ELECTRONIC CIGARETTES AND SUBSEQUENT CIGARETTE SMOKING IN YOUNG PEOPLE: METHODOLOGICAL CONSIDERATIONS AND RESULTS FROM A COCHRANE REVIEW

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Acknowledgements and declarations of interest

I have never received funding from tobacco, vaping, or pharmaceutical industries.

I have no conflicts of interest to declare.

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Most important acknowledgement – our team!

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PLUS freelance support from Kate Tudor and Karen Rees, UK, and support from our panel of PPI members

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'Competing' hypotheses

Though data consistently show that young people who vape are more likely to smoke, it is highly contested as to whether this is a causal relationship.

It is possible that vaping could act as:
- a 'gateway' into smoking
- a 'diversion' from smoking
- an 'off ramp' from smoking

Some people describe these as competing, but at an individual level they could all hold true.

'Net' impact

- Public health practitioners and policymakers have a particular interest in what happens at the population level – if, overall, vaping is contributing to more people starting to smoke than would have otherwise, then the net public health effect of vaping is going to be negative.
- We also are (or should be) interested in whether patterns differ based on socially stratifying characteristics –smoking rates differ by groups, and this is a leading driver of health inequalities – 'net' effects can sometimes mask important differences.

Our program of work

Evidence and Gap Map currently under pe[...] studies and reviews on multiple dimensions [...] characteristics

Cochrane Review to assess the eviden[...] and availability of e-cigarettes and subse[...] (aged 29 years or less), and whether the[...] status, gender, or other demographic cha[...]

!

Findings have been submitted for publication. They are confidential and not for wider distribution at this point. Please do not take pictures or share results on social media

Recommendations consensus exercise to guide further research (ongoing – we want your help!)

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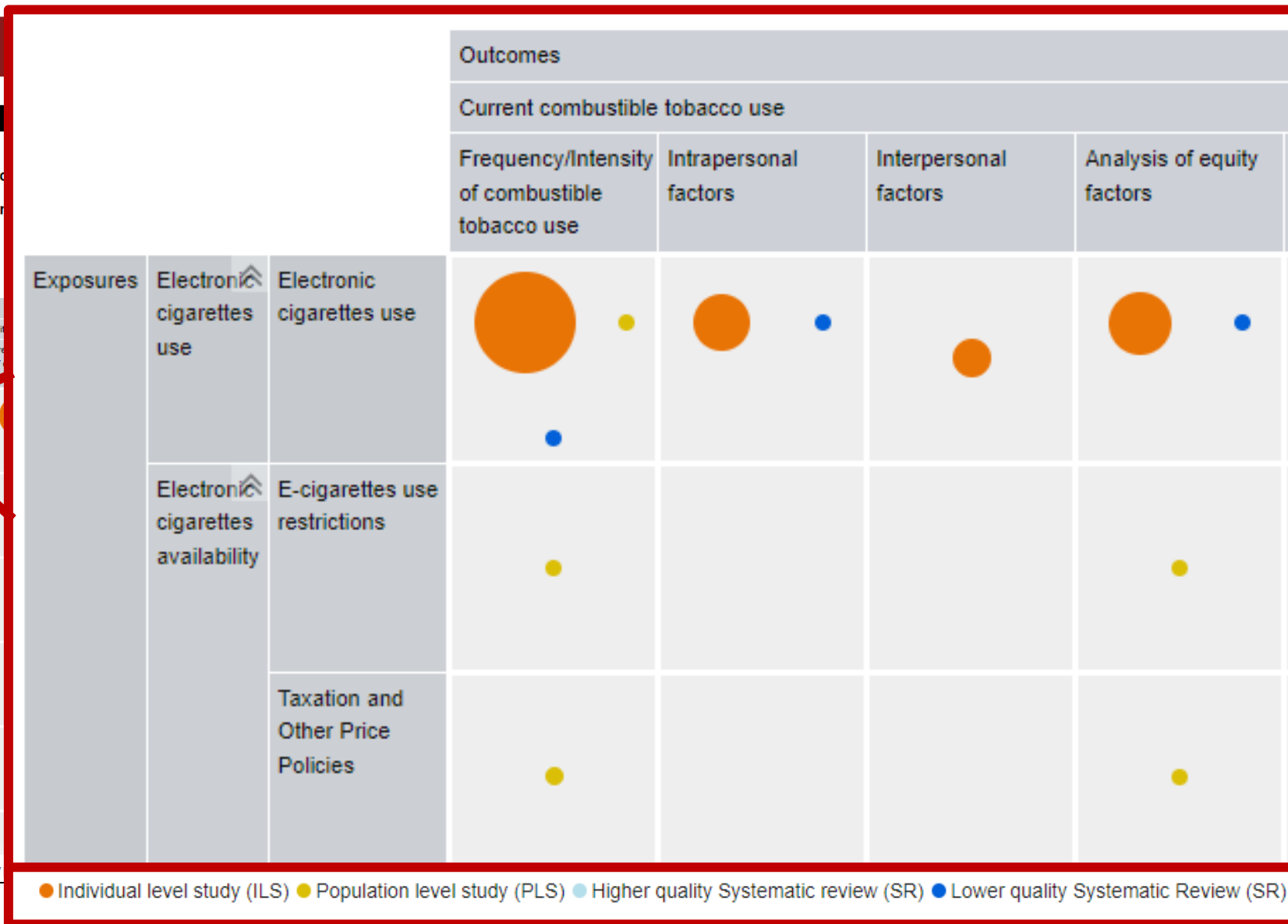
Methodological considerations

