

# Risk of Bias for Nutrition Observational Studies (RoB-NObs) Tool\*

<b>Bias due to confounding</b>	
<p>1.1 Is there potential for confounding of the effect of exposure in this study?</p> <p><i>If N or PN: skip all remaining questions (1.2 to 1.8) and go to Bias due to confounding: Risk of bias judgement; the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered.</i></p> <p><i>If Y or PY, answer question 1.2 to determine whether there is a need to assess time-varying confounding.</i></p>	
<p>1.2. <u>If Y or PY to 1.1</u>: Was the analysis based on splitting follow-up time according to exposure received?</p> <p><i>If N or PN, skip 1.3 and answer questions 1.4 to 1.6, which relate to baseline confounding.</i></p> <p><i>If Y or PY, go to question 1.3.</i></p>	
<p>1.3. <u>If Y or PY to 1.2</u>: Were exposure discontinuations or switches likely to be related to factors that are prognostic for the outcome?</p> <p><i>If N or PN, answer questions 1.4 to 1.6, which relate to baseline confounding only. Do not answer 1.7 and 1.8, which relate to both baseline and time-varying confounding.</i></p> <p><i>If Y or PY, skip questions 1.4 to 1.6, and answer questions 1.7 and 1.8, which relate to both baseline confounding and time-varying confounding.</i></p>	
<p>1.4. <u>If N or PN to 1.2 or 1.3</u>: Did the authors use an appropriate analysis method that adjusted for all the critically important confounding variables at baseline?</p> <p><i>Go to 1.5</i></p>	
<p>1.5. Were confounders that were adjusted for measured validly and reliably by the variables available in this study?</p> <p><i>Go to 1.6</i></p>	
<p>1.6. Did the authors avoid adjusting for post-exposure variables?</p> <p><i>(Skip to Bias due to confounding: Risk of bias judgement)</i></p> <p><i>Questions related to baseline and time-varying confounding</i></p>	
<p>1.7. <u>If Y or PY to 1.3</u>: Did the authors use an appropriate analysis method that adjusted for all the critically important confounding variables, including baseline and time-varying confounding?</p> <p><i>If N or PN to 1.7, skip to Bias due to confounding: Risk of bias judgement.</i></p> <p><i>If Y or PY to 1.7, answer question 1.8.</i></p>	
<p>1.8. <u>If Y or PY to 1.3 and Y or PY to 1.7</u>: Were confounders that were adjusted for measured validly and reliably by the variables available in this study?</p>	
<b>Bias due to confounding: Risk of bias judgement</b>	
<p>Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)</p>	<p>No confounding expected.</p>

<p>Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)</p>	<p>(i) Confounding expected, all known important confounding domains appropriately measured and controlled for;  <i>and</i>  (ii) Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.</p>
<p>Serious risk of bias (the study has some important problems)</p>	<p>(i) At least one key confounder was not appropriately measured, or not controlled for;  <i>or</i>  (ii) Reliability or validity of measurement of a key confounder was low enough that we expect serious residual confounding.</p>
<p>Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)</p>	<p>(i) Confounding is inherently not controllable;  <i>or</i>  (ii) The use of negative controls strongly suggests unmeasured confounding.</p>
<p>No information on which to base a judgement about risk of bias for this domain</p>	<p>No information on whether confounding might be present.</p>

<b>Bias in selection of participants into the study</b>	
<p>2.1. Was selection of participants into the study <i>or</i> into the analysis based on participant characteristics observed after the start of exposure?</p> <p><i>If N or PN, go to 2.4 (skip 2.2 and 2.3).</i></p> <p><i>If Y or PY, go to 2.2 and 2.3.</i></p>	
<p>2.2. <i>If Y or PY to 2.1:</i> Were the post-exposure variables that influenced selection of participants (into the study or analysis) associated with exposure?</p> <p><i>Go to 2.3</i></p>	
<p>2.3. <i>If Y or PY to 2.1:</i> Were the post-exposure variables that influenced selection of participants (into the study or analysis) associated with the outcome?</p> <p><i>Go to 2.4</i></p>	
<p>2.4. Do start of follow-up and start of exposure coincide for most participants?</p> <p><i>If N or PN to 2.4, answer 2.5.</i></p> <p><i>If Y or PY to 2.4, go to Bias in selection of participants into the study: Risk of bias judgement.</i></p>	
<p>2.5 <i>If Y or PY to 2.2 and 2.3, or N or PN to 2.4:</i> Were adjustment techniques that were likely to correct for the presence of selection biases used?</p> <p><i>Go to Bias in selection of participants into the study: Risk of bias judgement.</i></p>	
<b>Bias in selection of participants into the study: Risk of bias judgement</b>	
<p>Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)</p>	<p>(i) All participants who would have been eligible for the target trial were included in the study; <i>and</i> (ii) For each participant, start of follow up and start of exposure coincided.</p>
<p>Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)</p>	<p>(i) Selection into the study may have been related to exposure and outcome; <i>and</i> The authors used appropriate methods to adjust for the selection bias; <i>or</i> (ii) Start of follow up and start of exposure do not coincide for all participants; <i>and</i> (a) the proportion of participants for which this was the case was too low to induce important bias; <i>or</i> (b) the authors used appropriate methods to adjust for the selection bias; <i>or</i> (c) the review authors are confident that the rate (hazard) ratio for the effect of exposure remains constant over time.</p>

