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Evidence for Stratified Conflicts of Interest Policies in Research Contexts: A Scoping Review

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Abstract

Objectives: The purpose of this study was to conduct a scoping review the evidentiary foundation for stratified conflicts of interest (COI) policies in research contexts.

Design: Scoping review.

Search Strategy: We searched OVID for studies published between 1986 and 2021 conducting quantitative assessments of relationships between industry funding or COI and four target outcomes. Outcomes of interest included: positive study results, evidence of methodological biases, study reporting quality, and results-conclusions concordance. To assess if the available data could support stratified COI policies in research contexts, we analyzed the independent variable and dependent variable types in each article as well as details on variable definitions, assessments, and target outcomes.

Results: Of the 167 articles included in this study, a substantial majority (98.2%) evaluated the effects of industry sponsorship. None of the collected articles evaluated any associations between funding magnitude and outcomes of interest. Seven studies (4.3%) stratified industry funding based on mechanism of disbursement or funder relationship to product. Thirty-four articles (19.8%) assessed the effects of author COI on target outcomes. None evaluated COI magnitude, and three studies (9.1%) stratified COI by disbursement type and/or reporting practices. Ten of the studies (6.0%) evaluated identifiable COI strata. Participation of an industry-employed author showed the most consistent effect on favorability of results across studies.

Conclusions: Most COI policies stratify guidelines, distinguishing between COIs based on the nature or magnitude of financial relationships, but these policies may not be well grounded in evidence. Although the overall data on the association of industry funding and author COI suggests that such policies are an important part of protecting the integrity of the biomedical research enterprise, significant evidence gaps persist with respect to support for current approaches to differentiation types and magnitudes of industry funding and COI types in research contexts.

Background

Substantial evidence indicates that industry funding and conflicts of interest (COI) can bias research results.[1–7] Associations between industry funding or COI and positive outcomes, such as results favorable to the sponsor, are the most well studied.[2–5,7] Available evidence indicates that industry-funded trials can be up to 5.4 times more likely to return positive results,[8] and trials with author COI may be as much as 8.4 times more likely to return favorable results.[6] Additional research has demonstrated that industry funding and COI may be associated with reduced drug and device safety[6,9] and can have adverse effects on the methodological quality of clinical trials.[10–12] Recent research also suggests that industry sponsorship may be associated with premature trial termination and non-reporting of trial results.[13,14] Calls for more evidence documenting that industry funding and COI have measurable effects on biomedical research persist even though overarching relationship has been repeatedly replicated.[15]

Recognizing the risks in the well-documented relationships among funding, COI, and research outcomes, many organizations involved in biomedical research have adopted specific policies designed to address these risks. But although their existence is well-established, the efficacy of particular policies is less clear. Biomedical researchers, professional medical organizations, research funders, and government agencies have promulgated best practices for COI policies at academic medical centers (AMCs). Research evaluating these policies uses the American Medical Student Association (AMSA) scorecard of COI policies, which integrates recommendations from several professional medical organizations.[16,17] An updated AMSA scorecard has since been used to evaluate COI policies at AMCs in the United States,[17] France,[18] and Germany. [19] Similar guidelines are available from the Association of Academic Medical Centers (AAMC), the British Medical Association (BMA), professional

organizations, and researchers working in various national contexts. These policies depend on stratifying by types of COI, acknowledging that not all COI present the same degree of risk.

Competing guidelines for stratified COI policy are not uniform but share many common features. In general, guidelines suggest that some types of COI should be prohibited outright, others should be subjected to specific restrictions, and some should merely require disclosure. The recommendations typically advise a total prohibition on gifts from industry and ghostwriting, specific restrictions on industry-sponsored travel, and disclosure requirements for industry-funded research. Table 1 describes recommendations by the AMSA,[17] AAMC,[20] BMA,[21] and Brennen et al.[22]. Each also include recommendations for disclosure of COI beyond the specific types mentioned. The guidelines imply that all COI types should be subject to disclosure requirements.

Policies routinely make distinctions based on the method of remuneration (employment, consultancy, honoraria, fees), the nature of the funder (industry, nonprofit, government), the holder of the relationship (self, partner, family, collaborator), and the magnitude of the disbursement. They do not always agree on the severity of different COI. They may distinguish between acceptable and prohibited COI based on the monetary value of the relationship in question. Since 1995, the US Department of Health and Human Services has required AMCs and other entities that receive federal research funding to adopt policies that require disclosure of COI over a certain threshold.[23] This value was lowered from $10,000 to $5,000 in 2011.[24] Policies also stratify COI rules by type and amount. For example, the BMA sets the declaration threshold for gifts at £500 and for equity holdings at greater than 1% of the value of the company or greater than £25,000.[21] The substantial investments in establishing differential policies involve stratifying the risk to the research enterprise based on COI type and magnitude. The goal

of this scoping review is to evaluate the extent to which available research supports these stratifications.

COI	AMSA	AAMC	BMA	Brennen et al.
Attendance at unaccredited industry-sponsored events	Prohibit			Prohibit
Consulting	Restrict			
Donations			Disclose	
Ghostwriting	Prohibit	Prohibit		Prohibit
Gifts	Prohibit	Prohibit	Prohibit	Prohibit
Grants			Disclose	
Industry access- device representatives	Restrict	Restrict		Restrict
Industry access- pharmaceutical representatives	Prohibit	Restrict	Restrict	Prohibit
Industry sponsored CME	Restrict	Restrict		Restrict
Industry sponsored scholarships		Restrict		
Meals	Prohibit			Prohibit
Pharmaceutical samples		Restrict		
Research contracts			Disclose	
Speakers bureaus	Prohibit			Prohibit
Travel funds		Restrict		
Travel for industry sponsored meetings		Prohibit		
Travel funds for trainees	Prohibit		Prohibit	Prohibit
Treatment inducements	Prohibit			

Table 1: Illustrative Recommendations for Strata-Specific COI Policies. This table shows AMSA,[17] AAMC,[20] BMA,[21] and Brennen et al.'s[22] recommendations for whether AMC COI policies should prohibit, restrict, or require disclosure of specific COI strata. Where entries are blank, the guidance provided no specific recommendations for that type of relationship.

Methods

We conducted a scoping review[25] in three phases: First, we conducted a systematic search for articles that fit inclusion criteria modeled on a previous study of the effects of industry

funding and author COI on biomedical research.[2] Second, we added the more recent studies the screening strategy identified through 2021, and we collected additional data beyond the scope of the previous research on the methodological design of all included studies. Finally, we synthesized the evidence for evaluating different types of industry funding or author COI on target outcomes in biomedical research.