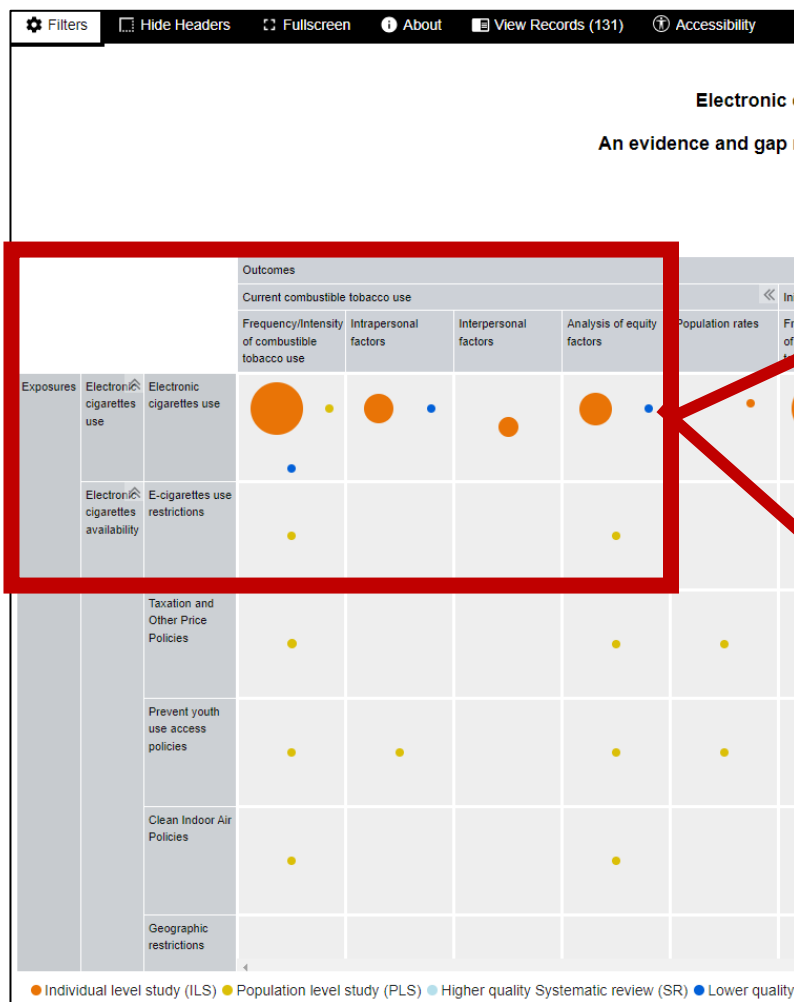We developed a set of recommendations for future research exploring e-cigarette use and subsequent cigarette smoking in young people.

We would like to invite you to provide your input on these recommendations by answering our anonymous survey.

~15 minutes

Have your say!


http://tinyurl.com/3u7me7n9

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Evidence and

Evidence and gap map

Evidence gaps identified in the EGM	Systematic reviews identified in the EGM
• Geographic restrictions on e-cigarettes and their association with current combustible tobacco use, initiation of combustible tobacco use and cessation of combustible tobacco use • E-cigarette use and its association with population rates of initiation and cessation of combustible tobacco use. • How associations between e-cigarette use/availability and subsequent combustible tobacco use vary based on social stratifying characteristics, including occupation, religion, and LBGTQIA+.	• Nine systematic reviews met our inclusion criteria • 3 of the 9 were judged to be of higher quality • All consistently reported that young people who vaped were more likely to smoke • None were able to establish causality

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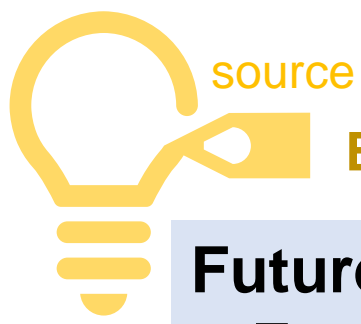
Evidence and Gap Map

Future studies should:

- Examine and report possible causes of differences in vaping-smoking transitions and associations, including sociodemographic characteristics and contextual factors
- Generate and use representative data from countries other than the USA, Canada and UK
- Examine associations between e-cigarette use/availability and smoking cessation in young people (especially at the population level).

Have your say!

http://tinyurl.com/3u7me7n9

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The Cochrane review

- We searched electronic databases and issued a call for evidence up to April 2023

- Primary outcome: association between EC use/availability and change in population rate of combustible tobacco use in young people, assessed through the proportion reporting current cigarette use.

- Secondary outcomes: association between EC use/availability and incidence, progression, and cessation of cigarette smoking

Cochrane Library — Trusted evidence. Informed decisions. Better health.

Cochrane Database of Systematic Reviews | Protocol - Intervention

Electronic cigarettes and subsequent cigarette smoking in young people

Jamie Hartmann-Boyce[a], Rachna Begh[a], Nicola Lindson, Jonathan Livingstone-Banks, Thomas R Fanshawe, Ann McNeill, Lion Shahab, Nancy A Rigotti, Dylan Kneale, James Thomas, Paul Aveyard   Authors' declarations of interest

Version published: 24 March 2022   Version history

https://doi.org/10.1002/14651858.CD015170

Review has been submitted and is under review.

Hartmann-Boyce J, Begh R, Lindson N, Livingstone-Banks J, Fanshawe TR, McNeill A, Shahab L, Rigotti NA, Kneale D, Thomas J, Aveyard P. Electronic cigarettes and subsequent cigarette smoking in young people. Cochrane Database of Systematic Reviews 2022, Issue 3.

