The Risk Of Bias In Non-randomized Studies – of Exposures (ROBINS-E) assessment tool

for

Systematic Review of Caries Risk Factors in Adults: Toward a Population-Based Screening Tool

Table of content

1. Tobacco use and caries increment in young adults : a prospective observational study (1)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Socioeconomic Status (SES): SES can influence both tobacco use and oral health outcomes, as individuals with lower SES may have limited access to dental care and education about oral hygiene.
2. Oral Hygiene Practices: Variations in personal oral hygiene habits, such as frequency of brushing and flossing, can affect caries development and may differ among tobacco users and non-users.
3. Dietary Habits: Consumption of sugary foods and beverages is a significant risk factor for dental caries. Tobacco users may have different dietary patterns compared to non-users.
4. Age: Age can influence both the likelihood of tobacco use and the risk of developing dental caries, making it a critical factor to consider in studies.
5. Gender: Gender differences in tobacco use prevalence and oral health behaviors can confound the relationship between tobacco use and caries increment.
6. Other Substance Use: The use of other substances, such as alcohol, can also impact oral health and may be associated with tobacco use.
7. Access to Dental Care: Regular dental visits and preventive care can significantly influence caries outcomes and may differ between tobacco users and non-users.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

The risk of bias was assessed in terms of the relationship between habitual smoking and caries increment in young adults. The numerical result being assessed was the relative risk (RR) of caries development over a 3-year period in young adults who were habitual smokers compared to non-smokers. The study found that the RR for caries development was 1.4 (95% CI 1.3-1.8) for habitual smokers, indicating a significantly increased risk compared to non-smokers

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	the authors did not explicitly mention any specific attempts to control for confounding factors in their analysis of the relationship between tobacco use and caries increment in young adults. However, they did acknowledge that caries is a complex multifactorial disease influenced by various biological, behavioural, psychosocial, and socioeconomic risk factors that were not assessed in their study
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	Given the acknowledgment by the authors that caries is a complex multifactorial disease influenced by various factors not assessed in their study, there is a potential for confounding that could impact the relationship between tobacco use and caries increment in young adults. While the study found a significant association between habitual smoking and caries development, the presence of unmeasured confounding factors suggests that the unadjusted results should be interpreted with caution.
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	In this study, the use of self-reported data on tobacco use may introduce measurement bias, as individuals may underreport or overreport their tobacco habits. However, since the study aimed to investigate the relationship between tobacco use and caries increment over a 3-year period, the method of measuring exposure through self-reporting was appropriate for the study design and objectives.

B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	The method of measuring the outcome in the study involved scoring caries as decayed and filled surfaces according to WHO criteria and recording the individual caries increment by counting the number of surfaces that changed from "sound" to "decayed/filled" over the study period. Additionally, digital bitewing radiographs were used to evaluate caries progression. The method of measuring the outcome in the study can be considered appropriate for evaluating caries increment in young adults over a 3-year period.

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The outcome of interest in this analysis is the caries increment, which was assessed by counting the number of surfaces that changed from "sound" to "decayed/filled" over the study period. The study found a statistically significant relationship between habitual smoking and caries increment, with a relative risk of 1.5 for smoking and a number needed to harm of 6.8. The analysis assessing the association between habitual smoking and caries increment in young adults is the focus of evaluating the risk of bias in the study.

C2. Specify the participant group on which this result was based.

The result regarding the relationship between habitual smoking and caries increment in young adults was based on a participant group of 19-year-olds. The baseline cohort consisted of 1295 19-year-olds, with 982 participants reexamined after 3 years

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study is habitual tobacco use, specifically smoking and the use of smokeless tobacco (Swedish snus). This exposure was assessed through a structured questionnaire administered at baseline to collect information on the participants' tobacco habits. Participants were asked about their smoking habits and use of smokeless tobacco, with smoking defined as habitual smoking and snuffing defined as the use of Swedish snus. The questionnaire was self-reported and developed by health authorities in the Skåne region for mandatory use at all public dental clinics to gather information on tobacco habits. Participants were categorized based on their reported tobacco use as smokers, non-tobacco users, or dual users (both smoking and snuffing).
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / <u>PN / N</u>
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / <u>PN / N</u>
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / <u>PN / N</u>
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / <u>Y / PY</u> / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / <u>PN / N</u>
C9. **If N/PN to C7**, how were repeat measurements used?	In the study, repeat measurements were not used in the analysis of the relationship between tobacco use and caries development. The study primarily relied on baseline assessments of tobacco habits and caries status to investigate the association between smoking, snuffing, and caries increment over the 3-year observation period.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The study calculated the relative risk (RR) with confidence intervals to assess the risk of caries increment associated with smoking and snuffing compared to non-tobacco users. The results indicated that habitual smoking was a significant risk factor for caries increment in young adults, with a relative risk of 1.5 (95% CI 1.2–1.7) compared to non-tobacco users.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The eligible participants in the study were 19-year-old patients from eight Public Dental Clinics in southern Sweden, meeting specific criteria and excluding those with planned relocation, leaving the public dental service, or severe medical/mental disability. Differences between the eligible and study participants could lead to selection biases, affecting the generalizability of the findings to the broader population of 19-year-olds in the region.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study was tobacco use, specifically smoking and snuffing, assessed through self-reported habits at baseline. This exposure was distinct from the method of measurement and was investigated for its causal effect on caries development in young adults over a 3-year period.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	The exposure window of interest in the study was the baseline assessment of tobacco habits (smoking and snuffing) in young adults. This exposure window captured the period at the beginning of the study when participants reported their tobacco use status. The exposure window was defined by the time of onset, which was at baseline examination, and the period of exposure, which was the start of the study. The study aimed to assess the impact of tobacco habits reported at baseline on caries development over a 3-year period.

D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	The exposure was categorized into ever/never exposed groups based on the participants' self-reported tobacco use status at the beginning of the study. This classification allowed for the comparison of caries development over a 3-year period between individuals with a history of tobacco use and those without any reported tobacco habit. The study focused on the impact of baseline tobacco exposure on caries increment in young adults, summarizing exposure status at a single time point to evaluate its association with the outcome of interest.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance

Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Dietary habits	not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Access to Dental Care	not explicitly mentioned	N	N	N	Benefit of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written

Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
-	-	-	-	-	--	-
-	-	-	-	-	--	-

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	SN. While the study did not explicitly mention controlling for all potential confounding factors, the authors recognized the complexity of caries development and the involvement of various factors beyond tobacco use. Despite the lack of explicit control for all confounders, the authors' acknowledgment of the multifactorial nature of caries suggests that uncontrolled confounding may not have been substantial enough to significantly impact the study's conclusions.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	-
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	(No). The study did not provide information indicating the use of negative controls or other specific considerations to suggest serious uncontrolled confounding. While the study acknowledged the complexity of caries development and the involvement of various factors beyond tobacco use, there is no direct indication in the excerpts that the authors employed additional methods to assess or address potential uncontrolled confounding.

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the Risk of bias (due to confounding) in the estimated effect of exposure on the outcome would be assessed as "Some concerns." While the study did not explicitly mention controlling for all potential confounding factors and did not provide information on the use of negative controls or specific considerations to address serious uncontrolled confounding, the authors' recognition of the complexity of caries development and the acknowledgment of various factors beyond tobacco use suggest that uncontrolled confounding may not have been substantial enough to significantly impact the study's conclusions. However, the lack of explicit control for all confounders and the absence of specific methods to assess or address serious uncontrolled confounding raise some concerns about the potential impact of confounding on the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding in the is towards harm of the higher exposure. Given that smoking was found to be significantly related to caries increment over a 3-year period in young adults and considering the known detrimental effects of smoking on oral health and general health, the bias due to uncontrolled confounding is likely to exaggerate the harmful association between smoking and caries development. Therefore, the predicted direction of bias due to confounding in this study is towards harm of the higher exposure.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	In the context of the likely direction of bias towards harm of the higher exposure and the magnitude of the estimated exposure effect showing a significant relationship between smoking and caries increment in young adults, it is reasonable to conclude that the risk of bias due to confounding is not sufficiently high to threaten the conclusions about whether smoking has an important effect on the outcome. Given that smoking was found to be a significant risk factor for caries development in young adults and considering the known detrimental effects of smoking on oral health, the study's findings align with existing knowledge and support the importance of considering smoking as a risk factor for caries. While there were some concerns regarding confounding in the study, the direction of bias and the strength of the association suggest that the conclusions about the impact of smoking on caries development remain valid.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	Based on the information provided from the, there is no explicit mention of the authors using an analysis method that was specifically designed to control for time-varying as well as baseline confounding. Therefore, the assessment would be "N" (No). The study did not indicate the use of an analysis method tailored to control for both time-varying and baseline confounding.
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	there is no explicit mention of the authors controlling for time-varying factors or other variables measured after the start of the exposure window being studied. Therefore, the assessment would be NO. The study did not indicate that the authors controlled for time-varying factors or other variables measured after the start of the exposure window.

Signalling questions	Response options	Comments
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	There is no explicit mention of the use of negative controls or other considerations that suggest uncontrolled confounding. Therefore, the assessment would be “No”. The study did not indicate the use of negative controls or other considerations that would suggest uncontrolled confounding.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the Risk of bias (due to confounding) in the estimated effect of exposure on the outcome would be assessed as "Some concerns." While the study did not explicitly mention controlling for all potential confounding factors and did not provide information on the use of negative controls or specific considerations to address serious uncontrolled confounding, the authors' recognition of the complexity of caries development and the acknowledgment of various factors beyond tobacco use suggest that uncontrolled confounding may not have been substantial enough to significantly impact the study's conclusions. However, the lack of explicit control for all confounders and the absence of specific methods to assess or address serious uncontrolled confounding raise some concerns about the potential impact of confounding on the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding in the is towards harm of the higher exposure. Given that smoking was found to be significantly related to caries increment over a 3-year period in young adults and considering the known detrimental effects of smoking on oral health and general health, the bias due to uncontrolled confounding is likely to exaggerate the harmful association between smoking and caries development. Therefore, the predicted direction of bias due to confounding in this study is towards harm of the higher exposure.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Based on the information provided in the study, the risk of bias due to confounding does not appear to be sufficiently high to threaten conclusions about whether the exposure (tobacco use) has an important effect on the outcome (caries development). Therefore, the assessment would be "No." The study findings suggest a significant relationship between smoking and caries increment in young adults, indicating that the exposure (smoking) may have an important effect on the outcome (caries development). While the study may have limitations and areas for improvement, the results do not suggest a high risk of bias due to confounding that would undermine the conclusions regarding the impact of tobacco use on caries development.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure (habitual smoking and use of Swedish snus) appears to well-characterize the exposure metric specified to be of interest in this study. Therefore, the assessment would be "Y" (Yes). The study collected information on smoking and snuffing habits through a structured questionnaire at baseline, which aligns with the exposure metric of interest (tobacco use) in investigating its relationship with caries increment in young adults. The study's approach to measuring the exposure appears to be appropriate for the research question at hand.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	There is no indication that the exposure (habitual smoking and use of Swedish snus) was likely to be measured with error or misclassified. Therefore, the assessment would be "N" (No). The study does not suggest that the measurement of tobacco use was prone to substantial error or misclassification. The structured questionnaire used to collect information on smoking and snuffing habits at baseline likely provided a reliable basis for assessing the exposure in relation to caries development in young adults.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome could be considered Some concerns. While the questionnaire used to assess tobacco use was developed by health authorities and mandated for use at all public dental clinics in the Skåne region, the lack of explicit mention of validation for this specific study raises some concerns about the reliability and accuracy of the self-reported tobacco use data collected through the questionnaire. Without validation, there is a potential risk of measurement error or misclassification of exposure, which could introduce bias into the estimated effect of tobacco use on the outcome of caries increment in young adults.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The assessment would be "Towards harm of (higher) exposure." The study findings indicate a significant relationship between smoking and caries increment in young adults, suggesting that higher exposure to smoking is associated with an increased risk of caries development. In this context, any potential bias in the measurement of exposure would likely lead to an underestimation of the harmful effects of tobacco use on caries outcomes, indicating a direction of bias towards the harm of higher exposure.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	"No." The study's findings indicate a significant relationship between smoking and caries increment in young adults, and the measurement of exposure, although self-reported, was conducted using a structured questionnaire. While there may be limitations associated with self-reported data, the study does not suggest that the risk of bias in exposure measurement is high enough to undermine the conclusions regarding the important effect of tobacco use on caries development in young adults

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	PY Follow-up began at or close to the start of the exposure window for most participants. This minimizes the risk of bias in the selection of participants into the study or analysis, as it ensures that the exposure and outcome assessments are temporally aligned, allowing for a more accurate evaluation of the relationship between tobacco use and caries increment in young adults.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	-
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	No. The selection of participants into the study or analysis was not based on participant characteristics observed after the start of the exposure window being studied. This reduces the risk of bias in participant selection, as it ensures that the characteristics used for inclusion in the study were determined prior to the exposure, minimizing the potential for confounding factors to influence the results.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-

Signalling questions	Response options	Comments
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The authors selected participants for the study based on a specific criterion. The study cohort consisted of all 19-year-old patients registered at eight Public Dental Clinics (PDC) located in southern Sweden, representing various socioeconomic backgrounds. Exclusion criteria included planned relocation, leaving the public dental service, or severe medical/mental disability. Eligible patients received a written invitation to participate in the project, and 76.2% of them consented and attended the baseline examination. After 3 years, 982 participants were reexamined, resulting in a dropout rate of 24.2%
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study is towards harm of (higher) exposure. This means that there may be a tendency for the study to overestimate the negative impact of tobacco use on caries increment in young adults. It suggests that the study design and participant selection may have favored finding a stronger association between tobacco use and caries development.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	No. The risk of bias due to the selection of participants into the study, while having some concerns, is not deemed to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Despite the potential for bias, the study design and analysis appear to have taken measures to mitigate these concerns and provide meaningful insights into the relationship between tobacco use and caries increment in young adults.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no indications that post-exposure interventions were influenced by prior exposure during the follow-up period. The study did not mention any interventions that were specifically tailored based on participants' prior tobacco use or caries status, indicating that there were no post-exposure interventions influenced by prior exposure in this context.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	-
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	While the study did not mention any post-exposure interventions influenced by prior exposure, there may still be some concerns about the risk of bias in the estimated effect of exposure on the outcome. It is important to consider the potential for unmeasured confounding factors or other interventions that could impact the validity of the study findings.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding is towards harm of (higher) exposure. This suggests that there may be a tendency for the study to overestimate the negative impact of tobacco use on caries increment in young adults due to potential confounding factors that could influence the association between exposure and outcome.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	No. Given the context provided and the assessment of the risk of bias due to post-exposure interventions, it does not appear that the risk is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns about bias, the overall impact on the study's conclusions does not seem significant enough to invalidate the findings regarding the relationship between tobacco use and caries increment in young adults.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	No. Complete data on exposure status were not available for all participants. The study mentioned a drop-out rate of 24.2%, indicating that not all participants had complete data on exposure status.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on the outcome were available for nearly all participants. The study mentioned that 982 out of 1295 participants could be reexamined after 3 years, indicating a high follow-up rate and availability of outcome data for the majority of participants.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	The information provided in the document does not explicitly state whether complete data on confounding variables were available for all or nearly all participants. Therefore, it is not possible to determine the extent of missing data on confounding variables in this study.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	No. The result is not based on a complete case analysis. The study mentioned a drop-out rate of 24.2%, indicating that not all participants were included in the final analysis. Therefore, the analysis is not based on a complete case approach.
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	-
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	No. The analysis was not based on imputing missing values. The study did not mention any imputation methods for handling missing data, indicating that missing values were not imputed in the analysis.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-

Signalling questions	Response options	Comments
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	The study does not provide information on whether appropriate alternative method was used to correct for bias due to missing data. Therefore, it is not possible to determine if an appropriate alternative method was used in this study.
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	There is no evidence provided in the document to suggest that the results were not biased by missing data. The study mentioned a drop-out rate of 24.2%, indicating that missing data could potentially introduce bias into the results.
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias due to missing data in the estimated effect of exposure on the outcome. The study mentioned a drop-out rate of 24.2%, which could introduce bias into the results. However, the document does not provide information on how missing data was handled or if appropriate alternative methods were used to correct for bias, leading to some concerns about the risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide sufficient information to determine the predicted direction of bias due to missing data. Without details on how missing data was handled or if appropriate methods were used to correct for bias, it is not possible to predict the direction of bias in this context.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Due to the lack of information provided in the document regarding how missing data was handled and the potential bias introduced by the drop-out rate, it is not possible to determine if the risk of bias due to missing data is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Further details on the handling of missing data would be needed to make a more informed assessment.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The risk of bias arising from the measurement of the outcome is "Yes" (Y) because there is a possibility that the measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure. This difference in measurement could potentially introduce bias into the study results.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The study does not provide explicit information regarding whether outcome assessors were aware of study participants' exposure history. Therefore, it is not possible to determine if outcome assessors were aware or unaware of the exposure history, resulting in a classification of "NI".
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The study does not provide specific details on whether the assessment of the outcome could have been influenced by knowledge of participants' exposure history. Without this information, it is not possible to determine the extent to which the assessment of the outcome may have been influenced by participants' exposure history, resulting in a classification of "NI".
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided in the study, the Risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome is categorized as "Some concerns." This classification is due to the lack of specific details regarding whether outcome assessors were aware of participants' exposure history and if the assessment of the outcome could have been influenced by this knowledge. The absence of this information raises some concerns about the potential for bias in the measurement of outcomes.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Insufficient information available The document does not provide explicit details on the predicted direction of bias arising from the measurement of outcomes in relation to participants' exposure history. Without this information, it is not possible to determine the predicted direction of bias, resulting in a classification of "Insufficient information available."

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Due to the lack of specific information regarding the predicted direction of bias arising from the measurement of outcomes and the magnitude of the estimated exposure effect in the document, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Therefore, the classification is "Cannot tell."

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The document does not provide explicit details regarding whether the reported result was in accordance with an available, pre-determined analysis plan. Without this information, it is not possible to determine if the result was reported following a pre-determined analysis plan, leading to a classification of "No Information (NI)."
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	The study does not provide information indicating that multiple exposure measurements within the exposure domain were considered or that the reported effect estimate was selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome. Therefore, the classification for this question is "Not Applicable (NA)."
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The document does not provide explicit details regarding whether the reported effect estimate was selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. Without this information, it is not possible to determine the likelihood of bias in the selection of the reported result, leading to a classification of "No Information (NI)."
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The document does not provide explicit details regarding whether the reported effect estimate was selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. Without this information, it is not possible to determine the likelihood of bias in the selection of the reported result, leading to a classification of "No Information (NI)."
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The document does not provide explicit details regarding whether the reported effect estimate was selected based on the desirability of the results, such as statistical significance, from different subgroups. Without this information, it is not possible to determine the likelihood of bias in the selection of the reported result, leading to a classification of "No Information (NI)."

Signalling questions	Response options	Comments
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	It appears that all relevant results related to the study objective were reported in the publication. The study focused on the impact of tobacco use on caries increment, and the results pertaining to this relationship were clearly presented in the study findings
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The document does not provide explicit details regarding the predicted direction of bias due to the selection of the reported result based on the desirability of the results. Without this information, it is not possible to determine the predicted direction of bias in the selection of the reported result, leading to a classification of "Insufficient information available."
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Due to the lack of explicit information in the document regarding the selection of the reported result based on the desirability of the results, it is not possible to determine if the risk of bias in the selection of the reported result is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Therefore, the answer is "Cannot tell."

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The overall risk of bias for this study is categorized as "Some concerns." This classification is based on the information provided in the document, which indicates potential concerns related to the selection of the reported result and the possibility of bias due to uncontrolled confounding factors. While the study design was longitudinal and aimed to investigate the association between tobacco use and dental caries increment in young adults, the presence of some concerns regarding bias in the selection of the reported results and uncontrolled confounding factors warrants this classification.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in this study cannot be determined definitively due to insufficient information provided in the document. Without explicit details on the potential direction of bias in the study, it is not possible to ascertain whether the bias would favor a specific direction (benefit or harm of exposure, towards or away from the null hypothesis). Therefore, the answer is "Insufficient information available."
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias in the study cannot be definitively assessed as sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome due to the lack of explicit information provided in the document regarding the direction and magnitude of bias. Without this critical information, it is not possible to determine if the bias could potentially impact the conclusions about the effect of the exposure on the outcome. Therefore, the answer is "Cannot tell."

2. Diabetes status affects long-term changes in coronal caries - The SHIP Study (2)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Age: Age is a significant confounder as both diabetes prevalence and caries experience increase with age. It is relevant across all exposure-outcome combinations.
2. Gender: Gender differences can affect both diabetes prevalence and dental health outcomes. For example, men may have different risk profiles for diabetes and caries compared to women.
3. Socioeconomic Status (SES): SES influences access to healthcare, dental care, and education about oral hygiene, which can affect both diabetes management and caries risk.
4. Smoking Status: Smoking is a known risk factor for both diabetes and dental diseases, including caries. It can confound the relationship between diabetes and caries.
5. Oral Hygiene Practices: Frequency of tooth brushing, use of interdental cleaning devices, and regular dental visits are critical factors influencing caries outcomes and may vary by diabetes status.
6. Dietary Factors: Sugar intake and overall diet quality can significantly impact caries risk and may differ between individuals with varying diabetes control.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

Change in Decayed Missing Filled Surfaces (DMFS):

Subjects with poorly-controlled diabetes had significantly higher rates of change in DMFS compared to subjects without diabetes.

Change in Missing Surfaces (MS):

Both poorly-controlled and well-controlled diabetes groups had significantly higher rates of change in MS compared to subjects without diabetes.

Change in Decayed Filled Surfaces (DFS):

Rates of change in DFS were significantly lower for subjects with well-controlled diabetes and higher for those with poorly-controlled diabetes compared to subjects without diabetes.

HbA1c Levels:

All rates of change in caries variables increased proportionally to HbA1c levels, indicating a direct relationship between higher HbA1c and increased caries progression.

Diabetes Duration:

The effects were more pronounced in subjects with a diabetes duration of ≥5 years, suggesting that longer disease duration correlates with greater caries progression.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They utilized covariate-adjusted linear mixed models to evaluate the rates of change in caries variables while accounting for various confounding factors. These factors included age, gender, school education, smoking status, partnership status, waist circumference, dental visit frequency, interdental cleaning practices, and tooth brushing frequency
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	

B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

Decayed Missing Filled Surfaces (DMFS):

The change in DMFS was assessed to evaluate the overall caries experience in relation to diabetes status.

Missing Surfaces (MS):

The change in MS was specifically analyzed to understand the impact of diabetes on the number of missing surfaces due to caries.

Decayed Filled Surfaces (DFS):

The change in DFS was measured to assess the effect of diabetes on the surfaces that were filled due to caries.

HbA1c Levels:

The relationship between HbA1c levels and the rates of change in caries variables was examined to determine how metabolic control influences caries progression.

Diabetes Duration:

The impact of diabetes duration (≥5 years) on caries progression was analyzed to see if longer disease duration correlates with increased caries experience.

C2. Specify the participant group on which this result was based.

No Diabetes: Individuals with HbA1c < 6.5% or non-fasting blood glucose < 11.1 mmol/l.

Well-Controlled Diabetes: Individuals with known or undetected diabetes mellitus and HbA1c ≤ 7%.

Poorly-Controlled Diabetes: Individuals with known or undetected diabetes mellitus and HbA1c > 7%.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	**Self-Reported Diagnosis**: Participants were asked about their physician's diagnosis of diabetes and whether they were taking glucose-lowering medications. **HbA1c Measurement**: HbA1c levels were measured using high-performance liquid chromatography at various time points (SHIP-0, SHIP-1, and SHIP-2). **Blood Glucose Measurement**: Non-fasting serum glucose levels were measured using specific analytical systems during the study.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The study analyzed the interaction between diabetes status (exposure) and time on the rates of change in caries variables (outcome). Specifically, it assessed how different levels of diabetes control, indicated by HbA1c levels, influenced coronal caries progression over an 11-year follow-up.

1. Interaction Terms: Mixed models included interaction terms between diabetes status (well-controlled, poorly-controlled, and no diabetes) and time, allowing evaluation of how caries rates changed based on exposure status.

2. Cumulative Exposure: The study considered the cumulative effects of diabetes duration on caries outcomes, indicating that longer diabetes duration correlated with more significant caries progression.

3. Risk Ratios and Odds Ratios: Linear regression coefficients (B) and odds ratios (OR) were reported to quantify the relationship between diabetes status and caries outcomes, comparing risks across different diabetes statuses.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study was adults aged 20 to 79 years residing in northeast Germany, specifically participants from the Study of Health in Pomerania (SHIP). **Eligible Participants:** 1. **Age Range**: Individuals aged 20 to 79 years were included, ensuring a broad representation of adult age groups. 2. **Diabetes Status**: Participants were categorized based on their diabetes status, which included those with no diabetes, well-controlled diabetes (HbA1c ≤ 7%), and poorly-controlled diabetes (HbA1c > 7%). 3. **Follow-Up Participation**: Eligible participants were those who provided baseline data and participated in at least one follow-up assessment (5-year or 11-year).
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study was **diabetes status**, specifically defined by the level of glycemic control as indicated by hemoglobin A1c (HbA1c) levels. The exposure categories included: 1. **No Diabetes**: Participants with HbA1c levels < 6.5% or non-fasting blood glucose < 11.1 mmol/l. 2. **Well-Controlled Diabetes**: Participants with known or undetected diabetes mellitus and HbA1c levels ≤ 7%. 3. **Poorly-Controlled Diabetes**: Participants with known or undetected diabetes mellitus and HbA1c levels > 7%.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the	The exposure window of interest in the study is defined as the **period from baseline assessment (SHIP-0) through the 11-year follow-up (SHIP-2)**. This encompasses the entire duration of the study, during which

	ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	participants' diabetes status and glycemic control (measured by HbA1c levels) were assessed at multiple time points. **Specification of the Exposure Window:** 1. **Time of Onset**: The exposure period begins at the baseline assessment (SHIP-0), which was conducted between 1997 and 2001. This is when participants' diabetes status was first evaluated. 2. **Period of Exposure**: The exposure period extends through the follow-up assessments at 5 years (SHIP-1) and 11 years (SHIP-2), allowing for the evaluation of changes in diabetes status and its impact on caries progression over time.

D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	1. **Categorical Exposure Status**: Participants' diabetes status is categorized at each assessment point (baseline, 5-year follow-up, and 11-year follow-up) into three groups:
		   - No diabetes
		   - Well-controlled diabetes (HbA1c ≤ 7%)
		   - Poorly-controlled diabetes (HbA1c > 7%)
		2. **Cumulative Exposure**: The study can also summarize exposure by considering the cumulative duration of diabetes. This involves tracking how long participants have been diagnosed with diabetes and categorizing them based on the duration (e.g., <5 years vs. ≥5 years). This approach allows for an assessment of how longer exposure to diabetes affects caries outcomes.
		3. **Average Exposure**: For participants with fluctuating diabetes status over time, an average HbA1c level could be calculated across the assessment points to represent their overall glycemic control during the exposure window.
		4. **Time-Varying Exposure**: Since diabetes status can change over time, the study employs mixed models that account for time-varying exposure. This means that the analysis considers the

diabetes status at each follow-up visit, allowing for a more nuanced understanding of how changes in diabetes control impact caries progression.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance

Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Dietary habits	not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Access to Dental Care	not explicitly mentioned	N	N	N	Benefit of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written

Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	-
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	-

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	The authors used linear mixed effects models with random intercepts and slopes for time across subjects to estimate longitudinal effects of exposure variables on outcome variables . These models included baseline levels for confounders, as well as baseline and follow-up visit levels of exposure variables, follow-up time, and interaction terms between the exposure variable and time to identify exposure-dependent differences in rates of change in caries variables over time. By incorporating time-varying levels of outcome variables as dependent variables and including interaction terms between the exposure variable and time, the authors addressed both baseline and time-varying confounding in their analysis. This approach allowed for the evaluation of long-term effects of diabetes status and HbA1c levels on coronal caries experience over an average follow-up time of 11 years. Therefore, the authors used an appropriate analysis method to control for both time-varying and baseline confounding, and the answer is "Y" (Yes).
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors controlled several important baseline confounding factors such as age, gender, education, smoking, waist circumference, dental habits, and diabetes duration using appropriate statistical methods like linear mixed effects models. These models included baseline levels for confounders and interaction terms to identify exposure-dependent differences in rates of change in caries variables over time. While the study did not explicitly mention controlling for variables that could have been affected by the exposure during the study period or the use of negative controls to assess serious uncontrolled confounding, the comprehensive control for baseline confounders suggests a thorough attempt to address potential confounding factors. Therefore, the authors likely controlled all the important baseline confounding factors for which it was necessary. The answer is "Y" (Yes).

Signalling questions	Response options	Comments
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The study measured several confounding factors such as age, gender, education, smoking, waist circumference, dental habits, and diabetes duration using valid and reliable methods, . These variables were collected through computer-assisted interviews, physical measurements, and clinical examinations, ensuring a standardized and systematic approach to data collection. While the study did not explicitly mention the validation of these measurements within the context of the study, the use of standardized protocols and methods in data collection likely contributed to the validity and reliability of the measured confounding factors. Therefore, the confounding factors that were controlled for in the study were likely measured validly and reliably by the variables available, and the answer is "Y" (Yes).
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	The study did not explicitly mention the use of negative controls to assess uncontrolled confounding . However, the comprehensive control for baseline confounders and the use of appropriate statistical methods to address time-varying confounding suggest that the authors made a concerted effort to minimize the impact of uncontrolled confounding factors. While the study did not provide specific information on the use of negative controls, the overall approach to controlling for confounders and the rigorous statistical methods employed indicate that uncontrolled confounding was likely not a significant concern in this study. Therefore, based on the information available, the answer is "N" (No).

Signalling questions	Response options	Comments
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	Based on the information provided in the study , there is no explicit mention of the use of negative controls to assess uncontrolled confounding. However, the study employed robust statistical methods, including linear mixed effects models with interaction terms to address time-varying confounding and control for baseline confounders effectively. While the study did not specifically mention the use of negative controls, the rigorous approach to controlling for confounders and the detailed statistical analysis suggest that the authors made significant efforts to minimize the impact of uncontrolled confounding. Therefore, based on the available information, the answer is "PN" (Possibly No), indicating that while the study did not explicitly mention the use of negative controls, the overall approach suggests that uncontrolled confounding was likely not a major concern.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to confounding in the estimated effect of exposure on the outcome is considered low in the study. This determination is supported by the study's adjustment for various confounding factors, utilization of robust statistical analysis methods, sensitivity analyses, and the controlled population-based study design. These factors collectively contribute to minimizing the potential influence of confounding variables on the relationship between diabetes status, HbA1c levels, and coronal caries experience.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Given that the study controlled for baseline and time-varying confounding factors using appropriate statistical methods like linear mixed effects models with interaction terms, it is likely that the predicted direction of bias due to confounding would be towards the null. By effectively addressing confounding variables, the study aimed to minimize the impact of potential biases and provide more accurate estimates of the true relationship between diabetes status and caries outcomes. Therefore, the predicted direction of bias due to confounding is "Towards null," indicating that the study's results are likely to be closer to the true effect size after accounting for confounding factors.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Based on the information provided in the study, where the analysis was based on splitting participants' follow-up time according to exposure status and changes in exposure status were likely related to factors predictive of the outcome, both baseline and time-varying confounding were addressed using appropriate statistical methods. The study employed rigorous statistical techniques to control confounding factors and utilized a comprehensive approach to address potential biases. Given the thorough approach to addressing confounding and the use of appropriate statistical methods, the risk of bias due to confounding is likely low. Therefore, the risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Therefore, the answer is "No," indicating that the risk of bias due to confounding is not sufficiently high to threaten conclusions about the important effect of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to	Yes / No / Cannot tell	-

Signalling questions	Response options	Comments
threaten conclusions about whether the exposure has an important effect on the outcome?		

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	In the context where the analysis was based on splitting participants' follow-up time according to exposure status and/or magnitude, the measured exposure, including changes over time, is likely to well-characterize the exposure metric specified to be of interest in this study. By splitting participants' follow-up time based on exposure status and/or magnitude, the analysis allows for a detailed examination of how different levels or changes in exposure influence the outcome over time. This approach provides a comprehensive understanding of the relationship between exposure and outcome, capturing the dynamic nature of exposure effects. Therefore, in this scenario, the measured exposure, including changes over time, is expected to well-characterize the exposure metric of interest in the study. The answer is "Y" (yes) in this context.
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	In the context where the analysis was based on splitting participants' follow-up time according to exposure status and/or magnitude, there was likely some error in the measurement or misclassification of the exposure at each single time point. However, this error was probably not substantial. Given the complexity of measuring exposure status and changes over time in a longitudinal study, some degree of error or misclassification in exposure measurement at individual time points is expected. However, the analysis approach of splitting participants' follow-up time based on exposure status and magnitude helps to mitigate the impact of this error by considering exposure patterns over time rather than relying solely on single time point measurements. Therefore, while there may have been some error in the measurement or misclassification of exposure at each single time point, it was likely not substantial due to the analytical approach used in the study. The answer is "WY" (yes, but probably not a substantial amount) in this context.
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	In the context where the analysis was based on splitting participants' follow-up time according to exposure status and/or magnitude, the

		mismeasurement or misclassification of exposure could have been differential, but likely to a small extent. When exposure status and changes over time are considered in the analysis by splitting participants' follow-up time based on exposure characteristics, any differential mismeasurement or misclassification of exposure is less likely to significantly impact the results. The approach of examining exposure patterns over time helps to reduce the influence of differential misclassification by capturing the overall exposure trends and variations within individuals. Therefore, while there may have been some potential for differential mismeasurement or misclassification of exposure, it was likely to a small extent due to the analytical strategy employed in the study. The answer is "WY" (yes, to a small extent) in this context.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	By considering exposure status and changes over time and analyzing participants' follow-up time based on exposure characteristics, the study design accounts for the overall exposure patterns and variations within individuals. This approach helps to mitigate the impact of non-differential measurement errors on the estimated effect of exposure on the outcome. Non-differential errors, when exposure misclassification is unrelated to the outcome, are less likely to introduce bias in the estimated exposure effect. Therefore, in this scenario, the nature of the (non-differential) measurement error is not likely to bias the estimated effect of exposure on the outcome, given the analytical approach used in the study. The answer is "WY" (yes, to a small extent) in this context.
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome is likely to be low. The approach of splitting participants' follow-up time based on exposure characteristics allows for a detailed examination of exposure patterns over time, which helps to capture the dynamic nature of exposure effects on the outcome. This methodological strategy reduces the risk of bias arising from exposure measurement errors by considering exposure status and changes over time, thus providing a more comprehensive and accurate assessment of the relationship between exposure and outcome.

What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure is likely towards the null. When exposure status and changes over time are considered in the analysis by splitting participants' follow-up time based on exposure characteristics, any measurement errors in exposure assessment are more likely to attenuate the estimated effect towards the null hypothesis. By capturing exposure patterns over time, the analysis approach helps to balance out potential overestimation or underestimation of the exposure effect, leading to a bias towards the null.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Given that the predicted direction of bias is towards the null and the analytical approach considers exposure status and changes over time, any potential measurement errors in exposure assessment are likely to have a minimal impact on the conclusions regarding the importance of the exposure effect on the outcome. The methodological strategy used in the study helps to mitigate bias and provides a comprehensive evaluation of the relationship between exposure and outcome.

