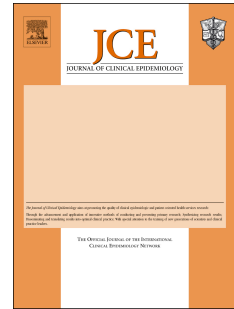


Accepted Manuscript

An overview of systematic reviews found suboptimal reporting and methodological limitations of mediation studies investigating causal mechanisms

Aidan G. Cashin, Hopin Lee, Sarah E. Lamb, Sally Hopewell, Gemma Mansell, Christopher M. Williams, Steven J. Kamper, Nicholas Henschke, James H. McAuley



PII: S0895-4356(18)31001-1

DOI: <https://doi.org/10.1016/j.jclinepi.2019.03.005>

Reference: JCE 9843

To appear in: *Journal of Clinical Epidemiology*

Received Date: 7 November 2018

Revised Date: 8 March 2019

Accepted Date: 12 March 2019

Please cite this article as: Cashin AG, Lee H, Lamb SE, Hopewell S, Mansell G, Williams CM, Kamper SJ, Henschke N, McAuley JH, An overview of systematic reviews found suboptimal reporting and methodological limitations of mediation studies investigating causal mechanisms, *Journal of Clinical Epidemiology* (2019), doi: <https://doi.org/10.1016/j.jclinepi.2019.03.005>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**An overview of systematic reviews found suboptimal reporting and methodological
limitations of mediation studies investigating causal mechanisms**

Aidan G Cashin ^{a,b}	Email: a.cashin@neura.edu.au
Hopin Lee ^{c,d*}	Email: hopin.lee@ndorms.ox.ac.uk
Sarah E Lamb ^c	Email: sarah.lamb@ndorms.ox.ac.uk
Sally Hopewell ^c	Email: sally.hopewell@csm.ox.ac.uk
Gemma Mansell ^e	Email: g.mansell1@aston.ac.uk
Christopher M Williams ^d	Email: christopher.m.williams@hnehealth.nsw.gov.au
Steven J Kamper ^f	Email: steven.kamper@sydney.edu.au
Nicholas Henschke ^f	Email: nicholas.henschke@sydney.edu.au
James H McAuley ^{a,g}	Email: j.mcauley@neura.edu.au

^aNeuroscience Research Australia, Sydney, Australia

^bPrince of Wales Clinical School, Faculty of Medicine, University of New South Wales,
Sydney, Australia

^cCentre for Statistics in Medicine & Rehabilitation Research in Oxford, Nuffield Department
of Orthopaedics Rheumatology and Musculoskeletal Sciences (NDORMS), University of
Oxford, UK

^dSchool of Medicine and Public Health, University of Newcastle, New South Wales, Australia

^eDepartment of Psychology, School of Life and Health Sciences, Aston University,
Birmingham, UK

^fSchool of Public Health, University of Sydney, Sydney, Australia

^gSchool of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney,
Australia

***Corresponding Author:**

Dr Hopin Lee

Botnar Research Centre

Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences,

University of Oxford, Windmill Road, Headington, Oxford, UK OX3 7LD

Tel: +44 018 652 26493

Email: hopin.lee@ndorms.ox.ac.uk

Abstract

Objective: To investigate whether systematic reviews of mediation studies identify limitations in reporting quality and methodological conduct.

Study Design and Setting: An overview of systematic reviews. We searched four databases (MEDLINE, PsycINFO, Cochrane Database of Systematic Reviews and PubMed) to identify systematic reviews of studies that used mediation analysis to investigate mechanisms of healthcare interventions or exposures in clinical populations between 2007 and 2017. Two reviewers independently screened titles and abstracts. Summary data on the characteristics, reporting quality and methodological conduct of the studies included in the systematic reviews were extracted independently by two reviewers. The protocol was prospectively registered on PROSPERO (CRD42017059834).

Results: 54 systematic reviews were included, representing 11 healthcare fields, 26 health conditions and 2008 mediation studies. 18/54 systematic reviews (33%) explicitly stated that the reporting of primary studies was suboptimal. Of these, 14/18 (78%) reviews noted incomplete reporting of effect sizes and precision estimates from mediation analyses. 29/54 systematic reviews (54%) identified limitations in the methodological conduct of primary studies.

Conclusion: The reporting and methodological conduct of studies investigating mechanisms in healthcare seems to be suboptimal. Guidance is needed to improve the quality, completeness and transparency of mediation studies.

Key words: Mechanism; mediation analysis; overview; quality of reporting; causal inference

Running title: Reporting and methodological quality of healthcare studies investigating mechanisms

Word count: 193 (abstract: 200max), 2673 (excluding imbedded text around figure titles and legends) (main text: 3000 max), 4 tables, 4 appendix files

ACCEPTED MANUSCRIPT

Key findings

- Mediation analysis is a popular method for studying the mechanisms by which health interventions or exposures exert their effects.
- This overview shows that over the past decade, there were 54 published systematic reviews including 2008 primary mediation studies, across 11 healthcare fields and 26 health conditions.
- Eighteen of fifty-four (33%) systematic reviews identified limitations in reporting quality and twenty-nine of fifty-four (54%) systematic reviews stated limitations in the methodological conduct of the primary mediation studies.

What this adds to what is known?

- Historically, mediation studies were common in fields such as psychology. This overview has shown that mediation studies are also conducted in health and medical fields across a range of health conditions.
- Systematic reviews of mediation studies have identified suboptimal reporting quality and methodological conduct of primary studies that study the mechanisms of health interventions and exposures.

What is the implication and what should change now?

There is a need to improve the reporting and methodological quality of studies investigating mechanisms. Improving reporting and methodological standards for mediation studies will enhance the ability to evaluate, reproduce and synthesise the findings of mediation studies. It may also minimise reporting bias in systematic reviews of mediation studies.

1. Introduction

Identifying the mechanisms that underpin the effect of healthcare interventions can help refine interventions to improve health outcomes and facilitate the translation of research findings into clinical practice and policy [1–3]. Recently, the US National Institute of Health (NIH) and UK National Institute for Health Research (NIHR) recommended embedding mechanism evaluations into clinical trial programs to explain *how* interventions work, so that they can be tailored for implementation (NIH Science of Behaviour Change Common Fund Program, and NIHR Efficacy and Mechanisms Evaluation program). The UK Medical Research Council have also endorsed the value of studying mechanisms as part of process evaluations of complex health interventions [3].