Search strategy and study selection

The previous systematic review evaluated the overall strength of the evidence base regarding the association of industry funding and author COI with results favorable to the sponsor, risks of bias associated with the methodological design, and the quality of reporting of the concordance between results and conclusions.[2] The review assessed 75 studies published between 1986 and 2016. The search strategy was designed to identify relevant articles indexed in the Ovid database. We retrieved each of the original 75 studies, and in June 2021, we replicated that search strategy to collect additional relevant articles published since 2016. Whereas the previous review focused on evaluating overall strength of the evidence, we conducted novel analyses focused at greater level of granularity on the specific operationalization of variables.

Eligible studies provided a quantitative assessment of the extent to which industry funding or author COI were associated with target outcomes of interest (positive results, methodological biases, reporting quality, and results-conclusions concordance) within research on drug and device products. All collected studies evaluated one of these outcomes on a dataset of clinical trials. Clinical trials data may come from published articles, clinical trials registries, or both. Studies of the effects of industry funding and/or COI in research areas related to smoking, nutrition, physical therapy, psychotherapy, biologics, and surgery were excluded except in cases where analyses were performed on separate identifiable drug or device data. Additionally,

studies that evaluated the effects of industry funding or COI on clinical practices, guidelines development, patient organizations, and regulatory policy were excluded.

Three evaluators screened titles and abstracts. After initial norming, a random sample of 255 titles and abstracts were selected by all three raters to assess reliability across screeners. A sample size of 255 was chosen to achieve 90% assurance using the intraclass correlation coefficient (ICC).[26] Overall agreement between the three raters was 94.9% with an ICC = 0.801. A secondary analysis of the random sample indicated that the abstracts for all articles selected for further screening included at least one of the following terms: "funding," "funded," "COI," "fCOI," "conflict," or "sponsor," which allowed us to develop an automated screening tool based on those terms. Articles selected for full-text review passed both automated and manual screening. The full article text of the remaining articles was evaluated by three raters.

Data Extraction and Synthesis

In an assessment of all articles selected for analysis, the investigators collected data on independent variable (IV) and dependent variable (DV) types as well as details on variable definitions, assessments, and target outcomes. Each funding and author COI IV was categorized as "stratified," "unstratified," or "magnitude." Here, "stratified," refers to identifiable subcategories such as "sponsor" or "competitor" for industry funding or "employment," "consulting," and "travel fees" for COI. An IV would be classified as "magnitude" if it assessed IVs as continuous variables, e.g. industry funding dollar amounts or number of COI per article. Investigators also noted whether author COI was used as a proxy for industry funding and if IVs had been dichotomized during data analysis. Each DV was also categorized according to the primary domain of interest: outcome favorability, drug or device safety; quality of study design or reporting; and if results were reported at all. Finally, for all articles with stratified IVs for

industry funding or author COI, we identified clinical area of interest, sample size used, each assessed stratum, outcome against which the stratum was assessed, significance of the results, and any reported effect sizes for significant results. A complete description of the criteria is available in Supplemental Table 1. Our analysis focuses on the prevalence of IV subtypes and the significance or effect sizes of identifiable strata.

Patients and public involvement

No patients or public were involved in the study.

Results

Our replication of the preexisting search strategy retrieved 3,884 unique records for articles published in 2016 and later. Automated screening removed 2,671 articles from consideration. Subsequent manual screening of titles and abstracts excluded another 926 articles. The remaining 287 articles were selected for full text review, and 92 studies were ultimately selected for inclusion. An additional 75 articles were included from the preexisting systematic review for a dataset of 167 articles (See Figure 1.)

Industry Funding and COI IV Types

Of the 167 articles included, a substantial majority (n = 164, 98.2%) evaluated the effects of industry sponsorship, and a smaller subset (n = 33, 19.8%) assessed COI (See Supplemental Table 2). Among the articles that assessed industry funding (n = 164), none evaluated associations between funding magnitude stratifications and outcomes of interest. Only seven (4.3%) stratified industry funding for analysis at all. Ten studies (6.1%) collected categorical data on industry funding but dichotomized the IV prior to analysis. Thirty-five studies (21.3%) assessed industry funding and used author employment or author COI as part of the inclusion

criteria for industry funding. Of the articles that evaluated author COI (n = 33), none evaluated COI magnitude, and only 3 studies (9.1%) stratified COI. Four studies (12.1%) collected stratified COI data but dichotomized it prior to analysis. Attention to unstratified IVs remained constant: Within each year, never more than one study assessed a stratified IV for industry funding or COI. Isolated assessments of author COI do not show up in the data until 2005 (Figure 2).

Outcomes Evaluation

Most studies (n = 108, 64.7%) evaluated the relationship between industry funding or COI and the favorability of outcomes. Sixty-six (39.5%) evaluated methodological or reporting quality. Nineteen (11.4%) assessed reporting of results, and 15 (9.0%) evaluated drug or device safety. Attention to specific DVs appears to have changed over time. The favorability of study outcomes had long been the dominant focus of research on industry funding and COI. Quality, safety and reporting, grew increasingly prevalent (Figure 2). This finding suggests that evolving research in this area is dominated by attention to different outcomes and demonstration of similar effects across subspecialties, but not to increasing precision about which types or magnitudes of funding relationships associate with risks to biomedical research.

Industry Funding and COI Stratification

Most of the studies examined did not assess different types of industry funding or COI. Within the 10 articles that differentiated among relationship types, evaluated strata were mostly associated with industry funding categories such as the nature of the sponsor (manufacturer vs. competitor) or the nature of the sponsorship (full study sponsorship, collaborative sponsorship, and provision of medications). Several of the studies included industry funding and author COI as different categories of a single IV. The few studies that assessed COI strata independently

tended to evaluate disclosure practices as opposed to COI types.[27–29] However, one article assessed the differential effects of author employment vs. other author COI, but only for first and corresponding authors.[30] On the whole, few of the category-specific assessments returned significant results (See Table 2). Three of the 10 studies included assessed differences in favorable outcomes based on funder relationship to the product evaluated (e.g., manufacturer vs. competitor company).[30–32] Only one study found significant results.[31] The review of 542 psychiatry studies found that a greater percentage of studies sponsored by the drug manufacturer have positive outcomes than those not sponsored by a pharmaceutical company (78% vs 48%), and that studies sponsored by a competitor had the lowest rate of favorable findings (28%). Pairwise comparisons between manufacturer-funded or competitor-funded and non-industry-funded studies were significantly different, but the study reports no effects measures. Three studies evaluated strata related to the mode of industry involvement.[33–35] These studies assessed the relationship between favorable outcomes and industry provision of medication, report of findings in an industry publication venue, and other (unspecified) industry involvement. One study found significant results, and reported that "other" industry involvement associates with favorable outcomes.[35]

Relationships between COI or funding disclosure practices and outcomes of interest were assessed in three studies.[27–29] These articles report on evaluations of the relationship between favorable outcomes or methodological quality and COI disclosure, lack of funding disclosure, incomplete disclosure, lack of disclosure requirements by journal, or affirmative statements of no author COI. Disclosure of COI and "full" disclosure of COI appear to be most strongly associated with results favorable to industry.[28,29] Here "full" disclosure means that all payments reported to the Open Payments Database were reflected in disclosure statements.