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The follow-up in the study began at the start of the exposure window for most participants. This is indicated by the fact that the baseline examinations were conducted between 1997 and 2001, and the average follow-up time was 11 years. Starting the follow-up close to the beginning of the exposure window ensures that participants were followed over an appropriate period to assess the long-term effects of diabetes status and HbA1c levels on coronal caries experience.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	-
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The selection of participants into the study (or into the analysis) was not based on participant characteristics observed after the start of the exposure window being studied. Participants were selected based on baseline examinations conducted between 1997 and 2001, which is before the exposure window of interest.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to the selection of participants into the study is at a low risk in the estimated effect of exposure on the outcome. This low risk is supported by the fact that participants were selected based on baseline

Signalling questions	Response options	Comments
		examinations conducted before the exposure window of interest, ensuring that the selection process did not introduce bias related to characteristics observed after the start of the exposure window. By starting the follow-up close to the beginning of the exposure window for most participants, the study design minimizes the risk of bias in estimating the effect of exposure on the outcome
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study is towards the null. This prediction is based on the fact that participants were selected based on baseline characteristics before the exposure window of interest. By starting the follow-up close to the beginning of the exposure window for most participants, any bias introduced by the selection process is likely to be towards the null, meaning that the estimated effect of exposure on the outcome is expected to be conservative and not exaggerated.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study design, which involved selecting participants based on baseline characteristics before the exposure window of interest, minimizes the risk of bias in estimating the effect of exposure on the outcome. Additionally, the predicted direction of bias is towards the null, indicating that any potential bias is likely conservative rather than exaggerated.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no post-exposure interventions that were influenced by prior exposure during the follow-up period in the study. The participants were selected based on baseline characteristics before the exposure window of interest, and there is no indication in the provided information that post-exposure interventions were influenced by prior exposure during the follow-up period.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	Since there were no post-exposure interventions that were influenced by prior exposure during the follow-up period in the study, it is not applicable to assess whether the analysis corrected for the effect of such interventions.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Given that there were no post-exposure interventions that were influenced by prior exposure during the follow-up period in the study, the risk of bias due to post-exposure interventions in the estimated effect of exposure on the outcome is low. The absence of such interventions minimizes the potential for bias introduced by post-exposure factors affecting the outcome, thereby reducing concerns about the validity of the estimated exposure effect on the outcome.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	In this study, the predicted direction of bias due to confounding is towards the null. The study design involved selecting participants based on baseline characteristics before the exposure window of interest, which helps control for potential confounders. By adjusting for baseline confounders and using mixed models to estimate long-term effects, the study aims to minimize the impact of confounding variables on the relationship between exposure and outcome.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to post-exposure interventions is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Since there were no post-exposure interventions that were influenced by prior exposure during the follow-up period in the study, the risk of bias due to such interventions is low. Therefore, the validity of the estimated exposure effect on the outcome is not significantly compromised by post-exposure interventions, and the

		conclusions about the importance of the exposure effect on the outcome remain robust.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on exposure status were available for nearly all participants in the study. The exclusion criteria and data handling procedures mentioned in the study ensured that subjects with missing data on exposure status were appropriately excluded from the analysis. This approach likely resulted in a high proportion of participants having complete data on exposure status
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on the outcome were available for nearly all participants in the study. The exclusion criteria and data handling procedures mentioned in the study likely ensured that subjects with missing data on the outcome were appropriately excluded from the analysis. This approach likely resulted in a high proportion of participants having complete data on the outcome, indicating that the risk of bias due to missing data related to the outcome is low.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on confounding variables were available for nearly all participants in the study. The study likely employed rigorous data collection methods and handling procedures to ensure that missing data on confounding variables were minimized.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	Exclusion from the analysis due to missing data was likely related to the true value of the outcome to some extent, but not strongly. The study likely employed appropriate exclusion criteria and handling procedures for missing data, which may have reduced the impact of missing data on the true outcome values. However, there may still be some relationship between missing data and the true outcome values, albeit not strong enough to significantly bias the results.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-

Signalling questions	Response options	Comments
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to missing data in the estimated effect of exposure on the outcome is considered low. The study likely had complete data on exposure, outcome, and confounding variables for nearly all participants, and the handling of missing data was conducted rigorously. This approach minimizes the potential for bias due to missing data, indicating a low risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Given that exclusion from the analysis due to missing data was likely related to the true value of the outcome to some extent, but not strongly, there is a possibility that the bias due to missing data could be towards harm of higher exposure. This means that the missing data may have a tendency to underestimate the true effect of exposure on the outcome, potentially leading to a bias that suggests a less favorable impact of the exposure on the outcome than what might be observed with complete data.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about	Yes / No / Cannot tell	The risk of bias due to missing data, considering its likely direction and the magnitude of the estimated exposure effect, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study likely employed robust methods to handle

Signalling questions	Response options	Comments
whether the exposure has an important effect on the outcome?		missing data, and any potential bias is not expected to significantly impact the overall conclusions regarding the important effect of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure. In the context of the study on the long-term changes in coronal caries in relation to diabetes status, there may have been variations in how caries were assessed or recorded among different exposure groups (e.g., no diabetes, well-controlled diabetes, poorly controlled diabetes). These differences in measurement or ascertainment could potentially introduce bias in the estimation of the exposure effect on the outcome.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The outcome assessors were partially aware of study participants' exposure history. In studies where the outcome assessors are not completely blinded to the exposure status of participants, there is a potential risk of bias. While the exposure history may not have been explicitly disclosed to the assessors, there could have been some indirect cues or information that may have influenced the outcome assessment, leading to a partial risk of bias in the measurement of the outcome.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The assessment of the outcome could have been influenced to a small extent by knowledge of participants' exposure history. While there may have been some potential for bias due to assessors having partial awareness of exposure history, the impact on the outcome assessment is considered minor. This small influence suggests a slight risk of bias in the measurement of the outcome, but it is not expected to significantly affect the overall study findings.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Half-Mouth Method, used to examine only one side of the mouth for dental conditions like coronal caries, can impact outcomes and introduce biases in studies
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes is towards the null. The partial awareness of exposure history by outcome assessors could potentially lead to a bias that diminishes the true effect of exposure on the outcome, tending to nullify any true associations that may exist. This bias could result in underestimating the actual impact of

Signalling questions	Response options	Comments
		exposure on the outcome, leading to a direction of bias towards the null hypothesis.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes, while present to some extent, is not considered sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Despite the potential for bias in outcome measurement due to partial awareness of exposure history, the magnitude of the estimated exposure effect and the likely direction of bias towards the null suggest that the overall conclusions regarding the impact of exposure on the outcome are not significantly compromised.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The result was reported in accordance with a partially available, pre-determined analysis plan. While some aspects of the analysis plan may have been predetermined and followed, there may have been some flexibility or modifications in reporting the results that were not explicitly outlined in the analysis plan.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple exposure measurements within the exposure domain. This suggests that there may be a risk of bias in the selection of the reported result, as the choice of which exposure measurements to report could be influenced by the desire to highlight significant or favorable effects.
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. This suggests a potential risk of bias in the selection of the reported result, as the choice of which outcome measurements to report could be influenced by the desire to emphasize significant or favorable effects.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. This suggests a potential risk of bias in the selection of the reported result, as the choice of which analyses to report could be influenced by the desire to highlight significant or favorable effects.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the results, such as statistical significance, from different subgroups. This suggests a potential risk of bias in the selection of the reported result, as the choice of which subgroup results to report could be influenced by the desire to emphasize significant or favorable effects.

Signalling questions	Response options	Comments
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	all results for each objective and for all groups were reported in the study. The researchers comprehensively analyzed the effects of diabetes status and metabolic control on long-term changes in coronal caries using data from the Study of Health in Pomerania. The study provided detailed associations between diabetes status, HbA1c levels, and various aspects of coronal caries experience, such as DMFS, DFS, and MS.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of the reported result is towards the benefit of higher exposure. This bias is likely to favor highlighting significant or favorable effects of the exposure on the outcome, potentially overemphasizing positive associations or effects.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result is sufficiently high, especially considering the predicted direction of bias towards the benefit of higher exposure. This bias could potentially influence the interpretation of the estimated exposure effect, leading to an overestimation of the importance or significance of the exposure on the outcome. Consequently, this bias threatens the validity of conclusions drawn about the impact of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The study demonstrated a low overall risk of bias through various strengths in its design and execution. Conducted on a large-scale population-based sample with 11-year follow-up data, the research provided a comprehensive assessment of the long-term effects of diabetes status and HbA1c levels on coronal caries outcomes. Results were reported for each objective and all groups, and mixed models were utilized for a detailed analysis, enhancing the understanding of the associations between diabetes status, metabolic control, and caries progression. Additionally, the well-trained and calibrated dental examiners ensured data accuracy, while appropriate statistical methods were employed for analysis. The study also transparently acknowledged potential limitations, further supporting the reliability and credibility of the findings regarding the impact of diabetes on coronal caries.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias is towards the benefit of higher exposure. This bias is primarily driven by concerns related to the selection of reported results, which may favor highlighting significant or favorable effects of the exposure on the outcome. Consequently, there is a potential for overestimating the positive impact of the exposure, leading to a bias towards the benefit of higher exposure.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study employed rigorous statistical techniques to control confounding factors and utilized a comprehensive approach to address potential biases related to confounding. By addressing both baseline and time-varying confounding using appropriate statistical methods, the risk of bias due to confounding is likely low. Therefore, the conclusions about the important effect of the exposure on the outcome are not significantly compromised by bias related to confounding factors.

3. Access to Fluoridated Water and Adult Dental Caries: A Natural Experiment (3)

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Age: Older individuals may have different dental health outcomes due to cumulative exposure to risk factors over time.
2. Sex: Gender differences can affect dental health behaviors and outcomes.
3. Income: Higher income levels often correlate with better access to dental care and oral health resources.
4. Education: Educational attainment influences health literacy and awareness of dental care practices.
5. Frequency of Dental Visits: Regular dental check-ups can significantly impact dental health outcomes.
6. Oral Hygiene Practices: Individual practices such as brushing and flossing can affect caries development.
7. Smoking: Tobacco use is associated with poorer oral health and increased risk of dental caries.
8. Diet: Sugar consumption and dietary habits can influence the risk of developing dental caries.
9. Previous Dental Treatments: History of dental caries or treatments can affect current dental health status.
10. General Health Conditions: Conditions such as diabetes can impact oral health.
11. Access to Dental Care: Geographic location and availability of dental services can influence dental health outcomes.
12. Community Water Fluoridation Levels: Variability in fluoridation practices across regions can affect exposure levels.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

Decayed, Missing, and Filled Teeth (DMFT) Index:

The study found that individuals with less than 50% lifetime exposure to fluoridated water had a higher DMFT rate ratio than those with greater exposure. Again, the excerpts did not detail specific numerical values for DMFT, but the results suggested a significant association between lower exposure and increased DMFT.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	Yes, the authors made several attempts to control for confounding factors in their analyses. They performed multiple regression models to adjust for various potential confounder
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The results being evaluated for risk of bias include:

Lifetime Access to Fluoridated Water: The categorization of participants based on their lifetime exposure to fluoridated water (>75%, 50% to 75%, and <50%) and its relationship to dental caries outcomes.

DMFT and DFT Indexes: The study's findings indicated that those with lower lifetime access to fluoridated water had higher DMFT and DFT rates, suggesting a correlation between reduced exposure and increased dental caries.

The potential risks of bias in this analysis could stem from factors such as:

Selection Bias: The study included only participants who had lived at the same address since age 7 or earlier, which may limit the generalizability of the findings.

Exposure Misclassification: Residential access to fluoridated water as a proxy for individual exposure may not accurately reflect actual fluoride intake.

Confounding Variables: Although the authors attempted to control for confounders, residual confounding from unmeasured variables could still influence the results.

C2. Specify the participant group on which this result was based.

The results of the study were based on a participant group from the EpiFloripa Adult cohort study, which included individuals aged 20 to 59 years. Specifically, the primary analyses focused on participants who had resided at the same address since the age of 7 years or younger. This criterion was established to assess the posteruptive effect of water fluoridation on dental caries in permanent teeth.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	lifetime residential access to fluoridated water. This exposure was assessed through a combination of participants' residency history and the implementation dates of water fluoridation in their respective areas.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N

C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

Rate Ratios: The study calculated rate ratios (RR) for DMFT and DFT outcomes based on the categories of lifetime access to fluoridated water:

Participants with 50% to 75% lifetime access had a DMFT rate ratio of 1.11 (95% CI, 0.85–1.44) compared to those with >75% access.

Participants with <50% lifetime access had a DMFT rate ratio of 1.39 (95% CI, 1.05–1.85) compared to those with >75% access.

Multivariable Models: The analysis included multiple regression models that adjusted for potential confounders, such as demographic and socioeconomic variables. The final model (model 3) showed the association between the level of access to fluoridated water and the DMFT and DFT indexes, indicating that lower lifetime access was associated with higher rates of dental caries.

Dose-Response Relationship: In unadjusted analyses, a dose-response relationship was observed, suggesting that longer lifetime exposure to fluoridated water was associated with lower dental caries experience. However, this relationship was attenuated after adjusting for confounders

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	Eligible Participants: Age Range: The study initially included adults aged 20 to 59 years at the time of the first wave of data collection in 2009. Residential History: Eligible participants were those who had resided at the same address since the age of 7 years or younger. This criterion was established to assess the posteruptive effect of water fluoridation on dental caries in permanent teeth. Access to Fluoridated Water: Participants needed to have a defined lifetime access to fluoridated water based on the implementation dates in their area (1982 and 1996). Inclusion Criteria: The primary analyses focused on participants who met the above criteria, which resulted in a final sample of 209 participants for the
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	Lifetime residential access to fluoridated water refers to the total number of years that participants have had access to water that has been fluoridated, starting from the time they were 7 years old or younger.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during	The exposure window of interest in the study is defined as lifetime exposure to fluoridated water, starting from age 7 years onward. Key Points: Time of Onset: Begins at age 7, when permanent teeth start to erupt. Period of Exposure: Extends throughout the participant's lifetime, categorized into: More than 75% of their lifetime

	ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	Between 50% to 75% of their lifetime Less than 50% of their lifetime
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	Exposure over time should be summarized as cumulative exposure to fluoridated water. This approach accounts for the total duration of time each participant had access to fluoridated water throughout their lifetime

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	number of years of education, income levels	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Access to Dental Care	classified as regular or irregular dental attenders	Y	Y	N	Benefit of (higher) exposure	

Age	categorized into different age groups	Y	Y	N	Insufficient information available	
Gender	categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	participants were categorized based on their smoking habits	Y	Y	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same

value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors of the study did control for important confounding factors such as demographic variables, socioeconomic variables, and dental caries-related behaviors. They used multiple regression models to adjust for these factors in their analysis. Therefore, the answer would be "Y" (Yes), as the authors made efforts to control for important confounding factors in their study.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The confounding factors that were controlled for in the study, such as demographic variables, socioeconomic variables, and dental caries-related behaviors, were measured using valid and reliable methods. The study assessed the reliability of examiner and interviewer measurements using appropriate statistical methods.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	The study did not mention controlling for any variables after the start of the exposure period that could have been affected by the exposure
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	The study did not mention the use of negative controls or other considerations to assess serious uncontrolled confounding
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to confounding in the estimated effect of exposure on the outcome is "Some concerns." While the study did control for important confounding factors such as demographic variables, socioeconomic variables, and dental caries-related behaviors, there is no mention of using negative controls or other considerations to assess serious uncontrolled confounding. Therefore, there may be some concerns regarding the potential impact of uncontrolled confounding on the estimated effect of exposure on the outcome.

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding is "Towards benefit of (higher) exposure." This prediction is based on the study's findings that participants with the shortest lifetime exposure to fluoridated water presented higher levels of dental caries compared to those with higher exposure levels
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to confounding is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns regarding confounding in the study, the predicted direction of bias is towards the benefit of higher exposure to fluoridated water. Given the study's findings and the control for important confounding factors, the bias is not likely to be significant enough to undermine the conclusions about the important effect of exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The single-point measurement of the exposure in this study does not adequately capture the complexity and variability of the exposure metric of interest, which is lifetime access to fluoridated water. Since the exposure was assessed based on participants' current residential status and historical implementation of water fluoridation in the area, it may not accurately reflect the long-term exposure patterns and cumulative effects of fluoride intake over an individual's lifetime. This limitation suggests that the measured exposure does not fully characterize the intended exposure metric specified in the study, indicating a substantial discrepancy between the actual exposure experience and the exposure measurement used in the analysis. As a result, the study may be at a high risk of bias due to the inadequate characterization of the exposure variable, potentially leading to biased estimates of the relationship between fluoridated water access and dental caries outcomes.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in this study, lifetime access to fluoridated water, was measured at a single point in time based on participants' current residential status and historical implementation of water fluoridation in the area. Given the dynamic nature of fluoride exposure over an individual's lifetime and the potential for changes in residential locations and water fluoridation practices, there is a high likelihood of measurement error and misclassification of the exposure. Since the measurement of lifetime access to fluoridated water was based on a snapshot of participants' current status and historical information, it may not accurately capture the full extent and variability of fluoride exposure experienced by individuals over their lifetimes. This could lead to misclassification of participants into exposure categories, potentially biasing the estimated effects of fluoridated water access on dental caries outcomes.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		

Signalling questions	Response options	Comments
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The mismeasurement or misclassification of exposure in this study, which was measured at a single point in time, could have been differential to a large extent. Since the exposure variable of interest, lifetime access to fluoridated water, was assessed based on participants' current residential status and historical implementation of water fluoridation in the area, there is a high likelihood that the measurement error or misclassification was related to the outcome or risk of the outcome. Differential misclassification occurs when the errors in exposure measurement are not random but are associated with the outcome or the risk of the outcome. In this case, if the mismeasurement or misclassification of lifetime access to fluoridated water is related to participants' dental caries status, it could introduce bias in the estimated effect of exposure on dental caries outcomes. For example, if individuals with higher levels of dental caries are more likely to have inaccuracies in reporting their lifetime exposure to fluoridated water, this could lead to an overestimation or underestimation of the true association between fluoridated water access and dental caries.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error in the exposure variable, lifetime access to fluoridated water, which was measured at a single point in time, is likely to bias the estimated effect of exposure on the outcome to a large extent. Since the exposure measurement errors are not related to the outcome or the risk of the outcome, they are considered non-differential. Non-differential measurement error can lead to bias in the estimated effect of exposure on the outcome by attenuating the true association towards the null hypothesis. In this study, if the inaccuracies in measuring lifetime access to fluoridated water are random and not associated with participants' dental caries status, the effect of exposure on dental caries outcomes may be underestimated or diluted.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome is categorized as "Some concerns." This assessment is based on the study's reliance on a single point in time measurement of lifetime access to fluoridated water, which may introduce potential errors and misclassification in the exposure variable. While efforts were made to categorize participants based on their residential status and historical implementation of water fluoridation, the possibility of differential misclassification due to the nature of the exposure assessment raises concerns about the accuracy and reliability of the exposure measurement.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure, which was assessed at a single point in time, is towards the null. Since the exposure variable of interest, lifetime access to fluoridated water, was measured based on participants' current residential status and historical implementation of water fluoridation in the area, any errors or misclassification in this measurement are likely to attenuate the true association between exposure and the outcome. In cases of non-differential misclassification or measurement error in exposure assessment, the estimated effect of exposure on the outcome tends to be biased towards the null hypothesis. This means that any inaccuracies in measuring lifetime access to fluoridated water, if not systematically related to participants' dental caries status, would likely lead to an underestimation or dilution of the true association between fluoridated water access and dental caries outcomes.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, particularly the potential for mismeasurement or misclassification of lifetime access to fluoridated water measured at a single point in time, is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Given the concerns regarding the accuracy and reliability of the exposure assessment, including the possibility of differential misclassification and non-differential measurement error, the risk of bias in the estimated effect of exposure on the outcome is significant. The likelihood of bias towards the null hypothesis due to measurement errors in the exposure variable raises concerns about the validity and interpretation of the study findings. These biases may impact the magnitude of the estimated exposure effect on adult dental caries outcomes, potentially leading to an underestimation of the true association between lifetime access to fluoridated water and dental caries.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	In the study where the analysis was based on splitting participants' follow-up time according to exposure status and/or magnitude, the follow-up began at or close to the start of the exposure window for most participants. This is indicated by the fact that participants were selected based on residing at the same address since the age of 7 years or younger, ensuring that the exposure to fluoridated water was captured from an early age. By focusing on participants who had been residing at the same address since childhood, the study aimed to assess the long-term effects of exposure to fluoridated water on dental caries. This approach suggests that the follow-up period closely aligned with the initiation of exposure to fluoridated water for the majority of participants, thereby reducing the risk of bias related to the timing of exposure and outcome assessment.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	The effect of exposure being constant over the period of follow-up analyzed is not clearly indicated in the information provided. Since the study did not explicitly mention whether the effect of exposure remained constant over time, it is not possible to determine if there were fluctuations or changes in the exposure effect during the follow-up period. Without specific details on the stability of the exposure effect over time, it is challenging to assess whether the effect of exposure was consistent throughout the follow-up period. Therefore, the rating for this question is "NI" (No Information), as the available information does not allow for a definitive evaluation of the constancy of the exposure effect over the period of follow-up analyzed.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The selection of participants into the study was not based on participant characteristics observed after the start of the exposure window being studied. Participants were included based on specific criteria related to their residential history and exposure to fluoridated water, such as residing at the same address since the age of 7 years or younger. This indicates that participant selection was determined by characteristics that predated the exposure window under investigation.

Signalling questions	Response options	Comments
		By focusing on participants who had a consistent residential history and exposure to fluoridated water from an early age, the study design ensured that participant selection was not influenced by characteristics observed after the start of the exposure window. Therefore, the rating for this question is "N" (No), indicating that the selection of participants into the study was not based on participant characteristics observed after the start of the exposure window being studied.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	The information provided does not explicitly state whether the analysis corrected for all potential selection biases identified in the risk of bias assessment for participant selection. While the study design included specific criteria for participant selection based on residential history and exposure to fluoridated water, it is unclear if the analysis accounted for all potential biases related to participant selection. Without detailed information on the specific methods used to address potential selection biases in the analysis, it is challenging to determine if all identified biases were adequately corrected for. Therefore, the rating for this question is "NI" (No Information), as the available information does not allow for a definitive assessment of whether the analysis corrected for all potential selection biases identified in the risk of bias assessment.
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	The study mentioned the performance of sensitivity analyses to test the impact of different selection criteria on the results. These alternative scenarios were used to assess whether other cut-off points for participant selection produced similar results. However, the specific findings or conclusions from these sensitivity analyses were not explicitly provided. Given that sensitivity analyses were conducted to test the impact of potential selection biases, the rating for this question is "PY" (Partially Yes), as the study indicated the use of sensitivity analyses to address potential

Signalling questions	Response options	Comments
		biases, but the extent to which these analyses demonstrated minimal impact is not explicitly stated.
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to the selection of participants into the study in the estimated effect of exposure on the outcome would be categorized as "Some concerns." This is because the study selected participants based on specific criteria, such as residing at the same address since the age of 7 years or before, which could introduce some selection bias. While this criterion was used to ensure a more homogeneous sample for analyzing the impact of lifetime exposure to fluoridated water on dental caries, it may also limit the generalizability of the findings to a broader population. Therefore, there are some concerns regarding the potential bias introduced by the selection criteria in the study
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study is "Towards benefit of (higher) exposure." This prediction is based on the study's selection criteria, which included participants with longer lifetime access to fluoridated water being associated with lower levels of dental caries. By selecting participants who had higher exposure to fluoridated water, the bias would likely favor finding a beneficial effect of fluoridation on dental caries outcomes.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study, while having some concerns, is not deemed to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study's sensitivity analyses and the selection criteria based on residential history and exposure to fluoridated water were implemented to address potential biases. While there may be some concerns about bias, the study's design and analyses suggest that the impact on the conclusions about the effect of exposure on the outcome is not significant enough to invalidate the findings

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	The study does not contain explicit information regarding post-exposure interventions that were influenced by prior exposure during the follow-up period. Therefore, it is not possible to determine whether there were post-exposure interventions that could have been influenced by prior exposure.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	-
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The study does not provide explicit information about post-exposure interventions that could have influenced the estimated effect of exposure on the outcome. Without this information, there are some concerns about the potential for bias due to post-exposure interventions. It is important to consider the influence of any interventions that occurred after exposure on the outcome to assess the risk of bias accurately.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding is "Towards benefit of (higher) exposure." This prediction is based on the study's selection criteria, which included participants with longer lifetime access to fluoridated water being associated with lower levels of dental caries. By selecting participants with higher exposure to fluoridated water, the bias would likely favor finding a beneficial effect of fluoridation on dental caries outcomes.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Given the information available, the risk of bias due to post-exposure interventions is not deemed to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns about potential bias, the study's design and analyses suggest that the impact on the conclusions about the effect of exposure on the outcome is not significant enough to invalidate the findings.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Yes. complete data on exposure status available for all, or nearly all, participants. Out of the 2,016 targeted participants, 1,720 were investigated in 2009 (85.3%) and 1,222 were interviewed and 1,140 then dentally examined in 2012.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study indicates that out of the 1,140 participants with dental clinical data, only those residing at the same address since the age of 7 years or younger were included in the primary analyses. This suggests that there were participants excluded based on the criteria of residing at the same address since a specific age, which may have led to missing data on the outcome for some participants.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	The document does not explicitly state whether complete data on confounding variables were available for all participants. However, it mentions that covariates such as sex, age, socioeconomic mobility, educational attainment, income, pattern of dental attendance, and smoking were included in the analysis. Since these variables were included in the analysis, it can be inferred that data on these confounding variables were likely available for all or nearly all participants.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	Participants were excluded from the analysis based on specific criteria related to exposure (residing at the same address since a certain age) and confounders. While this exclusion may introduce some bias, it may not be strongly related to the true value of the outcome as the criteria for exclusion were not directly related to the outcome itself.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-

Signalling questions	Response options	Comments
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	"Some concerns." This is because the study acknowledged the limitations of missing data and conducted sensitivity analyses to address potential biases related to incomplete data. By limiting the primary analysis to participants who had resided at the same address since the age of 7 years or before and performing sensitivity analyses with different scenarios, the researchers attempted to mitigate the impact of missing data on their findings
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is towards the benefit of higher exposure. Participants were excluded based on criteria related to exposure to fluoridated water, which may lead to underestimation of the actual effect of water fluoridation on dental caries prevention in adults. This exclusion could potentially bias the results towards showing a greater benefit of higher exposure to fluoridated water on dental caries.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to missing data, while present, is not considered to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study took measures to address missing data by excluding participants based on specific criteria related to exposure and confounders. While there are some concerns about bias, the overall impact on the conclusions is not significant enough to invalidate the findings.

Signalling questions	Response options	Comments

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	If the examiners were properly calibrated to ensure consistency and accuracy in measuring the outcome (dental caries using the DMFT index), then the risk of bias arising from measurement of the outcome would be minimized. In this case, if examiners were trained and standardized in their assessment of dental caries, the likelihood of measurement differences between exposure groups would be reduced, leading to a lower risk of bias in the study.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The information provided in the document does not specify whether outcome assessors were aware of study participants' exposure history. Without this information, it is not possible to determine if there was a risk of bias arising from measurement of the outcome due to assessors being aware of participants' exposure history.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	There is a possibility that assessment of the outcome could have been influenced by knowledge of participants' exposure history to fluoridated water. If outcome assessors were aware of participants' exposure levels, there could be a slight risk that this knowledge may have influenced how they assessed dental caries using the DMFT index. While efforts may have been made to standardize the assessment process, some degree of bias could still exist due to potential influence from knowledge of exposure history.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome. While efforts may have been made to calibrate examiners and standardize the assessment process, the potential influence of assessors' awareness of participants' exposure history could introduce some bias into the study results. This uncertainty warrants a classification of "Some concerns" for the risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null /	The predicted direction of bias arising from the measurement of outcomes is likely towards the null. If outcome assessors were aware of participants' exposure history to fluoridated water, there could be a slight risk that this knowledge may have influenced how they assessed dental caries using the

Signalling questions	Response options	Comments
	Insufficient information available	DMFT index. This potential bias may lead to an underestimation of the true effect of exposure on the outcome, resulting in a direction towards the null hypothesis.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes, while present to some extent, is not considered sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Despite the potential for bias due to assessors' awareness of participants' exposure history, the overall impact on the study conclusions is not significant enough to invalidate the findings regarding the association between lifetime access to fluoridated water and dental caries in adults.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The result was reported in accordance with a pre-determined analysis plan. The study likely followed a pre-defined analysis plan to analyze the association between lifetime access to fluoridated water and dental caries in adults. This adherence to a pre-determined plan suggests that the reported results are based on a planned analysis rather than post-hoc decisions, indicating a lower risk of bias in the selection of the reported result.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	the answer is NI (No Information) as the study does not provide explicit information to determine whether the reported effect estimate was selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple exposure measurements within the exposure domain.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The information provided does not specify whether the reported effect estimate was selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The information provided does not specify whether the reported effect estimate was selected based on the desirability of the results, such as statistical significance, from different subgroups.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The authors presented the results of their primary analysis, sensitivity analyses, and regression models examining the impact of lifetime exposure to fluoridated water on decayed, missing, and filled teeth (DMFT) and

Signalling questions	Response options	Comments
		decayed and filled teeth (DFT) outcomes. They reported rate ratios, confidence intervals, and statistical significance levels for the associations between different levels of residential access to fluoridated water and dental caries prevalence.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The text does not provide explicit details to determine the predicted direction of bias due to the selection of the reported result. Without specific information on how the reported results were selected or influenced, it is not possible to predict the direction of bias accurately. Therefore, the assessment for this question is inconclusive (Insufficient information available).
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The information provided does not offer sufficient details to determine if the risk of bias due to the selection of the reported result is high enough to threaten conclusions about whether the exposure has an important effect on the outcome. Without specific information on the selection process and its potential impact on the estimated exposure effect, it is not possible to make a definitive assessment in this context.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The overall risk of bias for this study is categorized as "Some concerns." This assessment is based on several factors contributing to potential biases in the study, including concerns about uncontrolled confounding, measurement of exposure, and selection of participants. While efforts were made to control for important confounding factors and conduct sensitivity analyses to address selection biases, there are still some uncertainties and limitations in the study design that raise concerns about the potential impact on the estimated effect of exposure on the outcome. Therefore, the overall risk of bias is considered to have some concerns.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding is "Towards benefit of (higher) exposure." This prediction is based on the fact that the study controlled for important confounding factors such as demographic variables, socioeconomic variables, and dental caries-related behaviors. However, there were no explicit mentions of using negative controls or specific considerations to address serious uncontrolled confounding. Therefore, the potential bias may lean towards overestimating the benefits of higher exposure to fluoridated water on dental caries outcomes.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	No, the overall risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are some concerns regarding confounding, measurement of exposure, and participant selection, the study made efforts to control for confounding factors, conduct sensitivity analyses, and address potential biases related to exposure measurement and participant selection. Additionally, the predicted direction of bias due to confounding is towards the benefit of higher exposure, suggesting that any potential biases may not significantly alter the conclusion regarding the association between lifetime access to fluoridated water and dental caries outcomes.

4. The Role of Behaviour in Inequality in Increments of Dental Caries among Finnish Adults (4)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Education Level: Affects both dental behaviors (e.g., knowledge about oral hygiene) and health outcomes (e.g., prevalence of dental caries).
2. Socioeconomic Status (SES): Influences access to dental care, ability to afford dental products, and health literacy.
3. Age: Affects both the likelihood of developing dental caries and the ability to maintain good dental hygiene.
4. Sex/Gender: May influence health behaviors and biological susceptibility to dental caries.
5. Oral Hygiene Practices: Directly impacts dental caries development.
6. Dietary Habits: Sugar intake and overall diet quality are critical factors in caries development.
7. Access to Dental Care: Affects the frequency of dental visits and preventive care.
8. Smoking Status: Associated with poorer oral health outcomes and can influence dental behaviors.
9. Health Literacy: Affects understanding of dental health information and the ability to engage in preventive behaviors.
10. Cultural Factors: Influences attitudes towards dental care and health behaviors.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They used sex- and age-adjusted regression models to assess the contribution of dental behaviors to inequalities in net DMFT and DT increments by education.
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The study utilized regression models to analyze these outcomes while adjusting for potential confounding factors, including sex, age, and various dental behaviors. The results indicated education gradients in caries increments, with the analysis assessing how dental behaviors contributed to explaining the inequalities observed in these outcomes.

C2. Specify the participant group on which this result was based.

The participant group on which the results were based consisted of 951 dentate adults who participated in both the Health 2000 survey and the Follow-Up Study on Finnish Adults' Oral Health. These participants had complete data on the selected measurements and were aged 30 years or older, with a mean age of 48.3 years. The group included a diverse representation of educational backgrounds, allowing for the analysis of the impact of education on dental caries increments.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study is the participants' dental behaviours, which include: 1. **Tooth brushing frequency with fluoridated toothpaste** 2. **Sugar consumption** 3. **Dental attendance patterns (e.g., visiting the dentist only for emergencies)** 4. **Daily smoking**
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study was a risk ratio for dental caries increments (net DMFT and net DT) comparing individuals with different levels of dental behaviors. The researchers used incidence rate ratios (IRRs) from negative binomial regression models to assess how dental behaviors influenced the risk of developing caries, showing that these behaviors significantly contributed to inequalities in dental health outcomes.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest was Finnish adults aged 30 years and older. Eligible participants for the causal effect were dentate adults who had complete data from both the baseline Health 2000 survey and the follow-up study, totaling 951 individuals. However, the causal effect may not apply to edentulous individuals or those with incomplete data, potentially introducing selection biases and limiting generalizability to all adults, especially those with poorer oral health or lower socioeconomic status.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure in the study was dental behaviors, which included factors such as frequency of tooth brushing with fluoridated toothpaste, sugar consumption, dental attendance patterns, and daily smoking.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	The exposure window in the study is defined as the four-year period between the baseline assessment (from the Health 2000 survey) and the follow-up oral re-examination.

D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	Exposure over time in the study should be summarized as average exposure for each participant during the four-year period. This involves assessing the frequency of dental behaviors (tooth brushing, sugar intake, dental attendance, and smoking) and calculating an average level of these behaviors, providing insight into their influence on dental caries increments.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Education level	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	sugar consumption	Y	Y	N	Harm of (higher) exposure	
Oral hygiene practices	tooth brushing frequency, use of fluoride toothpaste	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	dental attendance patterns	Y	Y	N	Benefit of (higher) exposure	

Age	Categorized into different age groups	Y	Y	-	Insufficient information available	
Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	participants were categorized based on their smoking habits	Y	Y	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same

value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors did not control for all the important confounding factors for which this was necessary. Therefore, the choice would be SN (no, and uncontrolled confounding was probably substantial). This decision is based on the acknowledgment that despite attempts to adjust for key confounding variables like tooth brushing frequency, sugar intake, dental attendance pattern, and smoking status, there is still a possibility of unmeasured factors such as dietary habits or genetic predisposition that could influence the results. The reliance on self-reported data for these variables and the potential for residual confounding indicate that uncontrolled confounding may have a substantial impact on the study outcomes.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	-
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	The use of negative controls or other considerations did not suggest serious uncontrolled confounding. Therefore, the choice would be N (No). This decision is based on the information provided, which did not indicate any specific negative controls or other factors that would suggest serious uncontrolled confounding beyond the acknowledged limitations in controlling for all important confounding factors at baseline.

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to confounding) in the estimated effect of exposure on the outcome is Some concerns. This rating is based on the acknowledgment that the study attempted to control for important confounding factors such as tooth brushing frequency, sugar intake, dental attendance pattern, and smoking status. However, there is a possibility of unmeasured confounders or residual confounding that could impact the results. The reliance on self-reported data for some variables and the potential for uncontrolled factors like dietary habits or genetic predisposition suggest that there are still some concerns regarding the risk of bias due to confounding in the study.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding is Towards harm of (higher) exposure. This prediction is based on the understanding that individuals with basic education, who are more likely to have unfavorable dental behaviors such as less frequent tooth brushing with fluoridated toothpaste, daily sugar consumption, dental visits only for emergencies, and daily smoking, had significantly greater increments of dental caries compared to those with higher education . These unfavorable behaviors are associated with poorer oral health outcomes, indicating that the presence of these confounding factors could lead to an underestimation of the true effect of exposure on the outcome, potentially biasing the results towards showing harm associated with higher exposure levels.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias (due to confounding) is Yes. This conclusion is drawn from the fact that the study indicates a significant association between lower education levels (linked to unfavorable dental behaviors) and greater increments of dental caries, suggesting that confounding factors may have influenced the observed effect of exposure on the outcome. Given the potential for confounding to bias the results towards showing harm associated with higher exposure levels, there is a concern that the magnitude of the estimated exposure effect may be influenced by these unmeasured or residual confounders, which could threaten the conclusions about whether the exposure has an important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

Domain 2, Variant (a): ***If N/PN to C5*** *(exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure in this study, which includes dental behaviors such as dental attendance pattern, tooth brushing frequency, use of fluoride toothpaste, sugar consumption, and smoking status , appears to well-characterize the exposure metric specified to be of interest. These behaviors are directly relevant to oral health and dental caries, which are the outcomes of interest in the study. The inclusion of these specific dental behaviors aligns with the study's focus on assessing the impact of behaviors on dental caries increments among Finnish adults. Therefore, the measured exposure well-characterizes the exposure metric specified in the study.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in this study, which includes dental behaviors like dental attendance pattern, tooth brushing frequency, use of fluoride toothpaste, sugar consumption, and smoking status, was likely measured with error or misclassified to some extent. Behavioral data collected at a single point in time may not fully capture the variability or changes in behaviors over time, potentially leading to misclassification or measurement error. Additionally, self-reported behaviors, such as tooth brushing frequency, sugar consumption, and smoking status, are subject to recall bias and social desirability bias, further increasing the likelihood of measurement error. Therefore, while the exposure was measured, there is a possibility of error or misclassification due to the nature of single-point measurements and self-reporting.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		

Signalling questions	Response options	Comments
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The potential for mismeasurement or misclassification of exposure in this study, which was measured at a single point in time , could have been differential to some extent. Since the exposure variables, such as dental behaviors, are related to oral health outcomes like dental caries, any misclassification or mismeasurement of these behaviors could be influenced by the participants' oral health status or risk of developing dental caries. For example, individuals with existing dental issues may report their behaviors differently compared to those without such issues, leading to differential misclassification. This differential misclassification could introduce bias into the study results, affecting the accuracy of the association between dental behaviors and increments of dental caries among Finnish adults. Therefore, the potential for mismeasurement or misclassification of exposure to be differential is present in this study.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error in the exposure, which was measured at a single point in time in this study, is likely to bias the estimated effect of exposure on the outcome to a small extent. Non-differential measurement error occurs when the misclassification of exposure is unrelated to the outcome or the risk of the outcome. In this context, if the measurement error in assessing dental behaviors is random and not systematically related to the development of dental caries, the bias introduced would likely be towards the null. While non-differential measurement error may slightly attenuate the true association between dental behaviors and increments of dental caries, it is less likely to substantially impact the overall findings of the study. Therefore, non-differential measurement error is expected to bias the estimated effect of exposure on the outcome to a small extent in this study.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	This determination is supported by the comprehensive approach to measuring exposure, which included self-reported information on dental behaviors and clinical assessments conducted by calibrated examiners. The calibration procedures ensured high reliability in recording dental findings, and specific criteria were used to identify decayed teeth during the examinations. The study's high reliability levels indicate a substantial agreement among examiners, contributing to a standardized and valid assessment process.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure, which was assessed at a single point in time in this study, is towards the null. Non-differential measurement error, which is likely in this scenario, typically biases the estimated effect towards the null hypothesis. In this context, any inaccuracies or misclassifications in measuring dental behaviors at a single time point are expected to dilute the true association between these behaviors and increments of dental caries among Finnish adults. Therefore, the bias arising from the measurement of exposure is predicted to push the estimated effect towards the null hypothesis, suggesting that the true association between dental behaviors and dental caries increments may be underestimated in the study results.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, particularly in the context of its likely direction towards the null and the magnitude of the estimated exposure effect in this study, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are concerns about measurement error and misclassification of exposure due to the single-point assessment, the predicted bias towards the null suggests that any potential impact on the estimated exposure effect is likely to be minimal. Given that the bias is expected to attenuate the association between dental behaviors and increments of dental caries, but not to a large extent, the overall conclusions regarding the importance of these behaviors on the outcome are not significantly compromised. Therefore, the risk of bias from the measurement of exposure is not sufficiently high to threaten the conclusions about the important effect of exposure on the outcome in this study.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	This suggests that there is partial certainty that the follow-up period started at or near the beginning of the exposure window for the majority of participants in the study. Starting follow-up close to the exposure window is important for minimizing bias related to the timing of exposure and outcome assessment.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	-
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The selection of participants into the study (or into the analysis) was not based on participant characteristics observed after the start of the exposure window being studied. This indicates a low risk of bias in terms of selecting participants based on characteristics that occurred after the exposure window, which could potentially introduce bias into the study results.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to the selection of participants into the study is considered low. This assessment is based on the fact that the selection of participants was not influenced by characteristics observed after the start of the exposure window being studied, indicating a lower likelihood of bias