The most frequently used quantitative method for evaluating causal mechanisms is *mediation analysis* [4,5]. Mediation analysis is used to provide insight into *how* health interventions or exposures exert their effects on outcomes. Mediation analyses are commonly used in epidemiological studies and randomised controlled trials. For example, in a randomised controlled trial of adults with type-2 diabetes mellitus, Rejeski et al. (2012) used mediation analysis to understand how a complex lifestyle programme (intervention) improved mobility (outcome) through its effect on weight loss (mediator) [6]. In an observational cohort study of premature infants, Chawla et al. (2016) investigated how the effect of antenatal steroids (exposure) on neurodevelopmental impairment (outcome) was mediated by reducing rates of severe intracranial haemorrhage (mediator) [7].

There are several analytical approaches to mediation analysis [8]. The fundamental goal is to decompose the ‘total effect’ of an intervention (or exposure) on an outcome into an

'indirect effect' that is channelled through a selected mediator, and a 'direct effect' that is not channelled through the selected mediator [4]. The goal of systematic reviews of mediation studies may be to estimate pooled average indirect or direct effects across studies. This may be challenging if primary mediation studies fail to adequately report the methods and results, including indirect and direct effects and their precision estimates.

Although there is guidance on how to conduct mediation analyses [4,5,9,10], there is a lack of guidance on how researchers should report mediation studies. Thus, it is possible that the accuracy and completeness in the reporting of mediation studies is varied in the literature. Inaccurate and incomplete reporting of mediation studies can limit the usability of the evidence, stifle reproducibility, and restrict the inclusion (or exclusion) of reliable information for systematic reviews and meta-analyses [11]. Although reporting practices for mediation studies may vary across healthcare fields and impose problems for evidence use and synthesis, it is unclear if a separate reporting guideline for mediation studies is needed, or whether a reporting guideline would significantly reduce the number of poorly reported studies.

The *Guidance for Developers of Health Research Reporting Guidelines* (Moher et al., 2010) [12] states that the first step in developing a reporting guideline is to identify the need for a new reporting guideline by evaluating published research [12]. Although the evidence for this need can be obtained in several ways, it is important to consider where inadequate reporting has the greatest impact [13]. Systematic reviews often experience limitations in synthesising and interpreting primary research findings due to inadequate or varied reporting of primary studies [14]. Systematically summarising the limitations identified by Cashin et al. (2018)

systematic reviews presents as a method to assess which common problems have been identified. There is precedent for this approach; Slade et al. (2012) [15] conducted an overview of systematic reviews which identified the need for better and standardised reporting of exercise prescription in the development of the Consensus on Exercise Reporting Template [16].

We conducted an overview of systematic reviews of studies investigating mechanisms in healthcare, published from 2007 to 2017. The overarching aim of this overview was to identify the need for a reporting guideline for mediation studies in healthcare research. The specific aims of this overview were to: 1) identify whether reporting and methodological problems of primary mediation studies are encountered by systematic reviews when synthesising the evidence; and 2) summarise and describe the reporting and methodological limitations highlighted by systematic reviews.

2. Methods

This overview is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. The protocol for this review was registered on the 22nd March 2017 on the PROSPERO International Prospective Register of Systematic Reviews (CRD42017059834), accessible at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=59834. Protocol deviations are reported in Appendix A1.

2.1. Eligibility criteria

We included articles that used systematic methods to identify and review primary mediation studies that aimed to investigate the mechanisms of health interventions or exposures. We included all clinical populations and populations of individuals at-risk of developing a health condition. We included systematic reviews published in the 10 year period from March 22, 2007, to March 22, 2017 that synthesised studies on human participants of any age. We excluded non-English publications, articles for which full texts were unavailable, articles for which the primary aim was not to review mechanisms, and articles describing only the design or protocol of a systematic review.

2.2. Search strategy

We searched MEDLINE (OvidSP), PsycINFO (OvidSP), Cochrane Database of Systematic Reviews (OvidSP) and PubMed databases (March 22, 2007, to March 22, 2017). The full search strategy is available in the Appendix A2. We downloaded the search results into EndNote™ and exported them to Microsoft Office Excel. Further, we hand searched the reference lists of included studies for eligible articles. AC and HL independently screened titles and abstracts and selected articles for full text review using the inclusion/exclusion criteria, and then independently reviewed the full texts to determine eligibility. AC and HL resolved disagreements through discussion and reaching consensus.

2.3. Data extraction

Two reviewers (AC, GM or HL) independently extracted data using a data extraction form developed for the study (Appendix Table A3). Disagreements were resolved through discussion. AC, GM and HL were not blinded to the journal or review authors. We extracted information about the systematic reviews, including: the year of publication, healthcare

field, target population, aim, number of studies included, data synthesis approach, and the types of effects that were pooled in a meta-analysis (if conducted). We also extracted information reported in the systematic reviews about the synthesised primary studies, including: study design, ratio of randomised and non-randomised study designs, and types of mediation analyses conducted. Finally, we extracted information about any limitations identified by the systematic reviews that were associated with the reporting and methodological conduct of the primary studies.

2.4. Data synthesis

Categorical variables were summarised using frequencies and percentages. Continuous variables were summarised using mean and standard deviation or median and interquartile range. Information on reporting quality and methodological conduct of the primary studies that were identified by the systematic reviews were extracted verbatim and grouped into common themes according to meaning and content. Themes were summarised using frequencies and percentages.

3. Results

3.1. Study selection

A total of 2457 records were identified through the database search and hand searching of reference lists (Figure 1). Following duplicate removal and title and abstract screening, 118 systematic reviews remained for full text screening. Sixty-four systematic reviews were excluded for the following reasons: not a clinical or at-risk population (n=22), not a systematic review (n=20), primary aim was not to review mechanisms (n=21), and non-

human sample (n=1). Finally, 54 systematic reviews met the inclusion criteria and were included in the overview [18,19,28–37,20,38–47,21,48–57,22,58–67,23,68–71,24–27].