<p>Serious risk of bias (the study has some important problems)</p>	<p>(i) Selection into the study was related (but not very strongly) to exposure and outcome;  <i>and</i>  This could not be adjusted for in analyses;  <i>or</i>  (ii) Start of follow up and start of exposure do not coincide;  <i>and</i>  A potentially important amount of follow-up time is missing from analyses;  <i>and</i>  The rate ratio is not constant over time.</p>
<p>Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)</p>	<p>(i) Selection into the study was very strongly related to exposure and outcome;  <i>and</i>  This could not be adjusted for in analyses;  <i>Or</i>  (ii) A substantial amount of follow-up time is likely to be missing from analyses;  <i>and</i>  The rate ratio is not constant over time.</p>
<p>No information on which to base a judgement about risk of bias for this domain</p>	<p>No information is reported about selection of participants into the study or whether start of follow up and start of exposure coincide.</p>

<b>Bias in classification of exposures</b>	
3.1. Is the exposure that was assessed clearly defined?	
3.2. Does the exposure that was assessed represent the exposure of interest?	
3.3. Were the methods used to assess the exposure clearly described?	
3.4. Were the methods used to measure the exposure valid and/or reliable?	
3.5. Were the same methods used to assess the exposure status for all participants/groups?	
3.6. Were the methods used to define exposure status for participants/groups clearly described?	
3.7. Were the methods used to define exposure status for participants/groups likely to result in minimal random or systematic exposure misclassification?	
3.8. Could classification of exposure status been affected by the presence of the outcome, knowledge of the outcome or risk of the outcome?	
<i>If Y or PY, there may be serious risk of bias.</i>	
<i>Go to Bias in classification of exposures: Risk of bias judgement.</i>	
<b>Bias in classification of exposures: Risk of bias judgement</b>	
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	(i) The exposure and the methods used to assess the exposure were well defined and represent the exposure of interest; <i>and</i> (ii) Methods were valid, reliable, the same across groups, and likely to result in <u>minimal</u> random or systematic exposure misclassification. <i>and</i> (iii) Exposure status was not affected by the presence of the outcome, knowledge of the outcome or risk of the outcome
Moderate risk of bias (the study is sound for a, observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) The exposure and the methods used to assess the exposure are defined and represent the exposure of interest; <i>and</i> (ii) Methods were valid, reliable, the same across groups, and likely to result in <u>minimal</u> random or systematic exposure misclassification. <i>or</i> Exposure status was not affected by the presence of the outcome, knowledge of the outcome or risk of the outcome
Serious risk of bias (the study has some important problems)	(i) Exposure status or the methods used to assess the exposure are <u>not</u> well defined or do not represent the exposure of interest; <i>and</i> (ii) Methods were not valid and reliable, the same across groups, or were likely to result in <u>some</u> degree of random or systematic exposure misclassification. <i>or</i> Exposure status was affected by the presence of the outcome, knowledge of the outcome or risk of the outcome
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) Exposure status and the methods used to assess the exposure are <u>not</u> well defined or do not represent the exposure of interest; <i>and</i> (ii) Methods were not valid and reliable, were not the same across groups, and were likely to result in <u>substantial</u> random or systematic exposure misclassification. <i>and</i>

	(iii) Exposure status was affected by the presence of the outcome, knowledge of the outcome or risk of the outcome
No information on which to base a judgement about risk of bias for this domain	No definition of exposure or no explanation of the source of information about exposure status is reported.