Signalling questions	Response options	Comments
		affecting the estimated effect of exposure on the outcome. This suggests that the study's internal validity regarding the relationship between exposure and outcome is less likely to be compromised by selection bias.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study is towards null. This is because the selection of participants was not based on characteristics observed after the start of the exposure window being studied, indicating that there is less likelihood of bias favoring either the benefit or harm of higher exposure. Therefore, the bias is more likely to be towards the null hypothesis, suggesting that the estimated effect of exposure on the outcome may be closer to the true effect without significant distortion caused by participant selection.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study is not considered sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. This assessment is based on the low risk of bias in participant selection, the predicted direction of bias towards null, and the overall study design and methodology. Therefore, the bias related to participant selection is unlikely to significantly impact the conclusions regarding the important effect of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no post-exposure interventions that were influenced by prior exposure during the follow-up period. This indicates that there were no interventions implemented based on the participants' prior exposure status, suggesting a lower risk of bias due to post-exposure interventions influencing the study outcomes.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	-
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the context of the study on dental caries increments among Finnish adults, the influence of education on dental behaviors and oral health outcomes may encompass both formal education (e.g., schooling, vocational training) and informal education (e.g., health literacy, self-care practices learned through community programs or personal experiences). Considering the broader concept of education beyond formal schooling is crucial for capturing the full spectrum of factors that may contribute to health disparities and inequalities. Informal education can influence individuals' health behaviors, decision-making processes, and access to health information, all of which can impact oral health outcomes such as dental caries increments.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	In this context, the predicted direction of bias due to confounding is towards null. This prediction is based on the assumption that any potential confounding factors that were not adequately controlled for in the study would likely bias the results towards the null hypothesis, meaning that the true effect of the exposure on the outcome may be underestimated. Therefore, the bias due to confounding is expected to push the results towards the null rather than towards a specific benefit or harm of the exposure.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to	Yes / No / Cannot tell	The risk of bias due to post-exposure interventions is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Since there were no post-exposure interventions influenced by prior exposure during the follow-up period, the impact of

threaten conclusions about whether the exposure has an important effect on the outcome?		bias related to post-exposure interventions on the estimated exposure effect is minimal. Therefore, the risk of bias in this context is not significant enough to undermine the conclusions regarding the important effect of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on exposure status were available for all participants in this study.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study, nearly all participants had complete data on the outcome variable, meaning that the information regarding the outcome (in this case, dental caries increments) was available for the vast majority of the participants. However, there might have been a small proportion of participants with missing outcome data, which is why the answer is "PY" (Probably Yes). This indicates that while the majority of participants had complete outcome data, there may have been a few individuals with missing outcome information.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on confounding variables were available for all participants in this study
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	Exclusion from the analysis due to missing data was likely related to the true value of the outcome, but not strongly so. This means that while there may have been some relationship between missing data and the true outcome value, it was not a significant or strong relationship that would introduce substantial bias into the analysis.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would	-

Signalling questions	Response options	Comments
	not be substantially reduced) / NI	
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias due to missing data in the estimated effect of exposure on the outcome. While efforts were made to address missing data and complete data on confounding variables were available for all participants, there may still be some potential for bias due to missing data. It is important to acknowledge these concerns and consider the potential impact on the study results.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is towards the null. This means that the missing data is more likely to lead to an underestimation or attenuation of the true effect of exposure on the outcome. In this case, the missing data is expected to bias the results towards showing a weaker relationship between the exposure and the outcome than actually exists.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to missing data, considering its likely direction and the magnitude of the estimated exposure effect, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are some concerns about missing data and its potential impact on the results, the overall risk of bias is not deemed high enough to significantly undermine the conclusions drawn from the study regarding the effect of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	In the study, the measurement or ascertainment of the outcome, which is the increment of dental caries, could have differed between exposure groups or levels of exposure. For instance, individuals with different education levels may have varying levels of awareness and understanding of oral health practices, leading to potential differences in how they report or perceive their dental health status. Higher-educated individuals may have better knowledge about oral hygiene and dental care, potentially leading to more accurate self-reporting of dental issues or better compliance with dental visits. On the other hand, individuals with lower education levels may have limited access to dental information or resources, which could result in underreporting of dental problems or less frequent dental visits.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The study " does not explicitly mention whether outcome assessors were aware of study participants' exposure history. Without specific information provided in the paper regarding blinding procedures or the blinding status of outcome assessors to participants' exposure history, it is not possible to definitively determine if outcome assessors were aware of the exposure status of the study participants. In research studies, blinding outcome assessors to participants' exposure history helps minimize the risk of bias by preventing potential knowledge of exposure status from influencing the assessment of outcomes. If outcome assessors were not blinded to participants' exposure history, there could be a risk of bias if their awareness of exposure status influenced the measurement or interpretation of the outcomes.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome. The paper mentions that dental examinations were conducted identically at baseline and follow-up by trained dentists using specific

Signalling questions	Response options	Comments
		criteria to assess dental caries increments. However, there is no explicit mention of blinding procedures or whether outcome assessors were aware of participants' exposure history. Without clear information on blinding procedures or the blinding status of outcome assessors, there is a possibility that knowledge of participants' exposure history could have influenced the measurement or interpretation of the outcomes, potentially introducing bias into the estimated effect of exposure on dental caries increments. Therefore, while the study employed standardized methods for dental examinations, the lack of information on blinding procedures raises some concerns about the risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes cannot be definitively determined due to insufficient information provided in the paper. Without specific details on blinding procedures, the blinding status of outcome assessors, or potential sources of bias in outcome measurement, it is challenging to predict the direction of bias with certainty. Given the lack of explicit information on how outcome assessment was conducted and whether outcome assessors were aware of participants' exposure history, it is not possible to accurately predict whether any bias would systematically favor the benefit of higher exposure, harm of higher exposure, lead towards null findings, or deviate away from null results. Therefore, the predicted direction of bias arising from the measurement of outcomes remains uncertain due to the insufficient information available in the study.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	the information provided does not explicitly state whether the reported results were in accordance with an available, pre-determined analysis plan. Without clear documentation or disclosure regarding the existence of a pre-specified analysis plan and whether the reported results align with this plan, it is not possible to definitively determine if the results were reported as planned. Due to the lack of explicit information on the adherence to a pre-determined analysis plan in reporting the results, the assessment falls under "NI" (Not Informative). Without this crucial detail, it is challenging to evaluate whether the reported results were based on a pre-defined analysis plan, which could impact the reliability and validity of the study findings.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	the information provided does not explicitly address whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. Without specific details on the selection process of the reported effect estimate, it is not possible to determine if the reported estimate was chosen selectively based on its desirability.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	the information provided does not explicitly address whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. Without specific details on the selection process of the reported effect estimate from multiple analyses, it is not possible to determine if the estimate was selectively chosen based on its desirability.

Signalling questions	Response options	Comments
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	the reported effect estimate is less likely to be selected based on the desirability of the results, such as statistical significance, from different subgroups. The study methodology and reporting do not suggest a bias towards selectively reporting results based on the statistical significance or desirability of outcomes from different subgroups. Therefore, the classification for this question is "N" (No), indicating that the reported effect estimate is not likely to be selected based on the desirability of the results from different subgroups. The study appears to have reported findings without bias towards statistically significant or desirable outcomes, enhancing the credibility of the reported results.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the data reported in the study appear to align with the objectives outlined, focusing on the relationship between dental behaviors, education, and inequalities in dental caries increments among Finnish adults. The study findings contribute to understanding the role of behavior in oral health disparities and provide insights into potential mechanisms underlying these inequalities.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	the predicted direction of bias due to the selection of the reported result could potentially be towards the benefit of higher exposure. This prediction is based on the fact that the study aimed to examine the role of dental behaviors in 4-year increments of dental caries among Finnish adults and specifically focused on the impact of dental behaviors on reducing inequality in dental caries increments. Given the emphasis on understanding how dental behaviors can attenuate or eliminate inequality in increments of dental caries, there may be a tendency to highlight results that support the importance of positive dental behaviors in reducing caries increments. This focus on the role of behaviors in addressing inequalities in oral health could potentially lead to a bias towards reporting results that show a beneficial effect of certain behaviors or interventions on dental caries outcomes.

Signalling questions	Response options	Comments
		Therefore, based on the study's objectives and emphasis on the role of dental behaviors in addressing inequalities in dental caries increments, the predicted direction of bias due to the selection of the reported result could be towards the benefit of higher exposure.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	it is challenging to determine the extent to which the risk of bias due to the selection of the reported result could threaten conclusions about whether the exposure has an important effect on the outcome. The lack of transparency regarding the selection process and the potential bias direction makes it difficult to assess the impact of this bias on the study's conclusions. Without a clear understanding of how the reported results were chosen and whether any bias was introduced during this selection, it is not possible to definitively determine if the risk of bias is sufficiently high to threaten the conclusions about the importance of the exposure effect on the outcome. Therefore, the classification for this question is "Cannot tell." Additional information on the selection process and its potential impact on the study findings would be needed to make a more informed assessment of the risk of bias and its implications for the conclusions drawn in the study.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	the Overall risk of bias in the study "The Role of Behaviour in Inequality in Increments of Dental Caries among Finnish Adults" can be classified as having Some concerns. This classification is based on the following considerations: Confounding: The risk of bias due to confounding is categorized as Some concerns. While the study attempted to control for important confounding factors such as tooth brushing frequency, sugar intake, dental attendance pattern, and smoking status, there is still a possibility of unmeasured confounders or residual confounding that could impact the results. This suggests that there are some concerns regarding the risk of bias due to confounding in the study. Measurement of Exposure: The risk of bias arising from the measurement of exposure is also categorized as Some concerns. Although the study included multiple dental behaviors and used regression models to adjust for these behaviors, there are concerns about potential measurement error, misclassification of exposure, and limitations associated with self-reported behaviors. These factors raise some concerns regarding the accuracy of exposure measurement and its impact on the estimated effect of exposure on the outcome. Missing Data: There are some concerns regarding the risk of bias due to missing data. While efforts were made to address missing data and complete data on confounding variables were available for all participants, there may still be some potential for bias due to missing data. This factor adds to the overall concerns about bias in the study.

What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias in this scenario, considering the information provided, would likely be towards the null. Given that the study attempted to control for important confounding factors such as tooth brushing frequency, sugar intake, dental attendance pattern, and smoking status, there is a lower risk of bias due to confounding. However, there are still concerns about unmeasured confounders or residual confounding that could impact the results. This suggests that while efforts were made to address confounding, there may still be some residual effects that could bias the results towards the null hypothesis. Additionally, the concerns regarding the accuracy of exposure measurement and potential misclassification of exposure raise some doubts about the precision of the estimated effect of exposure on the outcome. This uncertainty in exposure measurement could introduce some level of bias, albeit not high or very high, which could also contribute to bias towards the null hypothesis. Therefore, considering the potential residual confounding and measurement uncertainties, the overall direction of bias in this study is more likely to be towards the null hypothesis, indicating that the true effect of exposure on the outcome may be underestimated or not fully captured.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Based on the information provided, the overall risk of bias in the study does not appear to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study addressed important confounding factors such as tooth brushing frequency, sugar intake, dental attendance pattern, and smoking status, which suggests a low risk of bias due to confounding. While there were some concerns about unmeasured confounders or residual confounding, the study's efforts to control for known confounders indicate a relatively low risk in this aspect. Additionally, the study's approach to measuring exposure, although with some concerns about potential measurement errors and misclassification, was likely mitigated by the study design and data

		collection methods. The inclusion of multiple dental behaviors and the use of regression models to adjust for these behaviors also helped in addressing measurement issues. Furthermore, the low risk of bias related to participant selection and post-exposure interventions, as well as some concerns about missing data, suggest that the study's internal validity regarding the relationship between exposure and outcome is relatively sound. Therefore, considering the overall assessment of bias in the study, the risk does not seem to be high enough to significantly threaten the conclusions about whether the exposure has an important effect on the outcome.

5. The Shape of the Dose-Response Relationship between Sugars and Caries in Adults (5)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Age: Older individuals may have different caries experiences and dietary habits compared to younger individuals. This factor is relevant across various studies.
2. Sex: Males and females may exhibit different patterns of sugars consumption and dental health outcomes. This factor is generally applicable to most studies.
3. Education Level: Higher education levels may correlate with better health literacy and dietary choices, influencing both sugars intake and dental health. This is relevant across studies.
4. Toothbrushing Frequency: Regular toothbrushing is crucial for preventing dental caries, making this factor relevant in all studies examining sugars intake and caries.
5. Dental Attendance: Frequency of dental visits can affect caries detection and management, relevant to most studies.
6. Use of Fluoride Toothpaste: The use of fluoride toothpaste is a significant factor in caries prevention and is relevant in studies focusing on sugars intake.
7. Overall Diet Quality: The general quality of the diet (e.g., intake of fruits, vegetables, and other nutrients) can influence dental health and may confound the relationship between sugars and caries. This is relevant across studies.
8. Other Sources of Sugars: The presence of other dietary sources of sugars (e.g., processed foods, beverages) can impact the overall sugars intake and its effects on dental health.
9. Use of Mouthwash or Other Oral Care Products: The use of additional oral hygiene products can influence dental health outcomes and may need to be considered in studies.
10. Income Level: Higher income may allow for better access to dental care and healthier food options, influencing both sugars intake and dental health. This is relevant in many studies.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

1. **For every additional occasion of sugars consumption**: The DMFT increased by **0.15 units** (with a 95% confidence interval of **0.04 to 0.25**).
2. **For every 10 grams of sugars consumed**: The DMFT increased by **0.10 units** (with a 95% confidence interval of **0.04 to 0.15**).

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They adjusted their models for various sociodemographic factors, including sex, age, and education (Model 2). Additionally, they further adjusted for dental behaviors such as toothbrushing frequency, dental attendance pattern, and use of fluoride toothpaste (Model 3). In Model 4, they mutually adjusted for both frequency and amount of sugars intake to evaluate their relative contributions while controlling for these confounders
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

DMFT (Decayed, Missing, and Filled Teeth)

C2. Specify the participant group on which this result was based.

The participant group on which the results were based consisted of 1,702 adults aged 30 years and older from Finland

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study is sugars intake, which includes both the frequency and amount of sugars consumed by the participants.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study was a linear dose-response relationship between the amount of sugars intake and the levels of dental caries, measured using the DMFT (Decayed, Missing, and Filled Teeth) index.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	Age: Participants were required to be at least 30 years old.Dental Status: Only individuals who were dentate were included, meaning they had at least one natural tooth.Data Completeness: Participants needed to have complete data on their dental status and sugars intake from the surveys conducted. Study Participants: The study utilized data from three surveys conducted in Finland: The Health 2000 Survey (baseline) included 8,028 adults, of which 6,335 had clinical oral examinations. A follow-up study in 2004-2005 included 2,000 adults randomly selected from the original cohort. The Health 2011 Survey invited all participants from the Health 2000 Survey who were still alive. Ultimately, the analysis was based on 1,889 dentate adults who had caries data from at least two of the three surveys, with 1,702, 902, and 1,009 participants contributing data in 2000, 2004, and 2011, respectively
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study was the amount of sugars intake. This refers to the total quantity of sugars consumed by participants, measured in grams per day (g/d).
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should	Time of Onset: The exposure window begins at baseline, which corresponds to the time of the Health 2000 Survey when participants' sugars intake was first measured. Period of Exposure: The exposure period is defined as the 12 months prior to the baseline assessment. Participants were asked to report their sugars

	include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	consumption over the past year using a food frequency questionnaire (FFQ)
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	In the context of the study, exposure over time should be summarized as average exposure during the specified exposure window. Each participant's sugars intake will be quantified as the average daily intake of sugars (in grams per day) over the 12 months prior to the baseline assessment. This average is calculated based on the responses provided in the food frequency questionnaire (FFQ), which asked participants to estimate their consumption frequency of various sugary items.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Level of education	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Toothbrushing Frequency, Use of Fluoride Toothpaste	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Classified as regular or irregular dental attenders	Y	Y	N	Benefit of (higher) exposure	

Age	Categorized into different age groups	Y	Y	N	Insufficient information available	
Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	Based on the information provided in the study, the authors did control for important confounding factors at baseline. They considered demographic, socioeconomic, and behavioral factors as potential confounders in their analysis. Specifically, socioeconomic position was indicated by participants' education, and dental behaviors such as dental attendance were also taken into account.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The confounding factors that were controlled for in the study, such as demographic, socioeconomic, and behavioral factors, were measured using validated and reliable methods. The study utilized a validated food frequency questionnaire (FFQ) to measure food consumption, including sugars intake, which was considered a key confounding factor. Additionally, participants' education level and dental behaviors were also assessed as potential confounders.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	The information provided does not specify whether the authors controlled for any variables after the start of the exposure period that could have been affected by the exposure. Since there is no explicit mention of post-exposure variables being controlled for in the study, the answer is NI (No information).
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	Based on the information provided in the study, there is no indication that the authors used negative controls or other considerations to suggest serious uncontrolled confounding. Since there is no explicit mention of such methods being employed to assess uncontrolled confounding, the answer is N (No).

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided regarding the control for confounding factors at baseline, the measurement validity and reliability of these factors, and the absence of serious uncontrolled confounding, the risk of bias due to confounding in the estimated effect of exposure on the outcome is likely to be at a low risk. The study appears to have appropriately addressed and controlled for potential confounders, indicating a low risk of bias due to confounding.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	Based on the information provided regarding the study focusing on the relationship between sugars intake and dental caries, where higher sugar consumption is associated with increased caries risk, the predicted direction of bias due to confounding would indeed be towards harm of higher exposure. Therefore, the predicted direction of bias due to confounding in this context is towards harm of higher exposure. Thank you for pointing out the correction.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	In the context of the likely direction of bias due to confounding towards harm of higher exposure (higher sugar consumption leading to more caries) and the magnitude of the estimated exposure effect, the risk of bias due to confounding is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study has effectively controlled for potential confounders, reducing the risk of bias, and the relationship between sugar intake and dental caries is well-established. Therefore, the risk of bias due to confounding is considered to be low and not sufficient to threaten the conclusions about the important effect of exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

Domain 2, Variant (a): ***If N/PN to C5*** *(exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The exposure in this study, which is sugar intake, was measured using a validated food frequency questionnaire (FFQ) at baseline . While the FFQ included 128 commonly used or nutritionally important food items and mixed dishes to estimate the frequency and amount of sugars intake, it was assessed at a single point in time. Therefore, the measured exposure may not fully capture the variability in sugar intake over the entire study period. As a result, the exposure may not be well-characterized over time.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure, sugar intake, was measured using a food frequency questionnaire (FFQ) with a 12-month recall period and single average portion sizes at baseline. While FFQs are commonly used in epidemiologic studies to assess usual long-term diet, they are subject to measurement error due to under- and overreporting. Additionally, FFQs may not capture variations in food intake that occur over time or distinguish between food items consumed together or separately during the day, potentially leading to misclassification of exposure. Given these limitations associated with FFQs, it is likely that the exposure was measured with some degree of error or misclassification.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Mismeasurement or misclassification of exposure, in this case, sugar intake measured at a single point in time using a food frequency questionnaire (FFQ) , could potentially have been differential. Since the FFQ may not accurately capture variations in sugar intake over time and is subject to measurement error, individuals with different levels of caries or risk of caries may have different reporting behaviors regarding their sugar consumption. This differential misclassification could lead to biased estimates of the association between sugar intake and dental caries, particularly if the misclassification is related to the outcome or the risk of the outcome.

Signalling questions	Response options	Comments
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error in the measurement of exposure (sugar intake) at a single point in time using a food frequency questionnaire (FFQ) is likely to bias the estimated effect of exposure on the outcome to some extent. Non-differential measurement error tends to bias results towards the null hypothesis, potentially underestimating the true association between sugar intake and dental caries. In this case, if the FFQ does not accurately capture the true variability in sugar intake among participants, the estimated effect of sugar intake on dental caries may be attenuated due to this measurement error.
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of exposure (sugar intake) at a single point in time using a food frequency questionnaire (FFQ) is assessed to have "Some concerns." The use of an FFQ introduces the potential for measurement error and misclassification of exposure, which could lead to biased estimates of the effect of sugar intake on dental caries. While non-differential measurement error may attenuate the estimated effect towards the null hypothesis, the possibility of differential misclassification related to the outcome or risk of the outcome raises concerns about the accuracy of the estimated association. Therefore, there are some concerns regarding the risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure (sugar intake) at a single point in time using a food frequency questionnaire (FFQ) is towards the null. Non-differential measurement error typically biases results towards the null hypothesis, meaning that any bias introduced by inaccuracies in measuring sugar intake is likely to underestimate the true association between sugar intake and dental caries. Therefore, the predicted direction of bias is towards the null, indicating an underestimation of the true effect of exposure on the outcome.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure (sugar intake) at a single point in time using a food frequency questionnaire (FFQ) is not considered to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are some concerns regarding potential measurement error and bias towards the null hypothesis, the direction of bias is towards the null, which typically underestimates the true effect of exposure. Given this, the risk of bias, although present, is not deemed to be high enough to significantly impact the conclusions about the importance of the exposure effect on the outcome

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The information provided in the document does not explicitly state whether follow-up began at or close to the start of the exposure window for most participants. Therefore, the answer is "NI" (No information) as there is no direct indication in the text regarding the timing of follow-up in relation to the start of the exposure window for the participants.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	-
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	Based on the information provided in the document, there is no explicit mention of whether the selection of participants into the study or analysis was based on participant characteristics observed after the start of the exposure window being studied. Therefore, the answer is "NI" (No information) as there is no specific detail provided regarding the timing of participant selection in relation to the exposure window.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided regarding the selection of participants in the study "The Shape of the Dose-Response Relationship between Sugars and Caries in Adults," the risk of bias due to the selection of participants into the study would be categorized as "Some concerns." This is because

Signalling questions	Response options	Comments
		participants were selected through sampling methods, and there were exclusions based on criteria such as being edentate or residing in specific health center districts with fewer sampled subjects, which could potentially introduce some selection bias
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Given the lack of specific information in the document regarding the predicted direction of bias due to the selection of participants into the study or analysis, it is not possible to determine the exact direction of bias. Without details on the methods used for participant selection and potential biases, it is challenging to predict whether the bias would be towards benefit, harm, null, or away from null. Therefore, the answer remains "Insufficient information available."
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Given the limited information provided in the document regarding the risk of bias due to the selection of participants into the study, it is challenging to assess whether the risk of bias is sufficiently high to threaten conclusions about the exposure effect on the outcome. Without specific details on the methods of participant selection and potential biases, it is difficult to determine the impact on the conclusions of the study. Therefore, the answer is "Cannot tell" due to insufficient information available to make a conclusive assessment.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	Based on the information provided in the document, there is no mention of post-exposure interventions that were influenced by prior exposure during the follow-up period. Therefore, the answer is "No" as there is no indication of interventions being influenced by prior exposure in the context of the study described.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	Based on the information provided in the document, there is no explicit mention of whether the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure. Without specific details on how the analysis accounted for such interventions, it is not possible to determine if corrections were made. Therefore, the answer is "NA" as there is no information available to assess whether the analysis corrected for the effect of post-exposure interventions influenced by prior exposure.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided in the document, there is no explicit mention of post-exposure interventions that were influenced by prior exposure or whether the analysis corrected for such interventions. Therefore, the risk of bias due to post-exposure interventions is categorized as "Low Risk".
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Given the information provided in the document, there is no explicit indication of the predicted direction of bias due to confounding in the context of post-exposure interventions. Without specific details on the potential impact of confounding on the estimated effect of exposure, it is not possible to determine the predicted direction of bias. Therefore, the answer is "Insufficient information available" as there are no details provided to make an informed assessment of the predicted direction of bias due to confounding in this scenario.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Given the lack of specific information regarding the handling of post-exposure interventions and their potential impact on the estimated exposure effect, it is challenging to determine if the risk of bias due to post-exposure interventions is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Without clarity on how post-exposure interventions were addressed in the analysis,

		it is difficult to assess the potential impact on the conclusions drawn from the study. Therefore, the answer is "Cannot tell" as there is insufficient information available to determine if the risk of bias due to post-exposure interventions threatens the conclusions about the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Based on the information provided in the document, it is stated that there were 1,889 dentate adults who had caries data in at least 2 of the 3 surveys (baseline plus 2004–2005 and/or 2011), of which 187 (10%) were excluded for missing data on covariates. This suggests that complete data on exposure status were not available for all participants, as there were exclusions due to missing data on covariates. Therefore, the answer is "PN" (Probably no) as complete data on exposure status were not available for all participants.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	Based on the information provided in the document, it is mentioned that caries data were available for 1,702, 902, and 1,009 participants in 2000, 2004, and 2011, respectively. Furthermore, 1,493 (88%) contributed to 2 waves of caries data and 209 (12%) to all 3 waves. This indicates that there were participants with missing data on the outcome (caries data) across the different survey waves. Therefore, complete data on the outcome were not available for all participants. The answer is "PN" (Probably no) as complete data on the outcome were not available for all participants.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	Based on the information provided in the document, it is mentioned that 187 participants (10%) were excluded for missing data on covariates. This indicates that complete data on confounding variables were not available for all participants, as there were exclusions due to missing data on covariates. Therefore, the answer is "PN" (Probably no) as complete data on confounding variables were not available for all participants.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	Based on the information provided in the document, it is mentioned that 187 participants (10%) were excluded for missing data on covariates. This exclusion of participants with missing data indicates that the analysis was not based on a complete case analysis, as not all participants with missing data were included in the analysis. Therefore, the answer is "PN" (Probably no) as the result was not based on a complete case analysis.
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	Based on the information provided in the document, it is stated that 187 participants (10%) were excluded for missing data on covariates. The exclusion of participants with missing data on covariates suggests that the missing data may not be completely at random and could potentially be

Signalling questions	Response options	Comments
		related to the true value of the outcome (DMFT levels). Therefore, the exclusion from the analysis because of missing data is likely to be related to the true value of the outcome. The answer is "SY" (Yes, strongly related).
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	Based on the information provided in the document, there is no explicit mention of imputing missing values in the analysis. The document states that 187 participants (10%) were excluded for missing data on covariates, but it does not specify if imputation methods were used to handle missing data. Therefore, based on the information available, the answer is "N" (No) as there is no indication that the analysis was based on imputing missing values.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	Based on the information provided in the document, there is no explicit mention of an alternative method used to correct for bias due to missing data. The document states that 187 participants (10%) were excluded for missing data on covariates, but it does not specify if any specific method was employed to address potential bias due to missing data. Without information on an alternative method being used, the answer is "NI" (No information) as there is no clear indication in the document.
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	There is no explicit evidence provided in the document to suggest that the results were not biased by missing data. Without information on how bias due to missing data was addressed or mitigated, it is safer to assume that there is a possibility of bias in the results.
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to missing data in the estimated effect of exposure on the outcome is categorized as "Some concerns." This assessment is based on the fact that the document mentions that 187 participants (10%) were

Signalling questions	Response options	Comments
		excluded for missing data on covariates, but it does not provide detailed information on how missing data were handled or whether any methods were used to address potential bias. Without clear information on the handling of missing data, there are concerns about the potential impact of missing data on the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is "Insufficient information available." The document does not provide explicit details on how missing data were handled or whether any methods were used to address potential bias. Without this information, it is not possible to predict the direction of bias resulting from missing data.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The answer is "Cannot tell." Without detailed information on how missing data were handled and the potential bias addressed, it is challenging to determine if the risk of bias due to missing data is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Additional information or transparency regarding the handling of missing data is needed to make a more definitive assessment.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The answer is "Y" (Yes). The document mentions that identical clinical oral examinations were conducted at baseline and follow-ups, independent of participants' completion of questionnaires. However, it is possible that measurement or ascertainment of the outcome (DMFT levels) could have differed between exposure groups or levels of exposure due to variations in factors such as dental behaviors, dietary habits, or other unaccounted variables.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The answer is "NI" (No information). The document does not provide explicit information on whether outcome assessors were aware of study participants' exposure history. Without this information, it is not possible to determine if there was potential bias arising from outcome assessors being aware of the participants' exposure history.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome is "Some concerns." While the document mentions identical clinical oral examinations conducted at baseline and follow-ups, the lack of information on whether outcome assessors were aware of participants' exposure history and the potential for differences in outcome ascertainment between exposure groups or levels of exposure raises some concerns about the risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes is "Insufficient information available." Without specific details on how outcome assessors were blinded to participants' exposure history or if there were differences in outcome ascertainment between exposure groups, it is not possible to predict the direction of bias with certainty.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the	Yes / No / Cannot tell	The lack of detailed information on the risk of bias arising from the measurement of outcomes, including whether outcome assessors were

Signalling questions	Response options	Comments
magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?		aware of participants' exposure history and the potential impact on the estimated exposure effect, makes it difficult to determine if the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	Based on the information provided in the document, it is not explicitly stated whether the reported result was in accordance with an available, pre-determined analysis plan. Without clear information on the existence and adherence to a pre-determined analysis plan, it is challenging to determine if the reported result was based on a predefined analysis strategy.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	Based on the information provided in the document, it is not clear whether the reported effect estimate was likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. The document does not explicitly address the process of selecting the reported effect estimate in relation to the desirability of the effect size or statistical significance. Therefore, the answer is NI (No information) as there is no explicit information provided to make a determination regarding the selection of the reported result based on desirability of the effect estimate.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	Based on the information provided in the document, it is not explicitly stated whether the reported effect estimate was likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. The document does not provide details on the process of selecting the reported effect estimate in relation to the desirability of the effect size or statistical significance from various analyses conducted.

Signalling questions	Response options	Comments
		Therefore, the answer is NI (No information) as there is no specific information available to determine if the reported effect estimate was selected based on the desirability of the effect size or statistical significance from multiple analyses of the exposure-outcome relationship.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	Based on the information provided in the document, there is no explicit indication that the reported effect estimate was likely to be selected based on the desirability of the results, such as statistical significance, from different subgroups. The document does not mention any specific details regarding the selection process of the reported effect estimate based on the desirability of results from various subgroups analyzed. Therefore, the reported effect estimate is considered to be "Probably no" in terms of being selected based on the basis of desirability of the results from different subgroups, as there is no clear information provided to suggest intentional selection based on subgroup results.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The study on the dose-response relationship between sugars intake and dental caries in adults raised some concerns regarding bias due to the selection of reported results. The research focused on examining how sugars intake and exposure to fluoride toothpaste influenced caries levels in 1,702 Finnish adults using advanced statistical models. While the methodology was robust, concerns arose about the generalizability of the findings to the broader Finnish adult population due to potential participant biases in follow-up surveys. Additionally, the use of a food frequency questionnaire with a 12-month recall period for measuring sugars consumption raised concerns about measurement error, which could impact result accuracy. Despite providing valuable insights, these concerns highlight the need for cautious interpretation of the study's reported results. Therefore, the Risk of bias is categorized as "Some concerns" due to the lack of clarity on the selection process of the reported result, which may introduce potential biases in the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of	The predicted direction of bias due to the selection of the reported result is "Insufficient information available." Since there is no specific information

Signalling questions	Response options	Comments
	(higher) exposure / Towards null / Away from null / Insufficient information available	provided in the document regarding the selection process of the reported effect estimate based on desirability or statistical significance, it is not possible to predict the direction of bias resulting from this selection process. Without clear details on how the reported effect estimate was chosen, it is not feasible to determine whether the selection would introduce bias towards the benefit of higher exposure, harm of higher exposure, towards null, or away from null. Therefore, the predicted direction of bias is categorized as "Insufficient information available" due to the lack of specific information on the selection process and its potential impact on the estimated effect of exposure on the outcome.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are some concerns regarding the selection process of the reported effect estimate, the lack of specific information on the direction of bias and its magnitude makes it difficult to determine if it would significantly impact the conclusions about the exposure effect on the outcome. Without clear details on the potential bias direction and magnitude resulting from the selection process, it is challenging to assess whether the bias would be substantial enough to threaten the overall conclusions about the importance of the exposure effect on the outcome. Therefore, the answer is "Cannot tell" as the level of bias risk is not clearly defined to determine if it would threaten the conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	Based on the information provided, the overall risk of bias for this study can be categorized as "Some concerns." While the study appears to have addressed and controlled for potential confounders adequately, indicating a low risk of bias due to confounding, there are some concerns regarding the measurement of exposure (sugar intake) and the potential for bias in the estimated effect of exposure on the outcome. Specifically, the use of a food frequency questionnaire (FFQ) to measure sugar intake at a single point in time introduces the potential for measurement error and misclassification of exposure, raising concerns about the accuracy of the estimated association. Additionally, the measurement of exposure using multiple time points poses some concerns about the potential for differential misclassification of exposure, which could bias the results by distorting the true relationship between sugar intake and dental caries. While there are some concerns about the measurement of exposure in the study, the overall risk of bias is not high or very high, indicating that the study findings may still provide valuable insights despite these limitations. Therefore, the overall risk of bias for this study is categorized as "Some concerns" due to the potential issues related to the measurement of exposure and their impact on the estimated effect of exposure on the outcome.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in this study is towards the null. This prediction is based on the assessment that the study has addressed and controlled for potential confounders adequately, indicating a low risk of bias due to confounding. Additionally, while there are some concerns about the measurement of exposure (sugar intake) using a food frequency questionnaire (FFQ) and the potential for differential misclassification of exposure, these

		issues are likely to attenuate the estimated effect towards the null hypothesis. Furthermore, the use of linear mixed effects models to estimate the association between sugar intake and dental caries levels over 11 years, accounting for repeated measures and individual differences, suggests that the study has taken steps to minimize bias in the estimated effect of exposure on the outcome. Therefore, the overall risk of bias is predicted to bias the results towards the null hypothesis, indicating a more conservative estimate of the true relationship between sugar intake and dental caries.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias in this study is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study has addressed and controlled for potential confounders adequately, indicating a low risk of bias due to confounding. Additionally, the use of linear mixed effects models to estimate the association between sugar intake and dental caries levels over 11 years suggests that the study has taken steps to minimize bias in the estimated effect of exposure on the outcome. While there are some concerns about the measurement of exposure using a food frequency questionnaire and the potential for measurement error, the study's approach to analyzing the data and controlling for confounders supports the reliability of the findings.

6. Sugar-sweetened beverages and dental caries in adults: A 4-year prospective study (6)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Age: Older individuals may have different caries experiences and dietary habits compared to younger individuals. This factor is relevant across various studies.
2. Sex: Males and females may exhibit different patterns of sugars consumption and dental health outcomes. This factor is generally applicable to most studies.
3. Education Level: Higher education levels may correlate with better health literacy and dietary choices, influencing both sugars intake and dental health. This is relevant across studies.
4. Toothbrushing Frequency: Regular toothbrushing is crucial for preventing dental caries, making this factor relevant in all studies examining sugars intake and caries.
5. Dental Attendance: Frequency of dental visits can affect caries detection and management, relevant to most studies.
6. Use of Fluoride Toothpaste: The use of fluoride toothpaste is a significant factor in caries prevention and is relevant in studies focusing on sugars intake.
7. Overall Diet Quality: The general quality of the diet (e.g., intake of fruits, vegetables, and other nutrients) can influence dental health and may confound the relationship between sugars and caries. This is relevant across studies.
8. Other Sources of Sugars: The presence of other dietary sources of sugars (e.g., processed foods, beverages) can impact the overall sugars intake and its effects on dental health.
9. Use of Mouthwash or Other Oral Care Products: The use of additional oral hygiene products can influence dental health outcomes and may need to be considered in studies.
10. Income Level: Higher income may allow for better access to dental care and healthier food options, influencing both sugars intake and dental health. This is relevant in many studies.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

DMFT increment

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	Yes, the authors made several attempts to control for confounding in their analysis. They adjusted for a comprehensive set of potential confounders in their regression models.
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

DMFT increment

C2. Specify the participant group on which this result was based.

Finnish Adults

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	Consumption of sugar-sweetened beverages (SSBs). Participants reported their habitual consumption of selected sugary items at baseline
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study was a dose–response relationship between the frequency of sugar-sweetened beverage (SSB) consumption and the increment of dental caries, measured by the net DMFT (Decayed, Missing, and Filled Teeth) increment over a 4-year period.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study was Finnish adults aged 30 years and older who are dentate (having natural teeth). Eligible participants included those who participated in both the Health 2000 Survey and the Follow-Up Study of Finnish Adults' Oral Health, providing complete data on sugar-sweetened beverage (SSB) consumption and dental examinations.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study was the frequency of consumption of sugar-sweetened beverages (SSBs).
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	The exposure window of interest in the study was the 4-year period between the baseline assessment and the follow-up examination

D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	Exposure over time to sugar-sweetened beverages (SSBs) should be summarized as average exposure during the 4-year period. Participants reported their habitual consumption of SSBs at baseline, which was categorized into three groups: 0 SSBs per day, 1-2 SSBs per day, and 3 or more SSBs per day.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Level of education	Y	Y	N	(Benefit of (higher) exposure	
Oral hygiene practices	Toothbrushing Frequency, Use of Fluoride Toothpaste	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Dental attendance patterns	Y	Y	N	Benefit of (higher) exposure	
Age	Categorized into different age groups	Y	Y	N	Insufficient information available	

Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors of the study controlled for important confounding factors at baseline. They considered demographic factors (such as sex and age), socioeconomic status, and behavioral factors (including dental attendance pattern, toothbrushing frequency, and use of fluoride toothpaste) in their analysis. By including these factors in their models, the authors aimed to minimize the potential impact of confounding variables on the association between sugar-sweetened beverage (SSB) consumption and dental caries.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The confounding factors that were controlled for in the study, such as demographic factors, socioeconomic status, and behavioral factors, were likely measured validly and reliably based on the variables available in the study. The authors utilized established methods to assess these factors, including self-reported data on education level, dental behaviors, and SSB consumption frequency.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	The authors did not control for any variables after the start of the exposure period that could have been affected by the exposure. The study focused on assessing the relationship between baseline consumption of sugar-sweetened beverages (SSBs) and the development of dental caries over a 4-year period . Since the exposure (SSB consumption) was measured at baseline and the outcome (dental caries) was assessed over the follow-up period, there were no additional variables introduced after the start of the exposure period that could have been influenced by SSB consumption

Signalling questions	Response options	Comments
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	The study did not suggest serious uncontrolled confounding based on the measures taken to control for confounding variables. The use of negative controls or other considerations in the study did not suggest serious uncontrolled confounding. The authors controlled for important confounding factors at baseline, including demographic variables, socioeconomic status, and behavioral factors, to minimize the potential impact of confounding on the association between sugar-sweetened beverage (SSB) consumption and dental caries. By incorporating these factors into their analysis, the authors aimed to address potential sources of bias and confounding.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to confounding) in the estimated effect of exposure on the outcome in the study is Low risk. The authors controlled for important confounding factors at baseline, including demographic variables, socioeconomic status, and behavioral factors, to minimize the potential impact of confounding on the association between sugar-sweetened beverage (SSB) consumption and dental caries. By incorporating these factors into their analysis, the authors took appropriate steps to address potential sources of bias and confounding.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding in the study is Towards harm of (higher) exposure. The study aimed to explore the association between frequency of sugar-sweetened beverage (SSB) consumption and dental caries increment over a 4-year period in adults. Given the well-established detrimental effects of high sugar consumption on dental health, uncontrolled confounding factors that are associated with both higher SSB consumption and increased risk of dental caries could potentially bias the results towards showing a stronger harmful effect of SSB consumption on dental caries.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to confounding is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study controlled for important confounding factors at baseline, including demographic variables, socioeconomic status, and behavioral factors, to minimize the potential impact of confounding on the association between sugar-sweetened beverage (SSB) consumption and dental caries. By addressing these confounders, the study aimed to reduce the likelihood of bias affecting the conclusions drawn about the relationship between SSB consumption and dental caries.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure in the study well-characterizes the exposure metric specified to be of interest. The study focused on exploring the association between the frequency of sugar-sweetened beverage (SSB) consumption and dental caries increment over a 4-year period in adults. The exposure metric of interest, which is the frequency of SSB consumption, was clearly defined and categorized into meaningful groups (0 SSB/day, 1–2 SSB/day, 3+ SSB/day) to capture different levels of exposure.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in the study was likely not measured with error or misclassified. The frequency of sugar-sweetened beverage (SSB) consumption was assessed using a validated food-frequency questionnaire. The questionnaire was designed to capture participants' habitual intake of SSB over a specified period, providing a reliable estimate of their consumption patterns.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Given that the questionnaire used in the study to assess the frequency of sugar-sweetened beverage (SSB) consumption was not explicitly stated to be validated, there may be some concerns regarding the risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome. Without validation, there is a possibility of measurement error or misclassification of the exposure variable, which could introduce bias into the study results.

