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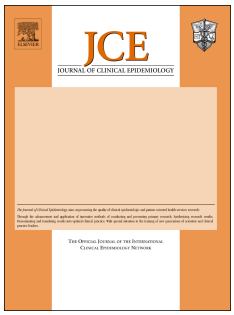

Most methodological characteristics do not exaggerate effect estimates in nutrition RCTs: findings from a meta-epidemiological study

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Most methodological characteristics do not exaggerate intervention effect estimates in nutrition RCTs: findings from a meta-epidemiological study

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To evaluate how risk of bias (RoB), as assessed using Cochrane RoB 2, influences effect estimates in nutrition intervention trials.

METHODS

Data source
RCTs selected from 183 nutrition meta-analyses

Process
Data extraction
Assessment with RoB2 tool

Analyses
Comparison of effect estimates (ratio of risk ratio)
RCTs with high risk or some concerns vs. low risk

RRR = RR / RR

RESULTS

N = 120 RoB assessments

Overall RoB did not affect intervention effect estimates

RRR = 0.99
(95% CI: 0.85 to 1.14)

No effects observed in **RoB domains**, except for possible exaggeration due to bias related to deviations from the intended intervention:

RRR = 1.29
(95% CI: 1.13 to 1.48)

CONCLUSION

Most methodological characteristics assessed with the RoB 2 tool do not lead to exaggerated effect estimates in nutrition RCTs. However, biases related to deviations from intended interventions warrant further investigation.

Most methodological characteristics do not exaggerate effect estimates in nutrition RCTs: findings from a meta-epidemiological study

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ABSTRACT

Objective: To evaluate the influence of bias from methodological characteristics on intervention effect estimates in nutrition randomised controlled trials (RCTs) using the Cochrane RoB2 tool.

Study design: Meta-epidemiological study

Methods: RCTs published until 2020 were selected from a representative sample of 183 nutrition meta-analyses. Pairs of reviewers conducted data extraction and risk of bias (RoB) assessments. Average estimates due to bias (ratio of risk ratio [RRR]) were computed through meta-analyses using a random-effects model, comparing RCTs rated as "high risk" or "some concerns" to those rated as "low risk" of bias. Subgroup analyses explored differences across RoB domains, types of interventions, and outcomes. Heterogeneity was assessed through I^2 and $\hat{\tau}^2$, and prediction intervals were calculated.

Results: We included 26 meta-analyses, encompassing 82 RCTs with 120 outcome-specific RoB assessments. Of these, 70% were rated as "some concerns", 18.3% as "low risk", and 11.7% as "high risk" of bias. Overall RoB did not affect intervention effect estimates (RRR 0.99, 95% confidence interval [CI] 0.85 to 1.14; I^2 = 36%; heterogeneity estimator [$\hat{\tau}^2$] = 0.03; prediction interval [PI] 0.66 to 1.47). Most RoB domains did not reveal differences in effect estimates, except for trials with biases related to deviations from the intended intervention (RRR 1.29, 95% CI 1.13 to 1.48; I^2 = 2%; $\hat{\tau}^2$ = 0.01; PI 0.97 to 1.72). We confirmed these findings in subgroup and meta-regression analyses.

Conclusion: Most methodological characteristics in nutrition RCTs, as assessed by RoB2, did not over- or underestimate intervention effect estimates. However, the unexpected finding that biases arising from deviations from intended interventions may lead to an underestimation of effects, rather than an overestimation, requires further research.

Keywords: Meta-epidemiological study; randomised controlled trials; nutrition; risk of bias; RoB2 tool, methodological trial characteristics

Running title: Most methodological characteristics do not exaggerate effect estimates in nutrition RCTs: findings from a meta-epidemiological study

Word count: 2,995

Plain language summary:

Randomised controlled trials (RCTs) are considered the most reliable method for determining whether an intervention is effective. However, weaknesses in study design or conduct can distort the results, a problem known as *bias*. The RoB 2 tool ("Risk of Bias") helps researchers check in a structured way whether bias is present and how much it might affect the results.

In this study, we looked at 82 RCTs on dietary interventions published up to 2020. We assessed 120 outcome-specific risk of bias assessments and identified whether they had a low, some concerns, or high risk of bias. We then compared the results of trials with a higher risk of bias to those with a low risk of bias to see whether bias influenced the reported treatment effects.

The reviewed trials showed variable levels of risk of bias and had little overall impact on the trial results. The main exception was how well participants followed the assigned diet and whether the researchers used the best available analysis methods. Problems in this area may have made the intervention's true effect seem smaller than it really was.

Our findings suggest that studies on nutrition interventions are mostly free from major bias and their results can be considered reliable. However, how well participants followed the assigned intervention and how good the analysis methods were seemed to play an important role. More research is needed to understand how study quality influences the results of nutrition trials.