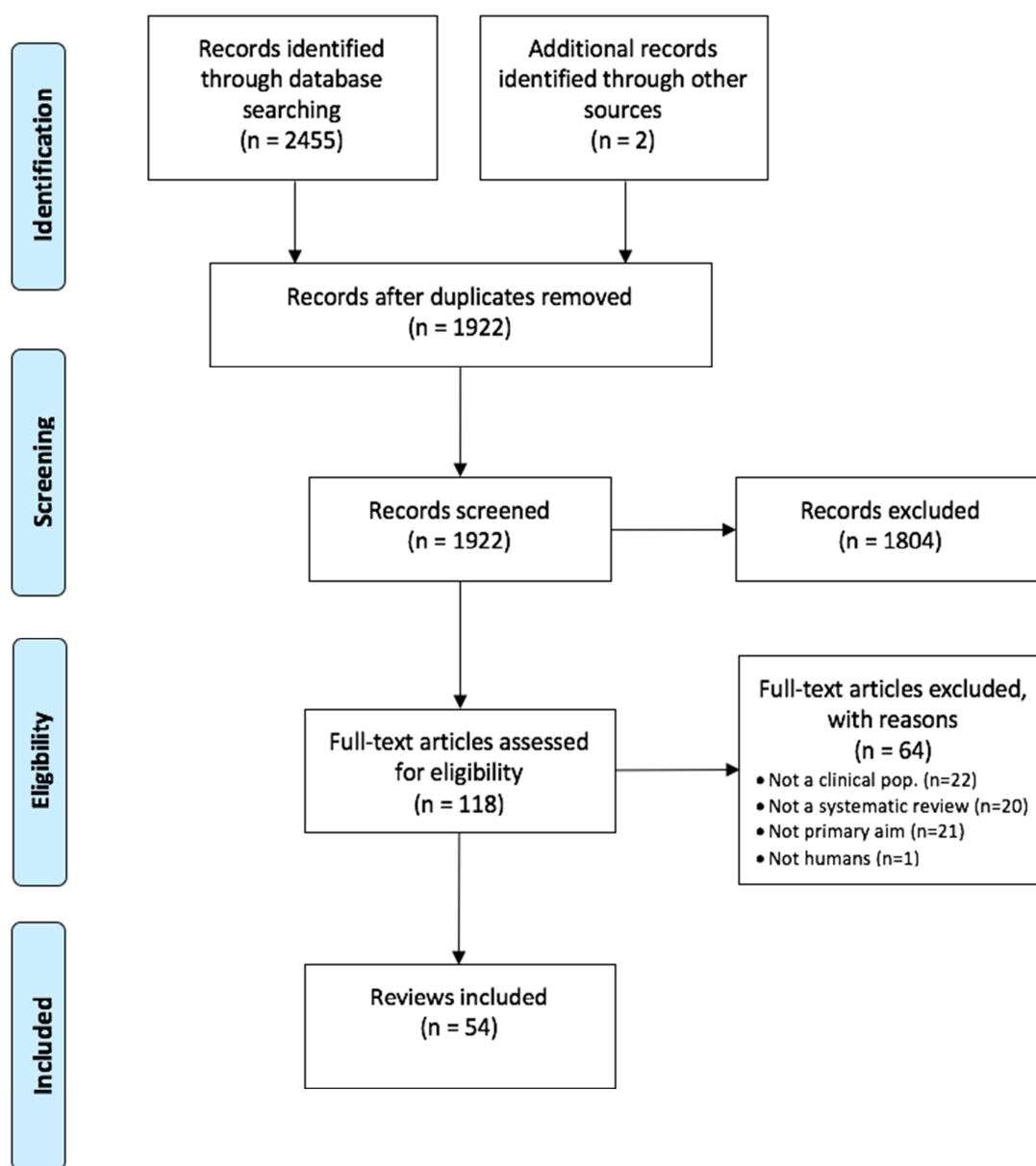


Figure 1. Prisma Flow Chart

3.2. Description of systematic reviews

Most reviews (n=33/54) were published between 2013 and 2017. The reviews were conducted across 11 healthcare fields and 26 healthcare conditions (Table 1).

Cashin et al. (2018)

Table 1. The fields and health conditions studied in the included systematic reviews

Characteristics	Number of Systematic Reviews (n=54)
Field	
Mental health	18 (32%)
General medicine	11 (20%)
Addiction	7 (13%)
Behavioural medicine	6 (11%)
Musculoskeletal	5 (9%)
Oncology	3 (5%)
Endocrinology	2 (4%)
Neurology	1 (2%)
Obstetrics	1 (2%)
Respiratory tract diseases	1 (2%)
Infectious diseases	1 (2%)
Health Condition	
Obesity	10 (12%)
Depression	9 (11%)
Substance abuse	8 (10%)
Diabetes	7 (9%)
HIV	6 (7%)
Anxiety	5 (6%)
Cancer	5 (6%)
Schizophrenia	4 (5%)
Asthma	4 (5%)
Osteoarthritis	3 (4%)
Spinal pain	3 (4%)
Multimorbidity	2 (2%)
Rheumatic disorders	2 (2%)
Stress	1 (1%)
Infertility related distress	1 (1%)
Panic disorder	1 (1%)
Alexithymia	1 (1%)
ADHD	1 (1%)
Eating disorder	1 (1%)
Metabolic syndrome	1 (1%)
Hypertension	1 (1%)
Chronic heart failure	1 (1%)
Multi-site/ widespread pain	1 (1%)
Fibromyalgia	1 (1%)
Very pre-term birth	1 (1%)
Multiple sclerosis	1 (1%)

The median number of primary mediation studies included in the systematic reviews was 27 (IQR 15-52). In total, the systematic reviews included 1213 non-randomised studies, 725 randomised studies, and 70 studies that were unclassified. The inclusion criteria for study design and the synthesis methods used by systematic reviews are presented in Table 2.

Table 2. Inclusion criteria and synthesis methods used by systematic reviews

Characteristic	Number of Systematic Reviews (n=54)
<i>Study design inclusion criteria used by systematic reviews</i>	
Only included experimental studies	22 (41%)
Only included non-experimental studies	20 (37%)
Combination*	12 (22%)
<i>Data synthesis methods used by systematic reviews</i>	
Only used narrative synthesis methods	39 (72%)
Only used quantitative synthesis methods	13 (24%)
Combination^	2 (4%)

*refers to systematic reviews that included experimental and non-experimental studies

^refers to systematic reviews that used narrative and quantitative synthesis methods

Of the 54 systematic reviews, 15 (28%) performed a meta-analysis of the primary studies. Of these studies, 3/15 (20%) pooled the indirect effect, 2/15 (13%) pooled the direct effect, 12/15 (80%) pooled the total effect, and 3/15 (20%) pooled fragments of the indirect effect (exposure-mediator effect and/or mediator-outcome effect). If data were available, reviews could have conducted an individual participant data meta-analyses (IPDMA). Only one review reported the results of an IPDMA [33].