Signalling questions	Response options	Comments
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure in this study, where exposure to sugar-sweetened beverages (SSB) was assessed at a single point in time and the questionnaire used was not explicitly validated, would likely be towards the null. Without a validated questionnaire, there is a higher likelihood of measurement error or misclassification of SSB consumption, which could lead to an underestimation or dilution of the true association between SSB intake and dental caries outcomes.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, particularly due to the lack of validation for the questionnaire used to assess sugar-sweetened beverage (SSB) consumption in the study, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns regarding the risk of bias from mismeasurement or misclassification of the exposure, the study findings still demonstrate a significant association between SSB consumption and dental caries in adults.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	Since the study focused on assessing the impact of SSB consumption on dental caries increment over time, it is likely that the follow-up began at or close to the start of the exposure window for most participants.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	The exposure of interest is the frequency of SSB consumption, which is assessed at baseline . Since dietary habits, including SSB intake, can vary over time due to changes in lifestyle, preferences, or external factors, the effect of exposure may not be constant over the 4-year follow-up period analyzed in the study.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	Since these participant characteristics were assessed at the beginning of the study, before the exposure window (SSB consumption) and outcome (dental caries) were measured, the selection of participants into the analysis was not influenced by characteristics observed after the start of the exposure window.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	The analysis accounted for participant characteristics observed at baseline, including demographic information, education level, and dental behaviors, to assess the association between SSB consumption and dental caries increment over a 4-year period . By considering these baseline characteristics in the analysis, the study attempted to address potential selection biases related to participant characteristics and exposure status.
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	There is no explicit mention of sensitivity analyses being conducted to assess the impact of potential selection biases related to participant characteristics on the study results. Without information on specific sensitivity analyses addressing these biases, it is challenging to determine whether the likely impact of these biases was minimal.

Signalling questions	Response options	Comments
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to the selection of participants into the study in the estimated effect of exposure on the outcome can be assessed as having "Some concerns". The study conducted clinical oral examinations at baseline and follow-up to assess dental caries increment in Finnish dentate adults. This process involved selecting participants based on certain criteria, such as dentate status and willingness to participate. While the study accounted for baseline demographic factors, education level, and dental behaviors in the analysis to address potential selection biases, there is no explicit mention of sensitivity analyses to evaluate the impact of these biases on the study results.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study in the estimated effect of exposure on the outcome is "Towards harm of (higher) exposure". The study included 939 dentate adults who participated in both the Health 2000 Survey and the Follow-Up Study of Finnish Adults' Oral Health. The selection of participants was based on their willingness to participate and meeting the inclusion criteria for the study. The study found a positive association between frequency of SSB consumption and dental caries increment over a 4-year period in Finnish adults. This suggests that higher SSB consumption was associated with a higher risk of dental caries.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study in the estimated effect of exposure on the outcome is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study on sugar-sweetened beverage (SSB) consumption and dental caries in adults included adjustments for demographic characteristics, education level, and dental behaviors in the analysis to address potential biases related to participant selection. While there may be some concerns about bias due to selection, the adjustments made in the analysis suggest that any bias is likely towards the null or towards underestimating the harmful effects of higher SSB consumption on dental caries.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no post-exposure interventions that were influenced by prior exposure during the follow-up period in the study.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	It is not applicable (NA) to consider the correction for the effect of post-exposure interventions that were influenced by prior exposure in the study. The study primarily focused on examining the association between the frequency of SSB consumption and dental caries increment over a 4-year period in adults . The analysis did not involve any post-exposure interventions or treatments that could have been influenced by prior exposure to SSBs during the follow-up period .
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There were no post-exposure interventions mentioned in the study that could have influenced the outcomes based on prior exposure to SSBs during the follow-up period.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding in the study is Towards null. The study adjusted baseline demographic characteristics, socioeconomic factors, and behavioral factors as confounders in the analysis to address potential biases related to participant characteristics. By including these confounders in the analysis, the study aimed to minimize the impact of potential confounding variables on the association between SSB consumption and dental caries increment.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The study did not involve any post-exposure interventions that could have influenced the outcomes based on prior exposure to sugar-sweetened beverages during the follow-up period.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on exposure status were available for all, or nearly all, participants in the study. The study collected data on SSB consumption as part of the baseline assessment for all participants . There is no indication in the study that exposure data on SSB consumption were missing for any participants during the follow-up period
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on the outcome were available for all, or nearly all, participants in the study. The study conducted baseline and follow-up clinical oral examinations for all participants to assess the outcome of dental caries increment over a 4-year period . There is no mention in the study of any missing data related to the outcome measure of dental caries during the follow-up assessments
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	Complete data on confounding variables were available for all, or nearly all, participants in the study
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	-
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would	-

Signalling questions	Response options	Comments
	not be substantially reduced) / NI	
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Risk of bias (due to missing data) in the estimated effect of exposure on the outcome is Low risk in the study. The study ensured complete data on exposure status (SSB consumption), outcome (dental caries), and confounding variables for all or nearly all participants. There is no mention in the study of missing data related to exposure, outcome, or confounding variables, indicating a low risk of bias due to missing data affecting the estimated effect of SSB consumption on dental caries.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is Towards null. The study had complete data on exposure (SSB consumption), outcome (dental caries), and confounding variables for all or nearly all participants. There is no indication in the study that missing data would systematically favor either an overestimation or underestimation of the association between SSB consumption and dental caries.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to missing data is not sufficiently high to threaten conclusions about whether the exposure (sugar-sweetened beverage consumption) has an important effect on the outcome (dental caries) in the study. The study had complete data on exposure, outcome, and confounding variables for all or nearly all participants, indicating a low risk of bias due to missing data.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The measurement or ascertainment of the outcome (dental caries) is consistent and the same for all exposure groups or levels of exposure in the study.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The clinical oral examinations to assess dental caries were conducted identically at baseline and follow-up in a blinded manner, indicating that the outcome assessors were independent and unaware of the participants' exposure history
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of outcomes in estimating the effect of exposure on dental caries is low. This is attributed to the rigorous blinding of outcome assessors, which ensured independence and minimized the potential influence of participants' exposure history on the assessment of dental caries outcomes. The study's adherence to robust blinding procedures contributes to the reliability and accuracy of the estimated effect of SSB consumption on dental health outcomes, indicating a low risk of bias in outcome measurement.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes is towards harm of higher exposure. The blinding of outcome assessors to participants' SSB consumption levels reduces the risk of bias that could favor either benefit or harm of higher exposure. Given the focus on dental caries outcomes, any potential influence on outcome assessment is more likely to reflect the true detrimental effects of higher SSB consumption on dental health, supporting a direction of bias towards harm of increased exposure to SSB.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes is not sufficiently high to undermine conclusions about the important effect of SSB exposure on dental health. The rigorous blinding procedures for

Signalling questions	Response options	Comments
threaten conclusions about whether the exposure has an important effect on the outcome?		outcome assessors and the predicted bias direction towards harm of higher exposure support the credibility of the study's findings.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The reported results were likely in accordance with an available, pre-determined analysis plan. The study's methodology and statistical analysis likely followed a predefined plan to analyze the association between SSB consumption and dental caries over a 4-year period.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The reported effect estimate is unlikely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect from multiple outcome measurements within the outcome domain. The study's methodology likely included analyzing various outcome measurements related to dental caries increment over a 4-year period, and the results were reported transparently without selectively choosing only the most favorable outcomes.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The reported effect estimate is unlikely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect from multiple analyses of the exposure-outcome relationship. The study likely conducted various analyses to explore the association between SSB consumption and dental caries increment, and all relevant results were transparently reported.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The reported effect estimate is unlikely to be selected based on the desirability of the results, including statistical significance, from different subgroups. The study analyzed the association between SSB consumption and dental caries across various subgroups (e.g., different age groups, education levels) and reported the results transparently for each subgroup. By presenting findings from diverse subgroups without selectively emphasizing statistically significant results, the study avoids bias in selecting only results that align with certain subgroup characteristics.

Signalling questions	Response options	Comments
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias due to the selection of the reported result in estimating the effect of exposure on the outcome is likely low. The study likely conducted multiple analyses, including subgroup analyses, and reported all findings transparently without selectively emphasizing specific results.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to selection of the reported result may be towards harm of higher exposure. This bias could occur if the researchers selectively highlight findings that demonstrate a significant and detrimental impact of frequent SSB consumption on dental caries, potentially overstating the association to emphasize the harmful effects.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study's methodological rigor, transparent reporting, and comprehensive analysis of the relationship between SSB consumption and dental caries support the reliability of the conclusions regarding the significant impact of SSB consumption on dental health in adults.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The overall risk of bias is low. The researchers meticulously conducted clinical oral examinations, ensured reliability in diagnosing dental caries, and transparently reported their methodology and results. By addressing potential confounders and controlling for biases, the study demonstrates a high level of methodological integrity, supporting the reliability of the findings regarding the association between SSB consumption and dental caries in adults.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Predicted direction of bias for the overall risk of bias in the is towards harm of higher exposure. The predicted direction of bias towards harm of higher exposure suggests that there may be a tendency for the study results to emphasize the negative impact of increased SSB consumption on dental caries, potentially overestimating the association. This bias could occur if there is a systematic inclination to highlight findings that demonstrate a significant and detrimental effect of frequent SSB consumption on dental health, leading to an exaggerated perception of the harm caused by higher SSB intake.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Despite the predicted bias towards harm of higher exposure, the study's methodological rigor, transparency, and comprehensive analysis support the reliability of the conclusions regarding the significant impact of SSB consumption on dental health in adults.

7. Daily smoking and 4-year caries increment in Finnish adults (7)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Socioeconomic Status (SES): SES can influence both tobacco use and oral health outcomes, as individuals with lower SES may have limited access to dental care and education about oral hygiene.
2. Oral Hygiene Practices: Variations in personal oral hygiene habits, such as frequency of brushing and flossing.
3. Dietary Habits: Consumption of sugary foods and beverages is a significant risk factor for dental caries.
4. Age: Age can influence both the likelihood of tobacco use and the risk of developing dental caries, making it a critical factor to consider in studies.
5. Gender: Gender differences in tobacco use prevalence and oral health behaviors can confound the relationship between tobacco use and caries increment.
6. Access to Dental Care: Regular dental visits and preventive care can significantly influence caries outcomes and may differ between tobacco users and non-users.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

Net DMFT Increment: This refers to the change in the total number of Decayed, Missing, and Filled Teeth (DMFT) over the 4-year follow-up period. It is a composite measure that reflects overall dental health.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They utilized a statistical modelling strategy that involved sequential adjustments for various confounders
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

C2. Specify the participant group on which this result was based.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study is **daily tobacco smoking**. The authors assessed smoking habits through a structured questionnaire administered during baseline home interviews.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / <u>PN / N</u>
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / <u>PN / N</u>
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	<u>NA</u> / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	<u>NA</u> / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	<u>NA</u> / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study to produce the results regarding daily smoking and caries increment was primarily a **risk ratio** for the outcome comparing exposed (daily smokers) with unexposed individuals (non-smokers).

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study was **Finnish adults aged 30 years and older**. **Eligible Participants:** 1. **Age**: 30 years or older. 2. **Dental Status**: Must be dentate (having at least one natural tooth). 3. **Smoking Status**: Required to provide information on smoking habits. 4. **Complete Data**: Only those with complete data on relevant variables were included.

Specification of the exposure metric of interest

D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study was **daily smoking**. This refers to individuals who reported smoking any tobacco product (cigarettes, cigars, or pipes) on a daily basis.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy.	4-year period following the baseline assessment of smoking habits. Time of Onset: The exposure period begins at the baseline assessment, where participants reported their smoking status and habits. Period of Exposure: The study specifically examines the impact of daily smoking on caries increment over the subsequent 4 years, allowing for an evaluation of how smoking behaviors during this time relate to changes in dental health.

	The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	Categorization: Participants were classified based on their reported average number of cigarettes smoked per day: Non-smokers (0 cigarettes/day) Low-level smokers (1–19 cigarettes/day) High-level smokers (20+ cigarettes/day)

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Level of education	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Sugar Intake Frequency	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Toothbrushing Frequency	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Classified as regular or irregular dental attenders	Y	Y	N	Benefit of (higher) exposure	

Age	Categorized into different age groups	Y	Y	N		
Gender	Categorized into 2 groups	Y	NI	NA		

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	"PY" (Probably yes). This is supported by the information provided that the study made efforts to adjust for demographic factors, socioeconomic position, and dental behaviors, indicating an attempt to address potential confounders. While there may still be unmeasured confounders that could influence the relationship between smoking and caries development, the authors' efforts suggest that they likely controlled for the important confounding factors to some extent.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	"PY" (Probably yes). The study likely measured confounding factors that were controlled for validly and reliably, as indicated by the use of demographic factors, socioeconomic position, and dental behaviors as variables for adjustment. While there may be some measurement error in these factors due to self-reported data, the study's efforts to control for these variables suggest that the extent of measurement error in the confounding factors was probably not substantial.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	(Yes). The authors likely controlled for variables after the start of the exposure period that could have been affected by the exposure. This is supported by the information provided that the study adjusted for demographic factors, socioeconomic position, and dental behaviors, which are variables that could potentially be influenced by smoking habits
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	(Probably no). The study did not explicitly mention the use of negative controls or other considerations to suggest serious uncontrolled confounding. However, based on the information provided about adjusting for demographic factors, socioeconomic position, and dental behaviors, it is likely that the authors accounted for important confounding variables. Therefore, serious uncontrolled confounding is probably not a major concern in this study.

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to confounding) in the estimated effect of exposure on the outcome is "Low risk." The study adjusted for baseline confounding factors such as demographic variables, socioeconomic position, and dental behaviors, which are likely to be important confounders in the relationship between smoking and caries development. By controlling for these factors, the authors minimized the potential bias due to confounding, indicating a low risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding is "Towards harm of (higher) exposure." Controlling for baseline confounding factors such as demographic variables, socioeconomic position, and dental behaviors likely reduces the potential for bias towards overestimating the benefits of smoking on caries development. By adjusting for these confounders, the study is more likely to capture the true harmful effects of smoking on caries increment, indicating that any bias due to confounding would likely be towards showing the harmful effects of higher smoking exposure on dental caries.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	"No." The risk of bias due to confounding is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study adjusted for baseline confounding factors and likely minimized the potential bias in estimating the effect of smoking on caries development. By controlling for these confounders, the study's conclusions about the important effect of smoking on caries development are likely to be valid and not significantly threatened by bias due to confounding.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure in the study, which is daily smoking and the level of tobacco consumption, may not well-characterize the exposure metric specified to be of interest due to the limitation of being measured at a single point in time. Daily smoking and tobacco consumption can vary over time, and a single measurement may not capture the full extent of exposure variability. This limitation could lead to misclassification or mismeasurement of the exposure, potentially biasing the results
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in the study, daily smoking and the level of tobacco consumption, was likely to be measured with error or misclassified due to being assessed at a single point in time. Daily smoking habits and tobacco consumption can fluctuate over time, and a one-time measurement may not accurately capture the true exposure status of individuals throughout the study period. This potential misclassification or measurement error could introduce bias into the results by misrepresenting the actual exposure levels of participants
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Mismeasurement or misclassification of exposure in this study, which was measured at a single point in time, could have been differential, meaning it could have been related to the outcome or the risk of the outcome. Daily smoking habits and tobacco consumption may change over time, and if the exposure measurement was not updated throughout the study period, individuals who experienced changes in their smoking behavior may have been misclassified. This differential misclassification could introduce bias into the estimated effect of exposure on caries development, potentially affecting the study's conclusions.

Signalling questions	Response options	Comments
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error in the exposure measurement, which was assessed at a single point in time, is likely to bias the estimated effect of exposure on the outcome to some extent. Non-differential misclassification of exposure would tend to bias the results towards the null hypothesis, potentially underestimating the true effect of daily smoking and tobacco consumption on caries development. This bias could impact the study findings by attenuating any true associations that may exist between smoking behavior and caries development.
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of exposure in this study, where exposure was assessed at a single point in time, is of "Some concerns." The potential for misclassification or mismeasurement of daily smoking and tobacco consumption due to the one-time assessment could introduce bias into the estimated effect of exposure on caries development. While there is a risk of bias, it is not at a high or very high level as the study likely considered and addressed this limitation in their analysis and interpretation of results.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure, where exposure was assessed at a single point in time, is "Towards null." Non-differential misclassification or mismeasurement of daily smoking and tobacco consumption is likely to bias the estimated effect of exposure on caries development towards the null hypothesis. This means that any true associations between smoking behavior and caries development may be underestimated or attenuated due to the measurement error. Therefore, the bias is expected to shift the results towards the null, indicating no significant effect of exposure on the outcome.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, particularly due to mismeasurement or misclassification of daily smoking and tobacco consumption assessed at a single point in time, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns regarding bias in the estimated effect of exposure, the direction of bias towards the null hypothesis and the overall study design likely considered and addressed this limitation. Therefore, the risk of bias is not high enough to significantly impact the conclusions about the important effect of exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2, Variant (b): ***If Y/PY to C5 and Y/PY to C6*** *(each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	--
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	No. The follow-up did not begin at (or close to) the start of the exposure window for most participants. This is evident from the study's design and the information provided, indicating that the exposure assessment was based on participants' smoking habits at baseline, which may not necessarily align with the exact start of the exposure window for all participants. The lack of alignment between the start of follow-up and the exposure window for most participants suggests that the exposure assessment may not accurately capture the true exposure status at the beginning of the study, potentially introducing bias in the selection of participants into the analysis.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	No. The effect of exposure is not likely to be constant over the period of follow-up analyzed. This is because the study involves assessing the impact of daily smoking on caries increment over a 4-year period, during which changes in smoking habits or other factors related to caries development may occur. Since smoking behavior and other relevant factors can vary over time, the assumption of a constant effect of exposure throughout the follow-up period may not hold true. This lack of constancy in the effect of exposure over time could introduce bias in the selection of participants into the study or analysis, affecting the validity of the conclusions drawn regarding the relationship between daily smoking and caries increment.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	No. The selection of participants into the study (or into the analysis) was not based on participant characteristics observed after the start of the exposure window being studied. The study design and methodology indicate that participants were selected based on their baseline characteristics, including smoking habits, which were assessed at the beginning of the study. Therefore, the selection of participants was not influenced by characteristics observed after the start of the exposure window. This reduces the risk of bias in the selection of participants into the study based on post-exposure characteristics and enhances the internal validity of the study findings.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-

Signalling questions	Response options	Comments
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	The analysis did not correct for all of the potential selection biases identified in the previous questions related to the selection of participants into the study. While the study design and methodology may have minimized certain biases, such as selection based on post-exposure characteristics, there are still concerns regarding the timing of follow-up in relation to the exposure window and the potential variability in the effect of exposure over time. These factors suggest that not all potential selection biases were fully addressed in the analysis.
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	There is no information provided regarding sensitivity analyses to assess the impact of potential selection biases on the study results. Without this information, it is not possible to determine whether sensitivity analyses were conducted to demonstrate the minimal impact of the identified biases on the study findings.
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	While the study design and methodology aimed to minimize biases in the selection of participants into the study, there are still some concerns regarding the potential impact of selection biases on the estimated effect of exposure on the outcome. Factors such as the timing of follow-up in relation to the exposure window and the lack of information on sensitivity analyses to assess the impact of biases suggest that there may be some residual risk of bias in the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Insufficient information available Without specific details on the direction and magnitude of potential biases in the selection of participants into the study, it is not possible to predict the direction of bias due to selection. Additional information or sensitivity analyses would be needed to assess the potential impact of selection biases on the estimated effect of exposure.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction	Yes / No / Cannot tell	There is no information provided regarding the magnitude of the estimated exposure effect or the specific direction of bias due to the selection of

Signalling questions	Response options	Comments
and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?		participants into the study. Without this information, it is not possible to determine if the risk of bias in participant selection is sufficiently high to threaten conclusions about the importance of the exposure effect on the outcome. Additional details or sensitivity analyses would be needed to make a more informed assessment.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	The provided document does not contain information regarding post-exposure interventions that may have been influenced by prior exposure during the follow-up period. Without this information, it is not possible to determine if there were any post-exposure interventions that could have impacted the study results.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	Based on the information provided in the document, there is no indication that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure. Since there is no mention of such corrections or interventions in the study design or methodology, the assessment is deemed not applicable.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The document does not provide explicit information on whether the analysis corrected for the effect of post-exposure interventions that may have been influenced by prior exposure
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide specific details on the predicted direction of bias due to confounding. Without this information, it is not possible to determine whether the bias would likely be towards the benefit of higher exposure, towards harm of higher exposure, towards null, or away from null. Additional information or analysis would be required to make an informed prediction about the direction of bias due to confounding in this study.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Without specific information on the risk of bias due to post-exposure interventions and their potential impact on the estimated exposure effect, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Further details or sensitivity analyses would be needed to assess the potential impact of post-exposure interventions on the study conclusions.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study mentions that the study is based on 955 dentate adults who participated in both surveys and had complete data on the variables selected for analysis, representing 77% of the original sampling frame. While the information indicates that there was a high level of participation and complete data for a majority of the participants, it is not explicitly stated that complete data on exposure status were available for all or nearly all participants. Therefore, it is probably yes that complete data on exposure status were available for most participants.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	The document mentions that the study is based on 955 dentate adults who participated in both surveys and had complete data on the variables selected for analysis, representing 77% of the original sampling frame. While the information indicates that there was a high level of participation and complete data for a majority of the participants, it is not explicitly stated that complete data on the outcome were available for all or nearly all participants. Therefore, it is probably yes that complete data on the outcome were available for most participants.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	The document does not explicitly state whether complete data on confounding variables were available for all participants. However, since the study is based on 955 dentate adults who had complete data on the variables selected for analysis, it is likely that complete data on confounding variables were available for most participants. Therefore, it is probably yes that complete data on confounding variables were available for all or nearly all participants.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	The document mentions that the study is based on 955 dentate adults who participated in both surveys and had complete data on the variables selected for analysis, representing 77% of the original sampling frame. While it is not explicitly stated whether the analysis was based on a complete case analysis, the information provided suggests that the analysis likely included participants with complete data. Therefore, it is probably yes that the result is based on a complete case analysis.

Signalling questions	Response options	Comments
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	While the document does not provide explicit information on the reasons for missing data or the relationship between missing data and the true value of the outcome, the study's high participation rate and the availability of complete data for a majority of participants suggest that exclusion from the analysis due to missing data may not be strongly related to the true value of the outcome. Therefore, it is weakly yes that exclusion from the analysis because of missing data was likely related to the true value of the outcome.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	While the study does not provide explicit details on the handling of missing data and its potential impact on the estimated effect of exposure on the outcome, the study's high participation rate and the availability of complete data for a majority of participants suggest that the risk of bias due to missing data may be low. However, since there is no specific information on how missing data were addressed in the analysis, there are some concerns regarding the potential impact on the estimated effect of exposure on the

Signalling questions	Response options	Comments
		outcome. Therefore, the risk of bias due to missing data is categorized as "Some concerns."
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide specific details on the predicted direction of bias due to missing data. Without this information, it is not possible to determine whether the bias would be towards the benefit of higher exposure, towards harm of higher exposure, towards null, or away from null. Therefore, the predicted direction of bias due to missing data is categorized as "Insufficient information available."
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Without specific information on the likely direction and magnitude of bias due to missing data, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Therefore, the assessment is categorized as "Cannot tell."

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The study mentions that clinical oral examinations were conducted at baseline and follow-up to assess the outcome variables related to caries increment. Since these examinations were performed by different dentists using specific criteria, there is a possibility that the measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure. Therefore, there is a concern that the measurement of the outcome may have differed, leading to a potential risk of bias in the study.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The document does not provide explicit information on whether outcome assessors were aware of study participants' exposure history. Without this information, it is not possible to determine if there was potential bias arising from outcome assessors being aware of the participants' exposure history
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome. The study does not provide detailed information on certain aspects that could potentially introduce bias, such as whether outcome assessors were aware of participants' exposure history or if the assessment of the outcome could have been influenced by knowledge of exposure history. Without this information, there is a possibility of bias in the measurement of outcomes.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Without specific details on whether outcome assessors were aware of participants' exposure history or if the assessment of the outcome could have been influenced by knowledge of exposure history, it is challenging to predict the direction of bias arising from the measurement of outcomes. The lack of information prevents a clear determination of whether the bias would be towards benefit, harm, null, or away from null.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Due to the lack of specific information on the direction of bias arising from the measurement of outcomes and the magnitude of the estimated exposure effect, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Without this critical information, it is challenging to assess the impact of bias on the study conclusions

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The study does not provide explicit information regarding whether the reported result was in accordance with an available, pre-determined analysis plan. Without details on the existence and adherence to a pre-determined analysis plan, it is not possible to determine if the reported result aligns with such a plan.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. Without this information, it is not possible to assess whether there was bias in the selection of the reported result.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. Without this information, it is not possible to assess whether there was bias in the selection of the reported result
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the results, such as statistical significance, from different subgroups. Without this information, it is not possible to assess whether there was bias in the selection of the reported result.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	--

Signalling questions	Response options	Comments
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Due to the lack of specific information provided in the study regarding the selection of the reported result based on the desirability of the magnitude or statistical significance of the estimated effect, it is not possible to predict the direction of bias. Without this information, it is unclear whether the reported results may be biased towards the benefit of higher exposure, harm of higher exposure, null effect, or away from the null.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result is not sufficiently clear from the information provided in the study to determine if it threatens conclusions about whether the exposure has an important effect on the outcome. Without specific details on the selection process of the reported results and its potential impact on the estimated exposure effect, it is challenging to assess the extent to which bias may affect the conclusions.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The overall risk of bias for this study is categorized as "Some concerns." While the study had a low risk of bias in terms of confounding, there were some concerns related to the measurement of exposure, potential biases in the selection of the reported results, and the handling of missing data. These factors could introduce bias into the estimated effect of exposure on the outcome, raising some concerns about the validity and reliability of the study findings. Further details or sensitivity analyses may be needed to address these concerns and ensure the robustness of the study results.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The risk of bias due to confounding is assessed to be low, indicating that the study adequately controlled for important confounding factors, minimizing potential bias in the estimated effect of exposure on the outcome. The risk of bias due to the measurement of exposure is categorized as having some concerns, suggesting a potential for misclassification or mismeasurement of daily smoking and tobacco consumption. This could introduce bias into the estimated effect of exposure on caries development. While there are concerns about biases in the selection of participants, handling of missing data, and measurement of outcomes, the low risk of bias due to confounding suggests that the study's findings are less likely to be biased towards showing a significant effect of exposure on the outcome. Therefore, the overall direction of bias is predicted to be towards null, indicating that the study results may not overestimate or underestimate the true effect of smoking on caries development.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The low risk of bias due to confounding indicates that the study adequately controlled for important confounding factors, minimizing potential bias in the estimated effect of exposure on caries development. While there are some concerns about the measurement of exposure and other potential biases, the low risk of bias due to

		confounding suggests that the study's findings are less likely to be biased towards showing a significant effect of exposure on the outcome. Therefore, the overall risk of bias is not high enough to threaten the conclusions about the important effect of smoking on caries development.

8. Risk score to predict dental caries in adult patients for use in the clinical setting (8)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Dietary Habits: The type and frequency of food and beverage consumption, particularly sugary and acidic items, can significantly influence caries development. This factor is relevant across various exposures and outcomes related to dental health.
2. Fluoride Exposure: The use of fluoride in dental products and community water supplies can affect caries risk. This is a general factor that applies to most studies on dental caries.
3. Salivary Flow: Saliva plays a crucial role in neutralizing acids and providing minerals for tooth remineralization. Variations in salivary flow can be a confounding factor in caries studies.
4. Socioeconomic Status: Socioeconomic factors can influence access to dental care, oral hygiene practices, and dietary choices, making it a common confounder in dental studies.
5. Oral Hygiene Practices: The frequency and effectiveness of brushing and flossing can impact caries risk and are relevant across various studies.
6. Microbiological Factors: The presence of specific cariogenic bacteria can vary among individuals and influence caries development. This factor may be more specific to certain exposures related to oral health.
7. General Health Conditions: Systemic diseases (e.g., diabetes, cardiovascular diseases) can affect oral health and caries risk, making this a relevant confounder in many studies.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes / No

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

The study identified several key risk factors with their corresponding risk ratios:

1. Presence of bacterial plaque/calculus
2. Restorations with more than 5 years
3. More than 8 teeth restored
4. History/active periodontitis
5. Presence of systemic condition

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They utilized univariate logistic regression to assess the relationship between independent variables (potential risk factors) and the outcome variable (dental caries). Variables that showed a significant relationship at the univariate level ($p < 0.100$) were then included in a multivariable logistic regression model.
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The study aimed to predict the likelihood of developing dental caries based on various identified risk factors, such as:

1. Bacterial Plaque: The presence and amount of plaque on teeth.
2. Restorations: The number and age of dental restorations (fillings).
3. Teeth Restored: The count of teeth that have been previously restored.
4. Periodontal Health: The presence of history or active periodontitis.
5. Systemic Conditions: The presence of systemic health issues that may influence oral health.

C2. Specify the participant group on which this result was based.

The participant group for the study consisted of adult patients who were part of a prospective epidemiological surveillance study on oral diseases. Specifically, the study included:

- A total of 397 patients who were eligible for inclusion, out of an initial cohort of 22,009 participants.
- Among these, 19,868 patients had natural teeth, and 5877 patients were without dental caries at the first observation.
- The final sample included 177 cases (patients who developed dental caries during the follow-up) and 220 controls (patients who remained free of dental caries)

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study relates to various risk factors associated with the development of dental caries. These risk factors include: 1. Bacterial Plaque: Assessed through clinical examinations where the presence and amount of plaque on teeth were evaluated. 2. Restorations: The number and age of dental restorations (fillings) were recorded. 3. Teeth Restored: The count of teeth that had been previously restored was documented. 4. Periodontal Health: The history of periodontal disease (periodontitis) was assessed through clinical evaluations. 5. Systemic Conditions: The presence of systemic health issues that could influence oral health was noted.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study to produce the results regarding the risk of developing dental caries was primarily a logistic regression analysis. This analysis aimed to determine the association between various risk factors (exposures) and the outcome of interest, which was the incidence of dental caries.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study consists of adults aged 18 years and older who are at risk for developing dental caries due to various risk factors. Eligible participants included those with natural teeth who were part of a dental care program and had documented dental histories and clinical evaluations. Exclusion criteria encompassed patients with significant systemic health issues, individuals who had dental caries at the initial observation, and those unable to provide informed consent. The study ultimately included 397 patients, comprising 177 cases with dental caries and 220 controls without, selected from a larger cohort of 5,877 patients. However, there are notable differences between the broader eligible population and the study participants, as the latter were drawn from a private practice setting, which may not fully represent the general adult population. This setting could introduce selection bias, as patients seeking care in private practices may have different socio-economic backgrounds and health-seeking behaviors, thereby limiting the generalizability of the findings to all adults at risk for dental caries.

Specification of the exposure metric of interest

D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure in this study refers to the risk factors associated with dental caries in adult patients. These risk factors include a combination of clinical and non-clinical variables that are believed to contribute to the development of dental caries. Specifically, the study assessed factors such as: 1. Bacterial Plaque: The presence and amount of bacterial plaque, which is a significant pathological factor associated with dental caries. 2. Previous Caries Experience: A history of dental caries, which is a strong predictor of future caries development.

		3. Systemic Conditions: The presence of systemic health issues (e.g., diabetes, cardiovascular disease) that may influence oral health and the host's response to plaque biofilm. 4. Number of Teeth: The total number of teeth present, as fewer teeth can be associated with higher caries risk. 5. Socio-economic Status: Evaluated based on the occupation of each patient, which can impact access to dental care and oral hygiene practices.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	The specified exposure window in this study is defined as the period from the initial clinical evaluation to follow-up assessments conducted over approximately three years (from July 2012 to December 2015). This window includes the time of onset, marked by the baseline assessment confirming the absence of dental caries, and extends through the follow-up period during which new carious lesions were monitored. This timeframe allows for a thorough evaluation of how risk factors, such as bacterial plaque and previous caries experience, influence the development of dental caries, ensuring that the exposure data accurately reflect participants' risk profiles during this critical period.
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	In this study, exposure over time should be summarized as ever/never exposed for each participant regarding the identified risk factors associated with dental caries. This approach categorizes participants based on whether they exhibited the presence of specific risk factors (e.g., bacterial plaque, previous caries experience, systemic conditions) at any point during the exposure window.

Additionally, for certain variables, cumulative exposure may also be considered, particularly for factors like the number of restored teeth or the duration of restorations in function, which can provide insight into the overall caries risk over time. This dual approach allows for a comprehensive assessment of both the presence of risk factors and their potential cumulative impact on the development of dental caries during the specified exposure period

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Categorized into 3 different groups	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Access to Dental Care	Not explicitly mentioned	N	N	N	Benefit of (higher) exposure	
Age	Categorized into different age groups	Y	Y	N	Insufficient information available	

Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Categorize as Non-smoker, smoker, use of Antidepressant medication.	Y	N	N	Harm of (higher) exposure	
Previous experience of caries	Categorized into 2 groups	Y	N	N	Harm of (higher) exposure	
Systemic condition	Categorized into 2 groups	Y	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors made efforts to identify and adjust for potential confounders related to dental caries risk using statistical analyses like logistic regression. While the study controlled for various confounding domains with measured variables, the complete control of all confounding factors in the multifactorial nature of dental caries remains challenging. Therefore, it is probable that the authors controlled for most important confounding factors, but there may still be some residual confounding present due to the complexity of dental caries risk factors.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The confounding factors that were controlled for in the study were likely measured validly and reliably by the variables available. The study used established criteria and definitions for variables such as systemic conditions, bacterial plaque, restorations, and periodontitis, which are commonly used indicators in dental caries risk assessment. While there may be some potential for measurement error in these factors, it is probable that the measurements were valid and reliable enough to control for the necessary confounding factors in the study.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	In the context of this study on dental caries risk assessment, the focus was on baseline confounding factors related to the presence of dental caries and associated risk factors. The study did not involve an exposure period or intervention where control for variables after the start of exposure would be relevant. Therefore, the question of controlling for variables after the start of the exposure period does not apply to this study on dental caries risk prediction in adult patients.

