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BMJ Open

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To cite: Jones L, Bellis MA, Butler N, *et al*. Interpreting evidence on the association between multiple adverse childhood experiences and mental and physical health outcomes in adulthood: protocol for a systematic review assessing causality. *BMJ Open* 2025;**15**:e091865. doi:10.1136/bmjopen-2024-091865

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-091865).

Received 31 July 2024
Accepted 07 February 2025

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ABSTRACT

Introduction Research suggests that adverse childhood experiences can have a lasting influence on children's development that result in poorer health outcomes in adulthood. Like other exposure-outcome relationships, however, there is uncertainty about the extent to which the relationship between adverse childhood experiences and health is causal or attributable to other factors. The aim of this systematic review is to better understand the nature and extent of the evidence available to infer a causal relationship between adverse childhood experiences and health outcomes in adulthood.

Methods and analysis A systematic review of evidence from cross-sectional and longitudinal studies will be conducted to examine the association between multiple adverse childhood experiences and mental and physical health outcomes in adulthood. A comprehensive search for articles will be conducted in four databases (Medline, CINAHL, PsycInfo and Web of Science) and Google Scholar. We will include studies published since 2014: (1) of adults aged 16 years or over with exposure to adverse childhood experiences before age 16 years from general population samples; (2) that report measures across multiple categories of childhood adversity, including both direct and indirect types and (3) report outcomes related to disease morbidity and mortality. Two reviewers will independently screen all titles and abstracts and full texts of potentially relevant studies. Included studies will be evaluated for risk of bias with the Risk Of Bias In Non-randomised Studies of Exposures tool. Data extraction will include extraction of study characteristics; measurement of adverse childhood experiences, outcome assessment and measurement of outcomes; details about confounding variables and contextual variables; methods of statistical analysis; and methods for assessing causal inference. We will carry out a meta-analysis and incorporate causal assessment with reference to the Bradford Hill criteria and the Grading of Recommendations Assessment, Development and Evaluation framework.

Ethics and dissemination This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. The findings from this systematic review will be disseminated via a peer-reviewed journal publication, professional networks and social media.

PROSPERO registration number CRD42024554563.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review will apply systematic and transparent methods to explore the extent to which the evidence supports the existence of a causal relationship between adverse childhood experiences and mental and physical outcomes in adulthood.
⇒ Assessing the risk of bias in observational studies is complex, and there are limitations in the currently available tools, so we will be careful to avoid applying a simple or mechanistic approach to risk of bias assessment.
⇒ The Bradford Hill viewpoints and Grading of Recommendations Assessment, Development and Evaluation framework will be used to structure and guide our descriptions of the nature and extent of the evidence available.

INTRODUCTION

Childhood experiences are fundamental in determining future health and social prospects, and preventing childhood adversity and moderating its impacts is essential for improving population health and reducing inequalities. In recent years, interest has grown in the concept of adverse childhood experiences (ACEs) which incorporates a wide range of highly stressful and potentially traumatic events that children can be exposed to while growing up.[1]

Research suggests that childhood adversities can have a lasting influence on children's development and mean that they may be more likely to have poorer health and social outcomes later in life.[2] The ACE concept recognises that adversities co-occur and may cluster or accumulate across a child's life. An

increasing number of studies have identified how exposure to multiple ACEs affects health-harming behaviours and the development of health conditions.[3] Importantly, these studies have shown that the more ACEs an individual suffers, the greater the risk of poor health outcomes in later life.[2 4]

As research on ACEs has proliferated, operationalisation of the concept has varied widely across studies with different numbers and types or categories of ACEs assessed. The original ACE study[5] focused on multiple types of childhood trauma that affected children either directly or indirectly through the environment in which they live and interact with. Recommendations have been made to expand the original list,[6] and more recent measures, such as the Adverse Childhood Experiences International Questionnaire,[7] incorporate a broader range of domains including experiences of peer and community violence and exposure to collective violence. Most ACE studies adopt a cumulative risk approach and report unweighted scores for cumulative risk with, for example, exposure to four or more individual ACEs being defined as 'high risk'. The use of scores has been criticised for simplifying the experience of ACEs, for example, by not accounting for differing levels of frequency or intensity of experiences or the differential impact of different ACEs on outcomes in later life.[8 9] Studies have therefore begun to use other methods alongside risk scores, including factor analysis and latent class analysis,[10 11] and dimensional models have also been proposed as an alternative conceptual approach.[12]