Assessments of these different disclosure practices returned non-significant results or noticeably smaller effect sizes. Two studies evaluated the relationship between participation of industry-employed authors and results favorable to industry.[33,34] An evaluation of 215 psychiatric studies published between 1998 and 2003 found that participation of industry authors was significantly associated with favorable outcomes.[33] Similarly, an assessment of 91 asthma product studies found that favorable outcomes were more likely for studies with industry-employed authors.[34] (See Table 2.)

Article	Area	Samp.	DV Type	Strata	Sig.	Effect Measure	Effect
Ahmer 2005	psychiatry	306	Outcome Favorability	Industry Provided Medications	0.053	-	-
				Author is Industry Employee	0.01*	OR	8.33 (1.64-50.0)
Bartels 2012	spine research	51	Outcome Favorability	Disclosed COI	<0.05*	OR	16.5 (4.7–58.1)
				Statement of No COI	-	-	-
				Disclosure Not Required by Journal	-	-	-
Bond 2012	asthma	91	Outcome Favorability	Industry Sponsorship	0.546	-	-
				Industry Publication Venue	0.191		-
				Other Industry Involvement	NR	-	-
				Author is Industry Employee	0.003*	RR	1.42 (1.10-1.82)
Jinapriya 2011	latanoprost	44	Outcome Favorability	Sponsorship by Parent Company	0.53	-	-
				Sponsorship by Competing Company	0.53	-	-
Kelly 2006	psychiatry	542	Outcome Favorability	Sponsorship by Manufacturer	0.001*	-	-
				Sponsorship by Competing Company	0.001*	-	-
Rattinger 2009	Thiazolidinediones	61	Outcome Favorability	Sponsorship by Manufacturer	0.7778	-	-
				Sponsorship by Competing Company	0.037*	OR	0(0,0.886)
				No Funding Disclosure	0.4153	-	-
				Corresponding Author COI	0.3939	-	-
				Corresponding Author is Sponsor Employee	0.5714	-	-
				Corresponding Author No Disclosure	0.4388	-	-

				Corresponding Author COI with sponsor	0.049*	OR	4.125(1.048;19.525
				First Author COI	0.1667	-	-
				First Author is Sponsor Employee	-	-	-
				First Author No Disclosure	-	-	-
				First Author COI with sponsor	0.4588	-	-
Vlad 2007	osteoarthritis	15	Outcome Favorability	Industry Sponsorship	0.05	-	-
				Other Industry Involvement	0.02*	random effects	0.55 (0.29-0.81)
				Author COI	0.04*	random effects	0.55 (0.27-0.84)
Cherla 2018	multiple	590	Outcome Favorability	Full Disclosure	0.001*	OR	8.65 (2.46-30.44)
				Incomplete Industry Disclosure	0.003*	OR	3.61 (1.53-8.51)
				Incomplete Self-Disclosure (Partial)	0.004*	OR	4.14 (1.58-10.82)
				Incomplete Self-Disclosure (None)	0.002*	OR	0.14 (0.37-1.15)
Saa 2018	probiotics	66	Outcome Favorability	Industry sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-
			Methodological or Reporting Quality	Industry Sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-

Table 2: Industry funding and COI Strata Assessed and Associated Results. This table describes the clinical area, methodological design (sample, DV Type, IV strata), and results of analysis presented in articles that evaluated identifiable industry funding and COI strata.

Discussion

Given the broad recognition of the risks associated with industry funding and COI, AMCs have adopted policies designed to mitigate these risks. At the same time, academic and professional medical organizations have disseminated guidelines designed to support effective industry funding and COI policies at AMCs. Although the overall data on industry funding and COI suggests that such policies are a critically important part of protecting the integrity of biomedical research, available evidence does not support current policy stratifications. The

overwhelming majority of studies evaluated in this review do not stratify industry funding or COI in their analyses. A number of studies collected data that could be used to assess differences in funding relationship types, but dichotomized IVs prior to analysis. Strikingly, no studies included in this review evaluated any relationship between the magnitude of industry funding or author COI and target outcomes of interest. The common treatment of author COI as an undifferentiated category of industry funding compromises the ability to meaningfully discriminate between the potential effects of industry funding or author COI.

Given the considerable investment in policies that distinguish between funding type and magnitude, the shortcomings identified here are weaknesses that should be addressed. When it comes to evaluation of different types or magnitudes of funding, little evidence supports these policies in the contexts of biomedical research. The lack of available evidence on magnitude is especially striking in the U.S. context given the regulatory emphasis on *de minimis* thresholds. With respect to stratified COI polices at AMCs specifically, at present no comparative evaluations of COI types provide an evidentiary foundation for the common distinctions between travel and consulting fees. Nevertheless, this distinction is central in the guidance.

In sum, the stratification of COI in policies enacted by AMCs does not appear to be governed by robust evidence or differential risk assessments. It is notable that the strictest criteria tend to associate with relationships of modest economic benefit to individuals (e.g., meals and travel) whereas relationships with well-documented risks but considerable economic benefit to institutions (e.g., industry grants and collaborations) are largely left out of COI policy recommendations. Additionally, it is noteworthy that the strongest evidence relates to author employment, although specific instructions about disclosing employment have been removed

from the latest ICMJE disclosure form. These findings support recent calls for greater attention to institutional COI at AMCs and other institutions that conduct biomedical research.[36–39]

This study has several limitations that should inform the reading of the findings. Our scoping review evaluates the methodological design and approaches to IV stratification for studies of the relationships between industry funding or author COI and four specified outcomes of interest in biomedical research. Although we are aware of studies that evaluate COI magnitude, for example, they were not returned by our search strategy either because they treat COI magnitude in the aggregate[40] or because they assess non-target outcomes such as associations with commercial publishing practices.[41] Additionally, AMC guidelines are designed to respond to COI risks in multiple domains including research, clinical practice, and medical education. We assume that COI strata related to industry-funded CME or pharmaceutical representative access to AMCs are designed primarily to address risks of bias associated with medical education and clinical practice. However, the literature collected does not assess clinical practice or educational domains. Additional research not covered by this scoping review is available that evaluates the relationships of industry funding and COI with prescription practices, guidelines development, policy decision-making, and other areas. Studies in these areas may offer further insights about different risk profiles associated with types or magnitudes of industry funding. AMC COI policies and related guidelines may be more responsive to research in these areas.