Signalling questions	Response options	Comments
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	The study did not explicitly mention the use of negative controls or other specific considerations to assess the presence of serious uncontrolled confounding. However, based on the comprehensive approach to identifying and including relevant confounding factors in the risk model, as well as the statistical methods employed to address confounding, it is likely that serious uncontrolled confounding was not a major issue in this study on dental caries risk prediction.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to confounding) in the estimated effect of exposure on the outcome is Low risk. The study demonstrated a thorough approach to controlling for baseline confounding factors related to dental caries risk, including the use of a risk model with significant predictors and good discrimination. The variables included in the model were carefully selected and analyzed using appropriate statistical methods, indicating a low risk of bias due to confounding in the estimated effect of exposure on the outcome of dental caries prediction in adult patients.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding is Towards harm of (higher) exposure. The risk factors included in the risk model for dental caries prediction, such as bacterial plaque/calculus, presence of restorations, history/active periodontitis, and systemic conditions, are typically associated with an increased risk of dental caries. Therefore, if there was any confounding present in the study, it would likely bias the results towards showing a higher risk of dental caries associated with these exposure factors.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to confounding, particularly baseline confounding, is not considered sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome of dental caries prediction in this study. The comprehensive approach to controlling for confounding factors, the development of a robust risk model, and the consideration of relevant predictors suggest that the study's conclusions regarding the impact of exposure on dental caries risk are likely valid and reliable.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

Domain 2, Variant (a): ***If N/PN to C5*** *(exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The exposure being measured at a single point in time may not fully characterize the exposure metric specified in the study. Single-point measurements may not capture variations or changes in exposure over time, leading to potential misclassification or mismeasurement of the exposure. This limitation could result in a large extent of mischaracterization of the exposure metric of interest.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	When exposure is measured at a single point in time, there is a higher likelihood of measurement error or misclassification due to the inability to capture changes or fluctuations in exposure levels over time. This can lead to a substantial amount of misclassification or error in the measurement of the exposure, potentially impacting the accuracy of the study results.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	When exposure is measured at a single point in time, there is a higher likelihood of differential misclassification or mismeasurement of exposure, especially if the exposure measurement is related to the outcome or the risk of the outcome. This can lead to a large extent of bias in the estimated effect of exposure, potentially affecting the validity of the study results.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error, which is more likely when exposure is measured at a single point in time, may bias the estimated effect of exposure on the outcome to a small extent. While non-differential measurement error can still introduce some bias, its impact on the estimated effect is typically less pronounced compared to differential measurement error.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome in the study "Risk score to predict dental caries in adult patients for use in the clinical setting" can be categorized as Low. In the study, the exposure variables related to potential risk factors for dental caries, such as the presence of bacterial plaque/calculus, restorations with more than 5 years, >8 teeth restored, history/active periodontitis, and presence of systemic conditions, were measured by trained and calibrated clinicians. The measurements were performed using standardized methods, and the clinicians were trained to diagnose and differentiate between sound surfaces and caries lesions both clinically and radiographically. The use of trained clinicians and standardized methods for measuring exposure variables suggests a low risk of bias in the measurement of exposure. This indicates that the exposure variables were likely measured accurately and consistently, reducing the potential for measurement error or bias in assessing the effect of exposure on the outcome of dental caries in the study.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure at a single point in time is "Towards null." Mismeasurement or misclassification of exposure in this scenario is likely to bias the estimated effect of exposure towards the null hypothesis, meaning that the true effect of exposure on the outcome may be underestimated or attenuated. This bias could lead to an underestimation of the true association between exposure and outcome, potentially affecting the interpretation of the study results.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	While there may be some concerns regarding bias arising from the measurement of exposure at a single point in time, the risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The potential bias, although present, is not expected to be of such magnitude that it would significantly alter the overall interpretation of the relationship between exposure and outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	In studies where follow-up begins at or close to the start of the exposure window for most participants, there is a higher likelihood of minimizing bias related to the timing of exposure and outcome assessment. This approach enhances the validity of the study findings by reducing the potential for misclassification or bias due to variations in the timing of exposure initiation and outcome assessment.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	-
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	If the selection of participants into the study or analysis was not based on participant characteristics observed after the start of the exposure window being studied, it indicates a lower risk of bias. By selecting participants based on characteristics that were present before the exposure window, the study is less likely to introduce bias related to the timing of exposure and outcome assessment. This approach helps ensure that the exposure-outcome relationship is not influenced by characteristics that develop after the exposure period has begun.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-

Signalling questions	Response options	Comments
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias in the selection of participants into the study "Risk score to predict dental caries in adult patients for use in the clinical setting" is categorized as Some concerns. While the study had ethical approval, obtained informed consent, and employed a prospective case-cohort design, there are potential concerns regarding participant selection bias due to the exclusion criteria, recruitment process, and generalizability of the study sample. These factors may introduce some level of bias in how participants were selected for the study.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	This prediction suggests that there may be a tendency for the selection process to favor participants with characteristics that could lead to an overestimation of the harmful effects associated with higher levels of exposure. This bias could potentially skew the results towards showing a stronger negative impact of the exposure on the outcome than what might be observed in a more representative sample.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. This assessment is based on the consideration that while there are some concerns regarding bias in participant selection, the magnitude of the estimated exposure effect and the likely direction of bias do not pose a significant threat to the overall conclusions drawn about the impact of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	Post-exposure interventions that were influenced by prior exposure during the follow-up period were present in the study. This indicates that there were interventions or actions taken after exposure that may have been influenced by the participants' prior exposure status, potentially introducing bias into the study results.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	It is likely that the analysis did not correct for the effect of post-exposure interventions that were influenced by prior exposure in the study. Since the study did not explicitly mention post-exposure interventions or how they were accounted for in the analysis, there is a probability that the potential influence of these interventions on the outcomes was not adequately addressed. This lack of information suggests that the analysis may not have corrected for the impact of post-exposure interventions influenced by prior exposure, leading to a potential risk of bias in the study results.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias due to post-exposure interventions in the estimated effect of exposure on the outcome in the study "Risk score to predict dental caries in adult patients for use in the clinical setting" can be categorized as Low. In the study, after measuring the exposure variables related to potential risk factors for dental caries at baseline, no post-exposure interventions or modifications were introduced that could have influenced the relationship between the exposure and the outcome (development of dental caries) during the follow-up period. The study focused on predicting dental caries based on the measured exposure variables and did not involve any interventions or changes in exposure status that could have affected the outcome independently of the exposure. Therefore, the risk of bias due to post-exposure interventions influencing the estimated effect of exposure on the outcome is considered low in this study.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null /	Given the context provided, where post-exposure interventions involve treatments that aim to reduce the occurrence of dental caries, it is reasonable to predict that the direction of bias due to these interventions would be "Towards benefit of (higher) exposure." The interventions, such as

	Insufficient information available	preventive measures or treatments, are likely to have a positive impact on reducing the risk or occurrence of dental caries, which would favor the group with higher exposure to these interventions. Therefore, in this scenario, the bias resulting from post-exposure interventions is expected to favor the benefit of higher exposure in terms of reducing the risk of dental caries.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Risk of bias due to post-exposure interventions Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome? Please choose either: Yes / No / Cannot tell (Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information) Please explain your answe

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	The answer is "PN" (Probably no). This is because the presence of missing data on exposure status for some participants suggests that complete data on exposure status may not have been available for all or nearly all participants. The likelihood of missing data on exposure status raises concerns about the potential impact on the validity and reliability of the study findings, as incomplete data may introduce bias and affect the accuracy of the exposure-outcome relationship analysis
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	This is because complete data on the outcome were likely available for all or nearly all participants in the study. Having comprehensive outcome data for the majority of participants suggests a lower risk of bias due to missing outcome data, which enhances the reliability and validity of the study results. However, the term "probably" indicates some uncertainty, as the exact extent of missing outcome data is not explicitly stated in the information provided.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	This is because the presence of missing data on confounding variables for some participants suggests that complete data on confounding variables may not have been available for all or nearly all participants. Incomplete data on confounding variables can introduce bias and affect the accuracy of the analysis, potentially impacting the validity of the study findings by not adequately accounting for potential confounders in the relationship between exposure and outcome.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	This is because the information provided does not explicitly state whether the results were based on a complete case analysis. However, the likelihood of a complete case analysis being conducted is high, considering the detailed statistical methods and risk model development described in the study. Complete case analysis involves using only the participants with complete data on all variables of interest, which may lead to potential bias if the missing data are not missing completely at random.
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	the likelihood of exclusion from the analysis due to missing data being related to the true value of the outcome is not strong. If missing data are related to the true outcome value, it can introduce bias and affect the validity of the study results. However, without specific information on the

Signalling questions	Response options	Comments
		reasons for missing data and their potential relationship to the outcome, it is uncertain whether the missing data were related to the true outcome values.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	the information provided does not explicitly state whether all predictors of missingness were included in the analysis model. However, based on the detailed statistical methods described in the study, it is likely that most predictors of missingness were considered in the analysis model. Including predictors of missingness in the analysis helps to account for potential biases introduced by missing data and strengthens the validity of the study results.
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	the information provided does not explicitly state whether the analysis was based on imputing missing values. However, given the complexity of the statistical methods and risk model development described in the study, it is probable that missing values were imputed to address missing data. Imputing missing values is a common approach to handle missing data and ensure that all available information is utilized in the analysis, thereby reducing potential bias and improving the robustness of the results.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	the study did not provide specific details on the imputation methods used for handling missing data. However, given the comprehensive statistical analysis and risk model development described in the study, it is likely that imputation was performed appropriately. Proper imputation methods help to minimize bias introduced by missing data and ensure the robustness of the study findings.
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	Although the study did not explicitly mention the use of alternative methods to correct for bias due to missing data, the detailed statistical analysis and risk model development suggest that appropriate measures were likely taken to address missing data. While the specific alternative methods are not specified, the comprehensive approach to statistical analysis indicates that efforts were made to minimize bias related to missing data, thereby enhancing the validity of the study results.
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	While the study did not explicitly provide evidence that the results were not biased by missing data, the detailed statistical methods and risk model development suggest that efforts were made to address missing data

Signalling questions	Response options	Comments
		appropriately. The comprehensive approach to handling missing data in the analysis indicates that steps were likely taken to minimize bias, although direct evidence confirming the absence of bias related to missing data was not explicitly stated.
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias due to missing data, including response rate, in the estimated effect of exposure on the outcome in the study "Risk score to predict dental caries in adult patients for use in the clinical setting" can be categorized as Some concerns. While the response rate, which indicates the proportion of participants who completed the study or provided data, was not explicitly mentioned in the provided excerpts, it is an important factor in assessing the potential bias due to missing data. A low response rate could lead to missing data and potentially introduce bias if the characteristics of non-responders differ significantly from those who participated in the study.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is "Insufficient information available." While the study did not provide explicit details on the direction of bias resulting from missing data, the comprehensive statistical analysis and risk model development suggest that efforts were made to address missing data appropriately. Without specific information on the predicted direction of bias, it is not possible to determine whether the missing data would lead towards benefit, harm, null effect, or away from null effect regarding the exposure and outcome relationship.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	While the study did not provide explicit information on the direction and magnitude of bias due to missing data, the comprehensive statistical analysis and risk model development suggest that efforts were made to handle missing data appropriately. Without specific details on the impact of missing data on the estimated exposure effect and the overall conclusions of the study, it is not possible to determine if the risk of bias due to missing data is sufficiently high to threaten conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	There is a possibility that the measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure in the study. This uncertainty arises from the lack of explicit information provided in the study regarding the consistency of outcome measurement across different exposure groups or levels. Without specific details confirming the uniformity of outcome assessment, there is a probable chance that measurement differences could have existed, leading to potential bias in the estimation of the exposure effect on the outcome.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	There is a likelihood that outcome assessors were aware of study participants' exposure history in the study. This potential bias arises from the lack of explicit information provided in the study regarding blinding procedures for outcome assessors. Without specific details confirming that outcome assessors were blinded to participants' exposure history, there is a probable chance that assessors were aware of this information, which could introduce bias in the measurement of the outcome based on the participants' exposure status.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	There is a strong possibility that the assessment of the outcome could have been influenced by knowledge of participants' exposure history in the study. This significant risk of bias arises from the potential for assessors to be influenced by participants' exposure status when evaluating the outcome, especially if blinding procedures were not implemented or if assessors were aware of the exposure history. The lack of information on blinding or procedures to mitigate the influence of exposure history on outcome assessment suggests a high likelihood that such influence could have occurred, leading to a substantial risk of bias in the measurement of the outcome.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias arising from the measurement of the outcome in the study "Risk score to predict dental caries in adult patients for use in the clinical setting" can be categorized as Low risk. The study mentions that examinations were performed by 22 clinicians who were trained and calibrated to diagnose and differentiate between sound surfaces and caries lesions both clinically and radiographically. The fact that

Signalling questions	Response options	Comments
		the clinicians underwent training and calibration indicates a structured and standardized approach to outcome measurement. Given the training and calibration of the clinicians involved in assessing the outcome (presence of dental caries), the risk of bias related to the measurement of the outcome is considered low. This suggests that the outcome assessment was likely conducted in a consistent and reliable manner, reducing the potential for measurement bias.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes is "Towards harm of (higher) exposure." The lack of blinding procedures, the potential for outcome assessors to be aware of participants' exposure history, and the likelihood of assessment being influenced by knowledge of exposure status suggest that there is a significant risk of bias in the measurement of outcomes. This bias could lead to an overestimation of the harmful effects associated with higher exposure levels, potentially skewing the results towards indicating a greater harm from increased exposure.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The significant risk of bias, particularly towards harm of higher exposure, combined with the lack of blinding procedures and the potential influence of exposure history on outcome assessment, raises concerns about the validity and reliability of the estimated exposure effect. This level of bias could distort the interpretation of the exposure-outcome relationship and compromise the ability to draw accurate conclusions regarding the importance of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The result was reported in accordance with an available, pre-determined analysis plan. This is indicated by the strong likelihood that the reported result aligns with a pre-defined analysis plan, ensuring transparency and adherence to a structured approach in reporting the findings of the study.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. This potential bias in selecting the reported result could lead to a distortion in the presentation of the effect estimate, favoring outcomes that support the researchers' preferences or expectations.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. This potential bias in selecting the reported result could lead to a preference for results that support the researchers' expectations or desired conclusions, influencing the interpretation of the exposure-outcome relationship.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The reported effect estimate is likely to be selected based on the desirability of the results, such as statistical significance, from different subgroups. This bias may lead to the preferential reporting of results that align with the researchers' expectations or desired outcomes within specific subgroups, potentially influencing the overall interpretation of the study findings.

Signalling questions	Response options	Comments
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias in the selection of the reported result in the study "Risk score to predict dental caries in adult patients for use in the clinical setting" can be categorized as Low risk. The study objectives were focused on estimating and evaluating a risk score to predict dental caries in adult patients. The reported outcomes, including the risk model with good discrimination, distribution of patients into risk groups, and conclusions regarding the predictive ability of the risk score, appear to align with the study's objectives. There is no indication of selective reporting of outcomes based on favorable results, suggesting a low risk of bias in the selection of the reported results.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of the reported result is towards the benefit of higher exposure. In cases where there is a high risk of bias in selectively reporting results based on the desirability of outcomes, such as statistical significance, there is a tendency for researchers to emphasize and highlight positive findings that support the effectiveness or benefits of higher exposure levels. This selective reporting may lead to an overestimation of the positive effects associated with higher exposure levels on the outcome of interest, potentially skewing the interpretation of the study results towards showing a greater benefit than actually exists. It is important to be aware of this potential bias and take measures to mitigate its impact on the validity and reliability of the study findings.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The high risk of bias, combined with the predicted direction of bias towards the benefit of higher exposure, raises concerns about the validity and reliability of the study conclusions. The potential for selectively reporting results that emphasize positive outcomes associated with higher exposure levels may lead to an overestimation of the exposure effect on the outcome, potentially influencing the interpretation of the study findings. This level of bias threatens the ability to draw accurate and unbiased conclusions about the true impact of the exposure on the outcome, highlighting the importance of addressing and mitigating bias in the reporting of study results.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	Based on the information provided from the study "Risk score to predict dental caries in adult patients for use in the clinical setting" , the Overall risk of bias can be categorized as Low risk. The study demonstrates structured training and calibration of clinicians for outcome assessment, aligns reported results with study objectives without selective reporting bias, and provides transparent information on risk score development and validation. These factors collectively suggest a low risk of bias in the study overall.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in this study is towards the benefit of higher exposure. The concerns about bias, particularly in the selection of reported results and potential uncontrolled confounding factors, suggest a tendency to emphasize positive outcomes associated with higher exposure levels. This bias may lead to an overestimation of the effects of higher exposure on the outcome, potentially skewing the interpretation of the study results towards showing a greater benefit than actually exists. Being aware of this predicted bias direction is important for critically evaluating the study findings and considering the potential impact on conclusions drawn from the research.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias in this study is sufficiently high, considering its likely direction towards the benefit of higher exposure and the potential overestimation of the exposure effect on the outcome. This high risk of bias threatens the validity and reliability of the study conclusions, particularly in assessing whether the exposure has a significant effect on the outcome. The potential for bias to influence the interpretation of the study results raises concerns about the accuracy of conclusions regarding the impact of the exposure on predicting dental caries in adult patients. Addressing and mitigating bias in future research will be essential to ensure the credibility and robustness of conclusions drawn from studies in this field.

9. Risk Indicators for Third Molar Caries and Periodontal Disease in Senior Adults (9)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

Age: Older age is often associated with increased caries risk due to factors like decreased saliva production and cumulative exposure to cariogenic bacteria.

Gender: There may be differences in caries prevalence between males and females, potentially due to behavioral factors or biological differences.

Race/Ethnicity: Different racial or ethnic groups may have varying levels of access to dental care and differing prevalence of caries.

Education Level: Higher education levels are often associated with better oral health literacy, which can influence caries risk.

Socioeconomic Status: Lower socioeconomic status can limit access to dental care and preventive measures, increasing caries risk.

Tobacco Use: Tobacco use is a known risk factor for various oral health issues, including caries.

Dietary Habits: High sugar intake and poor dietary choices can significantly increase the risk of caries.

Oral Hygiene Practices: Regular brushing and flossing can reduce the risk of caries, making oral hygiene a critical confounding factor.

Dental Visits: Frequency of dental visits for check-ups and cleanings can influence caries risk, as regular visits can lead to early detection and management of caries.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

1. Caries Experience: This is often measured as the number of teeth with carious lesions (decayed teeth), filled teeth (restorations), or missing teeth due to caries (DMFT index - Decayed, Missing, Filled Teeth).
2. Coronal Caries Experience: Specifically assessing the presence of caries on the coronal surfaces of teeth, including third molars.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	Yes, the authors made attempts to control for confounding factors in their analysis of caries risk. They utilized **unconditional logistic multivariate models** to derive odds ratios (OR) and 95% confidence intervals (CI), which allowed them to adjust for various explanatory variables that were found to be significant in bivariate analysis
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The outcome to which the result relates, particularly in caries risk, is the experience of coronal caries on third molars. This includes the presence of carious lesions, filled teeth, or missing teeth due to caries specifically affecting the third molars in the study population

C2. Specify the participant group on which this result was based.

The participant group on which the result related to caries risk was based consists of 810 dentate subjects aged 65 years and older from the Piedmont 65 Dental Study. This group was representative of community-dwelling older adults in five contiguous counties in North Carolina.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in relation to caries risk is the presence of various risk indicators that may influence the experience of caries. These risk indicators include factors such as: 1. Race: Caucasian and African American participants were compared to assess differences in caries experience. 2. Education Level: Participants were categorized based on whether they had less than or at least a high school education. 3. Tobacco Use: The presence or absence of tobacco use among participants was recorded. 4. Dental Visit History: Participants were assessed based on whether they had visited a dentist within the last three years or not.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N

C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed to produce the results regarding caries risk was a risk ratio (odds ratio) comparing exposed individuals with unexposed individuals. The study examined categorical risk indicators (race, education level, tobacco use, and dental visit history) and their association with coronal caries experience on third molars.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest for the analysis of caries risk specifically included senior adults aged 65 and older from the Piedmont 65 Dental Study. Eligible participants were community-dwelling individuals who were dentate (having at least one natural tooth) and had visible third molars at the time of enrollment.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the analysis of caries risk specifically pertains to the presence of risk indicators that may influence the likelihood of coronal caries experience. These risk indicators include: 1. Race: Specifically, being Caucasian versus African American. 2. Education Level: Having at least a high school education versus less education. 3. Tobacco Use: Current tobacco users versus non-users. 4. Dental Visit History: Having had a dental visit within the last three years versus not.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy.	The exposure window of interest for assessing caries risk in the study pertains to the period of time leading up to the dental examination, specifically focusing on the three years prior to enrollment in the Piedmont 65 Dental Study. This window is meaningful as it captures recent behaviors and conditions that could influence the development of coronal caries on third molars. The exposure period includes: • Time of Onset: The onset of exposure is considered to begin at least three years before the dental examination, as participants

	The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	were asked about their dental visit history and tobacco use during this timeframe. • Period of Exposure: The exposure period encompasses the entire duration leading up to the examination, reflecting the cumulative effects of risk indicators such as race, education level, and tobacco use on caries experience
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	1. Ever/Never Exposed: Classify participants as "ever exposed" (e.g., used tobacco or had a dental visit in the past three years) or "never exposed." 2. Cumulative Exposure: Count the number of dental visits or frequency of tobacco use during the exposure period. 3. Average Exposure: Calculate the average level of exposure, such as average dental visits or tobacco use frequency.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Level of education	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Not explicitly mentioned	N	N	N	(Benefit of (higher) exposure	
Dental Visit History	Having had a dental visit within the last three years versus not.	Y	Y	N	Benefit of (higher) exposure	
Age	Categorized into 2 groups	Y	N	N	Insufficient information available	

Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Current tobacco users versus non-users	Y	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* "Validity" refers to whether the confounding variable or variables accurately measure the confounding factor, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors probably controlled for all the important confounding factors for which this was necessary (PY). The study mentions that efforts were made to address confounding variables like race, education, dental history, and tobacco use using multivariable models. While there are limitations in fully accounting for all important confounding factors and time-varying confounding in observational studies, the mention of controlling for these factors suggests that the authors likely considered and adjusted for baseline confounding variables to some extent.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The study does not provide explicit information on the validity and reliability of the measurement of confounding factors controlled for. However, given that the study used multivariable models to control for confounding variables like race, education, dental history, and tobacco use, it is likely that these factors were measured to some extent validly and reliably within the available variables. While there may be some measurement error in these confounding factors, it is probable that the extent of this error was not substantial enough to significantly impact the study's results.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	The study focused on baseline confounding factors and did not mention controlling for any variables that may have been affected by the exposure after the start of the exposure period. This indicates that the authors did not address potential confounding variables that could have been influenced by the exposure during the study period.
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	The study did not mention the use of negative controls or other considerations that would suggest serious uncontrolled confounding. While there may be limitations in fully addressing all important confounding factors, the study's use of multivariable models to control for various confounders indicates an attempt to minimize the impact of confounding on the results. Therefore, it is probable that serious uncontrolled confounding was not a major issue in this study.

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to confounding) in the estimated effect of exposure on the outcome is "Some concerns." While the study attempted to control for baseline confounding factors using multivariable models, there may still be some concerns regarding the potential impact of unmeasured or residual confounding on the estimated effect of exposure on the outcome. The lack of information on the validity and reliability of the measured confounding factors and the absence of controlling for variables affected by the exposure during the study period suggest that there could be some residual confounding that may have influenced the results to some extent.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	The predicted direction of bias due to confounding is "Insufficient information available." Without specific details on the potential direction of bias in the study, such as the magnitude and direction of any uncontrolled confounding factors, it is not possible to predict whether the bias would favor the benefit of higher exposure or the harm of higher exposure. Additional information on the specific confounding factors and their potential impact on the exposure-outcome relationship would be needed to determine the predicted direction of bias accurately.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	While there may be some concerns regarding the risk of bias due to confounding in the study, the use of multivariable models to control for baseline confounding factors suggests that the impact of confounding on the estimated exposure effect may have been minimized to some extent. Without clear evidence that the bias due to confounding is sufficiently high to threaten the conclusions about the exposure's effect on the outcome, it is reasonable to conclude that the risk of bias due to confounding is not high enough to significantly impact the study's conclusions about the exposure's important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure does not well-characterize the exposure metric specified to be of interest in this study. Since the exposure was measured at a single point in time, it may not fully capture the dynamic nature of the exposure over time. This limitation suggests that the exposure measurement may not adequately represent the exposure metric of interest in the study.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure was likely to be measured with error or misclassified. Since the exposure was measured at a single point in time, there is a higher likelihood of error or misclassification due to the potential variability of the exposure over time. This limitation suggests that the exposure measurement may not accurately reflect the true exposure status of the participants.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Mismeasurement or misclassification of exposure could have been differential, related to the outcome or risk of the outcome. Since the exposure was measured at a single point in time, any differential misclassification or mismeasurement of the exposure could potentially be related to the outcome or the risk of the outcome. This differential misclassification could introduce bias in the estimated effect of exposure, impacting the validity of the study results.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error is likely to bias the estimated effect of exposure on the outcome. Since the exposure was measured at a single point in time, any non-differential measurement error could lead to bias in the estimated effect of exposure on the outcome. Non-differential measurement error affects all groups equally, potentially diluting the true association between exposure and outcome. This bias could impact the validity of the study findings.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the measurement of exposure being categorized as "some concern" due to it being conducted at a single point in time, another factor contributing to this concern is the lack of detailed explanation provided by the authors on how they retrieved the data. Without a clear description of the data retrieval process, there is ambiguity surrounding the methods used to collect the exposure data in the Piedmont 65 Study. This lack of transparency can introduce uncertainty and potential biases into the study findings, further contributing to the overall risk of bias in the measurement of exposure.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure at a single point in time is towards the null. Mismeasurement or misclassification of the exposure in this scenario is likely to attenuate the true association between exposure and outcome, leading to an underestimation of the effect. This bias would tend to move the observed effect towards the null hypothesis of no association between exposure and outcome.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Yes, the risk of bias arising from the measurement of exposure, particularly in the context of mismeasurement or misclassification of exposure at a single point in time, is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The potential for bias towards the null due to mismeasurement or misclassification could lead to an underestimation of the true effect of exposure on the outcome. This underestimation may obscure or weaken the actual impact of the exposure on the outcome, potentially affecting the interpretation of the study results and the conclusions drawn. Therefore, the risk of bias in this aspect is significant enough to threaten the conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2, Variant (b): ***If Y/PY to C5 and Y/PY to C6*** *(each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	there is a likelihood that follow-up did begin at or close to the start of the exposure window for most participants, there may be some uncertainty or variability in the exact timing of exposure assessment relative to the start of follow-up. Overall, there is a reasonable expectation that the follow-up was initiated in proximity to the exposure window for the majority of participants in the study.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	while there is a likelihood that the effect of exposure remains relatively stable or consistent over the follow-up period, there may be some potential for variability or changes in the exposure effect over time. Overall, it is probable that the effect of exposure is relatively constant during the period of follow-up analyzed, but there could be some nuances or fluctuations that may impact the consistency of the exposure effect over time.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	it is unlikely that participant selection was influenced by characteristics observed after the start of the exposure window. This suggests that the selection process was likely based on pre-existing participant characteristics or factors that were known prior to the commencement of the exposure window under investigation.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	-

Signalling questions	Response options	Comments
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias due to the selection of participants into the study being categorized as "Some concerns" indicates that there are certain aspects of the participant selection process that raise potential issues but do not pose a high or very high risk to the validity of the study results. Here are some reasons why this category is chosen: Sampling Method: The study included community-dwelling individuals over 65 years of age from specific North Carolina counties. The selection of participants from this population may introduce some bias if the sample is not representative of the broader population of interest. However, without further details on the sampling method, it is challenging to assess the extent of this bias. Generalizability: The study's findings may be limited in their generalizability if the selection criteria for participants were narrow or if certain groups were underrepresented. This could impact the external validity of the study results. Potential Confounders: The selection process may not have adequately accounted for potential confounding variables that could influence the relationship between exposure and outcome. Failure to address confounders in participant selection could introduce bias into the estimated effect of exposure on the outcome. Transparency: The lack of detailed explanation provided by the authors on how participants were selected for the study may raise concerns about the transparency and rigor of the participant selection process. Without clear documentation of the selection criteria and methods, it is difficult to assess the risk of bias accurately.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study is "Towards harm of (higher) exposure." This suggests that there is a likelihood that the bias in participant selection may lead to an overestimation of the harmful effects associated with higher exposure levels. The bias is expected to skew the results towards indicating a greater

Signalling questions	Response options	Comments
		harm associated with higher levels of exposure, potentially influencing the interpretation of the study outcomes.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study is not considered sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome. This suggests that while there may be some concerns regarding bias in participant selection, it is not deemed significant enough to undermine the overall conclusions regarding the impact of the exposure on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no post-exposure interventions that were influenced by prior exposure during the follow-up period. This indicates that there were no interventions implemented after exposure that were influenced by the participants' prior exposure status, suggesting that the follow-up period did not introduce bias related to post-exposure interventions.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	Since there were no post-exposure interventions that were influenced by prior exposure during the follow-up period, it is not applicable to assess whether the analysis corrected for the effect of such interventions. In this case, the absence of post-exposure interventions influenced by prior exposure eliminates the need to consider correction for their effects in the analysis.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias due to post-exposure interventions in the estimated effect of exposure on the outcome is "Low risk." Since there were no post-exposure interventions that were influenced by prior exposure during the follow-up period, there is no indication of bias introduced through post-exposure interventions. This suggests that the estimated effect of exposure on the outcome is not significantly impacted by post-exposure interventions, leading to a low risk of bias in this regard.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Without specific details or information provided regarding the potential confounding factors and their influence on the exposure-outcome relationship, it is not possible to predict the direction of bias due to confounding accurately. Additional information on the confounding variables and their impact would be needed to determine the predicted direction of bias in this context.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Since there were no post-exposure interventions that were influenced by prior exposure during the follow-up period, the risk of bias due to post-exposure interventions is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. In this case, the absence of post-exposure interventions influenced by prior exposure indicates that the estimated exposure effect is not significantly impacted by

		bias related to post-exposure interventions, thus not threatening the conclusions about the exposure's effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	The information provided in the study does not explicitly state whether complete data on exposure status were available for all participants. However, based on the description of the study sample and methods, it is likely that complete data on exposure status were available for all or nearly all participants in the study. This assumption is made considering the detailed examination and data collection procedures described in the document, which suggest a thorough assessment of exposure status for the participants.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study does not explicitly state whether complete data on the outcome were available for all participants. However, based on the detailed methods described in the document and the thorough examination procedures conducted on the participants, it is likely that complete data on the outcome were available for all or nearly all participants in the study. This assumption is made considering the comprehensive data collection methods mentioned in the document, which suggest a high likelihood of complete outcome data for the participants.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study does not explicitly state whether complete data on confounding variables were available for all participants. However, based on the detailed methods described in the document and the thorough examination procedures conducted on the participants, it is likely that complete data on confounding variables were available for all or nearly all participants in the study. This assumption is made considering the comprehensive data collection methods mentioned in the document, which suggest a high likelihood of complete confounding variable data for the participants.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	The study does not provide explicit information on whether exclusion from the analysis due to missing data was likely to be related to the true value of the outcome. However, based on the information available, it is probable that exclusion from the analysis due to missing data was not strongly

Signalling questions	Response options	Comments
		related to the true value of the outcome. This assumption is made considering the detailed examination procedures and data collection methods described in the document, which suggest that missing data handling was likely conducted in a systematic and unbiased manner, minimizing the likelihood of exclusion being related to the true outcome value.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	The studt does not explicitly state whether the analysis was based on imputing missing values. However, given the detailed methods described in the document and the focus on analyzing risk indicators for third molar caries and periodontal disease in senior adults, it is probable that imputation of missing values may have been utilized to address any missing data. Imputation is a common technique used to handle missing data in statistical analyses, especially in studies where complete data are crucial for drawing accurate conclusions.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	The study does not provide specific details on the imputation methods used for handling missing data. However, based on the comprehensive nature of the study and the detailed examination procedures described, it is likely that imputation, if performed, was done appropriately. This assumption is made considering the rigorous data collection methods mentioned in the document, which suggest that proper imputation techniques may have been employed to address missing data and minimize bias in the analysis.
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	-

Signalling questions	Response options	Comments
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias due to missing data in the estimated effect of exposure on the outcome can be categorized as "high risk." This is because there is no mention of how missing data was handled in the study, which could potentially introduce bias if the missing data were not addressed appropriately. Additionally, Clinical data from a subset of 810 dentate participants in the Piedmont 65 Study were utilized for analysis and only 340 subjects with visible third molars, all underwent examination for caries experience.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The document does not provide specific details on the direction of bias that may result from missing data in the estimated effect of exposure on the outcome. Without explicit information on how missing data were handled and the potential impact on the estimated associations, it is not possible to predict the direction of bias accurately. Further clarification or additional information would be needed to determine the potential direction of bias resulting from missing data in the analysis.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Without specific information on the handling of missing data, the direction of potential bias, and the magnitude of the estimated exposure effect, it is challenging to determine if the risk of bias due to missing data is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Further details or clarification on the handling of missing data and its impact on the study results would be necessary to assess the potential threat to the conclusions drawn from the analysis.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The study indicates that the measurement or ascertainment of outcomes, specifically third molar caries and periodontal disease, may have differed between exposure groups or levels of exposure. Variations in the assessment of outcomes between different exposure groups could introduce bias or affect the comparability of results. Further details on how outcome measurements were standardized and whether potential differences in measurement between exposure groups were addressed would provide more clarity on the extent of this potential bias.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The study does not explicitly state whether outcome assessors were aware of study participants' exposure history. However, in studies where outcome assessors are involved in the research process, there is a likelihood that they may have been aware of participants' exposure history, potentially introducing bias in outcome assessment. Without specific information on blinding procedures or measures taken to prevent assessors from being aware of exposure history, it is probable that outcome assessors were aware of participants' exposure status.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The study does not provide explicit information on whether the assessment of the outcome could have been influenced by knowledge of participants' exposure history. However, in studies where outcome assessment may be subjective or influenced by prior knowledge of exposure status, there is a high likelihood that such knowledge could have influenced the outcome assessment to a large extent. Without specific details on blinding procedures or measures to prevent bias related to exposure history, it is reasonable to assume that the assessment of outcomes could have been influenced by participants' exposure history to a significant degree.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided, the risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome can be categorized as "Some concerns." This is because the clinical data collection involved comprehensive dental examinations that included assessments of all visible teeth and evaluation of caries experience through visual-tactile examination. While these methods are commonly used in dental research, the lack of specific details on the measurement techniques

Signalling questions	Response options	Comments
		and potential variability in the assessment of outcomes may raise some concerns about the accuracy and consistency of outcome measurements.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of outcomes is "Towards null." Given the lack of specific information on the direction of bias in the document, and considering the potential for measurement biases to affect the accuracy of outcome assessment, it is likely that any bias introduced by measurement issues would tend to shift the results towards the null hypothesis. This means that the bias would likely lead to underestimating the true effect of exposure on the outcome, moving the results closer to a null effect or no association between exposure and outcome.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes is sufficiently high, considering the potential for bias in outcome assessment due to factors such as assessors' awareness of exposure history and the likelihood of bias towards the null hypothesis. This level of bias could threaten the conclusions about whether exposure has an important effect on the outcome by potentially underestimating the true effect of exposure. Therefore, the risk of bias in outcome measurement is significant enough to impact the conclusions drawn from the study regarding the relationship between exposure and outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The document does not provide explicit information on whether the reported result was in accordance with an available, pre-determined analysis plan. Without details on the existence of a pre-determined analysis plan and whether the reported result aligns with it, it is not possible to determine if the result was reported in accordance with such a plan.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The study does not provide specific details on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. Without this information, it is not possible to assess whether there was bias in the selection of the reported result based on the desirability of the effect estimate from multiple outcome measurements.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The document does not provide specific details on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. Without this information, it is not possible to assess whether there was bias in the selection of the reported result based on the desirability of the effect estimate from multiple analyses.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The study does not provide specific details on whether the reported effect estimate was likely selected based on the desirability of the results, such as statistical significance, from different subgroups. Without this information, it is not possible to assess whether there was bias in the selection of the reported result based on the desirability of the results from different subgroups.

Signalling questions	Response options	Comments
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The level of risk of bias due to the selection of reported results is considered "Low risk." The reported results align closely with the study objectives, which focused on examining risk indicators for third molar caries and periodontal disease in senior adults using data from a subset of 810 dentate participants from the Piedmont 65 Study. The outcomes reported in the study are in line with the research goals, indicating a low risk of bias in the selection of reported results.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The document does not provide specific details on the selection process of the reported results, including whether the results were chosen based on the desirability of the magnitude or statistical significance of the estimated effect from various analyses and subgroups. Without this information, it is not possible to predict the direction of bias in the selection of the reported results.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Without specific information on the selection process of the reported results and the potential bias introduced by this selection, it is not possible to determine if the risk of bias due to the selection of the reported result is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	The overall risk of bias in the study can be categorized as "Some concerns." While certain aspects of the participant selection process and the measurement of exposure raise potential issues, they do not pose a high or very high risk to the validity of the study results. The risk of bias due to confounding and the measurement of exposure both have some concerns regarding the potential impact of unmeasured or residual confounding and the lack of detailed explanation on data retrieval methods, respectively. Additionally, the risk of bias due to missing data is categorized as "high risk," indicating a potential for bias if the missing data were not appropriately addressed. However, the risk of bias due to post-exposure interventions is considered "Low risk," as there were no post-exposure interventions that could have influenced the estimated effect of exposure on the outcome. Overall, while there are some concerns in various aspects of the study design and analysis, they do not significantly undermine the validity of the study results.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias due to confounding in the estimated effect of exposure on the outcome is "Towards null." This means that the bias is likely to shift the results towards showing no effect or a weaker effect of exposure on the outcome than actually exists. The text mentions concerns about uncontrolled confounding and the lack of information on how baseline and time-varying confounding factors were addressed in the analysis. This suggests that there may be residual confounding that could influence the results to some extent. In the presence of uncontrolled confounding, the estimated effect of exposure on the outcome may be attenuated or biased towards the null hypothesis, leading to an underestimation of the true effect size. Therefore, the predicted direction of bias in this case is towards null, indicating a potential underestimation of the true relationship between exposure and outcome.

Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	While there are some concerns regarding bias in the study related to confounding, measurement of exposure, selection of participants, post-exposure interventions, missing data, and measurement of outcomes, the overall risk of bias is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The text indicates that there may be some concerns and potential biases in various aspects of the study, but these concerns do not appear to be severe enough to significantly impact the validity of the conclusions regarding the effect of exposure on the outcome.

10. Factors of importance for changes in dental caries among adults: A follow-up study of Oslo citizens from the age of 35 to 50 years (10)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Socioeconomic Status (SES): SES can affect access to dental care, oral hygiene products, and education about oral health.
2. Age: Age can influence the risk of developing dental caries due to changes in oral health practices and biological factors.
3. Gender: Gender differences can affect oral health behaviors and susceptibility to dental caries.
4. Oral Hygiene Practices:Regular brushing, flossing, and dental visits are critical for preventing caries.
5. Dietary Habits: Sugar intake and overall diet quality can significantly influence caries development.
6. Fluoride Exposure:Use of fluoride toothpaste, mouth rinses, and community water fluoridation can reduce caries risk.
7. Psychological Factors:Stress, anxiety, and depression can affect oral hygiene practices and health-seeking behavior.
8. Access to Dental Care:Availability and affordability of dental services can influence treatment and preventive care.
9. Health Behaviors:Smoking, alcohol consumption, and other health behaviors can impact oral health.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

The total number of carious surfaces (DS + D_S). This includes both decayed surfaces that were previously filled and those that were not filled.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They utilized multivariate analyses to assess the impact of various independent variables on the changes in dental health. Specifically, the study employed multiple classification analysis (MCA) to evaluate the relationships between behavioral, environmental, human biology, and health care organization factors and the dependent variable of carious surfaces (DS + D_S).
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	-
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	-

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The multivariate analysis of the independent variables related to changes in dental caries among adults. Specifically, the study examines the relationship between various behavioral, environmental, human biology, and health care organization factors and the outcome of dental health, measured as the number of carious surfaces (DS + D_S) at ages 35 and 50.

The outcome to which this result relates is the change in dental caries status, categorized as stable/improved versus deteriorated dental health, based on the number of carious surfaces recorded at the two age points.

C2. Specify the participant group on which this result was based.

A random sample of 116 Oslo citizens who were 35 years old at the time of the initial examination in 1973. After a follow-up examination conducted in 1988, the final sample size was reduced to 81 individuals

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?

These exposures were assessed through a combination of methods:

1. Clinical and Radiographic Examination: Participants underwent clinical examinations to assess their dental health, including the number of carious surfaces (DS + D_S) and the presence of filled or missing surfaces. Radiographs were also used to detect carious lesions that may not have been clinically visible.
2. Saliva Samples: Saliva samples were analyzed for stimulated secretion rate, buffer capacity, and the number of *Streptococcus mutans* colony-forming units, which are relevant to caries development .
3. Questionnaires: Participants completed questionnaires that gathered information on psychosocial factors and dental health habits, which provided insights into behavioral aspects related to dental care

C4. Was exposure analysed as a quantitative (rather than a categorical) variable?

Y / PY / PN / N

C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / <u>PN / N</u>
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	<u>NA</u> / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	<u>NA</u> / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	<u>NA</u> / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The study analyzed the relationship between various independent variables (exposures) and changes in dental caries status (the outcome) over a 15-year period. Specifically, it focused on how behavioral factors, particularly psychologic status, influenced the likelihood of having stable/improved versus deteriorated dental health.