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Inclusion criteria

All studies

Participants
People aged 29 and younger

Exposure
Any type of e-cigarette use (ranging from one time experimentation to regular use, excluding exclusive cannabis vaping) or e-cigarette availability (policies affecting e-cigarette availability, aggregate data on e-cigarette use)

Outcomes
Primary: Association between e-cigarette use, availability, or both, and change in population rate of tobacco use in young people
Secondary: Association between e-cigarette use, availability, or both, and initiation, progression, or cessation of cigarette smoking

Population-level studies (repeated cross sectional)

Used repeated measures and evaluated cigarette use in young people in relation to e-cigarette use or availability in the same population

Individual-level studies (cohort)

Prospectively collect data on e-cigarette and smoking behaviors from the same individuals at a minimum of two time points
Consider at least one covariate related to propensity to smoke in their analysis

Tier 1 (>5,000 participants)

Tier 2 (<=5,000 participants)

Inclusion criteria

Future longitudinal cohort studies should include at least one (and ideally more than one) variable related to propensity to smoke as a covariate (for example, parental smoking, measure of susceptibility to smoking, or socioeconomic status)

Have your say!

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Risk of bias assessment

- Adapted risk of bias instrument from Morgan et al designed for non-randomized studies of exposures
- Each study assessed independently by two reviewers
- Domains include bias due to: confounding; participant selection; misclassification of/deviation from exposure; missing data; outcome measurement; selective reporting
- Overall studies could be at critical, serious, moderate or low risk of bias

Population level studies

Tier 1 individual level studies

For more detail on risk of bias assessment, see https://osf.io/svgud or the end of this slide deck
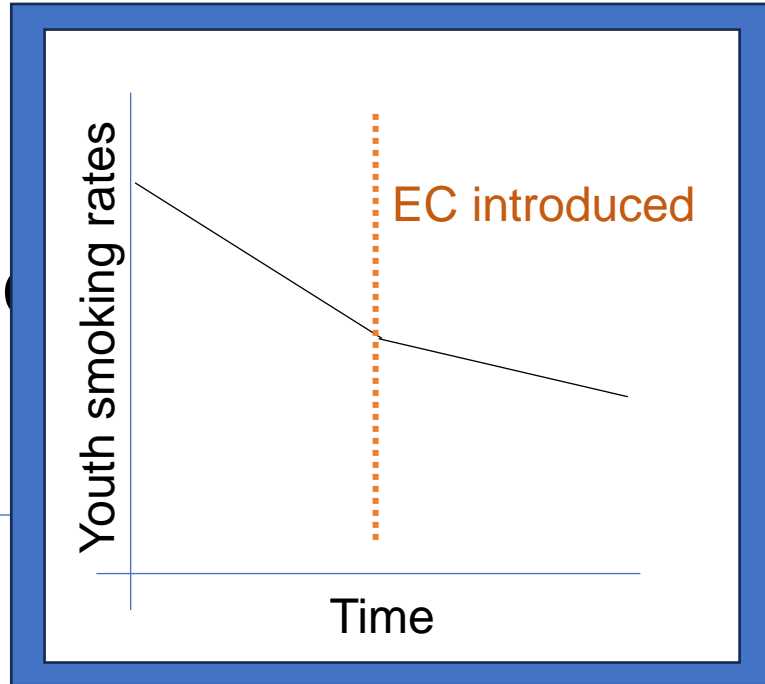
Data synthesis

- Heterogeneity in study designs, exposures and outcomes precluded meta-analysis.

- Followed Cochrane guidance on synthesis without meta-analysis.

- Association direction plots and qualitative comparative analysis were used for synthesis; in this presentation I will focus on results from the association direction plots as results from qualitative comparative analysis were hypotheses generating as opposed to hypothesis testing, and were largely inconclusive

- We assessed certainty using GRADE

Analysis plans registered in Open Science Framework.
(https://osf.io/4wycq/.)

Judging nature of associations

Direct associations

Inverse associations

Vaping

Smoking

Vaping

Smoking

Vaping

Vaping

Youth smoking rates

EC introduced

Time

Youth smoking rates

EC introduced

Time

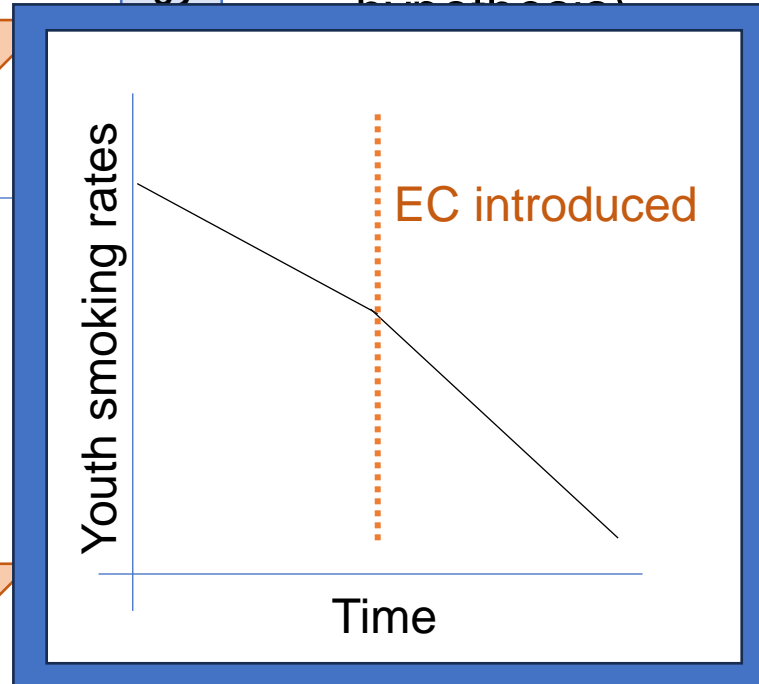Vaping might be causing young people to smoke who wouldn't have otherwise (consistent with gateway hypothesis)

reventing young ng who would onsistent with np hypotheses)

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Questions/comments before we move onto review results?