SUMMARY BOX

What is already known on this topic

- Randomised controlled trials (RCTs) are considered the reference standard for evaluating intervention effects. However, nutrition RCTs often encounter methodological challenges such as difficulties with blinding, low adherence, and high dropout rates, that may increase the risk of bias.
- Several meta-epidemiological studies have investigated the impact of study design characteristics, such as inadequate sequence generation on intervention effect estimates. Findings suggest heterogeneous influence of bias across clinical fields.

What this study adds

- This study is the first to conduct standardised, de-novo assessments in a large number of nutrition trials using the Cochrane RoB 2 tool.
- We advanced previous research by examining key methodological domains that may exaggerate intervention effects, providing new insights into the validity and application of risk-of-bias assessment criteria in nutrition research.
- Our findings suggest that, on average, most methodological characteristics assessed with the RoB 2 tool do not lead to exaggerated effect estimates in nutrition RCTs. However, biases related to deviations from intended interventions warrant further investigation.

1. BACKGROUND

Diet is a major modifiable risk factor in preventing non-communicable diseases, including cardiovascular diseases, cancer, and diabetes mellitus [1]. Although population-based observational studies are the main evidence source to investigate the long-term diet health impact, usually only (high certainty) evidence from randomised controlled trials (RCTs) allows reliable conclusions [2-4]. Intervention effect estimates in RCTs may, however, be influenced by various methodological characteristics leading to potential biases overestimating or underestimating true effects [5, 6]. In the field of nutrition RCTs, challenges of achieving blinding due to the nature of dietary interventions, low adherence, and high dropout rates may increase the risk of bias (RoB) [7]. Furthermore, the frequent lack of trial registration in nutrition RCTs undermines efforts to enhance transparency and rigor, and the reliability of research findings [7, 8]. This highlights the importance of systematic review authors assessing how specific methodological features might contribute to biases that could exaggerate effect estimates. Over the recent years, tools for evaluating RoB and identifying study limitations have been developed, guided by empirical evidence and theoretical considerations to ensure their suitability for RCTs [9].

Prior studies have shown that biases such as poor sequence generation, inadequate allocation concealment, and lack of blinding often lead to more favourable effect estimates in RCTs [5, 10, 11]. However, some studies have not confirmed these associations, suggesting that impact of biases may vary across clinical areas and warrant further investigation in specific fields [12, 13]. A previous meta-epidemiological study [14] investigated the average bias associated with methodological characteristics in nutrition RCTs, using the RoB tool [6].

This current meta-epidemiological study seeks to replicate and advance these findings using the revised Cochrane Risk of Bias (RoB2) tool [15]. Our study aims to evaluate how methodological features assessed by RoB2 influence intervention effect estimates in nutrition RCTs, synthesising evidence on average bias from five common trial characteristics and analysing variations across different interventions and outcomes in meta-analyses.

2. METHODS

This meta-epidemiological study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [16] and guidelines for meta-epidemiological research [17].

2.1. Data sources and study selection

RCTs published up to 2020 were selected from a representative sample of nutrition meta-analyses identified from two previous meta-epidemiological studies [18, 19]. A brief overview of the search strategy and selection process is provided in the supplementary appendix S1. In total, 183 meta-analyses were identified.

Meta-analyses of RCTs evaluating the effect of dietary interventions in adult populations, with a focus on patient-relevant outcomes were eligible. Moreover, we included meta-analyses containing at least two RCTs. To improve comparability, the sample was further refined to separate RCTs within a meta-analysis with heterogeneous interventions (e.g. vitamin C supplementation versus dietary intake). Inclusion and exclusion criteria are outlined in **table 1**.

2.2. Data extraction

Two reviewers (GB and JS) independently extracted data using a piloted extraction form. Discrepancies were discussed with a third reviewer (LS). For each individual RCT, we collected study characteristics, such as the first author, publication year, country, study name (and acronym), and study design (e.g. parallel, cross-over). We also extracted data on PICO characteristics: population (e.g. age, disease status), intervention (e.g. vitamin D supplementation), comparator (e.g. placebo), and outcomes (e.g. all-cause mortality), as well as intervention duration. For each outcome, we extracted the number of participants, number of events, type of effect measure (e.g. risk ratio [RR]), and effect estimates with their corresponding 95% confidence intervals (CI).

