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Reducing risk of bias in interventional studies during their design and conduct: a scoping review

Zhilin Ren[1], Angela Claire Webster[1], Kylie Elizabeth Hunter[1], Jiexin Zhang[2], Yi Yao[3], Ava Grace Tan-Koay[1] and Aidan Christopher Tan[1*]

Abstract

Background Interventional studies are intended to provide robust evidence. Yet poorly designed or conducted studies may bias research results and skew resulting evidence. While there have been advances in the assessment of risk of bias, it is unclear how to intervene against risks of bias during study design and conduct.

Objective To identify interventions to reduce or predict risk of bias in interventional studies during their design and conduct.

Search strategy For this scoping review, we searched three electronic bibliographic databases (MEDLINE, Embase, and Cochrane Library) and nine grey literature sources and Google from in September 2024. This was supplemented by a natural language processing fuzzy matching search of the top 2000 relevant publications in the electronic bibliographic databases. Publications were included if they described the implementation and effectiveness of an intervention during study design or conduct aimed at reducing risk of bias in interventional studies. The characteristics and effect of the interventions were recorded.

Result We identified, and reviewed the title and abstracts of, a total of 41,793 publications, reports, documents and grey literature, with 24,677 from electronic bibliographic databases and 17,140 from grey literature sources. There were 67 publications from bibliographic databases and 24 items from grey literature that were considered potentially eligible for inclusion, and the full-text of these were reviewed. Only three studies met the inclusion criteria. The first intervention was offering education and training to researchers during study design. This training included the implementation of a more rigorous participant screening process and systematic participant tracking program that reduced loss to follow-up and missing data, particularly for long-term follow-up trials. The second intervention was introducing an independent clinical events committee during study conduct. This was intended to mitigate bias due to conflicts of interest affecting the analysis and interpretation of results. The third intervention was to provide participants with financial incentives in randomized controlled trials, so that participants could more actively accomplish the requirements of the trials.

Conclusion Despite the major impact of risk of bias on study outcomes, there are few empirical interventions to address this during study design or conduct.

Keywords Interventional studies, Risk of bias, Study design, Study conduct

*Correspondence:
Aidan Christopher Tan
aidan.tan@sydney.edu.au
Full list of author information is available at the end of the article

Introduction

The number of publications in the field of medicine and health has rapidly increased over the past decade [1]. Yet many of these studies are at high risk of bias [2]. Bias refers to a systematic deviation of the observed effect from the true value and can result in overestimation or underestimation of an effect estimate [3–5]. While bias is difficult to quantify, risk of bias can be assessed, and studies with low risk of bias are more likely to produce results closer to the true value [3, 6, 7]. When included in evidence syntheses (e.g., systematic reviews and meta-analyses), such studies may compromise the reliability of results, which subsequently inform clinical guidelines and evidence-based practice. Low-quality medical research wastes resources [8–11] and funding [12]. High risk of bias studies can also be considered unethical, as participants put themselves at risk with the expectation that a study is designed and conducted appropriately and will advance science.

A review of 205 meta-analyses from the Cochrane database found that >40% of included randomized controlled trials (RCTs) were at high risk of bias [2]. Generally, this is secondary to poor design, incomplete description of methods and results, and selective reporting [13]. An analysis of 20,920 trials found that 33% had a high risk of bias in the blinding of personnel and 23% in the blinding of outcome assessors [14]. If considering the fact that reviewers frequently underestimated the risk of bias [15], and articles in journals with a low impact factor still have higher risks of bias in random sequence generation, allocation concealment, and blinding [14], the situation could be even less satisfactory. For non-randomized studies of interventions (NRSI), confounders may contribute to bias and requires more sophisticated tools for assessment [16–19].