Preliminary

Have your say!

http://tinyurl.com/3u7me7n9

Included studies

- **123 studies**

- 24 population level studies:
  - published 2016-2023
  - approx. 4 million participants

- 99 individual level studies (40 tier 1 and 59 tier 2)
  - published 2014-2023
  - approx. 500 000 participants

- Age range: 9-29 years

29 studies used data from Population Assessment of Tobacco and Health (PATH), 10 National Youth Tobacco Survey (NYTS), 5 Truth Longitudinal Cohort (TLC), 4 each Community Health Survey (CHS), COMPASS (CIHR) and Monitoring the Future Survey (MTFS)

Risk of Bias Assessment (population)
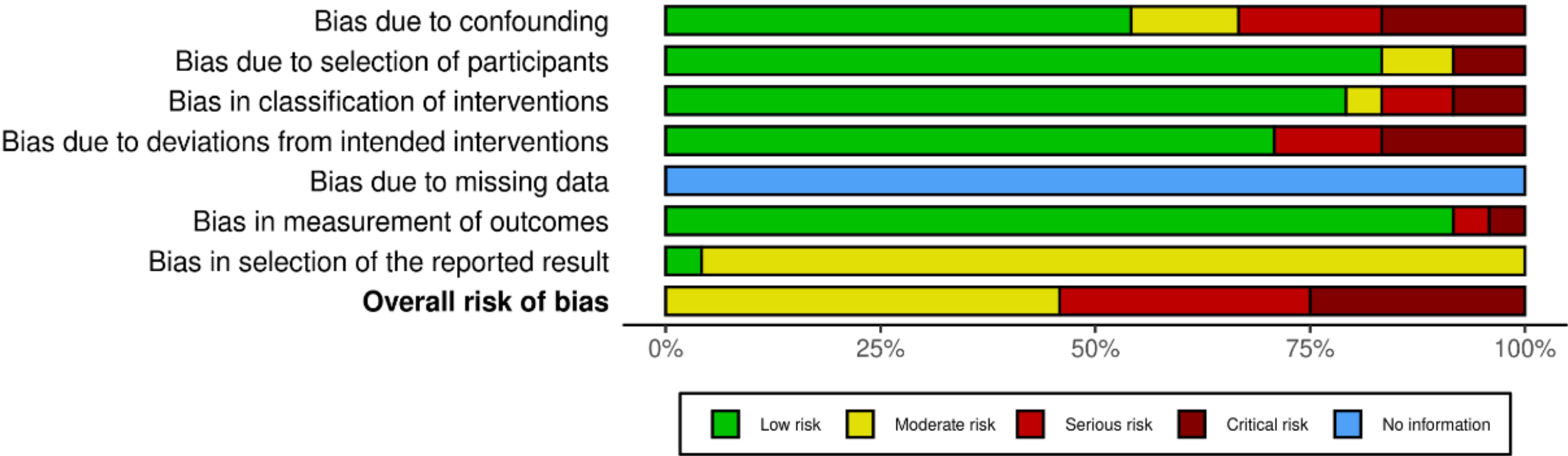
Risk of Bias summary – Population level studies

Risk of Bias Assessment (individual Tier 1)
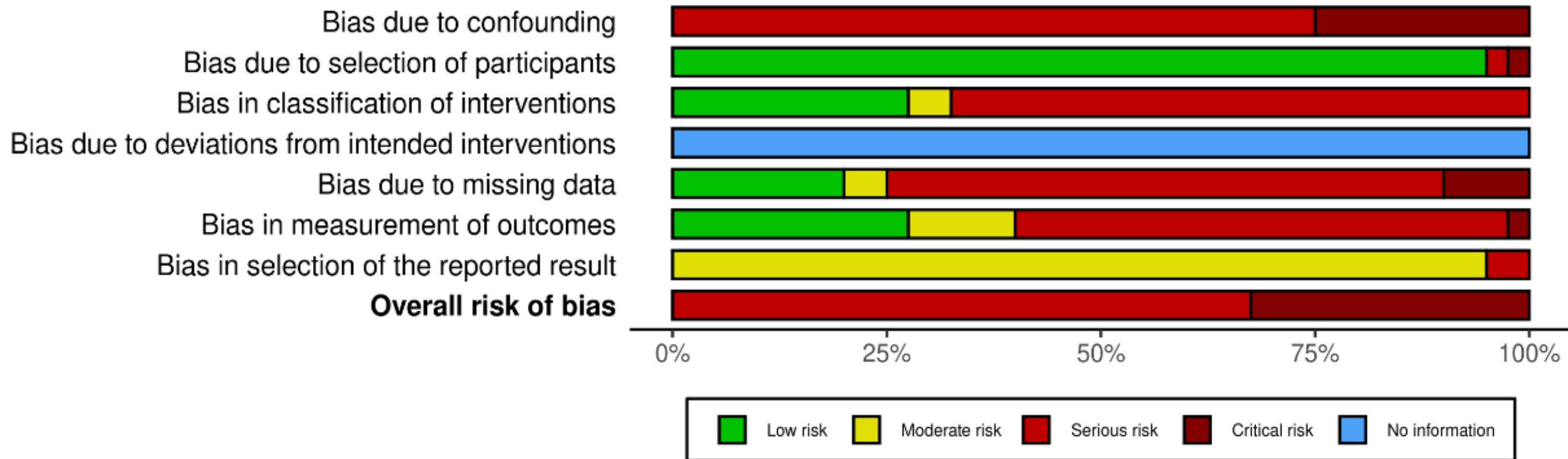
Risk of Bias summary – Tier 1 Individual level studies
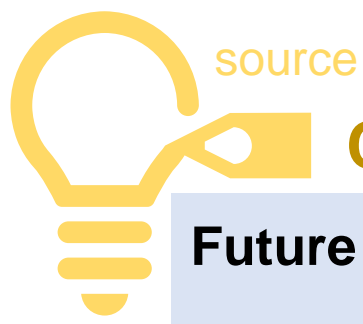
Critical appraisal tool

Future studies (individual and population-level) should:

- Pre-register research and/or analysis plans and/or study protocols on publicly available registers

- Ensure that participants are randomly selected from a national/state/province level representative survey or from a relevant subsample of a representative survey that is itself not impacted by the exposure variable

- Put in place and report on measures that ensure the anonymity of respondents, and report on the measures they undertook.