2.3. Assessment of risk of bias in included studies

We used the RoB2 tool to assess potential biases in RCTs [15]. Key domains include bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. In the case of cluster or cross-over RCTs, further

158 considerations were taken into account [20, 21]. Supplementary appendix S2 provides additional
159 guidance tailored to nutrition RCTs. Two reviewers (GB or JS) assessed the RoB for each included study
160 at the outcome level. Disagreements were addressed through discussion or by consulting the senior
161 author (LS). The RoB assessments were visualised using the Risk-of-bias VISualization tool (robvis)
162 [22].
163
164 **2.4. Statistical analysis**
165 To ensure consistency in the summary effect measures, we recalculated or converted effect estimates to
166 align with RR metrics (supplementary table S1). The data harmonisation process was in line with current
167 standards [18, 19].
168 To quantify differences in effect estimates, we calculated the ratio of risk ratios (RRR) for study pairs
169 [23], by comparing RCTs with a "high risk" or "some concerns" rating to those with a "low risk"
170 (reference category) rating. Additional information on how the RRR is generated can be found in
171 supplementary appendix S1. Briefly, an RRR <1 indicates an overestimation of studies rated as "high
172 risk" or "some concerns" compared to those with a "low risk" rating, whereas an RRR >1 represents an
173 underestimation of effects. Analyses were conducted for the overall RoB assessment and for each
174 individual domain. Comparisons are possible, when a meta-analysis provides at least two distinct RoB
175 judgements for overall RoB or individual RoB domains. For example, for the overall RoB, meta-
176 analyses had to include at least one study rated as "high" or "some concerns" and at least one study rated
177 as "low" RoB. As a result, the number of RoB assessments may vary across analyses. The pooled
178 estimates were obtained using a random-effects meta-analysis-model [24]. Between-study variability
179 (heterogeneity (τ^2) was estimated by the restricted maximum-likelihood method [25], which performs
180 well for both binary and continuous outcomes [26-28]. To account for heterogeneity, we used the
181 heterogeneity estimator ($\hat{\tau}^2$) and I^2 heterogeneity measure [24, 29]. We computed 95% prediction
182 intervals (PI) to provide the range of possible parameters for the differences between results of RCTs
183 with different bias ratings [30]. All statistical analyses were conducted using the R package meta
184 (version 8.0-2) [31].
185

2.5. Subgroup and meta-regression analyses

We conducted a priori planned subgroup analyses with respect to the different dietary interventions (dietary pattern, food groups, macronutrients, micronutrients), type of intake (dietary intake or supplementation), and cluster of outcomes (e.g. cardiovascular disease). We carried out additional analyses by examining various comparison combinations of RoB rating (e.g. "high" versus "some concerns", "high" vs. "low"). To further investigate potential influences on the summary effect estimates, we performed univariable meta-regressions for intervention cluster, intervention type, and outcome cluster, as well as multivariable meta-regressions for RoB ratings.

3. RESULTS

Figure 1 illustrates the selection process, resulting in 26 meta-analyses [32-49], with 82 individual RCTs comprising 120 outcome-specific assessments. Supplementary table S2 provides details on excluded meta-analyses and the reasons for their exclusion.

Figure 1: Flow diagram of the selection process

PI/ECO: population, intervention/exposure, comparator, outcome; RCTs: randomised controlled trials

3.1. Descriptive characteristics

Of the 26 included meta-analyses, 17 (65.48%) investigated the effect of micronutrients and five (19.2%) of dietary patterns. The most common outcome was cancer (n=7, 26.9%). The number of studies from RCTs ranged from 2 to 20 (median: 3). The total number of participants was 493,210 with a median of 6,730. Of the included 82 RCTs, most were conducted in the US (n=25, 30.5%), UK (n=12, 14.6%) and Australia (n=8, 9.8%). A detailed description of PICO characteristics for each included meta-analysis is depicted in supplementary table S3.

3.2. Risk of bias assessment

We conducted 120 outcome-specific RoB assessments. We classified 84/120 (70.0%) with "some concerns", 22/120 (18.3%) with "low risk of bias" and 14/120 (11.7%) with a "high risk of bias" rating.

The "high risk of bias" ratings (n=14) were primarily due to inappropriate handling of missing data (n=11) or deviations from the intended intervention (n=3). Supplementary table S38 summarises overall and domain-specific RoB ratings. Supplementary figure S1 provides an overview through a summary plot, and supplementary figure S2 depicts the forest plots of the meta-analyses with the effect estimates and RoB ratings of the included single RCTs.

3.3. Meta-epidemiological analyses

Table 2 presents the results of the association between the reported characteristics and the intervention effect estimates for the main analysis and subgroup analyses. The results of all meta-analyses conducted are presented in supplementary tables S4-S13 and illustrated as forest plots in supplementary figures S3-S8.

Overall risk of bias

The analysis of 79 RoB assessments found no difference in intervention effect estimates between trials with an overall judgement of "high risk" or "some concerns" compared to those rated with "low risk" (RRR 0.99, 95% CI 0.85 to 1.14; I^2 = 36%; τ^2 = 0.03; PI 0.66 to 1.47; see table 2). Subgroup analyses stratified by intervention type and outcome type, along with comparisons across bias ratings ("high", "some concerns", and "low") showed no differences in intervention effect estimates (see supplementary tables S4-S5).