Improving the quality of research reports could be achieved by reporting guidelines and improving researcher adherence, but reducing the risk of bias caused by flaws in research design and conduct is more challenging. Existing examples of initiatives with this intention include guideline references for researchers to rationalize study design [20], pre-registration requirements to improve study transparency [21], and open data and code that may reduce questionable research practices [22] Other examples of interventions with a more theoretical basis include training, mentoring, incentives, tools, assistance, and infrastructure. Another opportunity is through funding applications. The review, and provision of feedback, of research proposals in funding applications could be formalised to address likely risks of bias in interventional studies, if there were validated methods to predict risk of bias at study design. We would like to explore further whether there are more interventions capable of reducing the risk of bias at the study design and conduct stage.

Objective

The aim of this scoping review was to identify interventions to reduce or predict risk of bias in interventional studies during their design and conduct, and summarise the outcomes of these interventions.

Methods

Protocol and registration

This scoping review was conducted in accordance with the Joanna Briggs Institute methodology manual [23] and reported in accordance with the PRISMA-Scoping Review checklist [24]. The study protocol was prospectively registered on the Open Science Framework (https://osf.io/8vqp5).

Research questions

1. What interventions to reduce risk of bias of interventional studies during their design or conduct have been assessed, and what were the outcomes of these assessments?
2. Are there any methods to predict, during study design or conduct, the likely risk of bias in interventional studies?

Definition of terms

Interventional studies

Include randomised controlled trials, pseudo-randomized controlled trials, non-randomised controlled trials, and single-arm clinical trials.

Interventions

Action to influence the researchers' and participants' awareness, attitudes, and behavioural intentions (e.g. education, incentives, supervision, training, initiatives_.

Literature search

The Boolean logic search strategy for the bibliographic databases was designed in consultation with an information specialist from Cochrane (AT-K) and an experienced librarian from the University of Sydney. The Boolean logic search strategy was supplemented with natural language processing (NLP) fuzzy matching of the same bibliographic databases to identify any articles which might have been missed. The search strategy for the grey literature was designed in consultation with an expert in searching trial registries (KEH) [25], with separate search strategies for each source. Searches were not restricted by date, language or type of publication (e.g., abstracts were included). Publications in languages other than English and Chinese were reviewed with the aid of translation software (https://translate.google.com/).

Search strategy and information sources

Electronic databases

We searched MEDLINE, Embase, and Cochrane Library on 19th of September 2022 and again on the 29th September 2024 (see *Appendix A* for search strategies). After obtaining the results, SR-accelerator was used to automatically removed duplicate publications [26]. These publications were imported into *Rayyan* [27] and manually screened to remove any remaining duplicate records. De-duplicated publications were imported into Covidence (www.covidence.org) [28]. In order to capture publications we might have missed, we conducted a secondary screening of the three electronic bibliographic databases mentioned above by adopting a natural language processing search approach [29], details of which are documented in *Appendix C*.

Grey literature

We searched the sources in Table 1, initially from 6 December 2022 to 17 January 2023 and then again from 29 September 2024 and to 11 October 2024 (see *Appendix B* for search strategy).

During the screening process, we also identified systematic reviews and scoping reviews relevant to our study and screened their reference lists for potentially eligible publications.

Inclusion criteria

Publications were included if they implemented and assessed the effectiveness of an intervention to reduce or predict risk of bias in interventional studies during their design or conduct. We included and defined dimensions of risk of bias in accordance with the Cochrane risk-of-bias tool for randomized trials (RoB 2) [6] (e.g., flaws in the randomisation process, deviations from intended interventions, missing outcome data, flaws in outcome measurement) and the risk of bias in the non-randomized studies of interventions (ROBINS-I) tool [7] (e.g., confounding, selection of participants into the study, misclassification of interventions, deviations from intended interventions, missing data). If an intervention was ineffective at reducing or predicting risk of bias, we also included it as long as the authors attempted to assess the effect of the intervention to some degree.