- Clearly specify the frequency of vaping and smoking (e.g., experimental and regular) whether used as exposure variables or outcome variables

Have your say!

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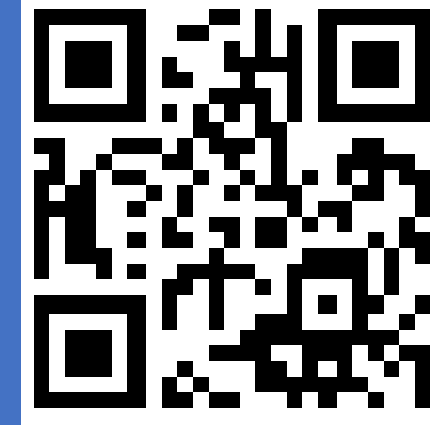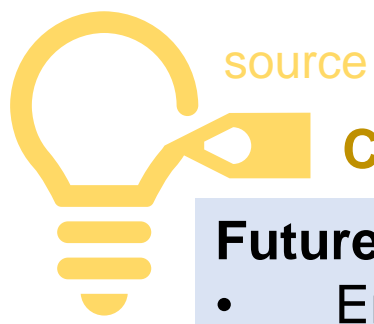
Critical appraisal tool

Future population-level studies should:
- Ensure parallel trends assumptions are met
- Compare outcomes of interest across different jurisdictions/contexts that vary based on a relevant exposure
- Investigate the possibility of dose-response effects
- Control for other relevant policies that occur simultaneously with the policy under evaluation
- Include fixed effects for place and time over which the exposure varies to eliminate confounding from unobserved time-invariant / area-specific sources, and area-invariant / time-specific sources.
- Discuss and/or account for implementation in studies where the exposure is a policy.
- Use instrumental variable designs, if an appropriate instrument becomes available, to identify the causal effect of vaping on subsequent smoking.

Have your say!

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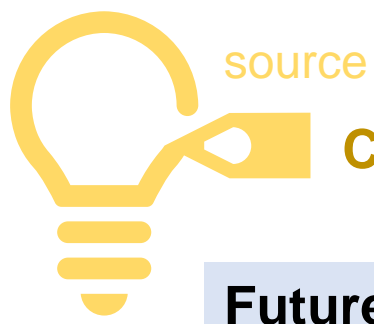
Critical appraisal tool

Future individual-level studies should:
- Control for combustible tobacco use at baseline
- Report differences in missing data by exposure group, and conduct and report sensitivity analyses to test the impact of missing data
- Report the proportion of participants lost to follow-up by exposure group and stratified by characteristics connected to combustible tobacco use

Have your say!

http://tinyurl.com/3u7me7n9
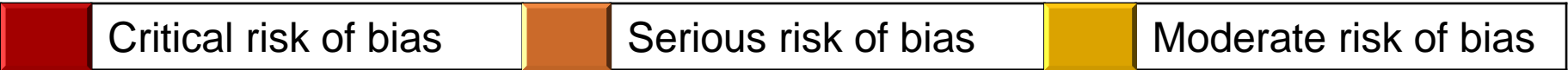
Associations between e-cigarette availability and smoking prevalence

Studies categorized by direction of association (n=19)

Category														
Statistically significant direct association	🟥	🟥												
Direct association, not statistically significant	🟥	🟧												
No association	🟥													
Inverse association, not statistically significant	🟥	🟧	🟨											
Inverse association, statistically significant	🟧	🟧	🟧	🟨	🟨	🟨	🟨	🟨	🟨	🟨				

🟥 Critical risk of bias	🟧 Serious risk of bias	🟨 Moderate risk of bias

Preliminary
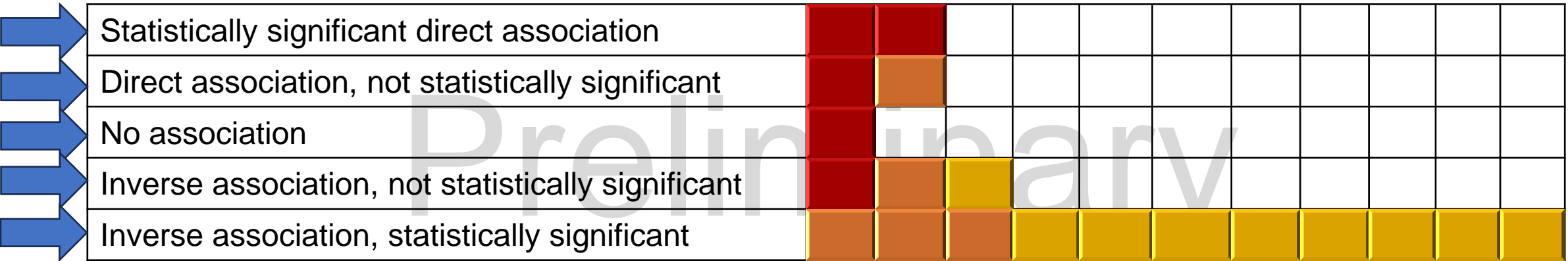
Associations between population level e-cigarette use and smoking prevalence

Studies categorized by direction of association (n=2)

Statistically significant direct association												
Direct association, not statistically significant												
No association	🟧											
Inverse association, not statistically significant												
Inverse association, statistically significant	🟥											

🟥 Critical risk of bias	🟧 Serious risk of bias	🟨 Moderate risk of bias

Associations between baseline *current e-cigarette use* and smoking initiation

Tier 1 studies categorized by direction of association (n=9)