<b>Bias due to departures from intended exposures</b>	
4.1. Is there concern that changes in exposure status occurred among participants that were unbalanced across groups and likely to impact the outcome?	
4.2. Were any critical co-exposures that occurred unbalanced between exposure groups and likely to impact the outcome?	
4.3. <i>If Y or PY to 4.1, or 4.2:</i> Were adjustment techniques that are likely to correct for these issues (i.e., changes in exposure status and/or unbalanced co-exposures) used?	
<i>Go to Bias due to departures from intended exposures: Risk of bias judgement.</i>	
<b>Bias due to departures from intended exposures: Risk of bias judgement</b>	
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	There were no changes in the exposure status that were likely to impact the outcome, and any important co-exposures were balanced across intervention groups.
Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) There were changes in exposures status <i>or</i> important co-exposures were not balanced across groups <i>and</i> (ii) the impact on the outcome is expected to be slight <i>or</i> measurement and/or adjustment techniques were used to correct for the issues
Serious risk of bias (the study has some important problems)	(i) There were changes in exposure status <i>or</i> important co-exposures were not balanced across groups that were likely to impact the outcome, <i>and</i> (ii) no or inappropriate measurement and/or adjustment techniques were used to correct for the issues
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) There were substantial changes in exposures status, or important co-exposures were not balanced across groups, that were likely to impact the outcome, <i>and</i> (ii) no or inappropriate measurement and/or adjustment techniques were used to correct for the issues.
No information on which to base a judgement about risk of bias for this domain	No information is reported on whether there is deviation from the intended exposure.

<b>Bias due to missing data</b>	
5.1. Were there missing outcome data?	
5.2. Were participants excluded due to missing data on exposure status?	
5.3. Were participants excluded due to missing data on other variables (besides outcome data and exposure status) needed for the analysis?	
5.4. <i>If Y or PY to 5.1, 5.2 or 5.3:</i> Are the proportion of participants and reasons for missing data similar across exposure groups?	
5.5. <i>If Y or PY to 5.1, 5.2 or 5.3:</i> Were appropriate statistical methods used to account for missing data?	
<i>Go to Bias due to missing data: Risk of bias judgement</i>	
<b>Bias due to missing data: Risk of bias judgement</b>	
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	(i) Data were reasonably complete; <i>or</i> (ii) Proportions of and reasons for missing participants were similar across exposure groups; <i>or</i> (iii) The analysis addressed missing data and is likely to have removed any risk of bias.
Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) Proportions of and reasons for missing participants differ slightly across exposure groups; <i>and</i> (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data.
Serious risk of bias (the study has some important problems)	(i) Proportions of missing participants differ substantially across exposures; <i>or</i> Reasons for missingness differ substantially across exposures; <i>and</i> (ii) The analysis is unlikely to have removed the risk of bias arising from the missing data; <i>or</i> Missing data were addressed inappropriately in the analysis; <i>or</i> The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) (Unusual) There were critical differences between exposures in participants with missing data; <i>and</i> (ii) Missing data were not, or could not, be addressed through appropriate analysis.
No information on which to base a judgement about risk of bias for this domain	No information is reported about missing data or the potential for data to be missing.

<b>Bias in measurement of outcomes</b>	
6.1. Could the outcome measure have been influenced by knowledge of the exposure received?	
6.2. Were outcome assessors aware of the exposure received by study participants?	
6.3. Were the methods of outcome assessment the same across exposure groups?	
6.4. Were any systematic errors during measurement of the outcome related to exposure received?	
<i>Go to Bias in measurement of outcomes: Risk of bias judgement</i>	
<b>Bias in measurement of outcomes: Risk of bias judgement</b>	
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	(i) The methods of outcome assessment were comparable across exposure groups; <i>and</i> (ii) The outcome measure was unlikely to be influenced by knowledge of the exposure received by study participants (i.e. is objective) or the outcome assessors were unaware of the exposure received by study participants; <i>and</i> (iii) Any error in measuring the outcome is unrelated to exposure status.
Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) The methods of outcome assessment were comparable across exposure groups; <i>and</i> (ii) The outcome measure is only minimally influenced by knowledge of the exposure received by study participants; <i>and</i> (iii) Any error in measuring the outcome is only minimally related to exposure status.
Serious risk of bias (the study has some important problems)	(i) The methods of outcome assessment were not comparable across exposure groups; <i>or</i> (ii) The outcome measure was subjective (i.e. vulnerable to influence by knowledge of the exposure received by study participants); <i>and</i> The outcome was assessed by assessors aware of the exposure received by study participants; <i>or</i> (iii) Error in measuring the outcome was related to exposure status.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.
No information on which to base a judgement about risk of bias for this domain	No information is reported about the methods of outcome assessment.