Justification for this review

Key methodological challenges are associated with estimating the causal effects of ACEs. Like other exposure–outcome relationships which are impossible to test in randomised controlled trials, such as exposures during pregnancy,[13] there is uncertainty about the extent to which the relationship between ACEs and health outcomes that occur in adulthood may be causal or attributable to other factors. The main biological pathway that has been used to link ACEs with poorer outcomes in later life proposes that children exposed to 'toxic stress' respond to these challenges through a process of adaptation.[14 15] ACEs have been associated both with physiological changes to the brain,[16] with dysregulation of the immune, endocrine and metabolic systems[17] and epigenetic changes.[18]

Understanding third-variable effects such as confounding, mediation and collider effects is critical in inferring causal relationships between exposure to ACEs and health outcomes in adulthood.[19 20] Socioeconomic position (SEP) in childhood, for example, is also a strong predictor of health in adulthood,[21 22] and there is a clear relationship between SEP in childhood and the risk of experiencing ACEs.[23] Understanding the causal pathway linking exposure to ACEs and health-related outcomes therefore requires careful consideration of the socioeconomic context.[24–26]

Although the authors are aware that evidence for a causal relationship between ACE exposure and health outcomes has been considered previously,[27 28] much of the recent work has focused on mental health outcomes only and we are not aware of any previous reviews that have applied full systematic and transparent methods to explore the extent to which the evidence infers the existence of a causal relationship between ACEs and both physical and mental health outcomes in adulthood. Furthermore, we are aware of an ongoing review that includes an explicit aim not to infer any causal relationships from the findings in their review.[29]

Aim, research question and objectives

Aim

The aim of this systematic review is to better understand the nature and extent of the evidence available to infer a causal pathway between ACEs and health outcomes in adulthood. Our approach incorporates an evaluation of the evidence available to justify causal claims with reference to the Bradford Hill viewpoints on causality,[30] a commonly used approach to causal assessment in systematic reviews[31 32] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[33 34]

Research questions

- What evidence is available about the relationship between multiple ACEs and health outcomes in adulthood?
- What is the strength and direction of the association between ACEs and health outcomes in adulthood?
- To what extent does the available evidence justify causal claims to be made about the relationship between exposure to ACEs and health outcomes in adulthood?

Objectives

Our primary objective is to assess the extent to which the evidence supports the existence of a causal relationship between ACEs and physical and mental health outcomes in adulthood. To achieve this primary objective, we will carry out a meta-analysis of new evidence published since 2014 and incorporate causal assessment with reference to the Bradford Hill criteria and GRADE framework.

METHODS AND ANALYSIS

This systematic review protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols guidelines. The systematic review protocol has been submitted to PROSPERO for registration (CRD42024554563). The systematic review started in June 2024 and has an anticipated end date of 31 March 2025.

Criteria for the consideration of studies

Types of participants

We will include studies of adult participants aged 16 years or over with exposure to ACEs drawn from general population samples. We will include studies of samples recruited both from birth or childhood and in adulthood. Studies based only on samples from socially excluded, high-risk or clinical populations will be excluded.

Types of exposures

We will include studies that report ACE measures across multiple categories of childhood adversity, including both direct (ie, child maltreatment) and indirect (ie, household dysfunction) types.[35] Inclusion will not be limited to specific ACE types, and studies that use expanded definitions of ACEs will be eligible, but measures of childhood adversity will need to be consistent with the operationalisation of the ACE concept and examine both direct and indirect exposures to adversity. Studies based on either a cumulative risk approach (including those involving the use of alternative methods such as factor analysis and latent class analysis) or dimensional models will be eligible for inclusion. We will exclude studies that report only single categories of adversities or individual ACEs. Studies of both prospective and retrospective childhood adversity measures will be eligible for inclusion.

Type of comparator

Studies of adult participants aged 16 years or over with no or singular ACE exposures.