Using multiple classification analysis (MCA), the study found that 26% of the variation in dental health outcomes was explained by these behavioral factors. While it did not specify a particular statistical model like a quadratic relationship or risk ratio, the analysis indicated a direct association where positive behavioral factors were linked to a lower likelihood of deteriorating dental health

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study consisted of adults aged 35 to 50 years living in Oslo, Norway. Eligible participants were those who were part of the original cohort examined at age 35 and were followed up at age 50. The study specifically focused on individuals who had complete data on dental health status and relevant independent variables at both time points. The study participants included those who had visited the dentist regularly and had varying levels of dental health, categorized as either stable/improved or deteriorated dental health based on the number of carious surfaces (DS + D_S) recorded at ages 35 and 50. Differences between the eligible population and the study participants could arise from selection biases, particularly if individuals with poorer dental health or those who did not regularly visit the dentist were less likely to participate in the follow-up. This could potentially limit the generalizability of the findings to the broader population of adults in the same age range, as the results may not fully represent those who are less engaged with dental care or have different health behaviors

Specification of the exposure metric of interest

D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure in the study refers to the various behavioral and psychosocial factors that may influence changes in dental caries status among adults. Specifically, the study examined factors such as: 1. Psychologic Status: This was identified as a significant predictor of changes in dental health. 2. Dental Care Behaviors: This includes regular dental visits and effective oral hygiene practices (e.g., tooth cleaning). 3. Substance Use: Factors such as alcohol consumption and smoking were also considered.

		4. Social and Environmental Factors: These may include socioeconomic status and changes in living conditions over the 15-year period.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	The exposure window of interest in the study is defined as the period from age 35 to age 50. This timeframe is significant as it encompasses the years during which the participants' dental health was monitored and assessed for changes in caries status. • Time of Onset: The exposure period begins at age 35, which is when the initial assessment of dental health and relevant behavioral factors was conducted. • Period of Exposure: The exposure period extends to age 50, when participants were reexamined to evaluate changes in their dental health status. This exposure window is meaningful for assessing the causal effect of the identified behavioral and psychosocial factors on dental caries outcomes, as it captures the critical years during which these factors could influence dental health.
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	In the study, exposure over time should be summarized using a combination of the following approaches: 1. Cumulative Exposure: This would involve assessing the total duration and frequency of exposure to the identified behavioral factors (e.g., regular dental visits, effective oral hygiene practices, and psychosocial conditions) over the entire exposure window from age 35 to age 50. For instance, participants could be categorized based on how consistently they engaged in positive dental health behaviors during this period. 2. Average Exposure: This could be calculated by determining the average level of engagement in the relevant behaviors (e.g.,

frequency of dental visits, average tooth cleaning practices) across the exposure window. This approach allows for a more nuanced understanding of how varying levels of exposure may impact dental health outcomes.

3. Ever/Never Exposed: For certain factors, such as smoking or alcohol use, participants could be classified as ever exposed (those who engaged in these behaviors at any point during the exposure window) versus never exposed (those who did not engage in these behaviors at all during the period).

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Education level (years at school) and social class	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Nutritional status, Sugar between meals	Y	N	N	Harm of (higher) exposure	
Oral hygiene practices	Toothbrushing and flossing Frequency.	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Classified as regular or irregular dental	Y	Y	N	Benefit of (higher) exposure	

	attenders and school dental care					
Age	Categorized into different age groups	Y	Y	N	Insufficient information available	
Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Alcohol, smoking	N	N	N	Harm of (higher) exposure	
Environmental Factors	fluoridated water	N	N	N	Benefit of (higher) exposure	
Host factors	Saliva buffer capacity, saliva secretion and presence of chronic disease	Y	Y	N		

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis?	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?*	If this confounding factor was not controlled for, is there evidence that	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher)	Comments

		(Y / N)	(NA / Y / PY / PN / N / NI)	controlling for it was unnecessary?** (NA / Y / PY / PN / N)	exposure / Insufficient information available)	

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors likely controlled for important confounding factors at baseline. This is inferred from the comprehensive nature of the study, which aimed to characterize changes in dental caries among adults over a 15-year period. Given the detailed examination of individual caries situations and the multifactorial approach employed in the study, it is probable that the authors considered and controlled for key confounding factors at baseline to ensure the validity and reliability of their findings.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	It is likely that the confounding factors controlled for in the study were measured validly and reliably. The study's detailed methodology and longitudinal design suggest that the variables used to assess confounding factors were carefully selected and measured to ensure accuracy and consistency. While there may be some potential for measurement error in any study, the robust nature of this research likely minimized such errors, indicating that the measurement of confounding factors was valid and reliable for the purposes of the study.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	The authors did not control for variables that may have been affected by the exposure after the start of the exposure period being studied. The focus of the study was on changes in dental caries among adults over a 15-year period, and it appears that the analysis primarily considered baseline confounding factors without adjusting for variables that could have been influenced by the exposure during the study period. This lack of control for post-exposure variables may introduce potential bias into the study results.

Signalling questions	Response options	Comments
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	There is likely no indication of serious uncontrolled confounding based on the information provided in the study. The comprehensive analysis of baseline confounding factors and the detailed examination of changes in dental caries over time suggest that the authors took appropriate measures to address potential confounders. Without specific details on the use of negative controls or other considerations in the study, it is probable that serious uncontrolled confounding was not a significant issue in this research.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias (due to confounding) in the estimated effect of exposure on the outcome in the study is categorized as "Some concerns." The study acknowledges the multifactorial nature of dental caries, involving various behavioral, environmental, human biology, and health care organization variables. While the study attempts to account for these factors in its analysis, there may still be residual confounding present that could influence the estimated effect of exposure on the outcome. The complexity of factors involved in dental caries development suggests that some concerns regarding confounding are warranted.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	Without specific details on the potential confounding variables, their relationship with the exposure and outcome, and the direction of their influence, it is not possible to predict the direction of bias due to confounding in this study. Additional information on the specific confounders and their potential impact on the exposure-outcome relationship would be needed to determine the predicted direction of bias accurately.
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Given the lack of specific information on the potential confounding variables, their impact on the exposure-outcome relationship, and the direction of bias, it is not possible to determine if the risk of bias due to confounding is sufficiently high to threaten conclusions about the importance of the exposure effect on the outcome. Without a clear understanding of the magnitude and direction of potential bias, it is challenging to assess the impact on the study's conclusions. Additional details would be needed to make a more informed judgment in this regard.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

Domain 2, Variant (a): ***If N/PN to C5*** *(exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure may not fully characterize the exposure metric specified in this study. The exposure was measured at a single point in time, which may not capture the full complexity of exposure over the entire study period. In the context of dental caries, factors such as long-term dietary habits, oral hygiene practices, and fluoride exposure could vary over time and influence the development of caries. Therefore, a single measurement of exposure may not fully capture the dynamic nature of factors contributing to dental caries development, suggesting a small extent of mischaracterization of the exposure metric.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in this study, which was measured at a single point in time, may have some degree of error or misclassification, but it is not likely to be substantial. Factors such as dietary habits, oral hygiene practices, and fluoride exposure can vary over time and may not be fully captured by a single measurement. While there may be some degree of misclassification due to the static nature of the exposure measurement, it is not expected to significantly impact the overall findings of the study.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	In this study where exposure was measured at a single point in time, there is a possibility of a small extent of differential misclassification of exposure, meaning that mismeasurement or misclassification of exposure could have been related to the outcome or risk of the outcome to some degree. Factors such as dietary habits, oral hygiene practices, and fluoride exposure, which are components of the exposure of interest (dental caries development), may be influenced by the individual's current dental health status or awareness of their oral health, potentially leading to differential misclassification . While the impact of this differential misclassification may be minor, it is important to acknowledge this potential source of bias in the estimated effect of exposure on the outcome.

Signalling questions	Response options	Comments
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error, resulting from exposure being measured at a single point in time, may introduce a small extent of bias in the estimated effect of exposure on the outcome in this study. Factors such as dietary habits, oral hygiene practices, and fluoride exposure, which are components of the exposure of interest (dental caries development), may vary over time and could lead to non-differential misclassification. While this non-differential error may introduce some bias, it is likely to be minor and may not significantly impact the overall estimated effect of exposure on the outcome.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Based on the information provided in the study , the risk of bias arising from the measurement of exposure in the estimated effect of exposure on the outcome can be categorized as "Some concerns." This classification is based on the following considerations: Validity and Reliability of Exposure Measurement: While the study utilized questionnaires and other tools to measure exposure factors such as psychosocial variables and dental health habits, the validation of these instruments was not explicitly mentioned. The lack of information on the validation process raises some concerns about the accuracy and reliability of the exposure measurements. Subjective Nature of Self-Reported Data: Self-reported data obtained through questionnaires may be subject to biases such as recall bias or social desirability bias. Although efforts were likely made to minimize these biases, the subjective nature of self-reported data introduces some concerns regarding the accuracy of exposure measurements. Selection Bias and Confounding Variables: The study did not provide detailed information on how potential selection bias or confounding variables were addressed in the measurement of exposure. Failure to adequately control for these factors could introduce bias and affect the estimated effect of exposure on the outcome. Measurement Error: While the study employed various tools and methods to measure exposure factors, the potential for measurement error, particularly in clinical examinations or saliva sample analyses, could impact the precision of exposure measurements and introduce some concerns about bias.

Signalling questions	Response options	Comments
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure at a single point in time is towards the null in this study. The static measurement of exposure may lead to some degree of misclassification or mismeasurement, potentially diluting the true effect of exposure on dental caries development. Since the exposure measurement is not capturing the dynamic changes in factors influencing dental caries over time, any bias introduced by this measurement error is more likely to attenuate the estimated effect towards the null hypothesis, indicating no association between exposure and outcome. Therefore, the predicted direction of bias is towards null in this context.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, particularly due to mismeasurement or misclassification of exposure at a single point in time, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome in this study. While there are some concerns about the potential bias introduced by the static measurement of exposure, the predicted direction of bias towards the null suggests that any impact on the estimated exposure effect is likely to be minimal and not substantial enough to significantly alter the conclusions regarding the importance of the exposure on dental caries development. Therefore, the risk of bias is not considered high enough to threaten the conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The study did not provide specific information regarding whether follow-up began at or close to the start of the exposure window for most participants. Without this information, it is not possible to determine if follow-up started at an appropriate time in relation to the exposure window for the majority of participants. Therefore, the answer is categorized as No Information (NI) in this case.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	The study did not provide specific information regarding whether the effect of exposure was likely to be constant over the period of follow-up analyzed. Without details on the stability of the exposure effect over time, it is not possible to determine if the effect of exposure remained consistent throughout the follow-up period. Therefore, the answer is categorized as No Information (NI) in this case
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The study did not provide specific information regarding whether the selection of participants into the study or analysis was based on participant characteristics observed after the start of the exposure window being studied. Without this information, it is not possible to determine if participant selection was influenced by characteristics that occurred after the exposure window began. Therefore, the answer is categorized as No Information (NI) in this case.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	-
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is	-

Signalling questions	Response options	Comments
	evidence of substantial impact)	
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias due to the selection of participants into the study in the estimated effect of exposure on the outcome can be categorized as "Some concerns." This classification is based on the following considerations: Participant Selection: The study initially included a random sample of 116 35-year-old Oslo citizens, which is a strength in minimizing selection bias. However, 17 individuals had moved from the region, and four had died during the 15-year follow-up period. The final sample size was reduced to 81 persons after excluding dropouts, resulting in an 85% attendance rate. The exclusion of participants due to relocation or mortality may introduce some concerns regarding the representativeness of the final sample and potential selection bias. Response Rate: Participants who did not respond after reminders were asked to complete a questionnaire about dental habits and reasons for not attending the examination. While efforts were made to gather information from non-responders, the reasons for non-participation could introduce bias if they are related to the exposure or outcome variables under study. Generalizability: The study population may have a somewhat better dental health status than the general population, as noted in the discussion. This difference in dental health status could impact the generalizability of the findings to the broader population and raise concerns about the selection of participants influencing the estimated effect of exposure on the outcome. Loss to Follow-up: The loss of participants over the 15-year follow-up period, particularly those with low education levels, may introduce bias if their characteristics or outcomes differ systematically from those who remained in the study. This loss to follow-up could affect the validity of the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null /	The study did not provide specific information regarding the predicted direction of bias due to the selection of participants in the study. Without this information, it is not possible to determine whether the selection of participants may have biased the results towards the benefit of higher

Signalling questions	Response options	Comments
	Insufficient information available	exposure, harm of higher exposure, towards null, away from null, or if there was insufficient information available.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Based on the information provided in the study, the risk of bias due to the selection of participants into the study does not appear to be sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study did not indicate any specific issues related to the selection of participants that would significantly impact the conclusions drawn regarding the effect of exposure on the outcome. Therefore, the answer is "No." The study did not highlight any concerns or biases related to the selection of participants that would cast doubt on the importance of the exposure effect on the outcome. Without evidence of a high risk of bias in participant selection affecting the conclusions, it is reasonable to conclude that the risk of bias in this aspect is not substantial enough to undermine the assessment of the exposure's impact on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	The study did not provide specific information regarding post-exposure interventions that were influenced by prior exposure during the follow-up period. Without this information, it is not possible to determine if there were any post-exposure interventions that may have been influenced by prior exposure. Therefore, the answer is categorized as No Information (NI) in this case.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	The study did not provide specific information regarding whether the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure. Without this information, it is not possible to determine if the analysis adequately accounted for any post-exposure interventions that may have been influenced by prior exposure. Therefore, the answer is categorized as No Information (NI) in this case.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	based on the information provided in the study, since there is no specific mention of post-exposure interventions that could have influenced the estimated effect of exposure on the outcome, it is reasonable to consider the risk of bias due to post-exposure interventions as low. Without evidence of such interventions impacting the estimated effect, the risk of bias in this aspect is likely low.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study did not provide specific information regarding the predicted direction of bias due to confounding. Without this information, it is not possible to determine the predicted direction of bias in this context. Therefore, the answer is categorized as No Information (NI) in this case.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The study did not provide specific information regarding the risk of bias due to post-exposure interventions and its potential impact on the conclusions. Without this information, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about the exposure effect on the outcome. Therefore, the answer is categorized as No Information (NI) in this case.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , it was mentioned that more persons with low education than with high education were lost in the recall study. This indicates that complete data on exposure status may not have been available for all participants, as there was differential loss to follow-up based on education level.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , it was mentioned that more persons with low education than with high education were lost in the recall study. This suggests that complete data on the outcome may not have been available for all participants, as there was differential loss to follow-up based on education level.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , it was mentioned that more persons with low education than with high education were lost in the recall study. This indicates that complete data on confounding variables may not have been available for all participants, as there was differential loss to follow-up based on education level.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	In the study , it was mentioned that more persons with low education than with high education were lost in the recall study. This suggests that the analysis may not have been based on a complete case, as there was differential loss to follow-up based on education level. Therefore, the answer is categorized as No (N) in this case.
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	In the study, it was mentioned that more persons with low education than with high education were lost in the recall study. This suggests that the exclusion from the analysis due to missing data was likely related to the true value of the outcome, as there was a differential loss to follow-up based on education level.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	-

Signalling questions	Response options	Comments
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	In the study, there is no mention of the analysis being based on imputing missing values. Since there is no indication of imputation methods being used for missing data, the answer is categorized as No (N) in this case.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	The study does not provide information on whether an appropriate alternative method was used to correct for bias due to missing data. Without details on any alternative methods used to address missing data, there is no information available to assess the appropriateness of such methods.
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	The study does not provide explicit evidence or discussion regarding the potential bias introduced by missing data. Without specific information on how missing data may have impacted the results and whether any steps were taken to address this bias, there is no evidence available to determine if the results were biased by missing data.
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias due to missing data in the estimated effect of exposure on the outcome can be categorized as "Some concerns." This classification is based on the following considerations: Reasons for Missing Data: The study mentioned that some individuals had moved from the Oslo region, and a few had died during the 15-year follow-up period. These reasons for missing data are known and documented, which reduces the risk of bias compared to missing data that are completely random or unexplained. Response Rate: Despite missing data due to individuals who had moved or passed away, the study still achieved an 85% attendance rate for the follow-up examination. This relatively high response rate helps mitigate the impact of missing data on the overall study findings. Handling of Missing Data: The study described efforts to contact non-responders and gather information through questionnaires about dental

Signalling questions	Response options	Comments
		habits and reasons for not attending the examination. While missing data were acknowledged, steps were taken to collect additional information from those who did not participate in the clinical examination. Impact on Generalizability: The missing data, particularly due to individuals who moved or died, may affect the generalizability of the study findings to the broader population. However, the known reasons for missing data allow for a more transparent assessment of potential biases.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide specific details on the predicted direction of bias due to missing data. Without information on how missing data were handled or imputed, it is not possible to determine the predicted direction of bias in this case.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to missing data in the study is categorized as "Cannot tell" in this case. This classification is based on the lack of information provided in the study regarding the handling of missing data and its potential impact on the estimated exposure effect. Without specific details on how missing data were addressed and the likely direction of bias, it is not possible to determine if the risk of bias is sufficiently high to threaten conclusions about the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	In the study , the risk of bias arising from the measurement of the outcome is categorized as "Yes." This classification is based on the possibility that the measurement or ascertainment of the outcome, which in this case is the number of dental caries lesions, could have differed between exposure groups or levels of exposure. Discrepancies in how the outcome was measured or assessed across different exposure groups may introduce bias and affect the validity of the study results. For example, if the methods used to detect or record dental caries lesions varied between individuals with different levels of exposure to certain risk factors, it could lead to differential misclassification of the outcome. This differential misclassification may result in an overestimation or underestimation of the true effect of exposure on the outcome, potentially influencing the study's conclusions regarding the relationship between exposure and dental caries lesions
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	the risk of bias arising from the measurement of the outcome is categorized as "No." This classification is based on the assumption that outcome assessors were not aware of the study participants' exposure history. When outcome assessors are blinded to the exposure status of participants, it helps minimize the risk of bias that could arise from their knowledge of the participants' exposure history. In this study, there is no indication or evidence provided that the outcome assessors were aware of the exposure history of the study participants. This lack of awareness suggests that the outcome assessment was conducted in a blinded manner, reducing the potential for bias related to the assessors' knowledge of participants' exposure status. Blinding of outcome assessors to exposure information enhances the objectivity and reliability of outcome measurements, contributing to the overall validity of the study findings.

Signalling questions	Response options	Comments
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	the risk of bias arising from the measurement of the outcome is categorized as "Yes, to a small extent." This classification suggests that while there is a possibility that the assessment of the outcome could have been influenced by knowledge of participants' exposure history, the impact of this influence is considered minimal. For example, if the individuals assessing the dental caries lesions were partially aware of the participants' exposure history, there might be a slight risk that this knowledge could subtly influence how the outcome is measured or recorded. However, since the study does not provide explicit information on the extent to which outcome assessment could have been influenced by exposure history, the potential bias is considered to be minimal. Therefore, while there is a small possibility that assessment of the outcome could have been influenced by knowledge of participants' exposure history, the impact of this influence is deemed to be minor and unlikely to significantly affect the overall validity of the study results.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias arising from the measurement of outcomes can be categorized as "Some concerns." This classification is based on the following considerations: Intraexaminer Calibration: The study mentioned that regular intraexaminer calibration tests were performed before and during the examination period, and the initial calibration period was terminated when it reached 90% consistency. This indicates a systematic approach to ensuring consistency and reliability in outcome measurements by the examiner. Lack of Information on Outcome Assessor Blinding: While the study did not provide explicit information about whether outcome assessors were aware of the study participants' exposure history, the absence of this information raises some concerns regarding the potential for bias. Blinding of outcome assessors to participants' exposure status is crucial to minimize measurement bias.

Signalling questions	Response options	Comments
		Transparency and Reporting: The study's lack of clarity on whether outcome assessors were blinded to exposure history introduces uncertainty about the objectivity of outcome assessments. Without explicit confirmation of blinding practices, there is a possibility of bias in outcome measurement. Calibration Consistency: Although intraexaminer calibration tests were conducted and consistency was monitored, the lack of information on blinding practices for outcome assessors leaves room for potential bias if assessors were not blinded to exposure history.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	outcomes. The study does not explicitly discuss the potential direction of bias in relation to the measurement of dental caries lesions and exposure history. Without specific details or indications within the study regarding the expected direction of bias, it is challenging to predict whether the measurement of outcomes would be biased towards the benefit of higher exposure, towards harm of higher exposure, towards null, or away from null. The lack of information on this aspect limits the ability to assess the potential direction of bias in the study's estimated effect of exposure on the outcome. Therefore, due to the absence of relevant details or insights within the study regarding the predicted direction of bias arising from the measurement of outcomes, the classification is marked as "Insufficient information available." This signifies the need for additional data or clarification to make an informed judgment on the potential direction of bias in the study's findings.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	In the context of the likely direction and magnitude of the estimated exposure effect, it is not possible to determine if the risk of bias arising from the measurement of outcomes is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The study does not provide explicit information on the extent of bias, the likely direction of bias, or the magnitude of the estimated exposure effect in relation to the outcome.

Signalling questions	Response options	Comments
		Without specific details or insights within the study regarding the potential impact of bias on the estimated exposure effect and its significance on the study conclusions, it is challenging to assess whether the risk of bias is high enough to threaten the conclusions about the importance of the exposure effect on the outcome. Therefore, due to the lack of relevant information or analysis within the study to evaluate the potential threat posed by bias on the conclusions regarding the exposure effect, the classification is marked as "Cannot tell." This indicates the need for further investigation or clarification to determine the impact of bias on the study's conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	the reported results were in accordance with an available, pre-determined analysis plan. There is no mention of a pre-specified analysis plan or details on how the results were reported in alignment with any predetermined analysis strategy. Without specific information within the study about the existence of a pre-determined analysis plan and the adherence to such a plan in reporting the results, it is not possible to determine if the reported results were based on a predefined analysis approach. Therefore, due to the lack of information or details on the presence of a pre-determined analysis plan and its influence on the reporting of results, the classification is marked as "NI" (No information). This signifies the absence of data within the study to assess whether the reported results were in accordance with a predetermined analysis plan
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	The study does not provide specific information regarding whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple exposure measurements within the exposure domain. There is no mention of the selection process for the reported effect estimate or any indication of potential bias in selecting the results based on desirability. Without explicit details or insights within the study about the criteria used for selecting the reported effect estimate and whether it was influenced by the desirability of the effect magnitude or statistical significance, it is not possible to determine if such selection bias occurred. Therefore, due to the absence of information or analysis within the study to evaluate the likelihood of bias in selecting the reported effect estimate based on desirability, the classification is marked as "NI" (No information). This indicates the lack of data within the study to assess whether the

Signalling questions	Response options	Comments
		reported effect estimate was influenced by the desirability of the effect magnitude or statistical significance.
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The study does not provide specific information regarding whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. There is no mention of the selection process for the reported effect estimate or any indication of potential bias in selecting the results based on desirability. Without explicit details or insights within the study about the criteria used for selecting the reported effect estimate and whether it was influenced by the desirability of the effect magnitude or statistical significance, it is not possible to determine if such selection bias occurred. Therefore, due to the absence of information or analysis within the study to evaluate the likelihood of bias in selecting the reported effect estimate based on desirability, the classification is marked as "NI" (No information). This indicates the lack of data within the study to assess whether the reported effect estimate was influenced by the desirability of the effect magnitude or statistical significance.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The study does not provide specific information regarding whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. There is no mention of the selection process for the reported effect estimate or any indication of potential bias in selecting the results based on desirability. Without explicit details or insights within the study about the criteria used for selecting the reported effect estimate and whether it was influenced by the desirability of the effect magnitude or statistical significance from

Signalling questions	Response options	Comments
		multiple analyses, it is not possible to determine if such selection bias occurred. Therefore, due to the absence of information or analysis within the study to evaluate the likelihood of bias in selecting the reported effect estimate based on desirability, the classification is marked as "NI" (No information). This indicates the lack of data within the study to assess whether the reported effect estimate was influenced by the desirability of the effect magnitude or statistical significance from multiple analyses of the exposure-outcome relationship.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The study does not provide specific information regarding whether the reported effect estimate was likely selected based on the desirability of the results, such as statistical significance, from different subgroups. There is no mention of the selection process for the reported effect estimate or any indication of potential bias in selecting the results based on desirability from different subgroups. Without explicit details or insights within the study about the criteria used for selecting the reported effect estimate and whether it was influenced by the desirability of the results from different subgroups, it is not possible to determine if such selection bias occurred. Therefore, due to the absence of information or analysis within the study to evaluate the likelihood of bias in selecting the reported effect estimate based on the desirability of the results from different subgroups, the classification is marked as "NI" (No information). This indicates the lack of data within the study to assess whether the reported effect estimate was influenced by the desirability of the results, such as statistical significance, from different subgroups.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the data reported align with the study objectives by providing insights into changes in dental caries among the study participants over time and examining the multifactorial aspects influencing these changes. The study aimed to:

Signalling questions	Response options	Comments
		a) Contrast the caries experience in a random sample of 35-year-old Oslo citizens investigated in 1973 and reexamined 15 years later. b) Describe any observed changes in dental caries over the 15-year period. c) Identify individuals with a stable or improved caries situation and compare them with individuals with an increased number of decayed surfaces from the first to the second examination. d) Characterize these two groups of individuals by means of a multifactorial approach, including environmental, behavioral, and other factors. The reported data in the study include information on the caries experience of the study participants at the initial examination in 1973 and the follow-up examination in 1988. The study presents findings on changes in dental caries status over the 15-year period, identifies individuals with different patterns of caries progression, and analyzes various factors related to dental health, behavior, and socioecological influences. Given the alignment of the reported data with the study objectives and the transparency in reporting findings related to changes in dental caries and multifactorial aspects influencing these changes, the risk of bias due to the selection of the reported results in estimating the effect of exposure on the outcome is categorized as "Low risk."
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide specific details on the predicted direction of bias due to the selection of the reported result. Without explicit information on the criteria used for selecting the reported effect estimate and whether it was influenced by the desirability of the results, it is not possible to determine the predicted direction of bias in the reported results. Since the study does not offer insights into the potential direction of bias resulting from the selection of the reported result, the classification is marked as "Insufficient information available." This indicates the lack of data within the study to assess the predicted direction of bias due to the selection of the reported result.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result in the study is classified as "Cannot tell." This classification is based on the lack of specific

Signalling questions	Response options	Comments
magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?		information provided in the study regarding the selection process for the reported effect estimate and its potential impact on the conclusions about the exposure effect on the outcome. Without explicit details on how the effect estimate was chosen and whether it could threaten the conclusions about the importance of the exposure effect on the outcome, it is challenging to assess the magnitude of bias and its potential impact on the study's conclusions. Therefore, due to insufficient information on the risk of bias and its potential threat to the conclusions, it is not possible to determine if the risk is sufficiently high to threaten the conclusions about whether the exposure has an important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	the risk of bias arising from the measurement of outcomes can be categorized as "Some concerns." This classification is based on the following considerations: Intraexaminer Calibration: The study mentioned that regular intraexaminer calibration tests were performed before and during the examination period, and the initial calibration period was terminated when it reached 90% consistency. This indicates a systematic approach to ensuring consistency and reliability in outcome measurements by the examiner. Lack of Information on Outcome Assessor Blinding: While the study did not provide explicit information about whether outcome assessors were aware of the study participants' exposure history, the absence of this information raises some concerns regarding the potential for bias. Blinding of outcome assessors to participants' exposure status is crucial to minimize measurement bias. Transparency and Reporting: The study's lack of clarity on whether outcome assessors were blinded to exposure history introduces uncertainty about the objectivity of outcome assessments. Without explicit confirmation of blinding practices, there is a possibility of bias in outcome measurement. Selection Bias: The reported data align well with the study objectives, providing insights into changes in dental caries and multifactorial influences. The risk of bias due to the selection of reported results is categorized as "Low risk," indicating that the reported data align with the study objectives and provide valuable insights into the research questions. Measurement Bias: The risk of bias arising from the measurement of outcomes is categorized as "Some concerns." While the study conducted intraexaminer calibration tests to ensure consistency and reliability in outcome measurements, the lack of information on outcome assessor blinding raises concerns. Blinding of outcome assessors to exposure history is crucial to minimize measurement bias,

		and the absence of explicit information on blinding practices introduces uncertainty about the objectivity of outcome assessments. Calibration Consistency: Although intraexaminer calibration tests were conducted and consistency was monitored, the lack of information on blinding practices for outcome assessors leaves room for potential bias if assessors were not blinded to exposure history.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in the study is categorized as "Insufficient information available." This classification is based on the lack of specific details provided in the study regarding the potential direction of bias that could impact the results and conclusions. Since the study does not offer explicit information on the predicted direction of bias in the overall risk assessment, it is not possible to determine whether the bias, if present, would favor a particular direction (benefit or harm of exposure, towards or away from null). Without clear insights into the expected direction of bias, the classification remains as "Insufficient information available." Therefore, due to the absence of information on the predicted direction of bias in the study, it is not feasible to determine how bias, if present, might influence the results and conclusions.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias in the study is classified as "Cannot tell" regarding whether it is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. This classification is based on the lack of specific information provided in the study to assess the impact of bias on the conclusions about the exposure effect on the outcome. Without explicit details on the likely direction and magnitude of bias, as well as the potential influence on the importance of the exposure effect on the outcome, it is challenging to determine if the overall risk of bias is high enough to threaten the study's conclusions. The absence

		of information on the impact of bias on the interpretation of the exposure effect hinders a definitive assessment. Therefore, due to insufficient information on the likely direction and magnitude of bias and its potential threat to the conclusions, it is not possible to determine if the overall risk of bias is sufficiently high to threaten the conclusions about whether the exposure has an important effect on the outcome.

11. Effect of Residence in a Fluoridated Community on the Incidence of Coronal and Root Caries in an Older Adult Population (11)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Socioeconomic Status (SES): SES can affect access to dental care, oral hygiene products, and education about oral health.
2. Age: Age can influence the risk of developing dental caries due to changes in oral health practices and biological factors.
3. Gender: Gender differences can affect oral health behaviors and susceptibility to dental caries.
4. Oral Hygiene Practices: Regular brushing, flossing, and dental visits are critical for preventing caries.
5. Dietary Habits: Sugar intake and overall diet quality can significantly influence caries development.
6. Fluoride Exposure: Use of fluoride toothpaste, mouth rinses, and community water fluoridation can reduce caries risk.
7. Psychological Factors: Stress, anxiety, and depression can affect oral hygiene practices and health-seeking behavior.
8. Access to Dental Care: Availability and affordability of dental services can influence treatment and preventive care.
9. Health Behaviors: Smoking, alcohol consumption, and other health behaviors can impact oral health.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

The numerical results being assessed in the study include the incidence rates of new coronal and root caries among older adult residents of fluoridated and non-fluoridated communities. Specifically, the study compares the mean number of new coronal caries surfaces and new root caries surfaces over an 18-month period for different groups based on their years of residence in either type of community.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	They used multivariate analyses with regression techniques to assess the effects of fluoridation on caries incidence while controlling for various confounding factors, including age, sex, and the number of teeth for coronal caries, and age, sex, and gingival recession for root caries.
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-
B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	-
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	-

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The outcome to which the result relates is the incidence of dental caries, specifically both coronal caries and root caries, among older adult residents of fluoridated and non-fluoridated communities. The study assesses how the duration of residence in these communities affects the development of new caries over an 18-month period.

C2. Specify the participant group on which this result was based.

The participant group on which this result was based consisted of older adults aged 65 and older who were residents of two rural Iowa counties. The study included a sample of 520 dentate individuals from the noninstitutionalized population, with a focus on those who had lived in either fluoridated or non-fluoridated communities.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	Residence in fluoridated versus non-fluoridated communities. This exposure was assessed by collecting residence histories from participants during baseline examinations. Specifically, the researchers identified the years of residence in communities with different fluoride levels in the drinking water using data from the 1982 Iowa fluoridation census and the 1975 national fluoridation census.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / PN / N
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / PN / N
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	NA / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	NA / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	NA / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study was the risk of developing new caries among elderly residents based on their duration of residence in fluoridated versus non-fluoridated communities. Specifically, the study calculated relative risks for the outcome of new caries, comparing the risk among residents of fluoridated communities to that of life-long residents of non-fluoridated communities.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study consists of elderly adults aged 65 and older residing in rural Iowa counties. The eligible participants for the causal effect being analyzed are those who have lived in either fluoridated or nonfluorinated communities for varying lengths of time, specifically focusing on long-term residents.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure of interest in the study is the duration of residence in fluoridated communities, specifically the long-term consumption of fluoridated drinking water. This exposure is considered the 'true' exposure because it is hypothesized to have a causal effect on the incidence of new caries (both coronal and root caries) among the elderly population. The study categorized participants based on the number of years they had lived in fluoridated communities, with specific attention to those who had resided there for 30 years or more. This long-term exposure to fluoridated water is believed to contribute to a reduction in caries incidence compared to those who have lived in non-fluoridated communities all their lives
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy.	The exposure window of interest in the study is defined as the duration of residence in fluoridated communities, specifically focusing on long-term exposure that begins from the time of first residence in those communities. For the purposes of the study, this exposure window is considered to encompass the entire period of residence in fluoridated communities, with particular emphasis on those who have lived there for 30 years or more. This means that the exposure window effectively starts from the time participants first moved to a fluoridated community and continues up to the time of the follow-up examination, which occurred 18 months after the baseline assessment. The study aimed to assess the cumulative effect of this long-term exposure on the incidence of new caries among elderly

	The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	adults, thereby suggesting that the benefits of fluoridation may accrue over many years of exposure
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	In the study, exposure over time should be summarized as cumulative exposure to fluoridated water, specifically categorized by the number of years participants have resided in fluoridated communities. This approach allows for a nuanced understanding of how varying lengths of exposure may influence the incidence of new caries.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Not explicitly mentioned	N	Y	N	(Benefit of (higher) exposure	
Dietary habits	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Not explicitly mentioned	N	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Not explicitly mentioned	Y	Y	N	Benefit of (higher) exposure	
Age	Categorized into different age groups	Y	Y	N	Insufficient information available	

Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Xerostomia drugs usage	Y	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors likely controlled for important confounding factors at baseline. The study mentioned that multivariate analyses were conducted using regression techniques to assess the effects of age, sex, number of teeth, and gingival recession on caries incidence. By controlling for these factors, the authors aimed to minimize the influence of potential confounders on the relationship between residence in fluoridated communities and caries incidence. While the specific details of all potential confounders controlled for were not explicitly stated, the use of regression techniques suggests that efforts were made to address baseline confounding factors.
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The confounding factors that were controlled for in the study, such as age, sex, number of teeth, and gingival recession, were likely measured validly and reliably based on the variables available in the study. While the specific details regarding the measurement validity and reliability of these factors were not explicitly discussed in the provided information, the use of these common variables in dental research suggests that they are typically well-defined and easily measurable. Therefore, it is probable that these confounding factors were measured accurately in the study.
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	Since we are focusing on baseline confounding in this analysis, the control for variables after the start of the exposure period being studied is not relevant to this specific assessment. The key consideration here is whether the authors adequately controlled for confounding factors at the baseline, before the exposure occurred, to minimize bias in the study results.

Signalling questions	Response options	Comments
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	Based on the information provided, there is no indication that serious uncontrolled confounding was present in the study. The authors conducted multivariate analyses using regression techniques to control for important confounding factors such as age, sex, number of teeth, and gingival recession. While the details of negative controls or other considerations were not explicitly mentioned, the use of regression analysis suggests that efforts were made to address potential confounders adequately at baseline. Therefore, serious uncontrolled confounding is probably not a significant concern in this study.
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the context of the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, the risk of bias due to confounding is categorized as "Some concerns." While the study attempts to control for potential confounders such as age, sex, and number of teeth, there are some concerns about unmeasured or residual confounding factors that could impact the validity of the results. Potential unmeasured confounders or residual confounding factors that could impact the results include socioeconomic status, dietary habits, oral hygiene practices, access to dental care, and behavioral factors. These factors were not fully accounted for in the analysis and could introduce bias, affecting the interpretation of the relationship between residence in a fluoridated community and caries outcomes.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	Without specific details on the direction and magnitude of potential confounding factors that were controlled for at baseline, it is not possible to predict the direction of bias due to confounding in this study. Additional information on the individual confounders, their relationships with the exposure and outcome, and the extent to which they were controlled for would be needed to make an informed prediction about the direction of bias.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Without detailed information on the specific confounding factors, their impact on the exposure-outcome relationship, and the extent to which they were controlled for, it is not possible to determine if the risk of bias due to confounding is sufficiently high to threaten conclusions about the exposure's effect on the outcome. Further clarification on the confounding variables and their management in the study would be needed to make a definitive assessment in this regard.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The exposure in this study was measured at a single point in time, which may not fully capture the dynamic nature of exposure over time. While the single measurement provides some information about exposure status, it may not fully characterize the exposure metric of interest, especially if exposure levels fluctuate or change over the study period. Therefore, the measured exposure may not well-characterize the exposure metric specified to be of interest, albeit to a small extent.
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	Given that the exposure was measured at a single point in time, there is a likelihood of some degree of error or misclassification in the measurement. However, since the exposure was assessed at a specific time point, the potential for substantial error may be lower compared to studies where exposure is measured repeatedly or over a longer period. Therefore, while there may be some degree of misclassification or error in the exposure measurement, it is likely not substantial.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Since the exposure was measured at a single point in time, there is a possibility of some degree of misclassification or mismeasurement. This misclassification may have a small extent of differential impact, meaning it could be related to the outcome or the risk of the outcome to some degree. However, without specific details on the nature and extent of misclassification, it is considered to have a small impact in this context.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error, which is likely when exposure is measured at a single point in time, may introduce some bias in the estimated effect of exposure on the outcome. This bias is expected to be to a small extent because non-differential misclassification tends to bias results towards the null hypothesis, potentially underestimating the true effect of exposure on the outcome. However, the impact of this bias is considered small in this context due to the nature of the measurement error being non-differential.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	There are some concerns regarding the risk of bias arising from the measurement of exposure in this study. The fact that exposure was measured at a single point in time introduces the potential for misclassification or mismeasurement, which could impact the estimated effect of exposure on the outcome. While the extent of bias may not be high or very high, there are still concerns about the accuracy of the exposure measurement and its influence on the study results.
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure at a single point in time is towards the null. Non-differential misclassification typically biases results towards the null hypothesis, meaning that any bias introduced by mismeasurement or misclassification of exposure is likely to underestimate the true effect of exposure on the outcome. Therefore, the direction of bias is expected to be towards the null in this scenario.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, considering its likely direction towards the null and the magnitude of the estimated exposure effect, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there are some concerns about bias due to the measurement of exposure at a single point in time, the predicted direction of bias towards the null suggests that any impact on the conclusions regarding the effect of exposure on the outcome is not significant enough to invalidate the overall findings.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The exposure in this study, derived from measurements at multiple time points, is likely to well-characterize the exposure metric specified to be of interest. By utilizing data from multiple time points, the exposure assessment is more comprehensive and provides a more accurate representation of the participants' exposure levels over time. This approach enhances the characterization of the exposure metric and increases the reliability of the exposure measurements in the study.
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	While there may be some error in the measurement or misclassification of exposure at each single time point due to factors such as variability or measurement limitations, the use of measurements made at multiple time points likely helps to mitigate this error to some extent. The cumulative data from multiple time points can help to average out any individual measurement errors, reducing the overall impact of measurement inaccuracies on the exposure assessment. Therefore, the error in measurement or misclassification of exposure is likely present but may not be substantial due to the multiple time point measurements.
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	While there is a possibility of some degree of mismeasurement or misclassification of exposure in a study where each individual's exposure level is estimated from measurements made at multiple time points, the likelihood of this being differential (related to the outcome or risk of the outcome) is relatively low. The use of measurements from multiple time points helps to reduce the impact of differential misclassification by providing a more comprehensive and averaged representation of exposure over time. Therefore, while there may be some potential for non-differential misclassification, the likelihood of differential misclassification is considered to be small in this context.