Bias arising from the randomisation process

Based on 86 RoB assessments, a judgement of "high risk" or "some concerns" compared to "low risk" in the randomisation process revealed no difference in intervention effect estimates on average (RRR 1.00, 95% CI 0.76 to 1.31; I^2 = 62%; τ^2 = 0.11; PI 0.45 to 2.20; see table 2). Subgroup analyses yielded mainly no differences, except bidirectional association by intervention type in effect estimates for "fatty acids" (RRR 0.74, 95% CI 0.59 to 0.92; I^2 = 0%; τ^2 = 0; PI 0.45 to 1.21) and "dietary patterns" (RRR 1.74, 95% CI 1.35 to 2.25; I^2 = 0%; τ^2 <0.01; PI 0.33 to 9.21). Additional analyses with various rating combinations found no differences (see supplementary tables S6-S7).

242

243 *Bias due to deviations from intended intervention*

244 The analysis of 72 RoB assessments revealed that a classification of "high risk" or "some concerns" –
245 compared to those classified as "low risk ", showed a difference in intervention effect estimates related
246 to deviations from the intended intervention, with an estimated average increase of 29% (RRR 1.29,
247 95% CI 1.13 to 1.48; I^2 = 2%; τ^2 = 0.01; PI 0.97 to 1.72; see table 2). Subgroup analyses by type of
248 intervention and outcome suggested a consistent underestimation in intervention effect estimates (see
249 supplementary table S8). The differences were also existent in additional analyses comparing
250 intervention effect estimates for trials with "some concerns" versus "low risk" (see supplementary table
251 S8).

252

253 *Bias due to missing outcome data*

254 Based on 96 RoB assessments no difference in intervention effect estimates was detected (RRR 0.90,
255 95% CI 0.78 to 1.03; I^2 = 20%; τ^2 = 0.03; PI 0.62 to 1.30; see table 2). None of the subgroup analyses,
256 showed exaggerated effect estimates, except for the outcome "cancer" (RRR 0.78, 95% CI 0.63 to 0.96;
257 I^2 = 0%; τ^2 = 0.02; PI 0.46 to 1.31; see supplementary table S10).

258

259 *Bias in measurement of the outcome*

260 In this domain, none of the RCTs were judged to have a "high risk" of bias. Based on 54 RoB
261 assessments, we found that a judgement of "some concerns", compared to "low risk", did not reveal a
262 difference in measurement of the outcome on average (RRR 0.91, 95% CI 0.72 to 1.15; I^2 = 0%; τ^2 = 0;
263 PI 0.65 to 1.27; see table 2). These findings were confirmed in subgroup analyses (Supplementary Table
264 S12).

265

266 *Bias in selection of the reported result*

267 None of the included RCT were rated as "high risk" of bias in this domain. An analysis of 96 RoB
268 assessments found that a judgement of "some concerns" versus "low risk" did not result in a difference
269 in average intervention effect estimates related to the selection of the reported results (RRR 0.96, 95%

CI 0.86 to 1.07; I^2 = 22%; τ^2 <0.01; PI 0.76 to 1.21; see table 2). Subgroup analysis confirmed the findings of the main analysis (see supplementary table S13).

Most meta-regression analyses did not identify statistically significant effects of potential confounding variables, including types of intervention, outcome categories, and RoB2 ratings, on trial characteristics (supplementary appendix S3, and tables S14-S37).

4. DISCUSSION

4.1. Summary of findings

In this meta-epidemiological study of nutrition RCTs, 120 outcome-specific RoB assessments were conducted and analysed. It is the first study to carry out standardised de-novo RoB assessments for RCTs using the Cochrane RoB2 tool. A majority of trials (70%) were rated as having "some concerns" regarding the overall RoB. While the overall RoB and most domains - including the randomisation process, missing outcome data, measurement of the outcome, and selection of the reported results – had no impact on effect estimates, the domain addressing deviations from intended interventions was associated with an estimated 29% underestimation of intervention effects (RRR 1.29, 95% 1.13 to 1.48). Subgroup analyses of the domain "randomisation process" revealed bidirectional differences by intervention type, including "fatty acids" (RRR 0.74, 95% CI 0.59 to 0.92) and "dietary patterns" (RRR 1.74, 95% CI 1.35 to 2.25).