Table 1 Grey literature sources searched

Grey literature	
Clinical Trial Registries	Australian New Zealand Clinical Trials Registry (ANZCTR)
	ClinicalTrials.gov
	International Clinical Trials Registry Platform (WHO)
Practice Guidelines	National Guideline Clearinghouse
	WHO Guidelines summaries
	Australian Practice Guidelines
Grey Literature Sources	Analysis & Policy Observatory (APO-Health section)
	Open Grey (ARCHIVE ONLY)
Others	MedNar
	Google

Exclusion criteria

Publications were excluded if they:

1. Were a simulation study which only demonstrated an interventions' effectiveness through virtual data.
2. Were a non-empirical study (e.g. theoretical studies of methodology).
3. Only described an improvement of research equipment, more appropriate statistical analysis methods, or financial incentives without reducing domains of risk of bias as an outcome.

The exclusion criteria were intended so as to focus on interventions that assist researchers to improve study design, reduce erroneous behaviours or decisions in the conduct of studies, and that have been have been used in practice.

Selection process

The titles and abstracts of all articles identified by the Boolean logic search and the top 2000 articles identified by the NLP fuzzy matching search were screened in duplicate by independent reviewers (ZR, YY, JZ) [27]. Conflicts were resolved by discussion between reviewers. All items, web pages, articles and other information identified from the grey literature search were screened by two reviewers (ZR, JZ). The full-text of publications which possibly met the inclusion criteria were then reviewed in duplicate by two independent reviewers (ZR, ACT) and the final included studies were confirmed by a third reviewer (ALS).

Data extraction

After all relevant articles had been identified, data extraction was undertaken by two reviewers (ZR, JZ) using a Microsoft excel spreadsheet. We documented the title, authors, year of publication, study type, name of the intervention, application stage of the intervention, target type of bias risk, and effectiveness of the intervention. Two reviewers cross-checked the extracted results. The final extraction data is saved in an Excel document and presented in the results section.

Data synthesis

The included studies were narratively synthesized due to significant heterogeneity. Interventions to reduce risk of bias were categorised by whether they were implemented during study design or conduct. The effectiveness of the included interventions was summarised.

Deviation from protocol

In the research protocol, we did not specifically declare whether intervention effectiveness was a criterion for inclusion. However, as unsuccessful interventions were still considered informative, we included these. Additionally, we extended the search of the grey literature database to obtain more studies that might meet the inclusion criteria.

Ethical statement

There was no patient or public involvement in this study, and no ethical review was required.

Results

Search

The results of our search are visualised in Fig. 1.

Boolean logic search

The search of the three electronic bibliographic databases identified 35,081 articles. After excluding duplicates, we screened the titles and abstracts of 24,677 articles. After excluding irrelevant articles, we reviewed the full-text of 67 articles. Of these, three articles met our inclusion criteria.

NLP fuzzy matching search

After reading the abstracts of 2000 records and excluding irrelevant articles, we reviewed the full-text of four articles. Of these, none met our inclusion criteria

Grey literature search

The search of the nine grey literature sources identified 17,140 publications, not including those from Google. The number of results obtained from Google searches is dynamic and difficult to record in total. Since the grey literature databases include a wide variety of types of publications or references, we were unable to report the number of duplicates as the results could not be input into Covidence or Rayyan. No publications or references met our inclusion criteria.

We recorded the reasons for exclusion after full-text review of articles identified in the Boolean logic search (see *Appendix D)*. The following Appendix D does not include 17 articles for which the abstract could not be displayed during the abstract screening process and were therefore reviewed in full-text during the initial screening, as none of these articles met our inclusion criteria.

Characteristics of included publications

We included three studies (see Table 2).

Synthesis of results

We identified three interventions during study design and conduct with evidence to reduce some risks of bias in interventional studies. The three interventions addressed two different domains of risk of bias: flaws in outcome measurement and missing data. We were unable to find any methods that predicted risk of bias during study design or conduct.