3.3 Reporting quality

Of the 54 systematic reviews, 18 (33%) provided information about limitations encountered through the reporting quality of the primary studies. The specific reporting limitations are summarised in Table 3. None of the systematic reviews explicitly aimed to assess the reporting quality of the synthesised studies, nor did they identify a specific reporting tool or existing reporting guideline for mediation studies.

Table 3. Reporting limitations of primary mediation studies identified by systematic reviews

Characteristic	Number of Systematic Reviews
Did not report effect sizes and precision estimates from mediation analysis	14
Did not report the theoretical rationale or specific intervention component that targets the mediators	7
Did not report sample size estimation to detect mediating effects	4
Did not describe methodology and analytical techniques used for mediation analyses	4

3.4 Methodological quality

Of the 54 systematic reviews, 29 (54%) provided information on the methodological quality of the primary studies, directly related to mediation. All 29 studies highlighted at least one methodological limitation specific to mediation analysis (Table 4).

Table 4. Methodological limitations of primary mediation studies identified by systematic reviews

Characteristic	Number of Systematic Reviews
Inappropriate study design to establish causation for mediating effects (eg. cross-sectional design)	17
Inappropriate statistical method to estimate mediating effects	15
Unable to establish temporal precedence of mediator (ie. possibility for reverse causation)	12
No consideration of statistical power to detect mediating effects	9
Measurement error for the mediator	7
Lack of adjustment for confounding	4
Lack of theoretical rationale for mediator	3

3.5 Risk of bias

Of the 54 systematic reviews, 33 (61%) reviews reported the use of a risk of bias tool; of these reviews, ten used a tool they had specifically adapted for mediation studies, and twenty-three used a general risk of bias tool (eg. Cochrane Collaboration's risk of bias tool [72], the Jadad criteria [73], Newcastle-Ottawa Scale [74]).

4. DISCUSSION

Our overview included 54 systematic reviews of 2008 primary mediation studies across 11 healthcare fields and 26 different health conditions. Most systematic reviews (n=33) were

Cashin et al. (2018)

published between 2013 and 2017, which suggests a recent increase in the volume of mechanism investigations in healthcare research. Specialist fields such as oncology [48], endocrinology [22], neurology [61] and infection control [62] are also beginning to utilise mediation analyses in randomised controlled trials and observational studies.

4.1 Reporting limitations

One-third of the systematic reviews reported limitations in synthesising primary mediation studies due to inadequate reporting. Most often, these reviews identified that the primary studies reported insufficient detail about the statistical analysis and did not report key effect estimates (e.g. indirect effects) that are critical for the interpretation of mediating effects. This overview did not aim to assess an extensive list of all possible items that should be reported in mediation studies. The findings from our overview are consistent with those of methodologically focussed reviews of mediation studies. For example, Gelfand et al. (2009) found that 52% of a random sample of 50 primary mediation studies did not report all relevant effects in a mediation model [75]; Wood et al. (2008) highlighted that 62-74% studies in organisational research did not report power calculations for mediating effects [76]; Hertzog (2018) and Lapointe-Shaw et al. (2018) identified that 23% and 65% of mediation studies in nursing and healthcare research did not report assumptions required for making valid causal inferences [77,78]; and Mansell et al. (2013) observed that 86% of mediation studies in the back pain literature did not report the measurement properties for both mediator and outcome variables [79]. Recently, Liu et al. (2016) and Lapointe-Shaw et al. (2018) both concluded that the reporting of mediation studies in epidemiology and time-to-event healthcare research was varied and suboptimal, and highlighted the need for formal guidance to improve reporting standards [78,80].

Cashin et al. (2018)

Only a quarter (28%) of reviews identified sufficient information and data to pool mediation effects in a meta-analysis. There could be several reasons for this. There may have been insufficient information reported in the primary mediation studies for systematic reviewers to decide whether it was appropriate to pool effect estimates. Some reviews may have decided not to pool effect estimates because key effect estimates were not reported (or reported inconsistently) across the primary studies that were reviewed. This is supported by our data showing that mediation studies often did not report key effect sizes and their precision estimates. The low number of meta-analyses may also be explained by issues unrelated to poor reporting practices. For instance, reviews may have found insufficient numbers of primary studies that tested consistent mediators across studies. For the small number of reviews that did pool effects, there was substantial heterogeneity in the types of effects that were pooled, with some reviews pooling fragmented components of the indirect effect. This in part may have resulted from poor reporting quality in the primary mediation studies or from heterogeneity between studies, such as different mediators being explored.

Following the *Guidance for Developers of Health Research Reporting Guidelines* (Moher et al. 2010) [12], the second step in developing a reporting guideline is to search for relevant existing guidance in the area. A search of the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network database in July 2016 showed that there are no existing guidelines or guidelines under development for mediation studies [81,82]. Our findings and those of others [78,80] suggest that existing guidelines such as the CONSORT for randomised controlled trials or STROBE for observational studies do not cover the

Cashin et al. (2018)

unique aspects of study design, analysis, and results that should be reported in a mediation study [78,80]. Requirements to justify the development of a reporting guideline have not been precisely defined [83]. However, our overview has shown that inadequate reporting of primary mediation studies can stifle systematic reviews; and the accumulating evidence of inadequate reporting of mediation studies [75–80], suggests that a guideline may help improve reporting standards.

4.2 Methodological limitations of mediation studies

We found that over half of the systematic reviews provided information about limitations in the methodological conduct of studies investigating mechanisms. A quarter of the reviews suggested that primary mediation studies used inappropriate study designs to infer causality (31%) and used inappropriate statistical methods to estimate mediating effects (28%). It was unclear how the review authors defined the use of appropriate methods and statistical analysis techniques. Given that several new methods for mediation analysis have been introduced during the past decade [4], the implicit definition of appropriate or inappropriate methods is likely to vary between reviews. Therefore, we cannot be sure about the extent of methodological issues in mediation studies. However, our findings are consistent with previous work. For example, Fairchild and McQuillin (2010) [84] concluded that studies were often underpowered, and cross-sectional study designs were used to examine causal mechanisms; Wood et al. (2008) [76] found strong publication bias for significant effects; and Cerin and MacKinnon (2009) [85] noted the use of incompatible (linear) analytic methods for binary outcomes, and a lack of adjustment for exposure-mediator interaction effects. Based on these observations, it seems that a risk of bias tool could help improve the quality of mediation analyses in applied health research.