Signalling questions	Response options	Comments
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	In the context where each individual's exposure level is estimated from measurements made at multiple time points, the nature of the non-differential measurement error is likely to bias the estimated effect of exposure on the outcome to a small extent. While there may be some degree of measurement error inherent in the exposure assessment, the utilization of data from multiple time points helps to reduce the impact of this error on the estimated effect. The averaging effect of multiple measurements over time can help to minimize the bias caused by non-differential measurement error, although some residual bias may still be present, albeit to a small extent.
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome: Some concerns In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, the risk of bias arising from the measurement of exposure is categorized as "Some concerns." While the exposure of residence in a fluoridated community was likely assessed through participant self-reporting or historical records, there may be some concerns regarding the accuracy and reliability of this measurement. Potential sources of bias related to the measurement of exposure include recall bias, misclassification of exposure status, or inconsistencies in defining and categorizing exposure levels. These factors could introduce errors in the assessment of participants' exposure to fluoridated water, leading to uncertainties in estimating the true effect of residence in a fluoridated community on caries outcomes.

Signalling questions	Response options	Comments
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure, where each individual's exposure level is estimated from measurements made at multiple time points, is towards the null. The use of measurements from multiple time points helps to average out potential errors or fluctuations in exposure assessment, which is likely to lead to a bias that tends towards the null hypothesis. While there may be some degree of measurement error, the averaging effect of multiple measurements is expected to mitigate any systematic bias towards either benefit or harm of higher exposure, resulting in a bias that is more likely to align with the null hypothesis.
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, where each individual's exposure level is estimated from measurements made at multiple time points, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While there may be some concerns regarding measurement error and potential bias, the use of data from multiple time points helps to improve the accuracy and reliability of the exposure assessment. The predicted direction of bias towards the null hypothesis suggests that any bias introduced is likely to be minimal and not substantial enough to significantly impact the conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	Follow-up beginning at or close to the start of the exposure window for most participants is probably yes. This suggests that the study likely initiated follow-up assessments promptly after participants were exposed to the relevant factors of interest, reducing the risk of bias related to the timing of exposure and outcome assessments. This alignment enhances the validity of the study findings by capturing the effects of exposure more accurately.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	The effect of exposure being likely constant over the period of follow-up analyzed is probably yes. This indicates that the exposure is expected to have a consistent impact on the outcome throughout the follow-up period, without significant fluctuations or changes in the relationship between exposure and outcome. A stable effect of exposure over time enhances the internal validity of the study results by providing more reliable estimates of the association between exposure and outcome.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The selection of participants into the study was probably yes based on participant characteristics observed after the start of the exposure window being studied. In the study, the baseline characteristics of participants, such as age, sex, number of teeth, smoking status, and dental conditions, were assessed after the exposure window had already begun. For example, the study compared individuals who had lived in fluoridated and nonfluoridated communities for over 30 years, indicating that participant selection was based on characteristics observed after the exposure had already started. This approach likely minimized bias related to selecting participants based on factors influenced by the exposure, thereby enhancing the study's internal validity.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	These characteristics were probably yes likely to be influenced by exposure or a cause of exposure. In the study, participant characteristics such as age, sex, number of teeth, smoking status, and dental conditions could be influenced by factors related to living in fluoridated or nonfluoridated communities, such as access to fluoridated water, oral health practices, and community health policies. For instance, individuals residing in fluoridated communities may have better access to preventive dental care or education

Signalling questions	Response options	Comments
		on oral health, which could impact their dental conditions and behaviors. Considering these characteristics as likely influenced by exposure or as potential causes of exposure enhances the understanding of how living in fluoridated communities may affect dental health outcomes, thereby improving the study's internal validity.
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	These characteristics were probably yes likely to be influenced by the outcome or a cause of the outcome. In the study, participant characteristics such as age, sex, number of teeth, smoking status, and dental conditions could potentially influence the development of dental caries, which is the outcome of interest. For example, older age, certain medications, and pre-existing dental conditions may predispose individuals to higher risks of dental caries, regardless of their exposure to fluoridated water. Considering these characteristics as potential influencers of the outcome helps in understanding the complex interplay between participant characteristics and the development of dental caries, thereby enhancing the study's internal validity.
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	The analysis probably yes corrected for most of the potential selection biases identified in the characteristics influencing exposure and outcome. The study likely considered factors such as age, sex, number of teeth, smoking status, and dental conditions in the analysis to account for any potential biases related to participant selection. By controlling for these characteristics, the study aimed to minimize the impact of confounding variables and ensure that the observed effects of living in fluoridated communities on dental caries were more accurately attributed to the exposure itself. This approach enhances the study's internal validity by addressing potential sources of bias that could have influenced the results.
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	There is no explicit mention of sensitivity analyses in the provided excerpts from the study. Without information on whether sensitivity analyses were conducted to assess the impact of potential selection biases, it is not possible to determine if the likely impact of these biases was minimal. Conducting sensitivity analyses would have provided insights into the robustness of the study findings in relation to participant selection biases and could have demonstrated the extent to which these biases influenced

Signalling questions	Response options	Comments
		the results. Without this information, the potential impact of selection biases on the study outcomes remains uncertain.
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, there are some concerns regarding the risk of bias in the selection of participants into the study. While the study included older adult residents from fluoridated and non-fluoridated communities, there may be potential issues that could introduce bias in participant selection. Some concerns related to the risk of bias in participant selection include the possibility of selection bias, where certain characteristics of participants in fluoridated communities may differ systematically from those in non-fluoridated communities. Additionally, the representativeness of the study sample in relation to the broader population of older adults may raise concerns about the generalizability of the findings. Therefore, due to some concerns about the risk of bias in the selection of participants into the study, there is a potential for biases that could impact the validity and generalizability of the study results.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	Without specific details on the direction of bias due to the selection of participants into the study, it is challenging to predict the exact direction of bias. The study did not provide explicit information on the potential biases introduced by participant selection or the expected impact on the exposure-outcome relationship. Therefore, there is insufficient information available to determine the predicted direction of bias resulting from the selection of participants into the study. Additional details or sensitivity analyses would be needed to assess the potential direction and magnitude of bias related to participant selection in influencing the exposure-outcome relationship.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study is not explicitly detailed in the provided excerpts from the study. Without specific information on the magnitude of bias, its likely direction, and its potential impact on the estimated exposure effect, it is challenging to determine if the risk of bias is sufficiently high to threaten conclusions about the effect

Signalling questions	Response options	Comments
threaten conclusions about whether the exposure has an important effect on the outcome?		of exposure on the outcome. Additional information or sensitivity analyses would be needed to assess the extent to which selection biases could influence the study's conclusions regarding the relationship between exposure and outcome. Therefore, based on the available information, it is not possible to definitively determine if the risk of bias in participant selection threatens the study's conclusions about the importance of the exposure effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	the study do not contain information regarding post-exposure interventions that may have been influenced by prior exposure during the follow-up period. Without explicit details on any post-exposure interventions or their potential relationship with prior exposure, it is not possible to determine if there were interventions that could have been influenced by the participants' prior exposure status. Additional information on post-exposure interventions and their potential impact on the study outcomes would be necessary to assess the presence and influence of such interventions on the results.
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	the study do not contain information regarding whether the analysis corrected for the effect of post-exposure interventions that may have been influenced by prior exposure. Without specific details on how post-exposure interventions were addressed in the analysis or whether adjustments were made for potential influences of prior exposure on these interventions, it is not possible to determine if the analysis adequately corrected for such effects. Additional information on the handling of post-exposure interventions and their potential relationship with prior exposure would be needed to assess the adequacy of correction in the analysis.
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, there were no post-exposure interventions mentioned or implemented as part of the study protocol. Since the study did not involve any post-exposure interventions or treatments related to fluoridation or dental care, there are no concerns about biases arising from such interventions influencing the study outcomes.
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide explicit details on how post-exposure interventions may have influenced the relationship between exposure to fluoridated water and the incidence of caries outcomes. Without specific information on the potential confounding effects of post-exposure interventions and their direction of bias, it is not possible to determine the predicted direction of bias due to confounding in this context. Additional data on the nature of post-exposure interventions and their impact on the

		exposure-outcome relationship would be required to assess the predicted direction of bias accurately.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	Due to the lack of specific information in the study regarding the influence of post-exposure interventions on the estimated exposure effect and the outcome, it is not possible to determine if the risk of bias due to post-exposure interventions is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Without detailed insights into the potential impact of post-exposure interventions and their magnitude on the exposure-outcome relationship, it is challenging to assess the level of bias and its implications for the study conclusions. Additional data or clarification on the role of post-exposure interventions would be needed to make a more definitive judgment in this regard.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study indicates that out of the original 520 dentate participants, 38 were not available for follow-up, leaving 482 individuals for analysis. While the study does not explicitly state the reasons for the missing data or whether exposure status was missing for any participants, the fact that 38 participants were not available for follow-up suggests that there may have been missing data on exposure status for these individuals. Since the study does not provide specific information on the completeness of exposure data for all participants, it is probable that there were missing data on exposure status for some individuals, indicating that complete data on exposure status may not have been available for all participants.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study mentions that out of the 482 individuals available for analysis, 451 participants participated in the second examination, resulting in a response rate of 94%. The participants were examined by dentists, and caries incidence was determined from tooth changes between the two examinations. The study does not explicitly state that outcome data were missing for any participants. Given the high response rate of 94% and the detailed description of the examination methods used to determine caries outcomes, it is probable that complete data on the outcome were available for nearly all participants. Therefore, it is likely that complete data on the outcome were available for all or nearly all participants in the study.
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	The study does not explicitly mention the availability of complete data on confounding variables for all participants. While it provides information on the collection of various data through interviews and examinations, it does not specifically address the completeness of data on confounding variables. Without explicit confirmation that complete data on confounding variables were available for all participants, it is probable that there may have been

Signalling questions	Response options	Comments
		missing data on confounding variables for some individuals. Therefore, it is likely that complete data on confounding variables were not available for all or nearly all participants in the study.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	The study does not explicitly state whether the results were based on a complete case analysis. It mentions that out of the original 520 dentate participants, 38 were not available for follow-up, and 451 participants participated in the second examination. The study does not provide details on how missing data were handled in the analysis. Given the lack of information on whether missing data were imputed or how they were addressed in the analysis, it is probable that the results were based on a complete case analysis, considering the high response rate of 94% for the second examination. However, without explicit confirmation, it cannot be definitively stated that a complete case analysis was conducted in this study.
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	The study does not provide explicit information on whether exclusion from the analysis due to missing data was likely to be related to the true value of the outcome. While it mentions that 38 participants were not available for follow-up, it does not specify the reasons for their unavailability or whether missing data were related to the true value of the outcome. Without specific details on the reasons for missing data or their potential relationship to the true outcome values, it is uncertain whether exclusion from the analysis due to missing data was likely to be related to the true value of the outcome. Therefore, it is probable that the exclusion from the analysis due to missing data was not strongly related to the true value of the outcome in this study.
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	The study does not provide explicit information on whether all or most predictors of missingness in exposure, confounders, or the outcome were included in the analysis model. It does not discuss the predictors of missing data or how missing data were handled in the analysis.

Signalling questions	Response options	Comments
		Without specific details on whether predictors of missingness were considered in the analysis model, it is uncertain whether all or most predictors of missingness were included. Therefore, it is probable that all or most predictors of missingness were not included in the analysis model in this study.
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	-
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	The study does not provide explicit evidence that the results were not biased by missing data. It does not discuss the potential impact of missing data on the results or provide information on the handling of missing data in the analysis. Without specific evidence or discussion on the potential bias introduced by missing data and how it was addressed, it is uncertain whether the results were biased by missing data. Therefore, it is probable that there is no evidence that the results were not biased by missing data in this study.
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, there were 38 participants who were not available for follow-up out of the original 520 dentate individuals. This missing data represents a proportion of approximately 7% of the initial sample.

Signalling questions	Response options	Comments
		While the response rate was high at 94%, the presence of missing data from those not available for follow-up raises some concerns regarding the potential bias introduced by the missing data. The impact of missing data on the study results and the representativeness of the sample could affect the generalizability and validity of the findings. Therefore, due to the presence of missing data from participants not available for follow-up, there are some concerns about the risk of bias associated with missing data in the study.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide sufficient information to determine the predicted direction of bias due to missing data. Without details on how missing data were handled, whether predictors of missingness were considered, or evidence that the results were not biased by missing data, it is challenging to predict the direction of bias introduced by missing data in this study. Due to the lack of information on the handling of missing data and its potential impact on the estimated effect of exposure on the outcome, it is not possible to determine the predicted direction of bias. Therefore, the predicted direction of bias due to missing data is categorized as "Insufficient information available" in this study.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to missing data is not sufficiently clear in the study to determine if it threatens conclusions about whether the exposure has an important effect on the outcome. Without detailed information on how missing data were handled, the potential impact of missing data on the estimated exposure effect, and whether the results were biased by missing data, it is challenging to assess the extent to which the conclusions may be threatened by this bias. Due to the lack of transparency regarding the handling of missing data and its impact on the estimated exposure effect, it is not possible to definitively determine if the risk of bias due to missing data is high enough to threaten

Signalling questions	Response options	Comments
		conclusions about the exposure effect on the outcome. Therefore, the assessment is categorized as "Cannot tell" in this study.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	There is a possibility that the measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure in the study. Variations in how the outcome (caries incidence) was measured or ascertained between individuals in fluoridated and nonfluoridated communities could introduce bias in the estimation of the effect of residence in a fluoridated community on caries incidence. For example, if there were differences in the methods used to detect and record caries between the fluoridated and nonfluoridated communities, this could lead to differential misclassification of caries status, potentially biasing the results towards or away from the null hypothesis. Therefore, the risk of bias arising from the measurement of the outcome is categorized as "Yes" in this study.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The study does not provide explicit information regarding whether outcome assessors were aware of study participants' exposure history. Without this information, it is not possible to determine if outcome assessors' knowledge of participants' exposure history could have influenced the measurement of the outcome (caries incidence) and potentially introduced bias. Since there is no clear indication in the study about whether outcome assessors were aware of participants' exposure history, the assessment for the risk of bias arising from outcome assessors' awareness is categorized as "No information (NI).
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, there are some concerns regarding the potential for bias arising from the measurement of the outcome. Even though the outcome of caries incidence was measured through dental examinations conducted by trained and standardized dentists. , The examiners who conducted the dental examinations were likely aware of the study participants' exposure history to fluoridated or nonfluoridated communities. The awareness of participants' exposure history to fluoridated water could introduce bias in outcome measurement due to the possibility of examiners being influenced by this information.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide explicit information on the predicted direction of bias arising from the measurement of outcomes (caries status). Without specific details on how the measurement of outcomes could potentially introduce bias in favor of or against the exposure (residence in a fluoridated community), it is not possible to determine the predicted direction of bias in this context. Since the study does not offer clear insights into the expected direction of bias arising from the measurement of outcomes, the assessment for the predicted direction of bias is categorized as "Insufficient information available (NI)."
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes in the study is not clearly defined in terms of its likely direction and the magnitude of the estimated exposure effect. Without a clear indication of the potential impact of bias on the conclusions regarding the effect of residence in a fluoridated community on caries outcomes, it is challenging to determine if the risk of bias is sufficiently high to threaten the conclusions about the importance of the exposure effect on the outcome. Since the study does not provide specific details on the likely direction and magnitude of bias in relation to the estimated exposure effect, it is not possible to definitively assess if the risk of bias is high enough to jeopardize

Signalling questions	Response options	Comments
		the conclusions about the importance of the exposure effect. Therefore, the assessment is categorized as "Cannot tell (NI)."

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The study does not provide explicit information regarding whether the reported results were in accordance with an available, pre-determined analysis plan. Without details on whether the analysis plan was established before conducting the study and if the reported results align with that plan, it is not possible to determine if the results were reported following a pre-determined analysis plan. Since the study does not offer insights into the presence or adherence to a pre-determined analysis plan, the assessment for whether the reported results were in accordance with such a plan is categorized as "No information available (NI)."
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple exposure measurements within the exposure domain. Without specific details on the selection process for the reported effect estimate, it is not possible to determine if the estimate was influenced by the desirability of the effect size or statistical significance. Since the study does not offer insights into how the reported effect estimate was selected in relation to the desirability of the effect magnitude or statistical significance, the assessment for this aspect is categorized as "No information available (NI).
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain. Without specific details on the selection process for the reported effect estimate in relation to the outcome measurements, it is not possible to determine if the estimate was influenced by the desirability of the effect size or statistical significance.

Signalling questions	Response options	Comments
		Since the study does not offer insights into how the reported effect estimate was selected based on the desirability of the effect magnitude or statistical significance from multiple outcome measurements, the assessment for this aspect is categorized as "No information available (NI)."
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship. Without specific details on the selection process for the reported effect estimate from various analyses of the exposure-outcome relationship, it is not possible to determine if the estimate was influenced by the desirability of the effect size or statistical significance. Since the study does not offer insights into how the reported effect estimate was selected based on the desirability of the effect magnitude or statistical significance from multiple analyses of the exposure-outcome relationship, the assessment for this aspect is categorized as "No information available (NI)."
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The study does not provide information on whether the reported effect estimate was likely selected based on the desirability of the results, such as statistical significance, from different subgroups. Without specific details on the selection process for the reported effect estimate from various subgroups based on desirability of the results, it is not possible to determine if the estimate was influenced by the desirability of the results. Since the study does not offer insights into how the reported effect estimate was selected based on the desirability of the results from different subgroups, the assessment for this aspect is categorized as "No information available (NI)."
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of the outcome is categorized as low. The study likely followed a pre-defined analysis plan to

Signalling questions	Response options	Comments
		ensure the appropriate statistical methods were applied consistently and transparently to analyze the data and report the results accurately.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The study does not provide specific details on the direction of bias that may result from the selection of the reported result in terms of the estimated effect of exposure on the outcome. Without information on how the reported effect estimate was selected and whether it was influenced by the desirability of certain outcomes, it is not possible to predict the direction of bias due to the selection of the reported result. Since the study does not offer insights into the potential direction of bias resulting from the selection of the reported result, the assessment for this aspect is categorized as "Insufficient information available."
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The study does not provide explicit information on the selection process for the reported result in terms of the estimated exposure effect on the outcome. Without details on how the reported effect estimate was chosen and whether it could potentially bias the conclusions about the importance of the exposure effect on the outcome, it is not possible to determine if the risk of bias in the selection of the reported result is high enough to threaten the conclusions. Since the study does not offer insights into the potential impact of bias in the selection of the reported result on the conclusions regarding the importance of the exposure effect on the outcome, the assessment for this aspect is categorized as "Cannot tell."

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	In the study on the effect of residence in a fluoridated community on the incidence of coronal and root caries in an older adult population, the overall risk of bias is categorized as "Some concerns." Here is a detailed breakdown of the specific concerns regarding bias in different aspects of the study: Confounding: While the study attempted to control for potential confounders such as age, sex, and number of teeth, there are concerns about unmeasured or residual confounding factors. Factors like socioeconomic status, dietary habits, oral hygiene practices, access to dental care, and behavioral factors were not fully accounted for in the analysis. These unmeasured confounders could introduce bias and affect the interpretation of the relationship between residence in a fluoridated community and caries outcomes. Measurement of Exposure: The risk of bias arising from the measurement of exposure is categorized as "Some concerns." Although exposure to residence in a fluoridated community was likely assessed through participant self-reporting or historical records, there are concerns about the accuracy and reliability of this measurement. Potential sources of bias related to exposure measurement include recall bias, misclassification of exposure status, and inconsistencies in defining exposure levels. These factors could introduce errors in assessing participants' exposure to fluoridated water, leading to uncertainties in estimating the true effect on caries outcomes. Selection of Participants: Some concerns exist regarding the risk of bias in the selection of participants into the study. While the study included older adult residents from fluoridated and non-fluoridated communities, there may be potential issues that could introduce bias in participant selection. Concerns include the possibility of selection

		bias and differences in characteristics between participants in fluoridated and non-fluoridated communities. The representativeness of the study sample in relation to the broader population of older adults raises concerns about the generalizability of the findings. Post-Exposure Interventions: Since there were no post-exposure interventions mentioned or implemented in the study, there are no concerns about biases arising from such interventions influencing the study outcomes. Missing Data: The presence of missing data from participants not available for follow-up raises concerns about potential bias introduced by the missing data. While the response rate was high at 94%, the missing data from 38 participants out of the initial sample could affect the generalizability and validity of the findings. Measurement of Outcome: Concerns exist regarding the potential bias arising from the measurement of the outcome. Even though caries incidence was measured through dental examinations conducted by trained dentists, the awareness of examiners regarding participants' exposure history to fluoridated or non-fluoridated communities could introduce bias in the outcome measurement.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in this study is categorized as "Insufficient information available." The study does not provide explicit details on the potential direction of bias that may result from the overall risk of bias assessment. Without specific information on how bias may impact the direction of the reported results or conclusions, it is not possible to predict the direction of bias for the overall risk of bias in this study.

		Since the study does not offer insights into the potential direction of bias resulting from the overall risk of bias assessment, the assessment for this aspect is categorized as "Insufficient information available."
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The overall risk of bias in this study is categorized as "Cannot tell" regarding whether it is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. While the study provides detailed information on various aspects such as participant characteristics, exposure, and outcomes, there are concerns about bias in the selection of reported results and the lack of transparency in reporting how the effect estimates were chosen. Without clear information on the potential impact of bias on the reported results and conclusions drawn from the study, it is challenging to determine if the overall risk of bias is high enough to threaten the conclusions about the importance of the exposure effect on the outcome. Therefore, due to the lack of specific details on the potential impact of bias on the conclusions, the assessment for whether the overall risk of bias threatens the conclusions is categorized as "Cannot tell."

12. Classification of a patient's caries activity based on lesion activity assessment among adults: findings from a prospective cohort study (12)

(for follow-up studies)

Template for completion

Version 20 June 2023

The ROBINS-E tool

At planning stage: list confounding factors and consider appropriateness criteria

P1. List the important confounding factors relevant to all or most studies on this topic. Specify whether these are particular to specific exposures-outcome combinations.

1. Age: Age is a significant confounder as caries experience and risk can vary widely across different age groups. It is often adjusted for in analyses due to its influence on both exposure and outcome.
2. Sex: Gender differences can affect caries prevalence and progression, making it an important confounding factor in many studies.
3. Socioeconomic Status (SES): SES can influence access to dental care, oral hygiene practices, and overall health, impacting caries risk and outcomes.
4. Educational Level: Higher educational attainment is often associated with better health literacy and oral health practices, which can confound the relationship between caries activity and outcomes.
5. Access to Dental Services: Regular access to dental care can significantly affect caries management and progression, serving as a confounder in studies.
6. Oral Hygiene Practices: Factors such as tooth brushing frequency and technique can influence caries risk and progression, making them relevant confounders.
7. Dietary Habits: Sugar intake and overall diet quality can impact caries development and progression, serving as confounding factors.
8. Fluoride Exposure: Access to fluoridated water and use of fluoride toothpaste can significantly affect caries risk and should be considered in analyses.
9. Health Status: General health conditions, including systemic diseases or conditions affecting oral health, can confound the relationship between caries activity and outcomes.

P2. Will the review use the ROBINS-E assessment of appropriateness (important aspects of “study sensitivity”)?

Yes

If Yes, complete sections Addressing appropriateness, Parts I and II in Appendix 1.

For each study result: preliminary considerations

A. Specify the result being assessed for risk of bias

A1. Specify the numerical result being assessed

The numerical result being assessed in the study regarding the risk for caries increment is the Incidence Risk Ratio (IRR) along with its 95% Confidence Intervals (CIs). The study utilized negative binomial regression models to estimate the risk for caries increment over the study period, specifically looking at the changes in DMFS (Decayed, Missing, and Filled Surfaces) scores from baseline to follow-up.

B. Decide whether to proceed with a risk-of-bias assessment

	Response options	Comments
B1. Did the authors make any attempt to control for confounding?	Y / PY / PN / N	Yes, the authors made attempts to control for confounding factors in their study. They included several predictor variables in their analysis, such as: 1. Age: Age was specifically mentioned as a confounding variable that was adjusted for in the analyses, given its significant influence on caries activity and outcomes. 2. Sex: The study adjusted for sex as a potential confounder in the negative binomial regression models. 3. Socioeconomic Status: Although not explicitly detailed in the results, socioeconomic factors are typically considered in studies of this nature and may have been accounted for in the broader analysis. 4. Other Variables: The authors also considered additional factors such as educational level, access to dental services, tooth brushing frequency, tooth type, arch (upper vs. lower), and surface type (free smooth vs. occlusal or proximal) in their analyses to control for potential confounding effects
B2. **If N/PN to B1**: Is there sufficient potential for confounding that an unadjusted result should not be considered further?	Y / PY / PN / N	-

B3. Was the method of measuring exposure inappropriate?	Y / PY / PN / N	-
B4. Was the method of measuring the outcome inappropriate?	Y / PY / PN / N	-

If the answer to any of B2, B3 or B4 is 'Yes' or 'Probably yes', the result should be considered to be at very high risk of bias and no further assessment is required. Otherwise, proceed to section C.

C. Specify the analysis in the current study for which results are being assessed for risk of bias

C1. Specify the outcome to which this result relates.

The outcome to which the result of the Incidence Risk Ratio (IRR) relates is the increment in caries experience, specifically measured by changes in the DMFS (Decayed, Missing, and Filled Surfaces) scores over the study period.

C2. Specify the participant group on which this result was based.

The participant group on which the results were based consisted of 413 individuals from southern Brazil, with a mean age of 54.1 years. These participants were part of a population-based prospective cohort study that followed individuals aged 35 years and older over a period of 4 years.

C3 to C8: Describe the exposure measurement(s) used to produce this result.

C3. What is the exposure being measured and how was it measured or assessed?	The exposure being measured in the study is the caries activity of the participants at baseline, classified as either caries-inactive or caries-active. This classification was determined based on a lesion activity assessment, which involved clinical examinations to evaluate the presence and status of carious lesions. The assessment of caries activity was conducted using the International Caries Detection and Assessment System (ICDAS) criteria, which categorizes carious lesions based on their clinical appearance and activity status. Specifically, the study looked at the presence of active and inactive non-cavitated lesions, as well as filled surfaces, to classify participants into the respective caries activity groups.
C4. Was exposure analysed as a quantitative (rather than a categorical) variable?	Y / PY / <u>PN / N</u>
C5. Did repeated measurements of exposure over time (for each participant) contribute to the analysis that produced this result?	Y / PY / <u>PN / N</u>
C6. **If Y/PY to C5**, was a single estimate of each participant's exposure level derived from the repeated measurements of exposure over time?	<u>NA</u> / Y / PY / PN / N
C7. **If N/PN to C6**, was the analysis based on splitting participants' follow up time according to exposure status and/or magnitude?	<u>NA</u> / Y / PY / PN / N
C8. **If Y/PY to C7**, were changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome?	<u>NA</u> / Y / PY / PN / N
C9. **If N/PN to C7**, how were repeat measurements used?	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable

C10. Specify the relationship analysed to produce this result. For example, this may be a quadratic relationship of cumulative exposure with the log odds of the outcome, or a risk ratio for the outcome comparing exposed with unexposed individuals.

The relationship analyzed in the study was a risk ratio for the outcome comparing caries-active individuals with caries-inactive individuals. Specifically, the study examined how the classification of a patient's caries activity at baseline (caries-active vs. caries-inactive) predicted the increment and progression of coronal and root caries lesions over the follow-up period.

D: Specify the causal effect of exposure being estimated by this result

D1. Specify the population of interest	Describe eligible participants (to whom the causal effect applies). These may be different from the study participants on whom the result was based (specified in C2). Such differences may give rise to selection biases.	The population of interest in the study consisted of adults aged 35 years and older from southern Brazil. The eligible participants were those who were dentate (having natural teeth) and were part of a representative sample selected through a multi-stage probabilistic sampling strategy. Eligible Participants: 1. Age: Individuals aged 35 years and older. 2. Dental Status: Participants had to be dentate, meaning they had at least one natural tooth. 3. Socio-Demographic Characteristics: The study included individuals from various socio-economic backgrounds, categorized into low, middle, and high socio-economic status based on consumption goods and educational level. 4. Informed Consent: Participants had to provide informed consent to be included in the study.
Specification of the exposure metric of interest		
D2. Specify the exposure	This is the factor whose causal effect on the outcome of interest is the subject of the study result being assessed. It may be thought of as the 'true' exposure of interest. It is distinct from the method with which exposure was measured.	The exposure in the study is the classification of a patient's caries activity at baseline, which is categorized as either "caries-inactive" or "caries-active." This classification serves as the primary factor whose causal effect on the outcomes of interest—specifically, the increment and progression of coronal and root caries lesions—is being assessed.
D3. Specify the exposure window	The exposure window of interest is the exposure period for which the result being assessed estimates the effect of exposure on the outcome. Specification of the exposure window is judged by the ROBINS-E user, who should aim to define a window that is both meaningful in answering the review question and broadly in line with when the study measured exposure. Specification should	The exposure window in this study is defined as the period immediately preceding the baseline assessment, specifically the time at which the participants' caries activity was classified as either caries-inactive or caries-active. Specification of the Exposure Window:

	include both the time of onset and period of exposure. For example, it may be lifetime exposure (from birth or from conception), during ages 50-55, the period from first employment in a particular occupation, time from birth to age 10, or during pregnancy. The specified exposure window is used to determine whether exposure data adequately reflect exposure during the window. Exposure before the start of the exposure window is addressed during the assessment of risk of bias due to confounding	• Time of Onset: The exposure is assessed at baseline, which corresponds to the initial clinical examination conducted between June 2011 and June 2012. This is when the participants' caries activity status was determined. • Period of Exposure: The exposure window is effectively the time leading up to the baseline assessment, which can be considered as the period during which the participants' oral health behaviors, dietary habits, and other factors influencing caries development were relevant. However, the study does not specify a precise duration for this period, as it focuses on the classification at a single point in time (baseline).
D4. Specify how exposure over time should be summarized	This may, for example, be ever/never exposed, cumulative exposure, average exposure, or peak exposure during the exposure period, for each participant. Alternatively, there may be only a single exposure event, or the exposure may be time invariant (such as a genetic variant or family history).	The exposure over time is summarized as a single exposure event based on the classification of caries activity at baseline. Each participant is categorized as either "caries-inactive" or "caries-active" at the time of the initial assessment, which serves as the primary exposure of interest for the study.

E. Evaluation of confounding factors

Complete a row for each important confounding factor listed in advance (subsection (i)). In addition, consider any further confounding factors that are either relevant to the setting of this particular study or which the study authors identified as potentially important (subsection (ii)).

"Important" confounding factors are those for which, in the context of this study, adjustment is expected to lead to an important change in the estimated effect of the exposure.

(i) Important confounding factors listed in advance						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments
Socioeconomic status	Level of education and Sociodemographic status	Y	Y	N	(Benefit of (higher) exposure	
Dietary habits	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	
Oral hygiene practices	Toothbrushing Frequency	Y	Y	N	(Benefit of (higher) exposure	
Access to Dental Care	Classified as regular or irregular dental attenders	Y	Y	N	Benefit of (higher) exposure	

Age	Categorized into different age groups	Y	Y	N	Insufficient information available	
Gender	Categorized into 2 groups	Y	NI	NA	Insufficient information available	
Other Substance Use	Not explicitly mentioned	N	N	N	Harm of (higher) exposure	

(ii) Additional confounding factors relevant to the setting of this particular study, or identified by study authors and considered to be important, or which were identified since the protocol was written						
Confounding factor	Measured variable(s) for this factor, if any	Was this variable (or were these variables) controlled for in the analysis? (Y / N)	If this confounding factor was controlled for, was it measured validly and reliably by this variable (or these variables)?* (NA / Y / PY / PN / N / NI)	If this confounding factor was not controlled for, is there evidence that controlling for it was unnecessary?** (NA / Y / PY / PN / N)	Is failure to adjust for this confounding factor expected to bias the effect estimate towards benefit or harm of (higher) exposure?*** (Benefit of (higher) exposure / Harm of (higher) exposure / Insufficient information available)	Comments

* “Validity” refers to whether the confounding variable or variables accurately measure the confounding factor, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

** In the context of a particular study, variables need not be included in the analysis: (a) if they are measured validly and reliably and are not associated with the outcome, conditional on exposure (noting that lack of a statistically significant association is not evidence of a lack of association); (b) if they are measured validly and reliably and are not associated with exposure; (c) if they are measured validly and reliably and adjustment makes no or minimal difference to the estimated effect of the primary parameter; (d) because the confounder was addressed in the study design, for example by restricting to individuals with the same value of the confounder; (e) because a negative control demonstrates that there was unlikely to have been confounding due to this variable or that uncontrolled confounding was likely to be minimal; or (f) because external evidence suggests that controlling for the variable is not necessary in the context of the study being assessed..

For each study: risk of bias assessment

Domain 1: Risk of bias due to confounding

Domain 1, Variant (a): ***If N/PN to C5 or Y/PY to C6 or N/PN to C7*** *(only baseline confounding needs to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	The authors of the study likely controlled for important confounding factors at baseline. Therefore, the response would be "PY" (Probably yes). In the study, the authors included various predictor variables such as sex, age, socioeconomic status, educational level, access to dental services, tooth brushing frequency, tooth type, arch, and surface type . By including these variables in their analysis, the authors likely accounted for potential confounders that could influence the relationship between caries activity and caries increment or progression. For example, age is a known confounding factor in caries studies, as older individuals may have different caries risk factors compared to younger individuals. By adjusting for age in their analysis, the authors likely controlled for this potential confounding factor. Therefore, based on the information provided in the study regarding the inclusion of various predictor variables, it is probable that the authors controlled for important confounding factors at baseline.

Signalling questions	Response options	Comments
1.2 **If Y/PY/WN to 1.1**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	The response to the question regarding the measurement validity and reliability of confounding factors controlled for in the study would be "PY" (Probably yes). In the study, the authors measured various confounding factors such as sex, age, socioeconomic status, educational level, access to dental services, tooth brushing frequency, tooth type, arch, and surface type . These variables are commonly used in caries research as they are known to influence caries risk. The authors likely used standardized methods to measure these variables, such as structured questionnaires for sociodemographic information and clinical examinations for oral health parameters. For example, age was categorized into three groups (35–47, 48–63, ≥ 64 years) based on self-reported information . While self-reported age may have some measurement error, it is a commonly used and reliable method for categorizing age in epidemiological studies. Similarly, variables like educational level and access to dental services were likely assessed using standardized questions that have been validated in previous research. Therefore, based on the information provided in the study regarding the measurement of confounding factors, it is probable that these factors were measured validly and reliably, supporting the response "PY" (Probably yes).

Signalling questions	Response options	Comments
1.3 **If Y/PY/WN to 1.1**: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA / Y / PY / PN / N / NI	In the study, the authors focused on assessing caries activity at baseline and its relationship with caries increment and progression over the study period . They included variables such as sex, age, socioeconomic status, educational level, access to dental services, and oral hygiene habits as potential confounders. These variables were likely measured at baseline and were not influenced by the exposure (caries activity) since they were characteristics of the participants at the beginning of the study. For example, variables like age, socioeconomic status, and educational level are typically stable characteristics that are not influenced by caries activity. Therefore, controlling for these variables at baseline helps to account for potential confounding effects on the relationship between caries activity and caries outcomes.
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	Y / PY / PN / N	In the study, the authors controlled for important confounding factors such as sex, age, socioeconomic status, educational level, access to dental services, and oral hygiene habits . By including these variables in their analysis, the authors likely addressed potential confounding effects on the relationship between caries activity and caries outcomes. For example, the authors adjusted for age as a confounding variable in their analysis of caries increment and progression. Age is a known factor that can influence caries risk, and by controlling for age, the authors accounted for this potential confounder.

Signalling questions	Response options	Comments
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to confounding in the estimated effect of exposure on the outcome would be "Low risk." In the study, the authors controlled for important confounding factors such as sex, age, socioeconomic status, educational level, access to dental services, and oral hygiene habits . These variables are known to influence caries risk and were likely measured reliably and accounted for in the analysis. By adjusting for these confounders, the authors minimized the potential impact of confounding on the relationship between caries activity and caries outcomes. For example, the authors adjusted for age as a confounding variable in their analysis of caries increment and progression. Age is a significant factor in caries risk, and by controlling for age, the authors reduced the risk of bias due to confounding.
What is the predicted direction of bias due to confounding?	(Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Insufficient information available)	In the study, the authors controlled for several potential confounding factors such as sex, age, socioeconomic status, educational level, access to dental services, and oral hygiene habits . By adjusting for these confounders, the authors aimed to minimize the impact of confounding on the relationship between caries activity and caries outcomes. However, without specific information on the magnitude and direction of the association between the confounding variables and the exposure (caries activity) or outcome (caries increment and progression), it is challenging to predict the exact direction of bias due to confounding. The effect of confounding on the estimated relationship between caries activity and caries outcomes could vary depending on the strength and direction of the associations between the confounders and the exposure or outcome variables.

Signalling questions	Response options	Comments
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The response to the question regarding whether the risk of bias due to confounding is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome would be "No." In the study, the authors controlled for potential confounding factors such as sex, age, socioeconomic status, educational level, access to dental services, and oral hygiene habits . By adjusting for these confounders, the authors aimed to minimize the impact of confounding on the relationship between caries activity and caries outcomes. Given that the authors considered and controlled for important confounding variables in their analysis, and there is no indication of serious uncontrolled confounding, the risk of bias due to confounding is considered low. Therefore, the risk of bias is not sufficiently high to threaten conclusions about whether the exposure (caries activity) has an important effect on the outcome (caries increment and progression).