Intervention 1 (Auerbach et al., 2013): Independent clinical events committee (CEC) [30]

Industry-sponsored studies often show positive clinical outcomes, with financial gain introducing potential bias [33, 34]. An independent CEC provides an unbiased, third-party assessment during study conduct, reducing risk of bias from outcome measurement [35, 36]. In the Auerbach trial on spinal stenosis treatment, a CEC of three unaffiliated spinal surgeons re-examined adverse event reports, resulting in the reclassification of 36% of events in the control group and 38% in the trial group [30]. The researchers attributed the causative factors for the adverse reactions to surgery and medical device and analysed them separately. There was no significant difference in the association with surgery and association with device domains, or in the reclassification of the severity of adverse events between the trial and control groups. The CEC increased the severity level of adverse events at a much higher relative frequency than it decreased the severity level of adverse events, and this was the area of most apparent conflict between the CEC and researchers. When patients treated by a researcher with a sponsored interest were analysed separately from patients treated by a researcher without a sponsored interest, it was found that for adverse events reported by sponsoring stakeholders, after reclassification by CEC, the odds of upgrading the adverse event level (compared to downgrading) were 8.9 times greater, regardless of device, compared to non-sponsoring stakeholders.

Researchers with a sponsored interest tended to underestimate adverse event severity more than their counterparts, influencing study conclusions. Although this bias did not differ between the trial and control groups, it still influenced the study conclusions. After validating