Conclusion

Current COI policies in research contexts devote considerable attention to distinguishing between different types and magnitudes of COI. Although substantial evidence exists that industry funding and COI in general have adverse effects on biomedical research, the current

evidence does not support the stratification by type or magnitude common to existing policy or capture why such stratification might be important. Appropriate and evidence-based COI policies are essential for safeguarding the integrity of the biomedical research enterprise. Therefore, it is critical that researchers in these areas develop standardized taxonomies of industry funding and/or author COI. These taxonomies combined with magnitudes allow for computation and aggregation of COIs essential for supporting rigorous research to guide COI policies in research contexts. Additionally, the results of this scoping review further support recent recommendations for attention to institutional COI at AMCs. Future COI policy guidelines should address institutional COI alongside individual COI. Finally, the results of this scoping review suggest that uniform COI policies designed to simultaneously address risks to clinical practice, medical education, and biomedical research may be predominantly informed by the first two domains. Additional efforts should be made to ensure that COI policies are responsive to risks associated with bias in biomedical research or AMCs should potentially consider differential policies based on institutional roles. Research should investigate the utility of separate COI policies for clinical, educational, and research staff. Of course, staff at AMCs often occupy more than one role. In such cases, it might be appropriate to require those staff to adhere to the most restrictive policy. Nonetheless, the policies should be developed based on an understanding of the differential effects of distinct strata and magnitudes of COI on outcomes across the multiple domains.

Contributors: SSG designed the study, coordinated the study, and is the guarantor. SSG, JBB, and JFR executed the search strategy and screened abstracts. SSG, MSK, JJ, and NS collected the data. SSG, JBB, JFR, and ZPM analyzed the data. SSG, MSK, and NS drafted the manuscript. SSG, JBB, JFR, and ZPM revised the manuscript. Guarantor: SSG.

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Data Availability: All data relevant to the study are included in the article or uploaded as supplementary information

Ethics Approval: This study did not require ethics approval as it did not involve human subjects.