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 1, variant (b): **If Y/PY to C7 and Y/PY to C8** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude and changes in exposure status and/or magnitude likely to be related to factors that are predictive of the outcome, so both baseline and time-varying confounding need to be addressed)*

Signalling questions	Response options	Comments
1.1 Did the authors use an analysis method that was appropriate to control for time-varying as well as baseline confounding?	Y / PY / PN / N / NI	-
1.2 **If Y/PY to 1.1**: Did the authors control for all the important baseline and time-varying confounding factors for which this was necessary?	NA / Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	-
1.3 **If Y/PY/WN to 1.2**: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	-
1.4 **If N/PN/NI to 1.1**: Did the authors control for time-varying factors or other variables measured after the start of the exposure window being studied?	NA / Y / PY / PN / N / NI	-
1.5 Did the use of negative controls, or other considerations, suggest uncontrolled confounding?	Y / PY / PN / N	-
Risk of bias (due to confounding) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-

Signalling questions	Response options	Comments
What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 2: Risk of bias arising from measurement of the exposure

*Domain 2, Variant (a): **If N/PN to C5** (exposure was measured at a single point in time)*

Signalling questions	Response options	Comments
Mismeasurement or misclassification of the exposure.		
2.1 Does the measured exposure well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	The measured exposure does not well-characterize the exposure metric specified to be of interest in this study. The response is "SN (no, to a large extent)." The exposure of interest in the study was the caries activity of the patients, which was classified as caries-inactive or caries-active. However, the exposure was measured at a single point in time, without considering potential changes in caries activity over the follow-up period. This single assessment may not fully capture the dynamic nature of caries activity, which can fluctuate over time due to various factors such as oral hygiene habits, dietary changes, and access to dental care. By only assessing caries activity at baseline and not accounting for any changes or fluctuations during the follow-up period, the exposure measurement may not accurately reflect the true exposure status of the participants throughout the study. This limitation could lead to misclassification of exposure and potentially bias the results towards null or obscure any true associations between caries activity and caries outcomes.

Signalling questions	Response options	Comments
2.2 Was the exposure likely to be measured with error, or misclassified?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	The exposure in the study was likely to be measured with error or misclassified. The response is "SY (yes, probably a substantial amount)." The exposure of interest, caries activity (caries-inactive or caries-active), was assessed at a single point in time. Since caries activity can vary over time due to factors like oral hygiene practices, dietary habits, and access to dental care, a one-time measurement may not capture the true exposure status of the participants throughout the study period. This limitation increases the likelihood of exposure misclassification, as individuals classified as caries-inactive or caries-active at baseline may have experienced changes in their caries status during the follow-up period. Misclassification of exposure can introduce bias and potentially impact the validity of the study findings. In this case, the potential for substantial misclassification of caries activity due to the single-point measurement suggests that the exposure was likely measured with error to a significant extent.
Bias in the estimated effect of exposure arising from mismeasurement or misclassification of the exposure		

Signalling questions	Response options	Comments
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Mismeasurement or misclassification of exposure in the study could have been differential, related to the outcome or risk of the outcome. The response is "SY (yes, to a large extent)." Given that the exposure of interest, caries activity, was assessed at a single point in time, there is a high likelihood that misclassification or mismeasurement of this exposure could have been differential. Since caries activity can influence the progression of caries lesions, any errors in classifying individuals as caries-inactive or caries-active may have had a direct impact on the estimated effect of exposure on the outcomes. For example, if individuals with misclassified caries activity were more likely to have their caries lesions progress or be incorrectly categorized as non-progressing, this differential misclassification could bias the estimated effect of caries activity on caries progression. The misclassification may have led to an underestimation or overestimation of the true association between caries activity and caries outcomes, potentially affecting the validity of the study results.
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	Non-differential measurement error in the exposure measurement is likely to bias the estimated effect of exposure on the outcome to a large extent. The response is "SY (yes, to a large extent)." In the study, caries activity (caries-inactive or caries-active) was measured at a single point in time. Non-differential measurement error occurs when the misclassification of exposure is random and not related to the outcome or other factors. However, since caries activity can influence the progression of caries lesions, any random misclassification of exposure status could still bias the estimated effect of exposure on the outcomes. For instance, if there were random errors in classifying individuals as caries-inactive or caries-active at baseline, this misclassification could lead to an underestimation or overestimation of the true association between caries activity and caries progression. The random nature of the measurement error may introduce noise into the data, potentially diluting any true effects or creating spurious associations.

Signalling questions	Response options	Comments
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	the risk of bias arising from the measurement of the exposure (caries activity status) is considered to be at a low risk level. Efforts were made to calibrate examiners, standardize protocols, and assess reliability, which helped minimize variability and subjectivity in the assessment of caries activity status based on lesion activity
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias arising from the measurement of exposure in the study, where exposure was measured at a single point in time, is "Towards null." Given the potential for misclassification or mismeasurement of caries activity (caries-inactive or caries-active) at a single point in time, the bias in the estimated effect of exposure on the outcomes is likely to be towards the null. This means that any errors in classifying individuals as caries-inactive or caries-active may lead to an underestimation or overestimation of the true association between caries activity and caries progression, ultimately biasing the effect estimate towards the null hypothesis of no association. For instance, if there were random errors in categorizing individuals as caries-inactive or caries-active, the misclassification could dilute any true effects or create spurious associations, resulting in an effect estimate that is closer to the null value of no association between caries activity and caries progression.

Signalling questions	Response options	Comments
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of exposure, in the context of its likely direction and the magnitude of the estimated exposure effect, is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. The response is "No." While there are concerns about misclassification or mismeasurement of caries activity (caries-inactive or caries-active) at a single point in time in the study, the predicted direction of bias was towards null. This suggests that any bias introduced by the measurement error is more likely to underestimate or overestimate the true effect towards the null hypothesis of no association. In this scenario, even though there may be some level of bias in the estimated effect of exposure on the outcomes due to measurement error, the direction of bias towards null indicates that the conclusions about whether the exposure has an important effect on the outcome are not significantly threatened. The effect estimate may still provide valuable insights into the relationship between caries activity and caries progression, despite the potential for bias.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (b): **If Y/PY to C5 and Y/PY to C6** (each individual's exposure level was estimated from measurements made at multiple time points)*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (derived from measurements at multiple time points) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

*Domain 2, Variant (c): **If Y/PY to C5, N/PN to C6 and Y/PY to C7** (the analysis was based on splitting participants' follow up time according to exposure status and/or magnitude):*

Signalling questions	Response options	Comments
2.1 Does the measured exposure (including changes over time) well-characterize the exposure metric specified to be of interest in this study? [*This was specified in the answers to D2, D3 and D4*]	Y / PY / WN (no, to a small extent) / SN (no, to a large extent) / NI	-
2.2 Was there error in measurement, or misclassification, of the exposure, at each single time point?	SY (yes, probably a substantial amount) / WY (yes, but probably not a substantial amount) / PN / N / NI	-
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e. related to the outcome or risk of the outcome)?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is the nature of the (non-differential) measurement error likely to bias the estimated effect of exposure on outcome?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	-
Risk of bias (arising from measurement of exposure) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	-
What is the predicted direction of bias arising from measurement of exposure?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	-
Is the risk of bias (arising from measurement of exposure) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	-

Y = Yes; PY = Probably yes; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 3: Risk of bias in selection of participants into the study (or into the analysis)

Signalling questions	Response options	Comments
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	In the study , the follow-up did not begin at (or close to) the start of the exposure window for most participants. The response is "N." The study followed 413 individuals from southern Brazil for 4 years to investigate the classification of a patient's caries activity based on lesion activity assessment and its effect on caries increment and progression. The exposure window, in this case, refers to the period when participants were classified as "caries-inactive" or "caries-active" based on their caries activity status. Ideally, follow-up should begin at or close to the start of this exposure window to accurately capture the effects of the exposure on the outcome. However, in this study, the baseline examination and classification of caries activity were conducted at the beginning of the study period, and participants were followed for 4 years thereafter. This means that the follow-up did not align with the exact start of the exposure window for most participants. As a result, there may have been variations in the duration of exposure assessment and follow-up for different individuals, potentially introducing bias or inaccuracies in estimating the effect of exposure on the outcome.
3.2 **If N/PN to 3.1**: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA / Y / PY / PN / N / NI	The effect of exposure is likely not constant over the period of follow-up analyzed in the study . The response is "PN" (Probably no). In longitudinal studies like the one described, where participants are followed over time to assess the impact of exposure on outcomes, the assumption of a constant effect of exposure throughout the follow-up period is crucial for valid interpretation of the results. However, in many health-related studies, the effect of exposure may vary over time due to changes in individual behaviors, disease progression, interventions, or other time-dependent factors. In the context of caries activity and progression, the impact of exposure (caries activity status) on caries development and progression may not remain constant over the entire follow-up period. Factors such as changes in oral hygiene habits, dietary patterns, access to dental care, or other

Signalling questions	Response options	Comments
		interventions could influence the progression of caries lesions differently at various time points during the study. Therefore, while the study aimed to investigate the effect of caries activity on caries increment and progression over a 4-year follow-up period, it is probable that the effect of exposure was not constant throughout this duration. Changes in participants' behaviors or external factors could have influenced the relationship between caries activity and caries outcomes at different stages of the study, potentially impacting the stability of the exposure effect over time.
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? [*The exposure window is specified in D3*]	Y / PY / PN / N / NI	The selection of participants into the study in was not based on participant characteristics observed after the start of the exposure window being studied. The response is "N." In the study, participants were selected based on their caries activity status at baseline, which was determined through clinical examination and assessment of lesion activity. The exposure window, representing the period when participants were classified as "caries-inactive" or "caries-active," was established at the beginning of the study. Therefore, participant selection into the study was not influenced by characteristics observed after the start of the exposure window. For example, individuals were included in the study based on their caries activity status and other baseline characteristics such as age, socioeconomic status, educational level, and oral hygiene habits. These factors were assessed at the beginning of the study and were not influenced by events or changes occurring after the exposure window had started. As a result, the selection of participants into the study was not based on participant characteristics observed after the start of the exposure window being studied. This approach helps to minimize bias related to the timing of participant selection and ensures that the study population is representative of the exposure statuses at the beginning of the investigation.
3.4 **If Y/PY to 3.3**: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA / Y / PY / PN / N / NI	-

Signalling questions	Response options	Comments
3.5 **If Y/PY to 3.4**: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	-
3.6 **If N/PN to 3.2 or Y/PY to 3.5**: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA / Y / PY / PN / N / NI	The analysis in the study likely did not correct for all of the potential selection biases identified in the previous assessments. The response is "PN" (Probably no). While the study had certain strengths in terms of participant selection and exposure assessment, there were potential biases related to the timing of follow-up initiation, the assumption of a constant effect of exposure over time, and the selection of participants based on characteristics observed after the start of the exposure window. These biases could introduce confounding factors or inaccuracies in the estimation of the relationship between caries activity and caries outcomes. For example, if the effect of exposure was not constant over the follow-up period and the analysis did not account for this variability, the results may not accurately reflect the true association between caries activity and caries progression. Similarly, if participant selection was influenced by characteristics observed after the exposure window had begun, there could be residual confounding that was not adequately addressed in the analysis.
3.7 **If N/PN to 3.2 or Y/PY to 3.5**: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA / Y / PY / WN (no, there were no sensitivity analyses or there is evidence of some impact) / SN (no, there is evidence of substantial impact)	Sensitivity analyses are essential in research to assess the robustness of findings and evaluate the influence of biases on study outcomes. Without conducting sensitivity analyses, there may be uncertainty about the extent to which potential selection biases could have affected the results. In this case, the absence of sensitivity analyses weakens the ability to fully understand and address the impact of selection biases on the study outcomes. For example, if sensitivity analyses had been performed and demonstrated that the impact of potential selection biases was minimal, it would have strengthened the validity of the study findings. Conversely, if sensitivity analyses had shown a substantial impact of selection biases, it would have raised concerns about the reliability of the results.

Signalling questions	Response options	Comments
		Therefore, the lack of information on sensitivity analyses in the study weakens the assessment of the likely impact of potential selection biases, highlighting the need for further investigation and transparency in addressing biases in research studies.
Risk of bias (due to selection of participants into the study) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to the selection of participants into the study in estimating the effect of exposure on the outcome would likely be categorized as "Some concerns." This is because the study was a population-based prospective cohort study that followed individuals from southern Brazil, which may introduce some potential biases related to the selection of participants. While the study employed a multi-stage probabilistic sampling strategy and included a representative sample of men and women aged 35 years and older, there could still be some concerns regarding the generalizability of the findings to broader populations. Additionally, factors such as non-response rates, discrepancies in demographic and socioeconomic characteristics between followed individuals and those lost to follow-up, and the use of weighting variables to adjust for participation bias may introduce some level of bias in participant selection.
What is the predicted direction of bias due to selection of participants into the study?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of participants into the study in the study is "Towards harm of (higher) exposure." The study mentioned some concerns regarding the selection of participants, including a higher proportion of men, younger individuals, and those with low socioeconomic status being lost to follow-up. This type of selection bias could potentially lead to an underestimation of the true association between caries activity and caries progression among adults. If individuals with higher caries activity or poorer oral health outcomes were more likely to drop out of the study, it could bias the results towards a more favorable outcome, masking the harmful effects of higher exposure to caries activity. For instance, if individuals with active caries lesions or higher caries risk factors were less likely to participate in the follow-up examinations, the

Signalling questions	Response options	Comments
		study may underestimate the actual risk of caries progression associated with caries activity. This bias could lead to a false impression that the impact of caries activity on caries progression is less significant than it truly is, potentially downplaying the importance of preventive measures and interventions.
Is the risk of bias (due to selection of participants into the study) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of participants into the study in the context of its likely direction and the magnitude of the estimated exposure effect is categorized as "Yes." In the study , the concerns related to the selection of participants, such as discrepancies between individuals lost to follow-up and those who remained in the study, could potentially bias the estimated exposure effect towards underestimating the true association between caries activity and caries progression among adults. This bias may threaten the conclusions about whether the exposure (caries activity) has an important effect on the outcome (caries progression). For example, if individuals with higher caries activity were less likely to participate in follow-up assessments, the study results may underestimate the impact of caries activity on caries progression, leading to potentially misleading conclusions about the importance of caries activity as a predictor of future caries development. This bias could affect the interpretation of the study findings and the implications for preventive strategies and clinical management.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SN = Strong no; WN = Weak no; NA = Not applicable; NI = No information

Domain 4: Risk of bias due to post-exposure interventions

Signalling questions	Response options	Comments
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	Y / PY / PN / N / NI	There were no explicit mentions of post-exposure interventions that were influenced by prior exposure during the follow-up period in the study. Therefore, the response is "N" (No). In the absence of information indicating that post-exposure interventions were influenced by prior exposure, it suggests that there were no specific interventions or treatments implemented during the follow-up period that were directly influenced by the participants' prior exposure status (caries activity). This lack of post-exposure interventions influenced by prior exposure reduces the risk of bias related to this aspect in the study. For example, if the study had included interventions that were tailored based on the participants' caries activity status at baseline, such as providing different preventive measures or treatments for caries-active individuals compared to caries-inactive individuals, it could have introduced bias in the estimated effects of exposure on the outcome. However, since there is no information indicating such post-exposure interventions in the study, the risk of bias due to post-exposure interventions influenced by prior exposure is considered low (No).
4.2 **If Y/PY to 4.1**: Is it likely that the analysis corrected for the effect of post-exposure interventions that were influenced by prior exposure?	NA / Y / PY / PN / N / NI	-
Risk of bias (due post-exposure interventions) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to post-exposure interventions in the estimated effect of exposure on the outcome is categorized as "Low risk." In the study, there were no explicit mentions of post-exposure interventions that were influenced by prior exposure during the follow-up period. Since the analysis did not involve adjusting for post-exposure interventions influenced by prior exposure and there were no indications of such interventions being present in the study, the risk of bias due to post-exposure interventions is considered low. Therefore, the risk of bias due to post-exposure interventions in the estimated effect of exposure on the outcome is considered low in this study.

What is the predicted direction of bias due to confounding?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to confounding in the study is "Towards null." In the study, the main predictor variable was patients' caries activity at baseline (caries-inactive or caries-active), and other predictor variables included sex, age, socioeconomic status, educational level, access to dental services, claimed tooth brushing frequency, tooth type, arch, and surface type. The analysis adjusted for age as a confounding variable. Given that the analysis adjusted for age as a confounding variable and considered various other potential confounders in the study, the predicted direction of bias due to confounding is towards null. This means that any potential confounding factors included in the analysis are likely to have minimized the bias, leading the estimated effect of caries activity on caries progression to be closer to the true underlying association. For example, if age was not adjusted for in the analysis, there could have been a bias towards either overestimating or underestimating the effect of caries activity on caries progression. However, by adjusting for age and other potential confounders, the study aimed to reduce the impact of confounding on the estimated association, leading to a predicted direction of bias towards null.
Is the risk of bias (due post-exposure interventions) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	In the context of the study , where there were no explicit mentions of post-exposure interventions that were influenced by prior exposure during the follow-up period, the risk of bias due to post-exposure interventions is considered low. Since the study did not involve adjusting for post-exposure interventions influenced by prior exposure and there were no indications of such interventions being present, the risk of bias due to post-exposure interventions is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Domain 5: Risk of bias due to missing data

Signalling questions	Response options	Comments
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , which followed 413 individuals from southern Brazil for 4 years, complete data on exposure status (patients' caries activity at baseline) were available for all participants. The study design and data collection methods ensured that exposure status was recorded for all individuals in the cohort, without missing data on this key variable. For example, the study mentions that the main predictor variable was patients' caries activity at baseline, and this information was collected through a questionnaire and clinical examination for all 413 individuals in the cohort. The availability of complete data on exposure status for all participants indicates that there were no missing data on this crucial variable in the study.
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , which followed 413 individuals from southern Brazil for 4 years, there were indications that complete data on the outcome (caries increment and caries progression) were likely available for all or nearly all participants. The study mentions that data collection included a questionnaire and clinical examination to record coronal/root caries and gingival recession, indicating a comprehensive approach to data collection on the outcomes of interest. For example, the study reports that a total of 413 individuals were reexamined at follow-up and included in the coronal caries analysis, with only a small number of individuals not examined for root caries. This suggests that the outcome data for coronal caries were available for the vast majority of participants. Additionally, the study provides details on the clinical characteristics of the sample at the tooth and surface levels, indicating a thorough assessment of the outcomes. While the study did not explicitly state the percentage of participants with complete outcome data, the detailed data collection methods and the inclusion of a large proportion of individuals in the analyses suggest that complete data on the outcome were likely available for all or nearly all participants, leading to a response of "PY" (Probably yes) for this question.

Signalling questions	Response options	Comments
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	In the study , which investigated the classification of a patient's caries activity based on lesion activity assessment among adults, there is an indication that complete data on confounding variables were likely available for all or nearly all participants. The study mentions that various confounding variables, such as sex, age, socioeconomic status, educational level, access to dental services, claimed tooth brushing frequency, tooth type, arch, and surface type, were included in the analysis. For example, the study reports that data analysis regarding decayed, missing, and filled tooth surfaces (DMFS) increment was performed using negative binomial regression models, adjusting for age as a confounding variable. Additionally, surface-level data analysis was conducted using SPSS, including variables at the tooth level as adjusting variables.
5.4 **If N/PN/NI to 5.1, 5.2 or 5.3**: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	-
5.5 **If Y/PY/NI**: Was exclusion from the analysis because of missing data (in exposure, confounders or the outcome) likely to be related to the true value of the outcome?	NA / SY (Yes, strongly related) / WY (Yes, but not strongly related) / PN / N / NI	In the study , which focused on the classification of a patient's caries activity based on lesion activity assessment among adults, the retention rate at follow-up was 40.5%, indicating that there was some loss to follow-up. The study mentioned that a significantly higher proportion of men, young individuals, and those with low socioeconomic status were lost to follow-up. However, there were no significant differences regarding educational level, caries experience, or access to dental services between the individuals lost to follow-up and those included in the analysis. Given that there were differences in characteristics such as sex, age, and socioeconomic status between individuals lost to follow-up and those included in the analysis, it is possible that the exclusion from the analysis due to missing data may not have been completely random and could be related to the true value of the outcome.

Signalling questions	Response options	Comments
5.6 **If N/PN to 5.5**: Were all or most predictors of missingness (in exposure, confounders or the outcome) included in the analysis model?	NA / SY (Yes, for sure) / WY (Yes, mostly or probably) / PN / N / NI	In the study , which examined the classification of a patient's caries activity based on lesion activity assessment among adults, the characteristics of individuals lost to follow-up were reported. The study mentioned that a significantly higher proportion of men, young individuals, and those with low socioeconomic status were lost to follow-up. However, there were no significant differences regarding educational level, caries experience, or access to dental services between the individuals lost to follow-up and those included in the analysis. While the study did not explicitly state whether all predictors of missingness were included in the analysis model, it did provide information on the characteristics of individuals lost to follow-up. By including details on the demographic and socioeconomic factors associated with loss to follow-up, the study likely considered important predictors of missingness in the analysis model.
5.7 **If N/PN to 5.4**: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the approach to handling missing data, specifically whether the analysis was based on imputing missing values, was not explicitly mentioned in the provided excerpts. Without specific information on whether imputation of missing values was used in the analysis, it is not possible to determine if the analysis was based on imputing missing values.
5.8 **If Y/PY to 5.7**: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-
5.9 **If N/PN to 5.7**: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	-

Signalling questions	Response options	Comments
5.10 **If PN/N/NI to 5.1, 5.2 or 5.3**: Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	In the study focusing on the classification of a patient's caries activity based on lesion activity assessment among adults, the retention rate at follow-up was 40.5%, indicating some loss to follow-up. The study mentioned that individuals lost to follow-up differed in characteristics such as sex, age, and socioeconomic status compared to those included in the analysis. While the study did not provide explicit evidence that the results were not biased by missing data, the differences in characteristics between individuals lost to follow-up and those included suggest the potential for bias due to missing data. Given the differences in characteristics between individuals lost to follow-up and those included in the analysis, and the lack of evidence provided to suggest that the results were not biased by missing data
Risk of bias (due to missing data) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias due to missing data in the estimated effect of exposure on the outcome would likely be categorized as "Some concerns." This is because the study reported a response rate of 40.5%, indicating that there was missing data due to individuals who were lost to follow-up. While the authors compared baseline characteristics between individuals lost to follow-up and those who remained in the study and used statistical methods and weighting variables to address potential biases, the presence of missing data could still introduce some concerns regarding the impact on the estimated effect of exposure on the outcome.
What is the predicted direction of bias due to missing data?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to missing data is "Towards harm of (higher) exposure." In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the retention rate at follow-up was 40.5%, indicating some loss to follow-up. The study mentioned that individuals lost to follow-up differed in characteristics such as sex, age, and socioeconomic status compared to those included in the analysis. Given that individuals lost to follow-up had different characteristics, particularly in

Signalling questions	Response options	Comments
		terms of socioeconomic status, there is a likelihood that the missing data may bias the results towards harm of higher exposure.
Is the risk of bias (due to missing data) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the retention rate at follow-up was 40.5%, indicating some loss to follow-up. The study mentioned that individuals lost to follow-up differed in characteristics such as sex, age, and socioeconomic status compared to those included in the analysis. Given the differences in characteristics between individuals lost to follow-up and those included, and the potential bias towards harm of higher exposure due to missing data, the risk of bias is sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome. Therefore, the risk of bias due to missing data is considered high enough to threaten conclusions about the effect of exposure on the outcome in this study.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 6: Risk of bias arising from measurement of the outcome

Signalling questions	Response options	Comments
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	Y / PY / PN / N / NI	The measurement or ascertainment of the outcome could have differed between exposure groups or levels of exposure, indicated by "Y" (Yes). In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the outcome of interest was caries increment and progression of coronal and root caries lesions. The study focused on assessing the effect of patients' caries activity on these outcomes. It is possible that the measurement or ascertainment of these outcomes may have differed between exposure groups (caries-active vs. caries-inactive patients) or levels of exposure, potentially introducing bias in the results. For example, if the assessment of caries increment or progression was conducted differently for caries-active patients compared to caries-inactive patients, this could lead to differential misclassification of the outcome, impacting the validity of the study findings.
6.2 Were outcome assessors aware of study participants' exposure history?	Y / PY / PN / N / NI	The outcome assessors were likely aware of study participants' exposure history, indicated by "Y" (Yes). In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the outcome assessors were responsible for assessing caries increment and progression of coronal and root caries lesions based on the patients' caries activity (caries-active or caries-inactive). Given that the exposure of interest was the patients' caries activity, it is likely that the outcome assessors were aware of this exposure history when evaluating the outcomes. For example, if outcome assessors knew whether a patient was classified as caries-active or caries-inactive, this knowledge could potentially influence

Signalling questions	Response options	Comments
		their assessment of caries increment or progression, leading to bias in the outcome measurement.
6.3 **If Y/PY/NI to 6.2**: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	The assessment of the outcome could have been influenced by knowledge of participants' exposure history to a small extent, indicated by "WY" In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the outcome assessors were responsible for evaluating caries increment and progression of coronal and root caries lesions based on the patients' caries activity (caries-active or caries-inactive). Given that the exposure history of patients was related to their caries activity, there is a possibility that the assessors' knowledge of this exposure could have influenced their assessment of the outcomes, albeit to a small extent. For example, if outcome assessors were aware of a patient's caries activity status, they might have been more attentive to detecting caries progression or increment in those classified as caries-active compared to caries-inactive patients, potentially introducing a slight bias in the outcome assessment.
Risk of bias (arising from measurement of outcomes) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The risk of bias arising from the measurement of outcomes in the estimated effect of exposure on the outcome is "Some concerns." In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, even though the study reported high intra- and inter-examiner reproducibility for assessing dental caries and gingival recession, indicating that the outcome measurements were reliable and consistent. there are indications that the outcome assessors were likely aware of the participants' exposure history, which could potentially introduce bias in the measurement of the outcomes.
What is the predicted direction of bias arising from measurement of outcomes?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards	The predicted direction of bias arising from the measurement of outcomes is "Towards harm of (higher) exposure."

Signalling questions	Response options	Comments
	null / Away from null / Insufficient information available	In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, the outcome assessors were likely aware of the participants' exposure history, and the assessment of the outcome could have been influenced to a small extent by this knowledge. This situation raises concerns that the measurement of outcomes may be biased towards detecting harm associated with higher exposure levels, in this case, caries activity. For example, if outcome assessors were more attentive to detecting caries progression or increment in patients classified as caries-active (higher exposure) compared to caries-inactive patients, there is a potential for overestimating the harm associated with higher caries activity levels.
Is the risk of bias (arising from measurement of outcomes) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias arising from the measurement of outcomes is not sufficiently high to threaten conclusions about whether the exposure has an important effect on the outcome, indicated by "No." In the study on the classification of a patient's caries activity based on lesion activity assessment among adults, while there are some concerns regarding the potential bias in outcome measurement due to assessors' awareness of participants' exposure history, the predicted direction of bias is towards harm of higher exposure levels. However, the magnitude of the estimated exposure effect and the overall study design suggest that the risk of bias is not high enough to significantly threaten the conclusions about whether the exposure (caries activity) has an important effect on the outcome (caries increment and progression). For instance, even though there may be some bias towards detecting harm associated with higher caries activity levels, the study's findings and statistical analyses likely account for potential confounders and adjust for relevant variables to minimize the impact of bias on the conclusions drawn.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; SY = Strong yes; WY = Weak yes; NA = Not applicable; NI = No information

Domain 7: Risk of bias in selection of the reported result

Signalling questions	Response options	Comments
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	The result reported in the study on the classification of a patient's caries activity based on lesion activity assessment among adults was likely reported in accordance with an available, pre-determined analysis plan, indicated by "PY" (Probably yes). In research studies, it is essential to have a pre-determined analysis plan to ensure transparency, rigor, and reproducibility of the results. While the study does not explicitly mention the existence of a pre-determined analysis plan, the detailed methodology and statistical analysis described in the study suggest that there was likely a plan in place before conducting the analyses. For example, the study outlines the main predictor variable (patients' caries activity at baseline), the other predictor variables included, the statistical methods used for data analysis (negative binomial regression models), and the outcomes assessed (caries increment and progression). These aspects indicate that the analysis plan was likely established before data collection and analysis.
7.2 **If N/PN/NI to 7.1**: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *exposure measurements* within the exposure domain?	NA / Y / PY / PN / N / NI	-
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *outcome measurements* within the outcome domain?	Y / PY / PN / N / NI	The reported effect estimate in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is not likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple outcome measurements within the outcome domain, indicated by "N" (No).

Signalling questions	Response options	Comments
		In this study, the outcomes assessed were related to caries development, specifically caries increment and progression on coronal and root surfaces. The exposure of interest was the classification of patients as caries-active or caries-inactive based on lesion activity assessment. The analysis focused on evaluating the association between caries activity and the progression of caries lesions. There is no indication in the study that the reported effect estimate was selectively chosen based on the desirability of the magnitude or statistical significance of the estimated effect from multiple outcome measurements within the outcome domain. The study appears to have systematically analyzed the relationship between caries activity and caries outcomes without selectively reporting results based on the desirability of the effect estimates.
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple *analyses* of the exposure-outcome relationship?	Y / PY / PN / N / NI	The reported effect estimate in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is not likely to be selected based on the desirability of the magnitude or statistical significance of the estimated effect of exposure on the outcome from multiple analyses of the exposure-outcome relationship, indicated by "N" (No). In the study, the analysis focused on evaluating the relationship between patients' caries activity status at baseline and the progression of caries lesions on coronal and root surfaces. The exposure of interest was the classification of patients as caries-active or caries-inactive based on lesion activity assessment. The study utilized appropriate statistical methods to assess the association between caries activity and caries outcomes. There is no indication in the study that the reported effect estimate was selectively chosen based on the desirability of the magnitude or statistical significance of the estimated effect from multiple analyses of the exposure-outcome relationship. The study appears to have conducted a

Signalling questions	Response options	Comments
		comprehensive analysis of the exposure-outcome relationship without selectively reporting results based on the desirability of the effect estimates.
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different *subgroups*?	Y / PY / PN / N / NI	The reported effect estimate in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is not likely to be selected based on the basis of desirability of the results (e.g., statistical significance) from different subgroups, indicated by "N" (No). In the study, the analysis focused on evaluating the relationship between patients' caries activity status at baseline and the progression of caries lesions on coronal and root surfaces. The exposure of interest was the classification of patients as caries-active or caries-inactive based on lesion activity assessment. The study included subgroup analyses to assess the impact of caries activity on different outcomes within specific subgroups. There is no indication in the study that the reported effect estimate was selectively chosen based on the desirability of the results, such as statistical significance, from different subgroups. The subgroup analyses were likely pre-specified and conducted to explore potential variations in the effect of caries activity on caries outcomes across different subgroups, rather than selectively reporting results based on the desirability of the findings.
Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome	Low risk / Some concerns / High risk / Very high risk	The Risk of bias (due to selection of the reported result) in the estimated effect of exposure on the outcome in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is assessed as "Low risk." In the study, the researchers investigated the relationship between patients' caries activity status at baseline and the progression of caries lesions on coronal and root surfaces. They utilized appropriate statistical methods, such as negative binomial regression models, to estimate the risk for caries increment and progression over the study period. The analysis included both unadjusted and adjusted models to account for potential confounding variables.

Signalling questions	Response options	Comments
		There is no indication in the study that the reported effect estimate was selectively chosen or biased based on the selection of the reported results. The researchers conducted a systematic analysis of the exposure-outcome relationship, considering various factors and adjusting for confounders where necessary. The study methodology and statistical analyses appear to have been conducted rigorously, without introducing bias in the selection of the reported results.
What is the predicted direction of bias due to selection of the reported result?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias due to the selection of the reported result in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is "Insufficient information available." In the study, the researchers investigated the relationship between patients' caries activity status and the progression of caries lesions on coronal and root surfaces. They reported the results of the analysis, including the risk estimates for caries increment and progression based on caries activity status. However, the study did not provide explicit information on any potential bias introduced through the selection of the reported results. Without specific details on the selection process of the reported results or any indication of bias introduced during result selection, it is not possible to predict the direction of bias in this context. The study may have followed rigorous methods to report the results accurately, or there could be potential biases that were not disclosed in the study report.
Is the risk of bias (due to selection of the reported result) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The risk of bias due to the selection of the reported result in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is assessed as "No." In the study, the researchers conducted a thorough analysis to investigate the relationship between patients' caries activity status and the progression of caries lesions on coronal and root surfaces. They utilized appropriate

Signalling questions	Response options	Comments
		statistical methods and adjusted for potential confounding variables to estimate the risk for caries increment and progression accurately. There is no indication in the study that the reported results were selectively chosen or biased in a way that would threaten the conclusions about whether the exposure (caries activity status) has an important effect on the outcome (caries progression). The researchers followed a systematic approach to analyze the data and report the results, ensuring the reliability and validity of their findings.

Y = Yes; PY = Probably yes; PN = Probably no; N = No; NA = Not applicable; NI = No information

Overall risk of bias

	Response options	Comments
Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Some concerns / High risk / Very high risk	Based on the information provided, the overall risk of bias in the estimated effect of exposure on the outcome in the study on the classification of a patient's caries activity based on lesion activity assessment among adults would be categorized as "Some concerns." While the study had low risk of bias in terms of confounding, post-exposure interventions, and selection of reported results, there are some concerns regarding bias due to the selection of participants, missing data, and measurement of outcomes. Selection of Participants: The study was a population-based prospective cohort study, but there were some concerns related to potential biases in participant selection, such as non-response rates and discrepancies in demographic and socioeconomic characteristics between followed individuals and those lost to follow-up. Missing Data: The study reported a response rate of 40.5%, indicating missing data due to individuals lost to follow-up. While efforts were made to address potential biases, the presence of missing data could still introduce concerns regarding the impact on the estimated effect of exposure on the outcome. Measurement of Outcomes: While the study reported high intra- and inter-examiner reproducibility for assessing dental caries and gingival recession, there were indications that the outcome assessors were likely aware of the participants' exposure history, which could potentially introduce bias in the measurement of outcomes.
What is the predicted direction of bias?	Towards benefit of (higher) exposure / Towards harm of (higher) exposure / Towards null / Away from null / Insufficient information available	The predicted direction of bias for the overall risk of bias in the study on the classification of a patient's caries activity based on lesion activity assessment among adults is "Insufficient information available." In this study, while there were some concerns identified regarding retention rate, sampling strategy, and non-response bias, the study did not explicitly provide information on the potential direction of bias

		that these concerns may introduce. Without specific details on how these factors could impact the exposure-outcome relationship, it is challenging to predict the direction of bias that may result from these concerns. For example, if there were systematic differences between individuals lost to follow-up and those who remained in the study, this could potentially bias the results towards either overestimating or underestimating the true effect of caries activity on caries progression. However, without detailed information on the extent and nature of these biases, it is not possible to determine the specific direction of bias.
Is the overall risk of bias sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Yes / No / Cannot tell	The study demonstrated some concerns related to retention rate, sampling strategy, and non-response bias. However, these concerns were not explicitly linked to a specific direction of bias that would threaten the conclusions about the important effect of caries activity on caries progression. The study employed appropriate statistical methods and adjusted for potential confounding variables, indicating a rigorous approach to analyzing the data. Example: While the retention rate and potential biases in the sampling strategy and non-response could introduce some level of uncertainty, the study's findings on the relationship between caries activity status and caries progression were based on robust statistical analyses. Therefore, the overall risk of bias is considered to be low enough not to threaten the conclusions about whether the exposure (caries activity) has an important effect on the outcome (caries progression).

References

1. Petersson GH, Twetman S. Tobacco use and caries increment in young adults: A prospective observational study. BMC Res Notes. 2019;12(1):1–5.
2. Schmolinsky J, Kocher T, Rathmann W, Völzke H, Pink C, Holtfreter B. Diabetes status affects long-term changes in coronal caries - The SHIP Study. Sci Rep. 2019;9(1):15685.
3. Peres MA, Peres KG, Barbato PR, Höfelmann DA. Access to Fluoridated Water and Adult Dental Caries. J Dent Res [Internet]. 2016;95(8):868–74. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84979086335&doi=10.1177%2F0022034516643064&partnerID=40&md5=85fea5c2398c631a0a0329782dd76597
4. Sabbah W, Suominen AL, Vehkalahti MM, Aromaa A, Bernabé E. The role of behaviour in inequality in increments of dental caries among finnish adults. Caries Res [Internet]. 2015;49(1):34–40. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84923557335&doi=10.1159%2F000366491&partnerID=40&md5=9d03dded8b08f3caaffc0a8e09a7925a
5. Bernabé E, Vehkalahti MM, Sheiham A, Lundqvist A, Suominen AL. The Shape of the Dose-Response Relationship between Sugars and Caries in Adults. J Dent Res [Internet]. 2016;95(2):167–72. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84955249851&doi=10.1177%2F0022034515616572&partnerID=40&md5=58c4c983a56093041d21bf4362c5ec19
6. Bernabé E, Vehkalahti MM, Sheiham A, Aromaa A, Suominen AL. Sugar-sweetened beverages and dental caries in adults: A 4-year prospective study. J Dent. 2014;42(8):952–8.
7. Bernabé E, Delgado-Angulo EK, Vehkalahti MM, Aromaa A, Suominen AL. Daily smoking and 4-year caries increment in Finnish adults. Community Dent Oral Epidemiol [Internet]. 2014;42(5):428–34. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84925679557&doi=10.1111%2Fcdoe.12101&partnerID=40&md5=f8c622708a5e5166091195065a43a73c
8. Nobre M de A, Sezinando A, Fernandes I, Maló P. Risk score to predict dental caries in adult patients for use in the clinical setting. J Clin Med. 2019;8(2).
9. Moss KL, Beck JD, Mauriello SM, Offenbacher S, White RP. Risk Indicators for Third Molar Caries and Periodontal Disease in Senior Adults. J Oral Maxillofac Surg. 2007 May;65(5):958–63.
10. Bjertness E, Eriksen HM, Hansen BF. Factors of importance for changes in dental caries among adults: A follow-up study of Oslo citizens from the age of 35 to 50 years. Acta Odontol Scand [Internet]. 1992;50(4):193–200. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0026901213&doi=10.3109%2F00016359209012763&partnerID=40&md5=9f692742e1b210bda14d5c921b741f2a
11. Hunt RJ, Eldredge JB, Beck JD. Effect of Residence in a Fluoridated Community on the Incidence of Coronal and Root Caries in an Older Adult Population. J Public Health Dent. 1989;49(3):138–41.
12. Rup AG, Izquierdo C de M, Rios FS, Costa R dos SA, Jardim JJ, Haas AN, et al. Classification of a patient's caries activity based on lesion activity assessment among adults: findings from a prospective cohort study. Clin Oral Investig [Internet]. 2023 [cited 2023 Sep 21];27(3):1123–31. Available from: https://link.springer.com/article/10.1007/s00784-022-04702-8