Statistically significant direct association										
Direct association, not statistically significant										
No association										
Inverse association, not statistically significant										
Inverse association, statistically significant										

Preliminary

■ Critical risk of bias	■ Serious risk of bias	■ Moderate risk of bias

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Associations between baseline *ever e-cigarette use* and smoking initiation

Tier 1 studies categorized by direction of association (n=19)

Statistically significant direct association																			
Direct association, not statistically significant																			
No association																			
Inverse association, not statistically significant																			
Inverse association, statistically significant																			

> After controlling for 'general liability to use tobacco products'

Preliminary

	Critical risk of bias		Serious risk of bias		Moderate risk of bias

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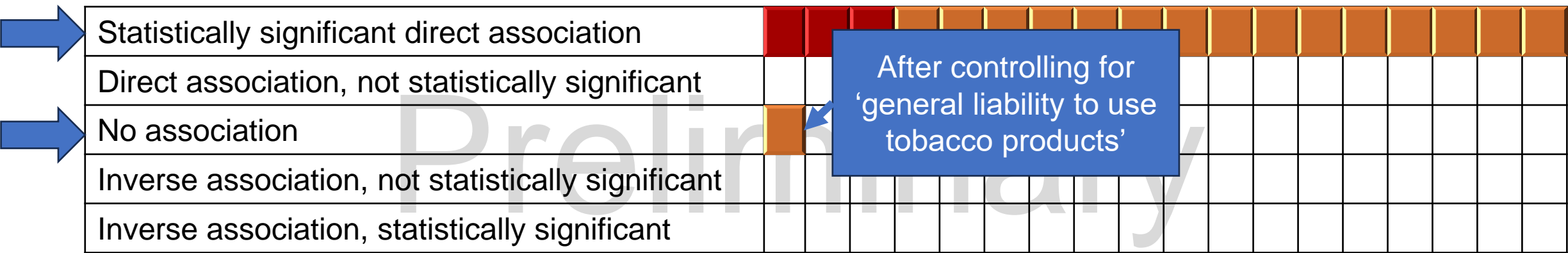
Associations between e-cigarette use and smoking progression

Tier 1 studies categorized by direction of association (n=5)

Statistically significant direct association	C	C	E								
Direct association, not statistically significant	C	E									
No association											
Inverse association, not statistically significant											
Inverse association, statistically significant											

	Critical risk of bias		Serious risk of bias		Moderate risk of bias

Exposure: C= current e-cigarette use at baseline; E= ever e-cigarette use at baseline

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Associations between e-cigarette use and smoking cessation

Tier 1 studies categorized by direction of association (n=3)

Statistically significant direct association											
Direct association, not statistically significant	E										
No association											
Inverse association, not statistically significant	C										
Inverse association, statistically significant	E										

	Critical risk of bias		Serious risk of bias		Moderate risk of bias

Exposures: C = current e-cigarette use at baseline; E = ever e-cigarette use at baseline

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Sociodemographic differences

Though there was no evidence of a difference at the population level, individual-level studies suggested vaping was more strongly associated with subsequent smoking in **males than females**.

Seven out of the nine individual level studies which examined associations based on **susceptibility to smoking** found that associations between vaping and subsequent smoking were **higher in those with lowest susceptibility at baseline**; the other two individual level studies found the opposite, and no population level studies provided breakdown by this category.

Data were mixed regarding: Rurality; Race/ethnicity; Income; Education; Age (within our eligible population)

No data available on any other variables, including mental health status, LGBTQ+, occupation, or religion

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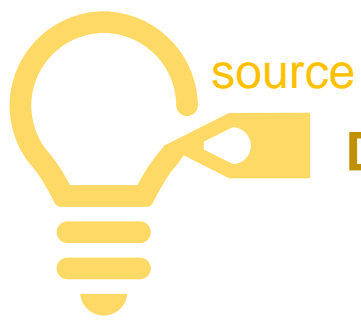
Future studies should follow relevant reporting guidelines, according to the type of study (e.g., The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for longitudinal studies).

Have your say!

http://tinyurl.com/3u7me7n9

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Certainty of Evidence (GRADE)

- Evidence can range from very low to high certainty

- Downgrading on five domains: risk of bias; unexplained inconsistency of results (statistical heterogeneity); indirectness of evidence; imprecision of results; probability of publication bias

- Observational evidence starts as 'low' and can be upgraded when there is evidence of a dose response effect or where all plausible unmeasured confounding would be in the opposite direction of the association detected

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Certainty of evidence: population rate

Outcomes	Direction of association	Number of studies	Certainty of the evidence
Population rate of combusted tobacco use	Inverse association; e-cigarette use/availability associated with less combustible tobacco use than would be otherwise expected	21	⊕⊖⊖⊖ VERY LOW

EC Availability

Smoking

Inverse association
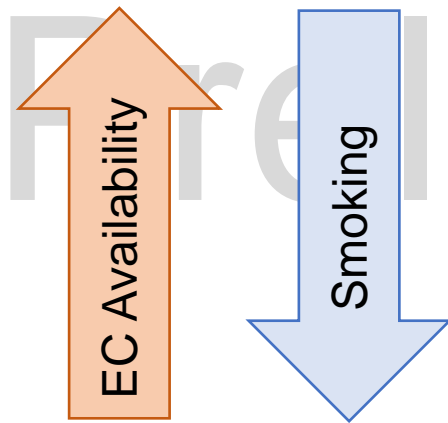
Downgraded one level for risk of bias; all studies judged to be at moderate, serious, or critical risk of bias.