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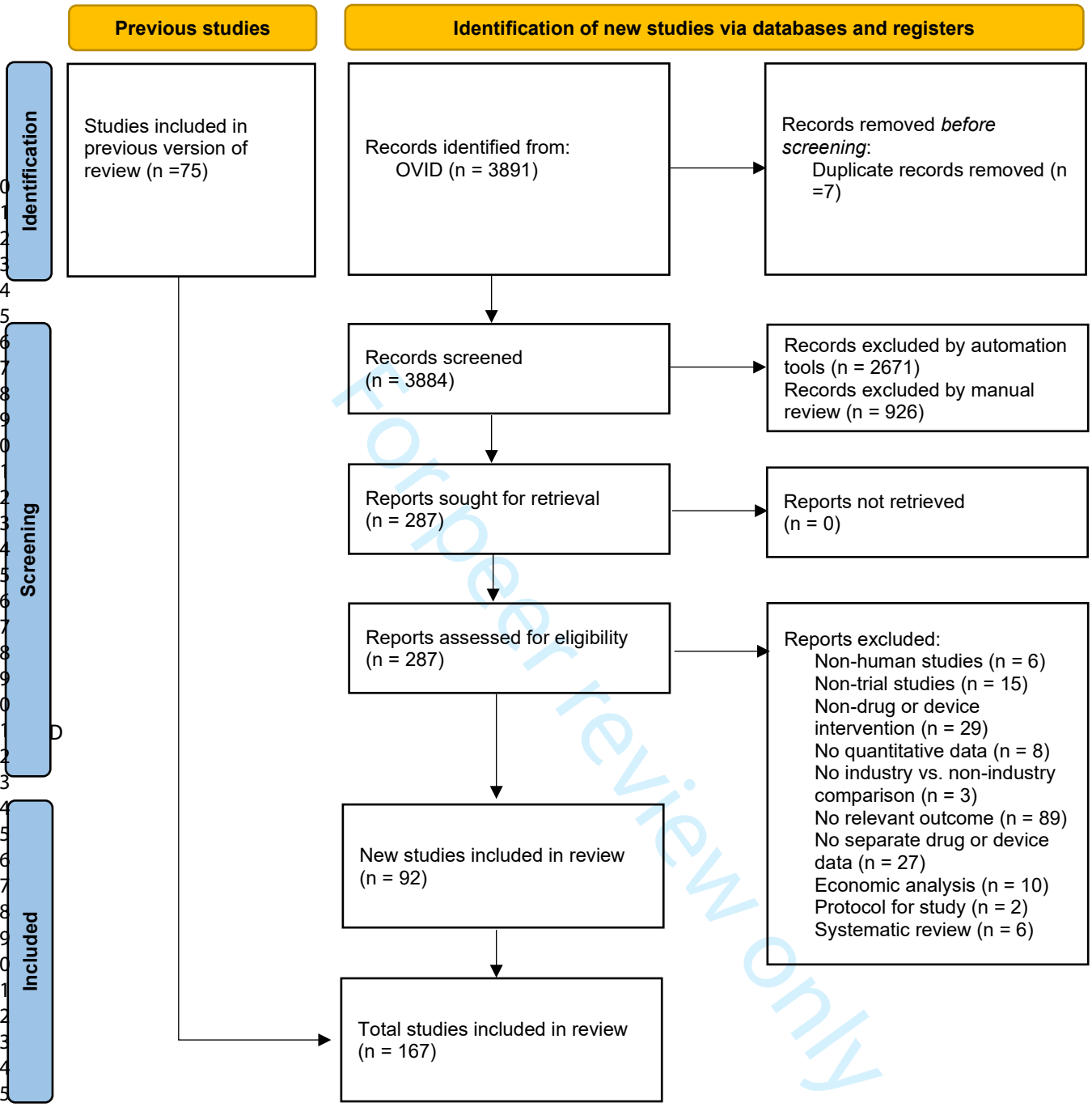
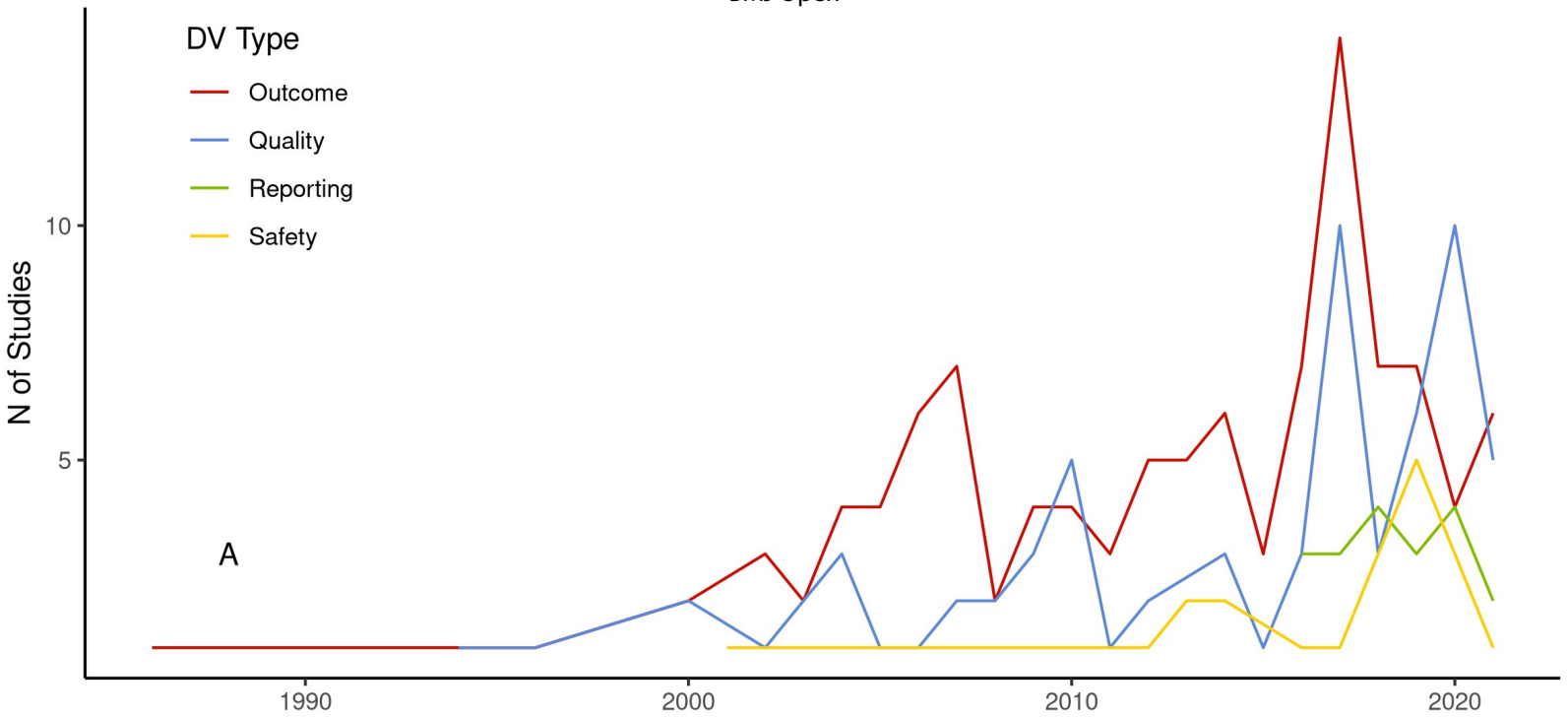
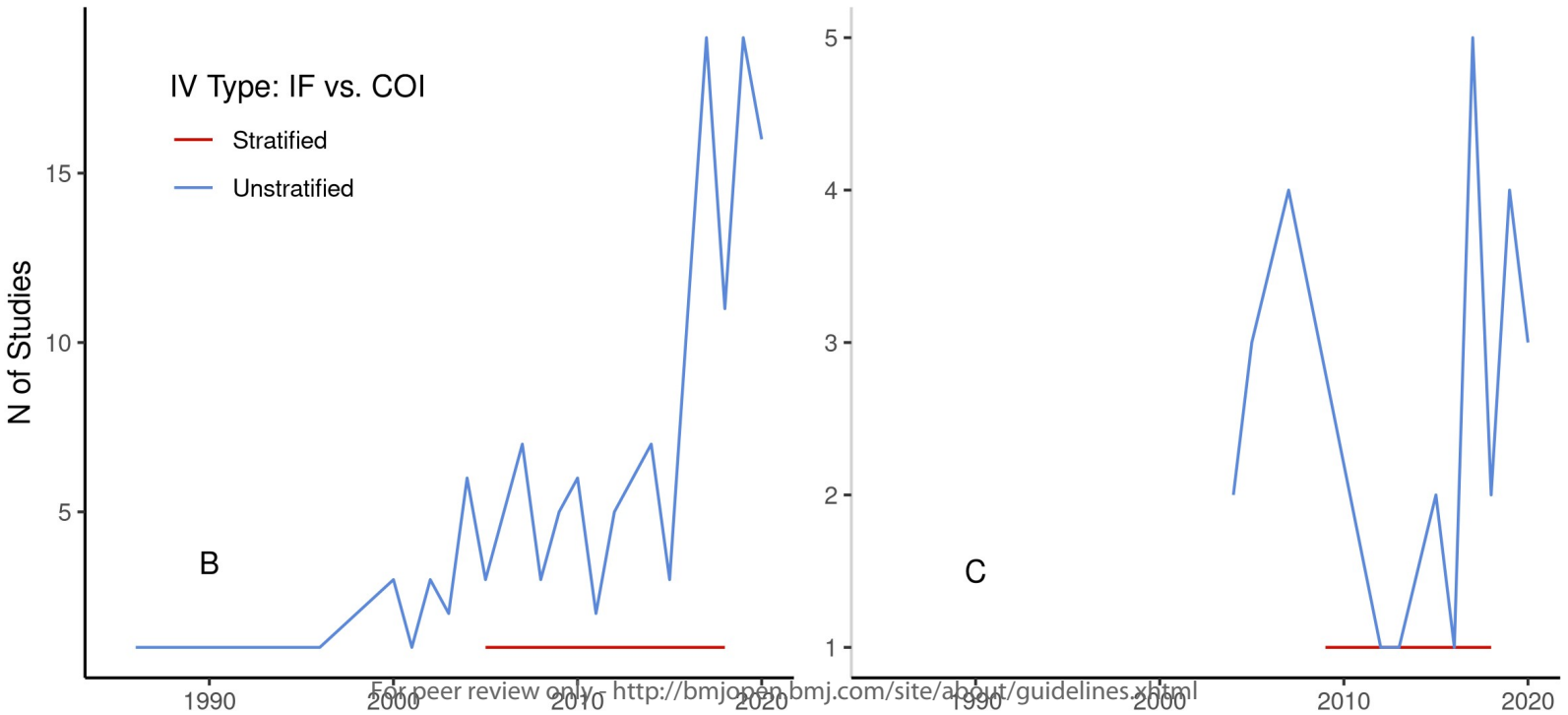
Figure 1: PRISMA-SCR Flow Diagram for Screening and Review.