4.3 Limitations

As our overview leveraged published systematic reviews, our indirect appraisal of primary studies may have underestimated the methodological and reporting problems of mediation studies in healthcare. For example, in 61% (n=33/54) of the included systematic reviews, it was not possible to determine which mediation analysis method was used by the primary studies. This may be due to inadequate reporting of the primary study, or because systematic reviews did not extract information on analytical methods. None of the included systematic reviews explicitly aimed to review limitations in the reporting or methodological conduct of primary mediation studies. Of those that did provide secondary information on limitations encountered due to reporting and methodological quality, the majority indicated that the quality was suboptimal. It is possible that systematic review authors may have encountered difficulties in summarising the evidence due to reporting and methodological limitations but chose not to report them. This means that we may have underestimated the reporting and methodological limitations of mediation studies. Because the purpose of this study was to determine the need for a reporting guideline, we conducted an overview of systematic reviews rather than a review of primary reports. The next step is to identify potentially important reporting items through a review of methodological papers and primary research reports.

4.4 Conclusion

Our overview of systematic reviews has shown that the reporting quality and methodological conduct of mediation studies in healthcare is suboptimal. Future work should aim to implement existing methodological guidance, and to develop a reporting

guideline to improve the completeness and transparency of mediation studies in health and medical research.

ACCEPTED MANUSCRIPT

Declarations**List of abbreviations**

None

Ethics approval and consent to participate

Ethics approval not required for this overview

Consent for publication

Not applicable

Submission declaration and verification

This article has not been previously published

Availability of data and materials

The dataset used and analysed during this study is available from the corresponding author on reasonable request.

Funding

This work was supported by project funding from the Berkeley Initiative for Transparency in the Social Sciences, a program of the Center for Effective Global Action (CEGA), with support from the Laura and John Arnold Foundation. AC is funded by the University of New South Wales Prince of Wales Clinical School Postgraduate Research Scholarship and a NeuRA PhD Candidature Supplementary Scholarship. HL is funded by the Australian National Health and Cashin et al. (2018)

Medical Research Council (grant no. APP1126767); National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust. SL is funded by the National Institute of Health Research OUH, NHS Biomedical Research Centre, and Collaboration for Leadership in Health Applied Research and Care at Oxford Health, NHS Trust, and Kadoorie Charitable Foundation.

Authors' contributions

AC, HL and JM conceptualised and designed the study. SL, SH, CW, SK and NH provided guidance and overviewed the project. AC, HL screened and selected articles. AC, HL and GM extracted data. AC analysed data. AC wrote the first draft of the manuscript. HL, SL, SH, GM, CW, SK, NH and JM provided feedback on the manuscript. All authors approved the final version of the manuscript.

Acknowledgments

None

Reference List

- [1] Lewis CC, Klasnja P, Powell BJ, Lyon AR, Tuzzio L, Jones S, et al. From Classification to Causality: Advancing Understanding of Mechanisms of Change in Implementation Science. *Front Public Heal* 2018;6:136. doi:10.3389/fpubh.2018.00136.
- [2] Dunn G, Emsley R, Liu H, Landau S, Green J, White I, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. *Health Technol Assess* 2015;19:1–115, v–vi. doi:10.3310/hta19930.
- [3] Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *Br Med J* 2015;350:h1258. doi:10.1136/bmj.h1258.
- [4] Vanderweele TJ. *Explanation in Causal Inference*. Oxford: Oxford University Press; 2015.
- [5] MacKinnon DP, Fairchild AJ, Fritz MS. Mediation Analysis. *Annu Rev Psychol* 2007;58:593–614. doi:10.1146/annurev.psych.58.110405.085542.
- [6] Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, et al. Lifestyle Change and Mobility in Obese Adults with Type 2 Diabetes. *N Engl J Med* 2012;366:1209–17. doi:10.1056/NEJMoa1110294.
- [7] Chawla S, Natarajan G, Shankaran S, Pappas A, Stoll BJ, Carlo WA, et al. Association of Neurodevelopmental Outcomes and Neonatal Morbidities of Extremely Premature Infants With Differential Exposure to Antenatal Steroids. *JAMA Pediatr* 2016;170:1164. doi:10.1001/jamapediatrics.2016.1936.
- [8] Lee H, Herbert RD, McAuley JH. *Mediation Analysis*. JAMA 2019. doi:10.1001/jama.2018.21973.
- [9] Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010;15:309–34. doi:10.1037/a0020761.
- [10] Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res* 2010;19:237–70. doi:10.1177/0962280209105014.
- [11] Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. *BMC Med* 2010;8:24. doi:10.1186/1741-7015-8-24.
- [12] Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med* 2010;7:e1000217. doi:10.1371/journal.pmed.1000217.
- [13] Altman DG, Simera I, Hoey J, Moher D, Schulz K. EQUATOR: reporting guidelines for health research. *Lancet* 2008;371:1149–50. doi:10.1016/S0140-6736(08)60505-X.
- [14] Jones PM. Guidelines for Reporting Health Research: A User's Manual. *Can J Anesth Can d'anesthésie* 2015;62:1357–8. doi:10.1007/s12630-015-0439-3.
- [15] Slade SC, Keating JL. Exercise prescription: A case for standardised Reporting. *Br J Sports Med* 2012;46:1110–3. doi:10.1136/bjsports-2011-090290.
- [16] Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med* 2016;50:1428–37. doi:10.1136/bjsports-2016-096651.
- [17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535–b2535. doi:10.1136/bmj.b2535.
- [18] Albers B, Kruse J, Giani G, Icks A. Diabetes and incident depression: Is the association mediated or modified by sociodemographic factors or co-morbidities? A systematic review. *Exp Clin Endocrinol Diabetes* 2011;119:591–8. doi:10.1055/s-0031-1280800.
- [19] Barth M, Klostermann S, Cipriani A, Kriston L, Linde K, Barbui C. Efficacy of selective serotonin reuptake inhibitors and adverse events: Meta-regression and mediation analysis of placebo-