Main outcome measures

The outcomes of interest are morbidity and mortality from disease grouped into two broad categories: (1) physical health conditions and (2) mental health conditions including substance use disorders. We will not place eligibility restrictions on the measurement of outcomes but will evaluate the validity and reliability of outcome measures on a study-by-study basis.

Types of studies

We will include all types of analytical, observational study designs, including cross-sectional, cohort and case-control studies. Risk of bias (RoB) will be assessed on a study-by-study basis rather than on a hierarchical by-design basis.

Search strategy

All relevant studies published since 1 January 2014 and up to the date on which the searches are run will be eligible for inclusion to align with the search period going forward from Hughes *et al*.[3] The search strategies will incorporate both subject headings/thesaurus terms and free-text terms as applicable to the databases searched, and the searches will be updated towards the end of the review in March 2025. Forward and backwards citation searching techniques will be used alongside the electronic searches to identify further relevant studies. Backwards citation searching will involve checking the reference lists of included studies. Forward citation will be carried out in Scopus using Felitti *et al*[5] (the original ACE study) and Hughes *et al*[3] (a highly cited systematic review) as the source studies.

Electronic searches

We will search for studies in four databases, MEDLINE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), PsycInfo and Web of Science, and Google Scholar. An example of the search strategy developed in Ovid MEDLINE is included in the online supplemental appendix.

Selection of studies

References identified through the searches will be imported into an Endnote library and deduplicated. Rayyan will be used to manage the review workflow through screening and study selection. Two reviewers will independently screen all titles and abstracts. In the first instance, a random 10% selection of articles will be screened and inter-rater agreement evaluated before proceeding to the screening of the remaining records. Full-text articles of potentially relevant studies will be independently screened by two reviewers. Any disagreements will be resolved through discussion with the wider team.

Data extraction and management

We will develop and pilot a standardised form to extract data from each study on study design, geographical location, characteristics of the study population and details on exposure to childhood adversities (definition of childhood adversity, theoretical foundation to measurement of childhood adversity, categories, scoring and clustering); operationalisation of the ACE concept; outcome assessment including measures of association (eg, OR, HRs, relative risks (RRs)) and measurement of outcomes; approach for identifying confounding variables; all confounding variables measured and adjusted for; contextual variables (ie, protective factors) that may moderate or mediate the impact of ACEs; methods of statistical analysis; and methods for assessing causal inference (if applicable). A single reviewer will extract data from the included studies, and a second reviewer will check the completed data extraction forms for accuracy against the full-text paper.

Quality and RoB assessment

There is no consensus on the best approach for assessing RoB in observational studies.[36 37] We will use the recently developed Risk Of Bias In Non-randomised Studies of Exposures (ROBINS-E) tool,[38] but we will avoid the application of a simple or mechanistic approach to RoB assessment.[32 39] The RoB assessment will be tailored to assessing the critical potential biases relevant to ACEs which include confounding, selection bias and operationalisation of the ACE concept.[20] Where feasible, we will consider the likely direction and magnitude of these potential biases and their impact on the effect estimates. Before beginning the methodological assessment, we will

prespecify relevant confounding variables for each of the categories of physical and mental health outcomes and agree on criteria for the valid measurement of ACEs. We will use the confounder matrix approach developed by Petersen *et al*[40] to support with this process.

Data synthesis and analysis

Analysis

Study findings will be reported as RRs, ORs or comparable statistics (eg, HRs or prevalence ratios) with 95% CI for dichotomous outcomes.

Assessment of heterogeneity

We will qualitatively assess potential sources of heterogeneity and assess statistical heterogeneity with the Cochran Q statistic and I^2 statistic (values greater than 50% to 75% are considered moderate to large). We will explore the suspected sources of heterogeneity between studies and, if the data allow, conduct meta-regression and subgroup analyses to explore potential moderators including sample size, participant age range, methods of ACE assessment and study design.

Meta-analysis

All meta-analyses will be conducted with a random effects model using the Hartung-Knapp-Sidik-Jonkman approach.[41 42] Meta-analysis will be performed using Comprehensive Meta-Analysis. We will also calculate the 95% prediction interval to quantify the dispersion of the effect estimates. If effect estimates are stratified within a study (eg, by sex or age groups), we will conduct a within-study fixed-effect meta-analysis to obtain a single overall estimate.