Figure 2: IV and DV Types By Year Number (1986-2021). Figure includes number of studies per year by DV Type (A), number of studies by IV type for studies assessing industry funding (B) and number of studies by IV type for studies evaluating COI (C).

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only







Supplementary Online Materials

Industry Funding Independent Variable (IV) Type.	
Stratified	Study provides a quantitative assessment of the relationship between different types of industry funding and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of industry funding categories. Funder stratifications may include level of involvement (primary, secondary), relationship to drug or device under study (manufacturer, competitor), or mode of sponsorship (study sponsor, medication provider, author employer).
Unstratified	Industry funding is analyzed as a dichotomous variable or as one category in a categorical variable, e.g. funder types might include industry, government, nonprofit.
Magnitude	Industry funding is a continuous variable representing either the total number of industry funders per study or total dollar value of contributions.
Author COI IV Type	
Stratified	Study provides a quantitative assessment of the relationship between different types of COI and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of COI categories. COI stratifications may include type of disbursement (employment, speaker fees, etc) and affiliation (trial sponsor vs. non-sponsor funder).
Unstratified	COI is analyzed as a dichotomous variable or as one category in a categorical variable, e.g., Industry funding, Author COI, Government Funding.
Magnitude	COI is a continuous variable representing either the total number of relationships or the total dollar value of contributions.
COI as Proxy for Industry Funding Study	
Yes	Disclosed author COI are used as inclusion criteria for industry funding.
No	Disclosed COI are not used as inclusion criteria for industry funding or industry funding is not measured.
IV Dichotomization	
NA	The IV used in the statistical analysis was stratified or an assessment of magnitude.
Yes	The categorical schema was converted to dichotomous variables that were used for analysis.
No	The IV was consistently treated as dichotomous throughout the article.
Dependent Variable Type (DV Type)	
Outcome	The analysis evaluates if chosen IVs are associated with results indicating the success of the intervention (drug, device, etc) or are otherwise favorable to trial sponsors. Includes drug efficacy, response rate, positive interpretation of findings, etc.
Safety	The analysis evaluates if chosen IVs associate with results related to drug safety.
Quality	The analysis evaluates if chosen IVs are associated with results related to methodological or reporting quality. Includes issues of statistical power, risk of bias, presence of hype or spin.
Reporting	The analysis evaluates whether or not trial results were reported at all. May include reporting to ClinicalTirals.Gov or publication of findings.

Supplemental Table 1. Methodological Design Feature Schema for Analyzed Studies. Definition and details for industry funding IV type, author COI IV type, COI as proxy for industry funding, dichotomization, and DV type analyses.

Article	*Year*	*IF IV Type*	*COI IV Type*	*DV Type*	*COI Proxy*	*IF Dichotomize*	*COI Dichotomize*
Abildgaard et al. (1)	2019	Unstratified	None	Outcome	yes	yes	NA
Addeo et al. (2)	2019	Unstratified	None	Outcome, Safety	no	no	NA
Ahmer et al. (3)	2005	Stratified	Unstratified	Outcome	no	NA	no
Ahn et al. (4)	2016	Unstratified	Unstratified	Outcome	no	no	yes
Alasbali et al. (5)	2009	Unstratified	None	Outcome, Quality	no	no	NA
Als-Nielsen et al. (6)	2003	Unstratified	None	Outcome	yes	NA	NA
Avni et al. (7)	2004	Unstratified	None	Quality	no	no	NA
Azad et al. (8)	2019	Unstratified	None	Quality	no	NA	NA
Azharuddin et al. (9)	2020	Unstratified	None	Quality	no	no	NA
Barden et al. (10)	2005	Unstratified	None	Outcome	yes	no	NA
Bariani et al. (11)	2013	Unstratified	Unstratified	Outcome	no	yes	yes
Bartels et al. (12)	2012	Unstratified	Stratified	Outcome	yes	no	NA
Bero et al. (13)	2007	Unstratified	Unstratified	Outcome	no	NA	no
Bhandari et al. (14)	2004	Unstratified	None	Outcome	no	yes	no
Bighelli et al. (15)	2020	Unstratified	Unstratified	Quality	no	no	NA
Bond et al. (16)	2012	Stratified	Unstratified	Outcome	yes	NA	no
Booth et al. (17)	2008	Unstratified	None	Outcome, Quality	no	NA	NA
Bourgeois et al. (18)	2010	Unstratified	None	Outcome, Quality	no	NA	NA
Brown et al. (19)	2006	Unstratified	None	Outcome, Quality	no	no	NA
Buchkowsky and Jewesson (20)	2004	Unstratified	Unstratified	Outcome	no	NA	no
Budhiraja et al. (21)	2021	Unstratified	None	Outcome	no	NA	NA
Bugano et al et al. (22)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Catillon (23)	2019	Unstratified	Unstratified	Quality	no	no	NA
Chang et al. (24)	2021	Unstratified	None	Quality	no	NA	NA
Chard et al. (25)	2000	Unstratified	None	Outcome, Quality	no	NA	NA
Chen et al. (26)	2016	Unstratified	None	Reporting	no	NA	NA
Cherla et al. (27)	2018	None	Stratified	Outcome	no	NA	NA
Cho and Bera (28)	1996	Unstratified	None	Outcome, Quality	yes	no	NA
Clark et al. (29)	2002	Unstratified	None	Outcome	no	no	NA
Clifford et al. (30)	2002	Unstratified	None	Outcome, Quality	no	NA	NA
Corona et al. (31)	2014a	Unstratified	None	Quality, Safety	yes	no	NA
Corona et al. (32)	2014b	Unstratified	None	Outcome, Quality	yes	no	NA
Cristea et al. (33)	2017	None	Unstratified	Outcome	no	NA	no
Crocetti et al. (34)	2010	Unstratified	None	Quality	no	NA	NA
Davidović et al. (35)	2021	Unstratified	None	Outcome, Reporting	no	no	NA
Davidson (36)	1986	Unstratified	None	Outcome	yes	no	NA