4.2. Comparison with other studies

Our findings align with those of another meta-research study in the field of nutrition by Stadelmaier and colleagues [14], which included 77 meta-analyses and investigated average bias related to methodological characteristics in RCTs using the 2011 Cochrane RoB tool [6]. Similar to our study, they concluded that most methodological characteristics as assessed by the original RoB tool may not over- or underestimate average intervention effect estimates. However, trials with a "high" or "unclear" RoB for blinding of outcome assessment appeared to exaggerate intervention effect estimates. Additionally, a "high" or "unclear" RoB for incomplete outcome data was associated with an

approximate 9% exaggeration of effect estimates, with bias primarily observed in trials reporting mostly subjectively assessed outcomes. In contrast, in our current study, we focused on objective outcomes. We used the Cochrane RoB2 tool, which differs from the original version (RoB1) primarily by excluding overall study level judgement, and instead requiring that the RoB is always assessed at the individual outcome measure level [15].

Several other meta-epidemiological studies with a broader thematic scope are available [10, 11, 50]. The most recent systematic survey conducted by Wang and colleagues in 2024 [5], explored the impact of potential RoB elements on effect estimates in RCTs. It integrated findings from multiple meta-epidemiological studies, differentiating between those that utilised within-trial and between-trial comparisons, and evaluated the certainty of evidence. Their analysis revealed that inadequate random sequence generation, adequate allocation concealment and the lack of blinding for participants and outcome assessors may lead to an overestimation of effect sizes.

4.3. Implications for nutrition research

High-quality systematic reviews are critical for providing trustworthy dietary guidance. Ideally, they are based on low-RoB RCTs characterised by rigorous methodology and transparent reporting. However, our sample highlight challenges specific to nutrition research, such as difficulties in blinding participants, high dropout rates, and inconsistent preregistration practices, factors that may influence effect estimates [7].

Blinding of participants and personnel is addressed in domain 2 of the RoB2 tool, and is a major challenge in nutrition RCTs, particularly in "whole diet" approaches, as participants are generally aware of their dietary choices [51]. Nevertheless, most trials in our sample focused on micronutrient supplementation, where blinding is feasible, similar to drug trials. Following the intention-to-treat (ITT) principle, we focused on the "effect of assignment to intervention", which maintains randomisation benefits, and generally yields less biased effect estimates than per-protocol analyses [52]. Most trials in our sample adapted this approach, consistent with the RoB2 guidance document [53]. Our analyses indicate that trials rated as "some concerns" or "high risk" in this domain underestimated intervention effects compared to those rated as "low risk". This may be due to low dietary adherence among

participants in unblinded trials. Additionally, ITT analysis has shortcomings in the presence of non-adherence, low adherence, or high dropout, and may thus bias true treatment effects [52].

High dropout rates - common in nutrition RCTs - are captured in domain 3. Among free-living populations, adherence to dietary regimens requires considerable effort from participants, often resulting in attrition rates of 40% to 50% [51, 55]. In our sample, missing outcome data, was the main factor contributing to an overall "high risk of bias" rating. However, 10% of the trials were classified as "high risk", indicating lower dropout rates in dietary supplement trials [56].

In our sample, most assessments did not report on a protocol, highlighting the lack of proper trial registration, including missing registration entries, protocols, and statistical analysis plans in nutrition RCTs. Furthermore, documented inconsistencies exist between blinding reports in trial publications and registries [57].

The overall RoB was judged mainly with "some concerns" (70%), driven by issues related to the randomisation process, missing data, and reported results, which revealed reporting problems and lack of reasons provided for the missing data. This highlights the need for improved trial design, conduct, and reporting practices. Implementing standardised frameworks, such as the CONSORT (Consolidated Standards of Reporting Trials) guideline for nutrition RCTs [59], will enhance transparency and completeness of information reported, thereby improving RoB judgement processes.

Another important aspect to consider is the validity of the assessment tool. The RoB2 is widely accepted as the reference standard for assessing RoB in RCTs. Insights from the original tool [60], empirical evidence from meta-epidemiological studies [50], and theoretical and conceptual considerations led to the development of the RoB2 tool. The lack of observed differences for several methodological characteristics in our study, can have various reasons: First, the RoB2 tool may not be able to fully capture certain biases, allowing them to go undetected and therefore resulting in an inaccurate estimation of bias. Second, the tool's domain structure and classification system may not accurately categorise outcomes, potentially impacting the assessment of bias.

4.4. Strengths and limitations

This study has several strengths. It is the first meta-epidemiological study to conduct de-novo RoB assessments for all included RCTs using the Cochrane RoB2 tool. Additionally, we evaluated a representative sample of dietary RCTs, covering a wide range of diet-disease associations. We used the Cochrane RoB2 tool [15], and ensured consistency in RoB judgments by having two reviewers independently assess all domains, with a third researcher resolving any discrepancies. Additionally, we followed a rigorous methodology that included standardised data extraction, independent screening and data extraction, and piloting of all research steps. However, several limitations must be considered: Although a representative sample of RCTs on diet-disease associations was included, not the full spectrum of diet could be assessed, e.g. food groups were not considered since solely RCTs on metabolic risk factors are available. Moreover, we did not consider continuous outcomes, such as metabolic risk factors, which are commonly used in short-term trials [7]. Trials reporting continuous outcomes were scarce within the overarching projects, and to maintain consistency in comparison, they were therefore omitted. Additionally, we evaluated methodological characteristics addressed by the RoB2 tool; however, other factors such as study setting, dietary adherence, provision of dietary supplements or food, and sample size, may also contribute to exaggerated effect estimates. Further research is needed to explore the impact of these factors.