Bias analysis

We will use funnel plot methods to assess small-study effects and publication bias. We will critically assess the sensitivity of estimates to the effects of unmeasured confounders and calculate E-values, as proposed by Mathur and VanderWeele,[43] where feasible.

GRADE

Following meta-analysis, we will use GRADE to assess the certainty of the evidence for each health outcome. GRADE is based on assessment across different domains, including RoB, inconsistency, indirectness, imprecision and publication bias. Our review will include non-randomised studies, and we will use the steps provided by Morgan *et al*[44] to integrate the RoB assessment from the ROBINS-E into a GRADE evidence profile.

Causal assessment

We will collate a narrative that describes the nature and extent of the evidence available and our confidence in making justified causal claims about the nature of the relationship between ACEs and different health outcomes in adulthood. This process necessarily involves some subjectivity and consideration of different perspectives,[45] so we will use an expert consensus process (such as a Delphi survey and/or an online consensus meeting) to further test our interpretations and confidence in the evidence. We will use the Bradford Hill viewpoints as a general framework for our assessments but acknowledge that some of the viewpoints will require consideration of evidence from beyond our included observational studies.[32 46] For the *Strength* criterion, we will consider the evidence with reference to the GRADE definition of a strong association between an exposure and an outcome. Pooled effect estimates from studies which examine the effects of ACE exposure on health outcomes will be explored with consideration of the RoB assessment of confounding factors and our assessment of the sensitivity of estimates to the effects of unmeasured confounders. We will consider the *Consistency* criterion with reference to the GRADE inconsistency domain[47] and in relation to our assessments of unexplained heterogeneity across effect estimates based on subgroup analyses and meta-regressions (where feasible). We will consider the *Biological Gradient* criterion based on studies that examine the association between different cumulative risk categories of ACEs compared with a reference level of exposure (eg, 0–1 ACEs) and considering the RoB assessment of adjustments for confounding. Longitudinal evidence is required for the evaluation of the *Temporality* criterion, but many studies of ACEs are cross-sectional and based on recall of childhood adversities in adulthood. We will therefore consider this criterion based on the evidence from prospective longitudinal ACE studies but with the recognition that there are important limitations that may arise with prospective ACE studies.[48] Following Blanchard,[49] under the *Specificity* criterion, we will consider evidence that the correlation between ACEs and health outcomes in adulthood might be due to confounding by social factors, with a particular focus on SEP in childhood. In relation to plausibility and coherence, we will draw on both relevant theoretical explanatory evidence and empirical evidence that explores the mechanisms underlying the relationship between ACEs and the health outcome under study (eg, mediation analysis).

Patient and public involvement

Patients and/or the public were not involved in this study.

ETHICS AND DISSEMINATION

This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. The findings from this systematic review will be disseminated via a peer-reviewed journal publication, professional networks and social media.

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Acknowledgements The authors acknowledge the contribution of Mennatallah Abdelgawad, Research Assistant in the Faculty of Health at Liverpool John Moores University for supporting with the development of the final version of the manuscript for publication.

Contributors All authors contributed to the conception and design of the protocol that this manuscript is based on. MAB acquired the financial support for the project, and LJ and MAB conceptualised the research goals and aims. LJ wrote a first draft of the manuscript and it was critically reviewed by MAB, ZQ, NB, KH and SM. LJ revised subsequent versions of the manuscript. All authors reviewed and approved the final version of the manuscript for publication. LJ and MAB assume the overall responsibility for the scientific integrity of this work, and LJ is the guarantor.

Funding This work is supported by discretionary funding from the Violence, Health and Society (VISION) consortium funded by the UK Prevention Research Partnership (UKPRP) (grant number MR/V049879/1).