Davis et al. (37)	2008	Unstratified	None	Outcome	yes	no	NA
de Souza Gutierres et al. (38)	2020	Unstratified	None	Quality	no	no	NA
DeFrance et al. (39)	2021	None	Unstratified	Outcome	no	NA	no
DeGeorge et al. (40)	2015	Unstratified	Unstratified	Outcome	no	NA	no
Del Paggio et al. (41)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Falk Delgado and Falk Delgaddo (42)	2017a	Unstratified	None	Outcome	no	NA	NA
Falk Delgado and Falk Delgaddo (43)	2017b	Unstratified	Unstratified	Reporting	no	NA	no
DePasse et al. (44)	2018	Unstratified	None	Reporting	no	NA	NA
DeVito et al. (45)	2020	Unstratified	None	Reporting	no	NA	NA
Djulbegovic et al. (46)	2013	Unstratified	None	Outcome	no	no	NA
Djulbegovic et al. (47)	2000	Unstratified	None	Quality	yes	no	NA
Etter et al. (48)	2007	Unstratified	None	Outcome	yes	no	NA
Finucane and Boult (49)	2004	Unstratified	None	Outcome	yes	no	NA
Flacco et al. (50)	2015	Unstratified	Unstratified	Outcome, Quality	yes	yes	no
Fraguas et al. (51)	2018	Unstratified	None	Quality	no	no	NA
Freemantle et al. (52)	2000	Unstratified	None	Outcome	no	no	NA
Fung et al. (53)	2017	Unstratified	None	Quality, Reporting	no	no	NA
Gabler et al. (54)	2016	Unstratified	None	Reporting, Quality	no	no	NA
Gan et al. (55)	2012	Unstratified	None	Quality	no	no	NA
Gao et al. (56)	2019	Unstratified	None	Quality	no	NA	NA
Gartlehner et al. (57)	2010	Unstratified	None	Outcome, Quality	yes	no	NA
Gaudino et al. (58)	2020	Unstratified	Unstratified	Outcome, Quality	yes	no	yes
Gonzalez et al. (59)	2019	Unstratified	None	Quality	no	NA	NA
Grey et al. (60)	2018	Unstratified	None	Outcome	no	no	NA
Gyawali et al. (61)	2019	Unstratified	None	Safety	no	NA	NA
Hajibandeh et al. (62)	2017	Unstratified	Unstratified	Outcome	no	no	no
Halpern et al. (63)	2004	Unstratified	None	Quality	no	NA	NA
Hanna et al. (64)	2016	Unstratified	None	Outcome	no	NA	NA
Hashemipour et al. (65)	2019	Unstratified	Unstratified	Outcome	no	no	no
Hengartner et al. (66)	2021	Unstratified	None	Safety	yes	no	NA
Heres et al. (67)	2006	Unstratified	None	Outcome	no	no	NA
Janiaud et al. (68)	2018	Unstratified	None	Outcome	no	yes	NA
Jefferson et al. (69)	2009	Unstratified	None	Quality	no	no	NA
Jellison et al. (70)	2020	Unstratified	None	Quality	no	yes	NA
Jinapriya et al. (71)	2011	Stratified	None	Outcome	no	NA	NA
Johnson et al. (72)	2020	Unstratified	None	Reporting	no	NA	NA

Jones et al. (73)	2010	Unstratified	None	Quality	no	NA	NA
Kakkar et al. (74)	2019	Unstratified	None	Quality	no	no	NA
Kapelios et al. (75)	2020	Unstratified	None	Outcome, Quality	no	no	NA
Kelly et al. (76)	2006	Stratified	None	Outcome	yes	NA	NA
Kemmeren et al. (77)	2001	Unstratified	None	Safety	no	no	NA
Khan et al. (78)	2012	Unstratified	None	Outcome, Quality	no	NA	NA
Killin et al. (79)	2014	Unstratified	None	Outcome	yes	no	NA
Kjaergard and Als-Nielson (80)	2002	Unstratified	None	Outcome	no	NA	NA
Lee et al. (81)	2012	Unstratified	None	COI, Outcome	no	no	NA
Lee et al. (82)	2020	Unstratified	None	Reporting	no	no	NA
Leite et al. (83)	2017	Unstratified	Unstratified	Outcome	no	no	no
Leucht et al. (84)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Leucht et al. (85)	2019	Unstratified	None	Outcome	no	no	NA
Linker et al. (86)	2017	Unstratified	None	Outcome, Quality	no	NA	NA
Liss (87)	2006	Unstratified	None	Outcome	yes	no	NA
Liu et al. (88)	2018	Unstratified	None	Outcome	no	NA	NA
Lubowitz et al. (89)	2007	Unstratified	None	Outcome	no	no	NA
Lynch et al. (90)	2007	Unstratified	None	Outcome, Quality	yes	NA	NA
Ma et al. (91)	2014	Unstratified	None	Outcome, Safety	no	no	NA
Magnani et al. (92)	2021	Unstratified	None	Reporting, Outcome	no	NA	NA
Maillet et al. (93)	2015	Unstratified	None	Outcome	no	no	NA
Malek et al. (94)	2017	Unstratified	None	Outcome	no	no	NA
Mian et al. (95)	2020	Unstratified	None	Quality	no	NA	NA
Mitchell and Patterson (96)	2020	Unstratified	None	Quality	no	NA	NA
Momeni et al. (97)	2009	Unstratified	None	Outcome	no	NA	NA
Moncrieff (98)	2003	Unstratified	None	Outcome	no	no	NA
Montgomery et al. (99)	2004	Unstratified	Unstratified	Outcome, Quality	no	no	no
Moraes et al. (100)	2017	Unstratified	Unstratified	Outcome	no	NA	no
Mossman et al. (101)	2021	Unstratified	None	Outcome	no	no	NA
Naci et al. (102)	2014	Unstratified	None	Outcome, Quality	no	no	NA
Ng et al. (103)	2016	Unstratified	None	Quality	no	no	NA
Nieto et al. (104)	2007	Unstratified	None	Safety	no	no	NA
Nithianandan et al. (105)	2020	Unstratified	Unstratified	Outcome	no	no	no
Odutayo et al. (106)	2017	Unstratified	None	Outcome	no	no	NA
Paggio et al. (107)	2021	Unstratified	None	Quality	no	no	NA
Pasalic et al. (108)	2020	Unstratified	None	Quality	no	no	NA
Pengel et al. (109)	2009	Unstratified	None	Quality	yes	NA	NA