- controlled trials. *Br J Psychiatry* 2016;208:114–9. doi:10.1192/bjp.bp.114.150136.
- [20] Belvederi Murri M, Respino M, Innamorati M, Cervetti A, Calcagno P, Pompili M, et al. Is good insight associated with depression among patients with schizophrenia? Systematic review and meta-analysis. *Schizophr Res* 2015;162:234–47. doi:10.1016/J.SCHRES.2015.01.003.
- [21] Black JJ, Chung T. Mechanisms of change in adolescent substance use treatment: How does treatment work? *Subst Abus* 2014;35:344–51. doi:10.1080/08897077.2014.925029.
- [22] Breland JY, McAndrew LM, Burns E, Leventhal EA, Leventhal H. Using the Common Sense Model of Self-Regulation to Review the Effects of Self-Monitoring of Blood Glucose on Glycemic Control for Non-Insulin-Treated Adults With Type 2 Diabetes. *Diabetes Educ* 2013;39:541–59. doi:10.1177/0145721713490079.
- [23] Brown H, Hume C, Pearson N, Salmon J. A systematic review of intervention effects on potential mediators of children’s physical activity. *BMC Public Health* 2013;13:165. doi:10.1186/1471-2458-13-165.
- [24] Byrne ML, Whittle S, Allen NB. The Role of Brain Structure and Function in the Association between Inflammation and Depressive Symptoms: A Systematic Review, 2016. doi:10.1097/PSY.0000000000000311.
- [25] Chu BC, Harrison TL. Disorder-specific effects of CBT for anxious and depressed youth: A meta-analysis of candidate mediators of change. *Clin Child Fam Psychol Rev* 2007;10:352–72. doi:10.1007/s10567-007-0028-2.
- [26] Copeland L, McNamara R, Kelson M, Simpson S. Mechanisms of change within motivational interviewing in relation to health behaviors outcomes: A systematic review. *Patient Educ Couns* 2015;98:401–11. doi:10.1016/j.pec.2014.11.022.
- [27] Curtiss J, Andrews L, Davis M, Smits J, Hofmann SG. A meta-analysis of pharmacotherapy for social anxiety disorder: an examination of efficacy, moderators, and mediators. *Expert Opin Pharmacother* 2017;18:243–51. doi:10.1080/14656566.2017.1285907.
- [28] Easton P, Entwistle VA, Williams B. Health in the “hidden population” of people with low literacy. A systematic review of the literature. *BMC Public Health* 2010;10:459. doi:10.1186/1471-2458-10-459.
- [29] Esch P, Bocquet V, Pull C, Couffignal S, Lehnert T, Graas M, et al. The downward spiral of mental disorders and educational attainment: a systematic review on early school leaving. *BMC Psychiatry* 2014;14:237. doi:10.1186/s12888-014-0237-4.
- [30] Fentz HN, Arendt M, O’Toole MS, Hoffart A, Hougaard E. The mediational role of panic self-efficacy in cognitive behavioral therapy for panic disorder: A systematic review and meta-analysis. *Behav Res Ther* 2014;60:23–33. doi:10.1016/j.brat.2014.06.003.
- [31] Frederiksen Y, Farver-Vestergaard I, Skovgard NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. *BMJ Open* 2015;5:e006592–e006592. doi:10.1136/bmjopen-2014-006592.
- [32] Gu J, Strauss C, Bond R, Cavanagh K. How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clin Psychol Rev* 2015;37:1–12. doi:10.1016/j.cpr.2015.01.006.
- [33] Haasova M, Warren FC, Ussher M, Janse Van Rensburg K, Faulkner G, Cropley M, et al. The acute effects of physical activity on cigarette cravings: Exploration of potential moderators, mediators and physical activity attributes using individual participant data (IPD) meta-analyses. *Psychopharmacology (Berl)* 2014;231:1267–75. doi:10.1007/s00213-014-3450-4.
- [34] Holla JFM, Sanchez-Ramirez DC, van der Leeden M, Ket JCF, Roorda LD, Lems WF, et al. The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. *J Behav Med* 2014;37:1226–41. doi:10.1007/s10865-014-9571-8.
- [35] Huebner DM, Perry NS. Do Behavioral Scientists Really Understand HIV-Related Sexual Risk Behavior? A Systematic Review of Longitudinal and Experimental Studies Predicting Sexual

- Behavior. *Arch Sex Behav* 2015;44:1915–36. doi:10.1007/s10508-015-0482-8.
- [36] Jack H, Reese Masterson A, Khoshnood K. Violent conflict and opiate use in low and middle-income countries: A systematic review. *Int J Drug Policy* 2014;25:196–203. doi:10.1016/j.drugpo.2013.11.003.
- [37] Jones L, Bates G, McCoy E, Bellis MA. Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: A systematic review and meta-analysis. *BMC Public Health* 2015;15:400. doi:10.1186/s12889-015-1720-7.
- [38] Kobayashi LC, Wardle J, Wolf MS, Von Wagner C. Aging and Functional Health Literacy: A Systematic Review and Meta-Analysis. *Journals Gerontol - Ser B Psychol Sci Soc Sci* 2016;71:445–57. doi:10.1093/geronb/gbu161.
- [39] Kramer MR, Hogue CR. What causes racial disparities in very preterm birth? a biosocial perspective. *Epidemiol Rev* 2009;31:84–98. doi:10.1093/ajerev/mxp003.
- [40] Lee H, Hübscher M, Moseley GL, Kamper SJ, Traeger AC, Mansell G, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain* 2015;156:988–97. doi:10.1136/bjsports-2013-092930.
- [41] Leeman J, Chang YK, Voils CI, Crandell JL, Sandelowski M. A mixed-methods approach to synthesizing evidence on mediators of intervention effects. *West J Nurs Res* 2011;33:870–900. doi:10.1177/0193945911402365.
- [42] Lindson N, Aveyard P. An updated meta-analysis of nicotine preloading for smoking cessation: Investigating mediators of the effect. *Psychopharmacology (Berl)* 2011;214:579–92. doi:10.1007/s00213-010-2069-3.
- [43] Maher CA, Lewis LK, Ferrar K, Marshall S, De Bourdeaudhuij I, Vandelandotte C. Are health behavior change interventions that use online social networks effective? A systematic review. *J Med Internet Res* 2014;16:e40. doi:10.2196/jmir.2952.
- [44] Malik S, Wells A, Wittkowski A. Emotion regulation as a mediator in the relationship between attachment and depressive symptomatology: A systematic review. *J Affect Disord* 2015;172:428–44. doi:10.1016/j.jad.2014.10.007.
- [45] Mantwill S, Monestel-Umaña S, Schulz PJ. The Relationship between Health Literacy and Health Disparities: A Systematic Review. *PLoS One* 2015;10:e0145455. doi:10.1371/journal.pone.0145455.
- [46] McAndrew L, Schneider SH, Burns E, Leventhal H. Does patient blood glucose monitoring improve diabetes control?: A systematic review of the literature. *Diabetes Educ* 2007;33:991–1011. doi:10.1177/0145721707309807.
- [47] Miles CL, Pincus T, Carnes D, Homer KE, Taylor SJC, Bremner SA, et al. Can we identify how programmes aimed at promoting self-management in musculoskeletal pain work and who benefits? A systematic review of sub-group analysis within RCTs. *Eur J Pain* 2011;15:775.e1-775.e11. doi:10.1016/j.ejpain.2011.01.016.
- [48] Moyer A, Goldenberg M, Hall M a, Knapp-Oliver SK, Sohl SJ, Sarma E a, et al. Mediators of change in psychosocial interventions for cancer patients: a systematic review. *Behav Med* 2012;38:90–114. doi:10.1080/08964289.2012.695412.
- [49] Norman H, Borrill J. The relationship between self-harm and alexithymia. *Scand J Psychol* 2015;56:405–19. doi:10.1111/sjop.12217.
- [50] Palmisano GL, Innamorati M, Vanderlinden J. Life adverse experiences in relation with obesity and binge eating disorder: A systematic review. *J Behav Addict* 2016;5:11–31. doi:10.1556/2006.5.2016.018.
- [51] Postma J, Karr C, Kieckhefer G. Community health workers and environmental interventions for children with asthma: A systematic review. *J Asthma* 2009;46:564–76. doi:10.1080/02770900902912638.
- [52] Rabin BA, Glasgow RE, Kerner JF, Klump MP, Brownson RC. Dissemination and Implementation Research on Community-Based Cancer Prevention. *Am J Prev Med* 2010;38:443–56. doi:10.1016/j.amepre.2009.12.035.