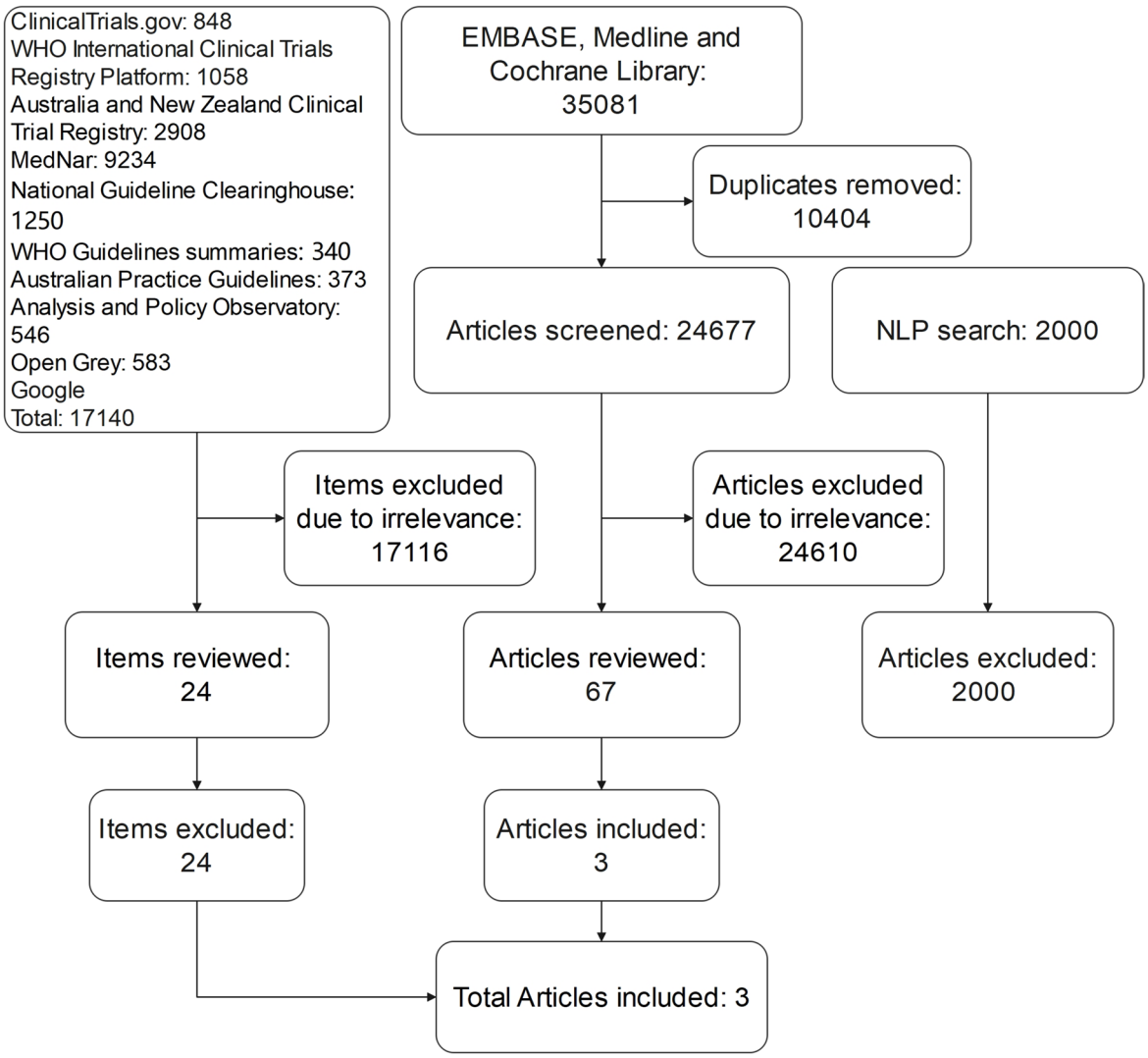

Fig. 1 Search flowchart

the reproducibility of CEC decisions and ensuring that CEC members were blinded, it was demonstrated that independent CECs can contribute to correcting outcome data.

Intervention 2 (Bhandari et al., 2008): Recruitment protocols and training [31]

The reasons for loss to follow-up in studies are diverse [37–39]. Minimizing loss to follow-up in studies is crucial, with interventions in the recruitment stage preferred over corrective measures during data analysis. The Bhandari (2008) study provides a systematic set of recruitment and follow-up interventions [40]. The recruitment approach yielded promising results in a multicentre RCT, with reduced selection bias. The core of recruitment protocols is establishing a central methods centre to manage participant individual information, monitor participant conditions, and train researchers. The recruitment process comprised three stages. Initially, participants were identified and recruited, excluding those unlikely to complete follow-up. Adequate information about the study's burden, risks, and benefits was provided. The second stage involved maintaining contact with patients, confirming their status and residence changes. Patients were encouraged to engage in trial-related activities during waiting periods. If patients withdrew voluntarily, their situation was confirmed promptly, with encouragement to continue. Researchers accommodated reasonable requests and attempted contact using collected information, systematically mobilizing the team to find patients in various ways [40]. Central to this intervention is the development of sound protocols around participants and training for research staff to help them cope with the different follow-up periods, as well as the

Table 2 Characteristics of included studies

Article	Study design	Population	Sample size	Type of risk of bias targeted	Intervention	Outcome	Implementation phase
Auerbach 2013 [30]	RCT	Spinal surgery patients	322	Flaws in outcome measurement	Clinical Events Committee (CEC)	The CEC reclassified the severity of 37% of the adverse events and the reasons for their occurrence, avoiding the influence of the personal bias of the researcher on the results of the study	Outcome measurement
Bhandari 2008 [31]	RCT	Adults with tibial shaft fracture	1319	Missing data (loss to follow-up)	A three-tiered intervention strategy to improve patient recruitment methods, reduce the loss of patients at the follow-up stage and actively counsel patients who may drop out	Only 6% of patients dropped out of the study mid-stream, significantly lower than the drop-out rate in randomized controlled trials of trauma patients	Mobilisation of research resources
High 2024 [32]	RCT	Participant in an online smoking cessation trial	204	Missing data (measure completion rates)	Provide appropriate monetary incentives to participants in randomised controlled studies.	The £20 incentive group required less manual follow-up than the £10 incentive group (OR = 0.53, $p < 0.05$). The time taken to complete the questionnaire was faster and the quality of the questionnaire responses was higher in the £20 incentive group.	Follow-up phase

need to improve the ability of different research staff to collaborate and follow a predetermined process at the first sign of a lost follow-up. At one year follow-up, the study achieved a 93% follow-up rate, significantly higher than other relevant studies in the same field [31, 40].