Competing interests MAB and SM are academic partners in the VISION consortium funded by the UKPRP (grant MR/V049879/1). The UKPRP is funded by the British Heart Foundation, Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Health and Social Care Research and Development Division (Welsh Government), Medical Research Council, National Institute for Health and Care Research, Natural Environment Research Council, Public Health Agency (Northern Ireland), the Health Foundation and Wellcome. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Bellis MA, Lowey H, Leckenby N, *et al*. Adverse childhood experiences: retrospective study to determine their impact on adult health behaviours and health outcomes in a UK population. *J Public Health (Oxf)* 2014;36:81–91.
2 Bellis MA, Hughes K, Leckenby N, *et al*. National household survey of adverse childhood experiences and their relationship with resilience to health-harming behaviors in England. *BMC Med* 2014;12:72.
3 Hughes K, Bellis MA, Hardcastle KA, *et al*. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* 2017;2:e356–66.
4 Anda RF, Felitti VJ, Bremner JD, *et al*. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci* 2006;256:174–86.
5 Felitti VJ, Anda RF, Nordenberg D, *et al*. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 1998;14:245–58.
6 Afifi TO. Considerations for expanding the definition of aces. In: *Adverse Childhood Experiences*. Elsevier, 2020: 35–44.
7 World Health Organization. Adverse childhood experiences international questionnaire: pilot study review and finalization meeting, 4-5 May 2011. 2011.
8 Butler N, Quigg Z, Bellis MA. Cycles of violence in England and Wales: the contribution of childhood abuse to risk of violence revictimisation in adulthood. *BMC Med* 2020;18:325.
9 Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol Bull* 2013;139:1342–96.
10 Mersky JP, Janczewski CE, Topitzes J. Rethinking the Measurement of Adversity. *Child Maltreat* 2017;22:58–68.
11 Lanier P, Maguire-Jack K, Lombardi B, *et al*. Adverse Childhood Experiences and Child Health Outcomes: Comparing Cumulative Risk and Latent Class Approaches. *Matern Child Health J* 2018;22:288–97.
12 McLaughlin KA, Sheridan MA. Beyond Cumulative Risk. *Curr Dir Psychol Sci* 2016;25:239–45.
13 Smith GD. Assessing Intrauterine Influences on Offspring Health Outcomes: Can Epidemiological Studies Yield Robust Findings? *Basic Clin Pharma Tox* 2008;102:245–56.
14 Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Med* 2017;15:135.
15 Ellis BJ, Del Giudice M. Developmental Adaptation to Stress: An Evolutionary Perspective. *Annu Rev Psychol* 2019;70:111–39.
16 Cassiers LLM, Sabbe BGC, Schmaal L, *et al*. Structural and Functional Brain Abnormalities Associated With Exposure to Different Childhood Trauma Subtypes: A Systematic Review of Neuroimaging Findings. *Front Psychiatry* 2018;9:329.
17 Nelson CA, Scott RD, Bhutta ZA, *et al*. Adversity in childhood is linked to mental and physical health throughout life. *BMJ* 2020;371:m3048.
18 Lang J, McKie J, Smith H, *et al*. Adverse childhood experiences, epigenetics and telomere length variation in childhood and beyond: a systematic review of the literature. *Eur Child Adolesc Psychiatry* 2020;29:1329–38.
19 MacKinnon DP, Lamp SJ. A Unification of Mediator, Confounder, and Collider Effects. *Prev Sci* 2021;22:1185–93.
20 Jaen J, Lovett SM, Lajous M, *et al*. Adverse childhood experiences and adult outcomes using a causal framework perspective: Challenges and opportunities. *Child Abuse Negl* 2023;143:106328.
21 Galobardes B, Lynch JW, Smith GD. Is the association between childhood socioeconomic circumstances and cause-specific mortality established? Update of a systematic review. *J Epidemiol Community Health* 2008;62:387–90.
22 Galobardes B, Lynch JW, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiol Rev* 2004;26:7–21.
23 Walsh D, McCartney G, Smith M, *et al*. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review. *J Epidemiol Community Health* 2019;73:1087–93.
24 Straatmann VS, Lai E, Law C, *et al*. How do early-life adverse childhood experiences mediate the relationship between childhood socioeconomic conditions and adolescent health outcomes in the UK? *J Epidemiol Community Health* 2020;74:969–75.
25 Suglia SF, Saelee R, Guzmán IA, *et al*. Child socioeconomic status, childhood adversity and adult socioeconomic status in a nationally representative sample of young adults. *SSM Popul Health* 2022;18:101094.
26 Houtepen LC, Heron J, Suderman MJ, *et al*. Associations of adverse childhood experiences with educational attainment and adolescent health and the role of family and socioeconomic factors: A prospective cohort study in the UK. *PLoS Med* 2020;17:e1003031.
27 Linden W, LeMoult J. Editorial Perspective: Adverse childhood events causally contribute to mental illness - we must act now and intervene early. *J Child Psychol Psychiatry* 2022;63:715–9.
28 Kelly-Irving M, Mabile L, Grosclaude P, *et al*. The embodiment of adverse childhood experiences and cancer development: potential biological mechanisms and pathways across the life course. *Int J Public Health* 2013;58:3–11.
29 Thurston C, Murray AL, Franchino-Olsen H, *et al*. Prospective longitudinal associations between adverse childhood experiences and adult mental health outcomes: a protocol for a systematic review and meta-analysis. *Syst Rev* 2023;12:181.
30 Bradford Hill A. The environment and disease: association or causation? Proceeding of the Royal Society of Medicine, Vol 58; 1965:295–300.
31 Shimonovich M, Pearce A, Thomson H, *et al*. Causal assessment in evidence synthesis: A methodological review of reviews. *Res Synth Methods* 2022;13:405–23.
32 Steenland K, Schubauer-Berigan MK, Vermeulen R, *et al*. Risk of Bias Assessments and Evidence Syntheses for Observational Epidemiologic Studies of Environmental and Occupational