- [53] Rauner A, Mess F, Woll A. The relationship between physical activity, physical fitness and overweight in adolescents: A systematic review of studies published in or after 2000. *BMC Pediatr* 2013;13:19. doi:10.1186/1471-2431-13-19.
- [54] Reeve S, Sheaves B, Freeman D. The role of sleep dysfunction in the occurrence of delusions and hallucinations: A systematic review. *Clin Psychol Rev* 2015;42:96–115. doi:10.1016/j.cpr.2015.09.001.
- [55] Riley KE, Park CL. How does yoga reduce stress? A systematic review of mechanisms of change and guide to future inquiry. *Health Psychol Rev* 2015;9:379–96. doi:10.1080/17437199.2014.981778.
- [56] Runhaar J, Luijsterburg P, Dekker J, Bierma-Zeinstra SMA. Identifying potential working mechanisms behind the positive effects of exercise therapy on pain and function in osteoarthritis; a systematic review. *Osteoarthr Cartil* 2015;23:1071–82. doi:10.1016/j.joca.2014.12.027.
- [57] Schmidt SJ, Mueller DR, Roder V. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: Empirical review and new results by structural equation modeling. *Schizophr Bull* 2011;37. doi:10.1093/schbul/sbr079.
- [58] Shahab L, McEwen A. Online support for smoking cessation: a systematic review of the literature. *Addiction* 2009;104:1792–804. doi:10.1111/j.1360-0443.2009.02710.x.
- [59] Sikorski C, Luppá M, Luck T, Riedel-Heller SG. Weight stigma “gets under the skin”-evidence for an adapted psychological mediation framework-a systematic review. *Obesity* 2015;23:266–76. doi:10.1002/oby.20952.
- [60] Smits JAJ, Julian K, Rosenfield D, Powers MB. Threat reappraisal as a mediator of symptom change in cognitive-behavioral treatment of anxiety disorders: A systematic review. *J Consult Clin Psychol* 2012;80:624–35. doi:10.1037/a0028957.
- [61] Streber R, Peters S, Pfeifer K. Systematic Review of Correlates and Determinants of Physical Activity in Persons With Multiple Sclerosis. *Arch Phys Med Rehabil* 2016;97:633–645.e29. doi:10.1016/J.APMR.2015.11.020.
- [62] Sweeney SM, Vanable PA. The Association of HIV-Related Stigma to HIV Medication Adherence: A Systematic Review and Synthesis of the Literature. *AIDS Behav* 2016;20:29–50. doi:10.1007/s10461-015-1164-1.
- [63] Teixeira PJ, Carraça E V., Marques MM, Rutter H, Oppert J-M, Bourdeaudhuij I De, et al. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. *BMC Med* 2015;13:84. doi:10.1186/s12916-015-0323-6.
- [64] van der Velden AM, Kuyken W, Wattar U, Crane C, Pallesen KJ, Dahlgard J, et al. A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder. *Clin Psychol Rev* 2015;37:26–39. doi:10.1016/j.cpr.2015.02.001.
- [65] Van Stralen MM, Yildirim M, Velde ST, Brug J, Van Mechelen W, Chinapaw MJM. What works in school-based energy balance behaviour interventions and what does not A systematic review of mediating mechanisms. *Int J Obes* 2011;35:1251–65. doi:10.1038/ijo.2011.68.
- [66] Haegen M Vander, Luminet O. Stress, Psychosocial Mediators, and Cognitive Mediators in Parents of Child Cancer Patients and Cancer Survivors: Attention and Working Memory Pathway Perspectives. *J Psychosoc Oncol* 2015;33:504–50. doi:10.1080/07347332.2015.1067279.
- [67] Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophr Res* 2009;113:189–99. doi:10.1016/j.schres.2009.03.035.
- [68] Wertli MM, Burgstaller JM, Weiser S, Steurer J, Kofmehl R, Held U. Influence of Catastrophizing on Treatment Outcome in Patients With Nonspecific Low Back Pain. *Spine (Phila Pa 1976)* 2014;39:263–73. doi:10.1097/BRS.000000000000110.
- [69] Wilson IM, Graham K, Taft A. Alcohol interventions, alcohol policy and intimate partner