Intervention 3 (High et al., 2024): Financial incentive [32]

Modest financial incentives in questionnaire distribution or respondent recruitment could increase response rates and sample sizes [41]. For intervention studies requiring long-term follow-up, financial incentives have other positive effects. High et al. nested a parallel randomized controlled study within a host trial of the Quit Sense mobile app to assist with smoking cessation [42] and verify whether offering participants £20 and £10 monetary incentives impacted six-month follow-up data collection. The results showed that there was no significant difference in the rate of loss to follow-up between the two groups, but only 46% of participants in the £20 incentive group required manual intervention to prompt questionnaire completion and saliva sample submission during the automated data collection process, a significant difference compared to 62% in the £10 incentive group (OR = 0.53, $p = 0.032$) [32]. Meanwhile, the £20 incentive group had higher data completeness in completing the questionnaire items, with a median questionnaire completion time of only 7 days, lower than the £10 incentive group's 14.9 days [32]. This study within a trial (SWAT) shows that financial incentives contribute to better compliance among participants in interventional studies, reducing the time and effort needed to reduce missing data and indirectly improving data quality and statistical power.

Discussion

In this scoping review, we identified three interventions during study design or conduct to reduce risk of bias in interventional studies. These interventions address flaws in outcome measurement and missing outcome data in RCTs.

In the Auerbach (2013) [30] trial, the independent CEC demonstrated a significant impact on outcome measures and reduced the influence of financial interests on outcome assessment. The necessary role of independent outcome adjudicators/committees is supported by other studies [35, 43, 44].To guarantee the operational integrity of this intervention requires rigorous trial design, safeguarding the independence of the CEC, assessing the level of expertise of CEC members and concealing treatment assignment to CEC members [45]. This may be limited by resource constraints of smaller study teams [45]. The recruitment protocol in the Bhandari (2008) trial achieved significantly higher follow-up rates than similar studies and is a useful strategy for addressing the problem of low follow-up rates. However, this recruitment protocol may contribute to selection bias, by excluding those with personal characteristics associated with loss to follow-up, such as homeless people, and those with mental disorders. Excluding such vulnerable populations may also reduce external validity. Balancing the internal validity of excluding specific populations to safeguard the trial with the external validity of generalizable trial results to obtain the optimal recruitment strategy requires a site-specific design approach by the researcher [46]. High (2024) trial shows that providing direct monetary incentives can reduce bias caused by missing data to some extent during the follow-up of interventional studies. This intervention can also be extended to surveys after the completion of clinical trials [47]. Still, it is necessary to consider the new selection bias caused by the fact that participants with poor economic conditions are more sensitive to monetary incentives [48], as well as the financial burden of the study due to unreasonable incentive amounts.

Regarding interventions to predict risk of bias, we did not find any relevant cases. The reason for adding this question to our scoping review is that all current bias assessment tools are designed for retrospective management after the study has been reported. Various types of handbooks actually describe in detail the sources of bias and errors in study design that can introduce high risk of bias [49, 50], and we wondered if it would be possible to adapt bias assessment tool so that it could be applied prospectively before the study is conducted to reduce the risk of bias. If there were researchers who could predict the risk of bias at the completion stage by understanding the characteristics of the study at the design stage and referring to any bias assessment tools, and improving the quality of their own study, we could incorporate these findings into help predict the risk of bias in the study proposal. We also found evidence of the feasibility of using AI for risk of bias assessment [51, 52], and machine learning can be used to assist in statistical analysis [53]. We would like to explore whether this technology can be used to assist in warning of bias in research at the study design or conduct stage. But this review failed to identify any relevant literature, even observational correlational studies or cross-sectional surveys.