Downgraded one level for inconsistency; association directions varied across studies and we were unable to identify the underlying causes of variation (though risk of bias was one)

Certainty of evidence: smoking initiation and progression

Outcomes	Direction of association	Number of studies[a,b]	Certainty of the evidence[c]
Initiation of cigarette smoking	Direct association; e-cigarette use was positively associated with subsequent initiation of combustible tobacco use	28	⊕⊖⊖⊖ VERY LOW
Progression of cigarette smoking	Direct association; e-cigarette use was positively associated with subsequent progression of combustible tobacco use	5	⊕⊖⊖⊖ VERY LOW

EC Availability
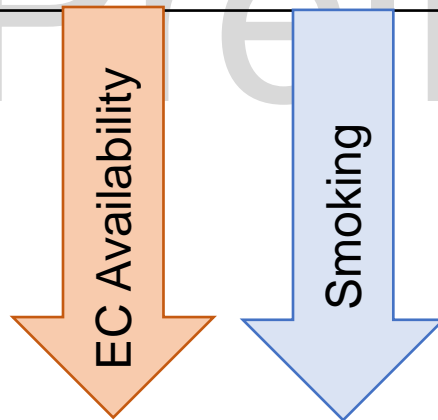
Smoking

Direct association

Downgraded two levels for risk of bias; all studies were judged to be at serious or critical risk of bias

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Certainty of evidence: smoking cessation

Outcomes	Direction of association	Number of studies	Certainty of the evidence
Cessation of cigarette smoking	Inconclusive. One study using 'current use' as an exposure and two using 'ever use' as an exposure found a statistically significant decrease in smoking cessation in people vaping at baseline; one found a non-statistically significant increase in cessation associated with ever use.	4	⊕⊖⊖⊖ VERY LOW

Downgraded two levels for risk of bias; all studies were judged to be at serious or critical risk of bias Downgraded two levels due to inconsistency; findings mixed across studies with no clear pattern.
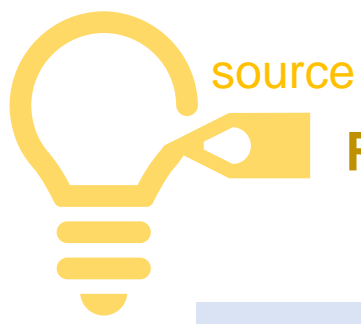
Recommendations for further research (Cochrane review)

Future studies should use triangulation methods (consider data from multiple methodological approaches, each with different sources of bias*) across a range of study designs capable of producing causal effects, but that vary in terms of internal and externality validity, to support stronger causal inference.

Have your say!

http://tinyurl.com/3u7me7n9

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*in Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol.* 2016;45(6):1866–1886.

We need more…

Consensus on how best to design these studies to evaluate causality – and then studies designed following these principles

Studies conducted outside of the USA, Canada and UK.

Studies looking at socially stratifying characteristics

Acknowledgement of uncertainty in this space

Thank you!

Preliminary

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Have your say!

http://tinyurl.com/3u7me7n9

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
1. Bias due to confounding	What are the confounding variables? Do authors adjust for these?	**Low** – Instrumental variable designs (e.g. Mendelian randomization) • Relevance condition (the instrument strongly predicts the exposure) is tested and met AND instrument conceptually impacts outcome only through the exposure. **Moderate** – Instrumental variable designs in which there are stated or otherwise well-documented conceptual concerns regarding exclusion restriction violation. **Serious** – Multiple factors related to propensity to smoke are measured at time of assessment of exposure. When confounders differ between groups, they are adjusted for/controlled using propensity score matching to assess the association of interest. **Critical** – All other studies	**Low** – Cross context designs including: • Natural experiments OR • Parallel trends assumptions are tested and met AND dose-response is tested for AND there are no concurrent policy changes or concurrent policy changes are controlled for AND fixed effects for place and time over which exposure varies are included. **Moderate** – Cross-context experiments in which parallel trend assumptions are met and there are no concurrent policy changes or those changes are controlled for, but dose-response is not tested for. **Serious** – Confounders evaluated and adjusted in: • Cross-context experiments which lack data before event (so cannot test parallel trend assumption) OR
	• Cross-context experiments that do not include time period and area fixed effects • Single context designs (e.g. interrupted time series in one setting)		
	Critical – All other studies		

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
2. Bias in selection of participants into the study	Is it a randomly selected sample (when applicable)?	**Low** – randomly selected from a national/state/province level representative survey OR relevant subsample from representative survey that is itself not impacted by the exposure variable (e.g., age is not impacted by e-cigarette use, but people with certain medical conditions could be) AND accounts for non-responders in weighting by population characteristics. **Moderate** – as per low but does not account for non-responders. **Serious** – randomly selected sample from non-nationally /province/state level representative population, or relevant subsample that is endogenously impacted by the exposure. **Critical** – convenience sampling	**Low** – as per individual level, or based on comprehensive data e.g. state level sales data). **Moderate** – as per individual level **Serious** – as per individual level **Critical** – as per individual level

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
3. Bias due to misclassification of exposure	How is e-cigarette use measured? Do they specify frequency of use Measuring exposure is difficult and the reference groups is assumed to be non-exposed. If non-differential, exposure misclassification will usually bias associations to the null.	**Low** – Authors specify frequency of e-cig use and measures are put in place to ensure anonymity of respondents (and this is known to participants; this is to reduce risk of misreport) OR if tobacco use was biochemically validated. **Moderate** – Authors specify frequency of e-cig use but do not report measures put in place to ensure anonymity of respondents. **Serious** – Specifies between ever-use and current e-cig use without further detail **Critical** – all other studies	**Low** – Authors specify frequency of e-cig use and measures are put in place to ensure anonymity of respondents (and this is known to participants) OR Exposure is not self-reported (e.g. sales data / e-cigarette ban). **Moderate** – Authors specify frequency of e-cig use but do not report measures put in place to ensure anonymity of respondents. **Serious** – Specifies between ever-use and current e-cig use without further detail **Critical** – all other studies

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
4. Bias due to deviations from intended ex-posures		N/A	**Low – All** other studies. **Moderate –** N/A **Serious – Exposure** is regulatory measure and no discussion of effectiveness of implementation AND failing to show that the exposure affects e-cigarette use. **Critical –** Exposure is regulatory measure and evidence of incomplete implementation is present but not accounted for in analyses.