Exposures: Strengths and Limitations. *Environ Health Perspect* 2020;128:95002.
33 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
34 Schunemann H, Hill S, Guyatt G, *et al*. The GRADE approach and Bradford Hill's criteria for causation. *J Epidemiol Community Health* 2011;65:392–5.
35 Dube SR, Felitti VJ, Dong M, *et al*. Childhood Abuse, Neglect, and Household Dysfunction and the Risk of Illicit Drug Use: The Adverse Childhood Experiences Study. *Pediatrics* 2003;111:564–72.
36 Bero L, Chartres N, Diong J, *et al*. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev* 2018;7:242.
37 Eick SM, Goin DE, Chartres N, *et al*. Assessing risk of bias in human environmental epidemiology studies using three tools: different conclusions from different tools. *Syst Rev* 2020;9:249.
38 ROBINS-E Development Group. Risk of bias in non-randomized studies - of exposure (ROBINS-E). Launch version. 2023. Available: https://www.riskofbias.info/welcome/robins-e-tool
39 Savitz DA, Wellenius GA, Trikalinos TA. The Problem With Mechanistic Risk of Bias Assessments in Evidence Synthesis of Observational Studies and a Practical Alternative: Assessing the Impact of Specific Sources of Potential Bias. *Am J Epidemiol* 2019;188:1581–5.
40 Petersen JM, Barrett M, Ahrens KA, *et al*. The confounder matrix: A tool to assess confounding bias in systematic reviews of observational studies of etiology. *Res Synth Methods* 2022;13:242–54.
41 IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;14:25.
42 Veroniki AA, Jackson D, Bender R, *et al*. Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. *Res Synth Methods* 2019;10:23–43.
43 Mathur MB, Smith LH, Yoshida K, *et al*. E-values for effect heterogeneity and approximations for causal interaction. *Int J Epidemiol* 2022;51:1268–75.
44 Morgan RL, Thayer KA, Santesso N, *et al*. 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;122:168–84.
45 Krieger N, Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *Int J Epidemiol* 2016;45:1787–808.
46 Bird A. The epistemological function of Hill's criteria. *Prev Med* 2011;53:242–5.
47 Guyatt G, Zhao Y, Mayer M, *et al*. GRADE guidance 36: updates to GRADE's approach to addressing inconsistency. *J Clin Epidemiol* 2023;158:70–83.
48 Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psychiatry* 2004;45:260–73.
49 Blanchard T. Specificity of association in epidemiology. *Synthese* 2022;200:482.