Beyond our inclusion criteria, several methods and initiatives that may reduce the risk of bias are worthy of discussion and replication. The proportion of prospective

registrations has increased over time, with significantly higher rates for studies published in high-impact speciality medical journals compared to lower-impact speciality medical journals and studies with prospective registrations have a lower risk of bias in all domains [54]. However, there remain issues, including retrospective registration after study completion (sometimes secondary to a lack of awareness of prospective registration [55]), modification of registration partway through the study conduct, and failure to adequately pre-specify outcomes [54, 56]. In contrast, registered reports allows for prior peer review of research design and methods, which may be more helpful in improving the quality of research design and reducing the risk of bias [57]. In the randomization process, the researchers used new scratch cards [58] and improved pharmaceutical allocation boxes [59] to ensure that the trial groups would not be unblinded due to artificial factors, and this has achieved satisfactory results in practice. Efforts to enhance study reporting include CONSORT, PRISMA, and STROBE guidelines [60, 61], aimed at improving reporting quality, though adherence remains suboptimal [62, 63]. COBWEB, a novel online writing aid aligned with CONSORT, could alleviate this situation [64].

Other proposed interventions to reduce the risk of bias are summarised in Table 3.

Despite an exhaustive search across multiple databases and sources using both traditional and artificial intelligence strategies and consulting various information specialists, because of the broad topic area there is a possibility that some intervention types may have been missed, especially those which used atypical terminology.

Table 3 Proposed interventions during study design and conduct to reduce risk of bias

Proposed interventions	Examples of implementation
Guidelines	Organisations such as the EQUATOR Network provide tutorials and resources on various reporting guidelines and are dedicated to raising awareness of the guidelines amongst researchers [65–67]
Training/education	Develop researcher's ability to design a study, write a protocol and conduct a study through training courses, workshops, seminars and other educational initiatives [68]
Initiatives	Open Science Initiative works to increase the transparency and sharing of clinical research data [69]; which may reduce questionable research practices [70]
Regulation/mandatory rules	Enforcement of requirements for prospective registration of studies [71]

We also realised that atypical studies that examine whether an intervention could reduce the risk of bias through an interventional study may be difficult to publish or fund. Researchers are more likely to validate the interventions we want to identify in the form of the Study Within a Trial (SWAT) [72], and our search strategy was not specifically designed for this situation. The above reasons may contribute to the extremely low hit rate we end up with.

Conclusion

After reviewing over 41,817 publications, reports, items, and grey literature, we found only three interventions during study conduct stage to reduce risk of bias in interventional studies. Existing research tends to focus more on statistical methods, reporting quality, and bias assessment. There is a lack of interventions that could be implemented at the more preliminary stage of study design to predict or reduce the risk of bias.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12874-025-02467-8.

Supplementary Material 1.

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Authors' contributions
Zhilin Ren. Conceptualization; Methodology; Investigation; Formal Analysis; Writing – Original Draft; Writing – Review & Editing. Zhilin Ren contributed to the study protocol, search strategy, review of search results, manuscript writing (all tables and figures), and revision of the manuscript. Angela Claire Webster. Conceptualization; Methodology; Writing – Review & Editing; Supervision. Angela Claire Webster was one of the supervisors of this study, made outstanding contributions to the study design, and was primarily responsible for the manuscript review. Kylie Elizabeth Hunter. Methodology; Investigation; Writing – Review & Editing. Kylie Elizabeth Hunter contributed to the search strategy and retrieval of publications for this study and was responsible for the manuscript review. Jiexin Zhang. Investigation; Writing – Review & Editing. Yi Yao. Investigation; Writing – Review & Editing. Ava Grace Tan-Koay. Methodology; Investigation; Writing – Review & Editing. Ava was the information consultant for this study, made a prominent contribution to the design of the search strategy and the study protocol, and was responsible for the revision and review of the manuscript. Aidan Christopher Tan. Conceptualization; Methodology; Investigation; Writing – Review & Editing; Supervision. Aidan Christopher Tan drafted the initial study protocol, designed the study methodology and search strategy, participated in the publications review, and was the primary supervisor of this study.

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

Author details
[1]NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, Sydney, NSW 1450, Australia. [2]Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia. [3]School of International Relations and Public Affairs, Fudan University, Shanghai, China.

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