5. Conclusion

This meta-epidemiological study is the first to investigate the impact of RoB on intervention effect estimates in nutrition RCTs through 120 de-novo assessments using the Cochrane RoB2 tool. Most trials in our sample were rated as having "some concerns" regarding the overall RoB. Surprisingly, while overall RoB and most domains did not influence effect estimates, the domain concerning deviations from intended interventions was associated with an underestimation of intervention effects. To support the findings of our study, we recommend a replication study, ideally with a larger sample size, to provide a more comprehensive understanding of how methodological quality influences effect estimates in nutrition RCTs.

List of abbreviations

$\hat{\tau}^2$: heterogeneity estimator; **CI:** confidence interval; **CONSORT:** Consolidated Standards of Reporting Trials**; HR:** hazard ratio; **ITT:** intention-to-treat analysis; **OR:** odds ratio; **PHS II:** Physicians' Health Study II; **PI:** prediction interval; **PI/ECO:** population, intervention/exposure, comparator, outcome; **PREDIMED:** Prevención con Dieta Mediterránea; **PRISMA:** the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCT:** randomised controlled trial; **REML:** the restricted maximum-likelihood method; **RoB:** risk of bias; **RoB2:** Revised Risk of Bias tool; **robvis**: the Risk-of-bias VISualization tool; **ROR:** ratio of odds ratios; **RR:** risk ratio; **RRR:** ratio of risk ratios

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566 **Table 1** Description of inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Population	**Adult population (≥18)**	**Children (<18)**
Intervention	**Dietary intervention (intake or supplementation)** - **Dietary pattern:** e.g. Mediterranean diet. - **Food groups:** e.g. grains, vegetables, oil - **Macronutrients:** *carbohydrates*, e.g. starch; *fat*, e.g. omega–3 fatty acids; *proteins*, e.g. amino acids. - **Micronutrients:** *vitamins*, e.g. B vitamins (thiamine, riboflavin, niacin, pyridoxine, cobalamin, folic acid); *minerals*, e.g. calcium, sodium. - **Other:** e.g. fibres, probiotics, prebiotics	- **Heterogeneous interventions:** e.g. vitamin C supplementation and dietary vitamin C intake
Control / Comparison	- **Low/ no intake or supplementation** of the above mentioned interventions. - **Placebo.** - **Usual care.**	
Outcome	- **Patient-relevant binary outcomes:** e.g. all-cause mortality, prostate cancer, type 2 diabetes	- **Continuous outcomes:** e.g. metabolic risk factors
Study design	- **Randomised controlled trials**: parallel, crossover, factorial, cluster design	- **Non-randomised studies:** *cohort studies,* e.g. nested case-control, case-cohort studies

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569 **Table 2** Overview of the main results

Methodological trial characteristics	N (assessments)	RRR (95% CI)	Heterogeneity (I^2 (%); τ^2)	95% PI
Main analysis				
Overall rating *high/some concerns vs. low*	79	0.99 (0.85 to 1.14)	36; 0.03	0.66 to 1.47
Bias arising from the randomisation process *high/some concerns vs. low*	86	1.00 (0.76 to 1.31)	62; 0.11	0.45 to 2.20
Bias due to deviations from intended intervention *high/some concerns vs. low*	72	1.29 (1.13 to 1.48)	2; 0.01	0.97 to 1.72
Bias due to missing outcome data *high/some concerns vs. low*	96	0.90 (0.78 to 1.03)	20; 0.03	0.62 to 1.30
Bias in measurement of the outcome *some concerns vs. low*	54	0.91 (0.72 to 1.15)	0; 0	0.65 to 1.27
Bias in selection of the reported result *some concerns vs. low*	96	0.96 (0.86 to 1.07)	22; <0.01	0.76 to 1.21

570 *CI*: confidence interval; I^2: Heterogeneity measure; *PI:* prediction intervals; *RRR*: Ratio of risk ratios; τ^2: heterogeneity value

571 with the restricted maximum-likelihood estimation method

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DECLARATIONS

Ethics approval and consent to participate: Not applicable since we did not include any human subject.

Consent for publication: Not applicable.

Availability of data and materials: Data were extracted from published studies (systematic review and randomised controlled trial). All data generated or analysed during this study are included in this published article and its additional files.