<b>Bias in selection of reported result</b>	
7.1. Is the reported effect estimate likely to be selected on the basis of the results from multiple <i>outcome measurements</i> within the outcome domain?	
7.2. Is the reported effect estimate likely to be selected on the basis of the results from multiple <i>analyses</i> of the exposure-outcome relationship?	
7.3. Is the reported effect estimate likely to be selected on the basis of the results from different <i>subgroups</i> ?	
<i>Go to Bias in selection of reported result: Risk of bias judgement</i>	
<b>Bias in selection of reported result: Risk of bias judgement</b>	
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.
Moderate risk of bias (the study is sound for an observational study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)	(i) The outcome measurements and analyses are consistent with an <i>a priori</i> plan; or are clearly defined and both internally and externally consistent; <i>and</i> (ii) There is no indication of selection of the reported analysis from among multiple analyses; <i>and</i> (iii) There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Serious risk of bias (the study has some important problems)	(i) Outcomes are defined in different ways in the methods and results sections, or in different publications of the study; <i>or</i> (ii) There is a high risk of selective reporting from among multiple analyses; <i>or</i> (iii) The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	(i) There is evidence or strong suspicion of selective reporting of results; <i>and</i> (ii) The unreported results are likely to be substantially different from the reported results.
No information on which to base a judgement about risk of bias for this domain.	There is too little information to make a judgement (for example if only an abstract is available for the study).

\*NESR created the RoB-NObs by making modifications to the ROBINS-I and a preliminary instrument designed to assess risk of bias in non- randomized studies of exposures.<sup>1,2</sup> These modifications were made to ensure that the tool was applicable to observational studies of food, nutrition, and public health.<sup>3,4</sup>

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<sup>1</sup> Morgan, R.L., Thayer, K.A., Santesso, N., Holloway, A.C., Blain, R., Eftim, S.E., Goldstone, A.E., Ross, P., Guyatt, G., Schunemann, H.J., 2018a. Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the 'target experiment' concept in studies of exposures: rationale and preliminary instrument development. *Environ. Int.* 120, 382–387.

<sup>2</sup> Morgan RL, Thayer KA, Santesso N, Holloway AC, Blain R, Eftim SE, Goldstone AE, Ross P, Ansari M, Akl E, Filippini T, Hansell A, Meerpohl JJ, Mustafa RA, Verbeek J, Vinceti M, Whaley P, Schünemann HJ; GRADE Working Group. A risk of bias instrument for non-randomized studies of exposures: A users' guide to its application in the context of GRADE. *Environ Int.* 2019 Jan;122:168-184. doi: 10.1016/j.envint.2018.11.004. Epub 2018 Nov 22 PMID: 30473382

<sup>3</sup> Hörnell A, Berg C, Forsum E, Larsson C, Sonestedt E, Åkesson A, Lachat C, Hawwash D, Kolsteren P, Byrnes G, De Keyzer W, Van Camp J, Cade JE, Greenwood DC, Slimani N, Cevallos M, Egger M, Huybrechts I, Wirfält E. Perspective: An Extension of the STROBE Statement for Observational Studies in Nutritional Epidemiology (STROBE-nut): Explanation and Elaboration. *Adv Nutr.* 2017;8(5):652-678. PMID: [28916567](https://pubmed.ncbi.nlm.nih.gov/28916567/)

<sup>4</sup> Bero, Lisa & Chartres, Nicholas & Diong, Joanna & Fabbri, Alice & Ghersi, Davina & Lam, Juleen & Lau, Agnes & McDonald, Sally & Mintzes, Barbara & Sutton, Patrice & Turton, Jessica & Woodruff, Tracey. (2018). The risk of bias in observational studies of exposures (ROBINS-E) tool: Concerns arising from application to observational studies of exposures. *Systematic Reviews.* 7. 10.1186/s13643-018-0915-2.