- violence: a systematic review. *BMC Public Health* 2014;14:881. doi:10.1186/1471-2458-14-881.
- [70] Cerin E, Barnett A, Baranowski T. Testing Theories of Dietary Behavior Change in Youth Using the Mediating Variable Model with Intervention Programs. *J Nutr Educ Behav* 2009;41:309–18. doi:10.1016/j.jneb.2009.03.129.
- [71] Lubans DR, Foster C, Biddle SJH. A review of mediators of behavior in interventions to promote physical activity among children and adolescents. *Prev Med (Baltim)* 2008;47:463–70. doi:10.1016/j.ypmed.2008.07.011.
- [72] Higgins JP, Altman DG. Assessing Risk of Bias in Included Studies. *Cochrane Handb. Syst. Rev. Interv. Cochrane B. Ser.*, Chichester, UK: John Wiley & Sons, Ltd; 2008, p. 187–241. doi:10.1002/9780470712184.ch8.
- [73] Jadad AR, Andrew Moore R, Carroll D, Jenkinson C, John Reynolds DM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17:1–12. doi.org/10.1016/0197-2456(95)00134-4.
- [74] Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa Hosp Res Inst* 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed October 29, 2018).
- [75] Gelfand LA, Mensinger JL, Tenhave T. Mediation Analysis: A Retrospective Snapshot of Practice and More Recent Directions NIH Public Access. *J Gen Psychol* 2009;136:153–76.
- [76] Wood RE, Goodman JS, Beckmann N, Cook A. Mediation testing in management research: A review and proposals. *Organ Res Methods* 2008;11:270–95. doi:10.1177/1094428106297811.
- [77] Hertzog M. Trends in Mediation Analysis in Nursing Research: Improving Current Practice. *West J Nurs Res* 2018;40:907–30. doi:10.1177/0193945916687782.
- [78] Lapointe-Shaw L, Bouck Z, Howell NA, Lange T, Orchanian-Cheff A, Austin PC, et al. Mediation analysis with a time-to-event outcome: a review of use and reporting in healthcare research. *BMC Med Res Methodol* 2018;18:118. doi:10.1186/s12874-018-0578-7.
- [79] Mansell G, Kamper SJ, Kent P. Why and how back pain interventions work: What can we do to find out? *Best Pract Res Clin Rheumatol* 2013;27:685–97. doi:10.1016/j.berh.2013.10.001.
- [80] Liu S-H, Ulbricht CM, Chrysanthopoulou SA, Lapane KL. Implementation and reporting of causal mediation analysis in 2015: a systematic review in epidemiological studies. *BMC Res Notes* 2016;9:354. doi:10.1186/s13104-016-2163-7.
- [81] EQUATOR Network. Reporting guidelines. EQUATOR Netw 2017. <https://www.equator-network.org/reporting-guidelines/> (accessed October 22, 2018).
- [82] EQUATOR Network. Reporting guidelines under development. EQUATOR Netw 2015:1. <https://www.equator-network.org/library/reporting-guidelines-under-development/> (accessed October 22, 2018).
- [83] Moher D, Weeks L, Ocampo M, Seely D, Sampson M, Altman DG, et al. Describing reporting guidelines for health research: a systematic review. *J Clin Epidemiol* 2011;64:718–42. doi:10.1016/J.JCLINEPI.2010.09.013.
- [84] Fairchild AJ, McQuillin SD. Evaluating mediation and moderation effects in school psychology: A presentation of methods and review of current practice. *J Sch Psychol* 2010;48:53–84. doi:10.1016/j.jsp.2009.09.001.
- [85] Cerin E, MacKinnon DP. A commentary on current practice in mediating variable analyses in behavioural nutrition and physical activity. *Public Health Nutr* 2009;12:1182–8. doi:10.1017/S1368980008003649.

APPENDICES

Appendix A. Supplementary files

A1. Deviations from preregistered PROSPERO protocol (no. CRD42017059834)

Protocol section	Deviations
Objectives	No Change
Searches	No Change
Types of studies to be included	We deviated from our original protocol to increase the scope and generalisability of this review by including: <ul style="list-style-type: none"> • Reviews including participants of any age • Reviews that aimed to investigate causal mechanisms but did not identify any primary studies conducting formal mediation analysis
Condition or domain being studied	No Change
Outcomes	No Change
Data extraction	It was not possible to ascertain whether the studies reviewed mechanisms of effective or ineffective interventions
Strategy for data synthesis	No Change

A2. Search Strategy

1. *mechanism evaluation*
2. *mediat**
3. *mediation analysis*
4. *mediation analyses*
5. *causal mediation analysis*
6. *causal mediation analyses*
7. *Combine 1-6 OR*
8. *systematic adj2 (review* or overview*)*
9. *systematic review*
10. *narrative review*
11. *meta analysis*
12. *meta-analysis*
13. *Combine 8-12 OR*
14. *7 AND 13*

Table A3. Data extraction template

Characteristics of systematic reviews
Study ID
Citation
Publication date
Healthcare field
Health condition / population of interest
Aim
Data synthesis type
Data synthesis approach
Presence of meta-analysis
Details of effects pooled
Characteristics of primary studies reviewed
Study design
Number of included studies
Number of randomised studies
Number of non-randomised studies
Number of included studies that performed mediation analysis
Types of mediation analysis performed
Verbatim quotes from systematic reviews
Limitations identified from reporting of primary studies
Limitations identified from methodological conduct of primary studies
Methods used to assess reporting quality
Methods used to assess methodological quality

What is new**Key findings**

- Mediation analysis is a popular method for studying the mechanisms by which health interventions or exposures exert their effects.
- This overview shows that over the past decade, there were 54 published systematic reviews including 2008 primary mediation studies, across 11 healthcare fields and 26 health conditions.
- Eighteen of fifty-four (33%) systematic reviews identified limitations in reporting quality and twenty-nine of fifty-four (54%) systematic reviews stated limitations in the methodological conduct of the primary mediation studies.

What this adds to what is known?

- Historically, mediation studies were common in fields such as psychology. This overview has shown that mediation studies are also conducted in health and medical fields across a range of health conditions.
- Systematic reviews of mediation studies have identified suboptimal reporting quality and methodological conduct of primary studies that study the mechanisms of health interventions and exposures.

What is the implication and what should change now?

There is a need to improve the reporting and methodological quality of studies investigating mechanisms. Improving reporting and methodological standards for mediation studies will enhance the ability to evaluate, reproduce and synthesise the findings of mediation studies. It may also minimise reporting bias in systematic reviews of mediation studies.

Authors' contributions

AC, HP and JM conceptualised and designed the study. SL, SH, CW, SK and NH provided guidance and overviewed the project. AC, HP screened and selected articles. AC, HP and GM extracted data. AC analysed data. AC and HP wrote the first draft of the manuscript. SL, SH, GM, CW, SK, NH and JM provided feedback on the manuscript. All authors approved the final version of the manuscript.