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Author Contributions: GB, JS, and LS designed the research. GB and JS extracted the data, and assessed the risk of bias of the included publications. GB, JS, and MP analysed the data. All authors (GB, JS, MP, JJM, and LS) interpreted the data. GB wrote the first draft of the paper. All authors (GB, JS, MP, JJM, and LS) read the manuscript and approved the final version. GB and LS are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

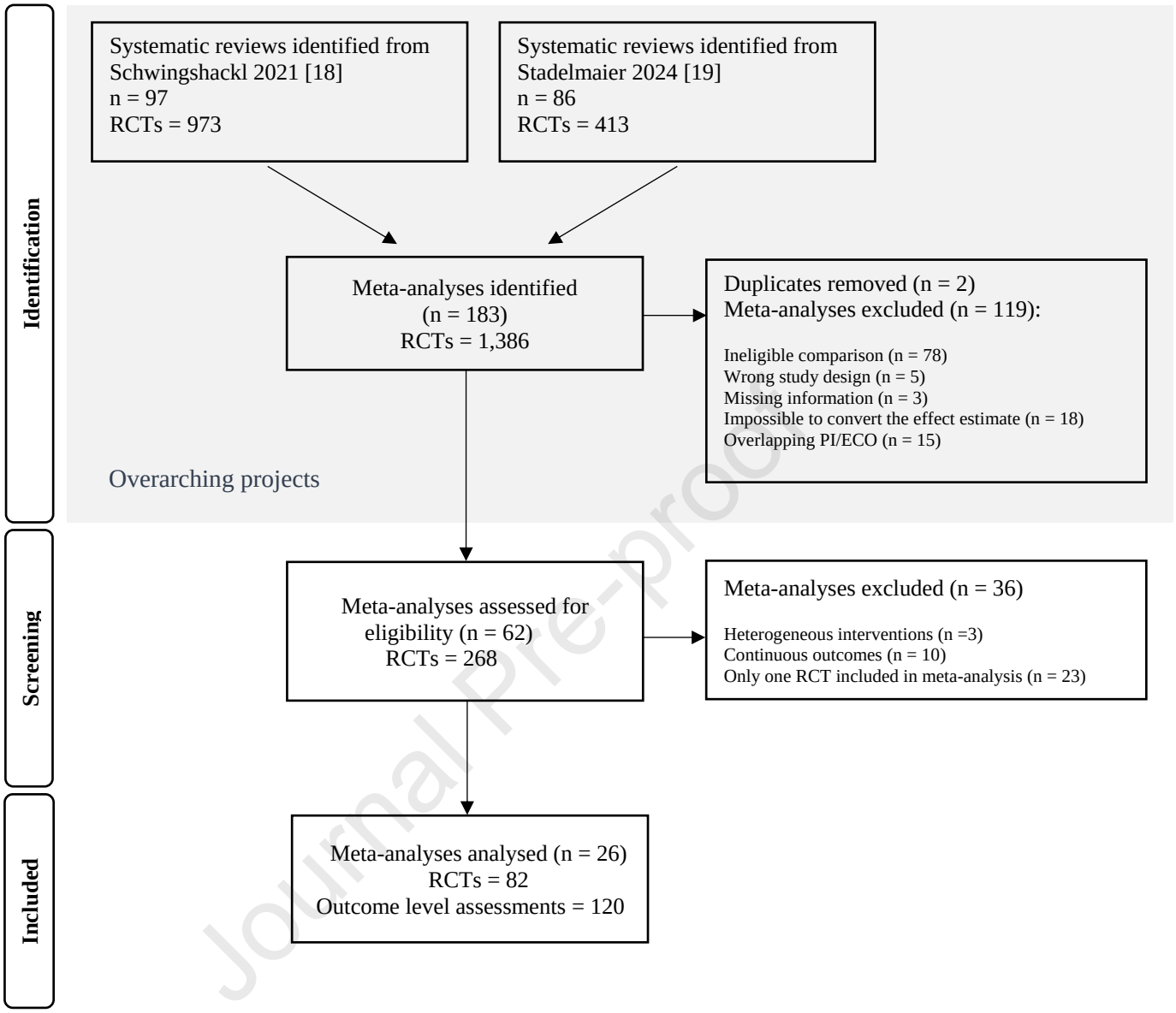
Data availability: Data were extracted from published studies (systematic review and randomised controlled trials). All data generated or analysed during this study are included in this published article and its additional files. Data and codes for statistical analysis can be found under the following link: https://osf.io/9bq83/

Patient and Public involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Supplementary Information