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
5. Bias due to missing data	Is there missing follow up data? Have the authors tested for whether missingness is associated with variables that are related to combustible tobacco use (e.g. propensity to smoke)? Was any data excluded from the final analyses? (e.g. participants excluded due to missing data).	**Low** – Follow-up is 80%+, there is <5% difference in groups by exposure, and there are no differences in Long-term follow-up (LTFU) based on characteristics related to Combustible Cigarettes (CC) use (other than the exposure). OR one or more of the above apply but analyses show results are insensitive to LTFU. **Moderate –** - Follow up is 80+% but difference between groups is between 5-10%. - There are no differences in LTFU based on characteristics related to CC use (other than the exposure). - AND no sensitivity analyses conducted OR they're conducted and do indicate issue. **Serious –** - Follow up is <80% but difference between groups is <10% OR difference between groups is not reported	**N/A** OR there are differences in LTFU characteristics related to CC use (other than exposure). - AND no sensitivity analyses conducted OR they're conducted and do indicate issue. **Critical –** - Follow up is <80% and difference is >10% between groups - AND no sensitive analyses conducted OR they're conducted and do indicate issue.

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
6. Bias in measurement of the outcome		**Low** – Authors specify frequency of CC use AND measures are put in place to ensure anonymity of respondents (and this is known to participants) (or the authors state the data comes from a government agency or if tobacco use was biochemically validated) AND CC use at baseline is controlled for. **Moderate** – Authors specify frequency of CC use but do not report measures put in place to ensure anonymity of respondents (or otherwise specify the data is from a government agency or if tobacco use was biochemically validated). CC use at baseline is controlled for.	**Low** – Authors specify frequency of CC use and measures are put in place to ensure anonymity of respondents (and this is known to participants) (or if tobacco use was biochemically validated). OR Outcome is not self-reported (e.g. sales data) **Moderate –** Authors specify frequency of CC use but do not report measures put in place to ensure anonymity of respondents or if tobacco use was biochemically validated).
		Serious – CC use at baseline is controlled for but no other specification given. **Critical** – all other studies	**Serious** – Specifies between ever-use and current CC use without further detail. **Critical** – all other studies

Bias Items	Things to consider	Individual Level Exposure Guidance	Population Level Exposure Guidance
7. Bias in selection of the reported results	Is the reporting of results consistent with a priori plan	**Low –** Authors have published study protocol / analysis plan in advance of conducting and reported as planned OR deviations are reported and justified. **Moderate – All expected outcomes and analyses reported in full.** **Serious –** N/A **Critical –** All other studies	**Low –** Authors have published study protocol / analysis plan in advance of conducting and reported as planned OR deviations are reported and justified. **Moderate – All expected outcomes and analyses reported in full.** **Serious –** N/A **Critical –** All other studies
Overall risk of bias	Overall ratings should be consistent with the most biased rating for a given item. I.e. if one bias item is 'critical' then overall rating should also be critical.		

Qualitative comparative analysis (QCA)

"Do policies to improve the accessibility of electronic cigarettes lead to decreases or increases in combustible tobacco use on a population level?"

The conditions considered for this analysis were:
- Age
- Socioeconomic status
- Gender/Sex
- Level of youth cigarette use
- Level of youth EC use
- Exposure
- Comparator
- Definition of smoking used
- Definition of vaping used

Sub-questions

•**Which study-level population characteristics explain whether policies to improve the accessibility of ECs lead to decreases or increases in combustible tobacco use on a population level?**

Conditions operationalised: Gender; Age <18 included; Age ≥ 18 included

Which study-level contextual characteristics explain whether policies to improve the accessibility of ECs lead to decreases or increases in combustible tobacco use on a population level?

Conditions operationalised: Level of youth cigarette use; Level of youth electronic cigarette use

Which study-level intervention and methodological characteristics explain whether policies to improve the accessibility of ECs lead to decreases or increases in combustible tobacco use on a population level?

Conditions operationalised: Exposure, Comparator, Definition of smoking used; Definition of vaping used

QCA - *Truth table of consolidated characteristics*

Definition of Smoking	Comparator	Full age distribution	Gender	Outcome	N (cases)	Sufficiency	PRI	Studies
0	1	0	1	1	4	1	1	Pesko 2021; Wu 2022; Abouk 2023b,Pesko 2023
0	1	0	0	1	1	1	1	Friedman 2015a
0	1	1	0	1	1	1	1	Friedman 2022
1	0	0	0	1	1	1	1	Nguyen 2021
1	1	0	0	1	1	1	1	Pesko 2019
1	1	1	1	1	1	1	1	Dave 2019
1	0	1	0	0	1	0.658	0.49	Hallingberg 2020
0	0	0	1	0	3	0.579	0.366	Beard 2022; Harrell 2022; Hawkins 2022
0	0	1	1	0	3	0.54	0.445	Abouk 2023a; Cantrell 2020; Schneller 2022
1	0	1	1	0	1	0.33	0	Kowitt 2022
0	1	1	1	0	1	0	0	Abouk 2017

Consistency/Sufficiency: A measure of the consistency of a subset relationship between the configuration of conditions and the outcome

PRI: Proportional Reduction in Inconsistency is an additional measure of consistency/sufficiency and refers to the extent in which a configuration reduces the level of inconsistency in predicting a is sufficient in triggering successful outcome, with higher values indicating greater reductions in inconsistency