Online Resource: Appendix S1 Additional methodological information. **Appendix S2** Additional guidance to assess the risk of bias in the included randomised controlled trials. **Appendix S3** Meta-regression. **Table S1** Overview of transformations made to the original data extraction. **Table S2** Reasons for exclusion. **Table S3** Characteristics of included meta-analyses. **Table S4-S5** Overview of results for RCTs – Overall risk of bias. **Table S6 – S7** Overview of results for RCTs – Bias arising from the randomisation process. **Table S8–S9** Overview of results for RCTs – Bias due to deviations from intended intervention. **Table S10 – Table S11** Overview of results for RCTs – Bias due to missing outcome data. **Table S12** Overview of results for RCTs – Bias in measurement of the outcome. **Table S13** Overview of results for RCTs – Bias in selection of the reported result. **Table S14** Multivariable meta-regression for risk of bias ratings: Overall risk of bias. **Table S15** Univariable meta-regression for cluster of intervention: Overall risk of bias. **Table S16** Univariable meta-regression for type of intervention: Overall risk of bias. **Table S17** Univariable meta-regression for cluster of outcomes: Overall risk of bias. **Table S18** Multivariable meta-regression for risk of bias ratings: Bias arising from the randomisation process. **Table S19** Univariable meta-regression for cluster of intervention: Bias arising from the randomisation process. **Table S20** Univariable meta-regression for type of intervention: Bias arising from the randomisation process. **Table S21** Univariable meta-regression for cluster of outcomes: Bias arising from the randomisation process. **Table S22** Multivariable meta-regression for risk of bias ratings: Bias due to deviations from intended intervention. **Table S23** Univariable meta-regression for cluster of intervention: Bias due to deviations from intended intervention. **Table S24** Univariable meta-regression for type of intervention: Bias due to deviations from intended intervention. **Table S25** Univariable meta-regression for cluster of outcomes: Bias due to deviations from intended intervention. **Table S26** Multivariable meta-regression for risk of bias ratings: Bias due to missing outcome data. **Table S27** Univariable meta-regression for cluster of intervention: Bias due to missing outcome data. **Table S28** Univariable meta-regression for type of intervention: Bias due to missing outcome data**. Table S29** Univariable meta-regression for cluster of outcomes: Bias due to missing outcome data. **Table S30** Multivariable meta-regression for risk of bias ratings: Bias in measurement of the outcome. **Table S31** Univariable meta-regression for cluster of intervention: Bias in measurement

of the outcome. **Table S32** Univariable meta-regression for type of intervention: Bias in measurement of the outcome. **Table S33** Univariable meta-regression for cluster of outcomes: Bias in measurement of the outcome. **Table S34** Multivariable meta-regression for risk of bias ratings: Bias in selection of the reported result. **Table S35** Univariable meta-regression for cluster of intervention: Bias in selection of the reported result. **Table S36** Univariable meta-regression for type of intervention: Bias in selection of the reported result. **Table S37** Univariable meta-regression for cluster of outcomes: Bias in selection of the reported result. **Table S38** Overview of risk of bias ratings overall and per domains. **Figure S1** Risk of bias in single randomised controlled trials (summary plot). **Figure S2** Effect estimates and risk of bias ratings in single randomised controlled trials. **Figure S3** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / overall risk of bias. **Figure S4** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / randomisation process. **Figure S5** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / deviations from intended intervention. **Figure S6** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / missing outcome data. **Figure S7** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / measurement of the outcome. **Figure S8** Forest plot of the comparisons between bodies of evidence from randomised controlled trials with high risk of bias or some concerns versus low risk of bias as pooled ratio of risk ratios / selection of the reported result.



HIGHLIGHTS

- Risk of Bias (RoB) tools are essential for critical appraisal of randomised controlled trials (RCTs)
- The RoB2 tool is used to assess how study design bias influences effect estimates in nutrition RCTs
- Most methodological characteristics in nutrition RCTs may not exaggerate effect estimates

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Lukas Schwingshackl reports financial support was provided by German Research Foundation. Maria Petropoulou reports financial support was provided by German Research Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

SUMMARY BOX

What is already known on this topic

- Randomised controlled trials (RCTs) are considered the reference standard for evaluating intervention effects. However, nutrition RCTs often encounter methodological challenges such as difficulties with blinding, low adherence, and high dropout rates, that may increase the risk of bias.
- Several meta-epidemiological studies have investigated the impact of study design characteristics, such as inadequate sequence generation on intervention effect estimates. Findings suggest heterogeneous influence of bias across clinical fields.

What this study adds

- This study is the first to conduct standardised, de-novo assessments in a large number of nutrition trials using the Cochrane RoB 2 tool.
- We advanced previous research by examining key methodological domains that may exaggerate intervention effects, providing new insights into the validity and application of risk-of-bias assessment criteria in nutrition research.
- Our findings suggest that, on average, most methodological characteristics assessed with the RoB 2 tool do not lead to exaggerated effect estimates in nutrition RCTs. However, biases related to deviations from intended interventions warrant further investigation.