Pepper et al. (110)	2019	Unstratified	None	Safety	no	no	NA
Peppercorn et al. (111)	2007	Unstratified	Unstratified	Outcome	yes	no	no
Perlis et al. (112)	2005a	Unstratified	Unstratified	Outcome, Quality	yes	no	no
Perlis et al. (113)	2005b	Unstratified	Unstratified	Outcome	yes	no	no
Popelut et al. (114)	2010	Unstratified	None	Outcome	no	NA	no
Pouwels et al. (115)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Prakash et al. (116)	2018	Unstratified	None	Quality	no	NA	NA
Price-Haywood et al. (117)	2019	Unstratified	None	Safety	no	NA	NA
Printz et al. (118)	2013	Unstratified	None	Outcome	yes	no	NA
Probst et al. (119)	2016	Unstratified	None	Outcome	no	no	NA
Punja et al. (120)	2016	Unstratified	None	Outcome, Safety	no	no	NA
Putman et al. (121)	2021	Unstratified	None	Quality	yes	no	NA
Raman et al. (122)	2018	Unstratified	Unstratified	Outcome	no	NA	no
Rasmussen et al. (123)	2009	Unstratified	None	Outcome	yes	yes	NA
Rattinger and Bero (124)	2009	Stratified	Stratified	Outcome	yes	NA	NA
Reda et al. (125)	2016	Unstratified	None	Outcome, Quality	no	yes	NA
Rees et al. (126)	2019	Unstratified	None	Reporting	no	NA	NA
Ridker and Torres (127)	2006	Unstratified	None	Outcome	no	NA	NA
Rios et al. (128)	2008	Unstratified	None	Quality	no	NA	NA
Rochon et al. (129)	1994	Unstratified	None	Outcome, Quality	yes	no	NA
Roddick et al. (130)	2017	Unstratified	None	Outcome	no	NA	NA
Roper et al. (131)	2014	Unstratified	None	Limitations, Outcome	no	NA	NA
Rosner et al. (132)	2010	Unstratified	None	Outcome, Quality	no	no	NA
Rosner et al. (133)	2011	Unstratified	None	Outcome	no	NA	no
Saa et al. (134)	2018	Stratified	None	Outcome, Quality	yes	NA	NA
Saleh et al. (135)	2020	Unstratified	None	Outcome	no	no	NA
Sendyk et al. (136)	2019	Unstratified	None	Quality, Reporting	no	no	NA
Shepard et al. (137)	2021	Unstratified	None	Quality	no	NA	NA
Silva et al. (138)	2017	Unstratified	None	Safety, Quality	no	no	NA
Simonetti et al. (139)	2019	Unstratified	None	Safety	no	no	NA
Sinyor et al. (140)	2012	Unstratified	None	Outcome, Safety	yes	no	NA
Son et al. (141)	2016	Unstratified	None	Outcome	no	no	NA
Spanemberg et al. (142)	2011	Unstratified	None	Outcome, Quality	no	no	NA
Sriganesh et al. (143)	2017	Unstratified	None	Quality	no	no	NA
Stefaniak et al. (144)	2017	Unstratified	None	Reporting, Quality	no	NA	NA
Steffens et al. (145)	2021	Unstratified	None	Quality	yes	no	NA

Sung et al. (146)	2013	Unstratified	None	Outcome	yes	no	NA
Tiabau et al. (147)	2018	Unstratified	None	Outcome	no	NA	NA
Trinquart et al. (148)	2018	Unstratified	None	Reporting	no	no	NA
Tulikangas et al. (149)	2006	Unstratified	None	Outcome	no	no	NA
Tungaraza and Poole (150)	2007	Unstratified	Unstratified	Outcome	no	no	no
Urrutia et al. (151)	2016	Unstratified	None	Reporting	no	no	NA
van den Bogert et al. (152)	2017	Unstratified	None	Quality	no	yes	NA
van Heteren et al. (153)	2019	Unstratified	None	Reporting	no	NA	NA
Van Lent et al. (154)	2014	Unstratified	None	Outcome	yes	NA	NA
Venincasa et al. (155)	2019	Unstratified	Unstratified	Outcome	no	no	no
Vlad et al. (156)	2007	Stratified	Unstratified	Outcome, Quality	no	NA	no
Walkup et al. (157)	2017	Unstratified	None	Outcome	no	no	NA
Walter et al. (158)	2020	Unstratified	None	Reporting	no	no	NA
Waqas et al. (159)	2019	Unstratified	Unstratified	Outcome	no	no	no
Welsh et al. (160)	2018	Unstratified	Unstratified	Reporting	no	NA	no
Wise et al. (161)	2021	Unstratified	Unstratified	Outcome	no	yes	yes
Wong et al. (162)	2019	Unstratified	None	Outcome	no	no	NA
Wortzel et al. (163)	2020	Unstratified	None	Quality	no	NA	NA
Xu et al. (164)	2013	Unstratified	None	Safety	no	no	NA
Yilmaz et al. (165)	2018	Unstratified	None	Reporting	no	no	NA
Youssef et al. (166)	2016	Unstratified	None	Outcome	no	no	NA
Zhang et al. (167)	2013	Unstratified	None	Outcome, Safety	no	no	NA

Supplemental Table 2. Methodological Design Analysis for All Collected Articles. Includes industry funding IV type, author COI IV type, DV type(s), COI as proxy, and dichotomization data.

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Evidence for Stratified Conflicts of Interest Policies in Research Contexts: A Methodological Review

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Abstract

Objectives: The purpose of this study was to conduct a methodological review of research on the effects of conflicts of interest (COI) in research contexts.

Design: Methodological review.

Methods: We searched OVID for studies published between 1986 and 2021 conducting quantitative assessments of relationships between industry funding or COI and four target outcomes: positive study results, evidence of methodological biases, study reporting quality, and results-conclusions concordance. We assessed included articles for key research design features. Our primary analysis identified whether studies stratified industry funding or COI variables by magnitude (i.e., number of COI or disbursement amount), and/or type (industry employment, travel fees, speaking fees) or if they were operationalized as dichotomous. Secondary analyses focused on target outcomes and available effects measures.

Results: Of the 167 articles included in this study, a substantial majority (98.2%) evaluated the effects of industry sponsorship. None of the collected articles evaluated any associations between funding magnitude and outcomes of interest. Seven studies (4.3%) stratified industry funding based on the mechanism of disbursement or funder relationship to product (manufacturer or competitor). A fifth of the articles (19.8%) assessed the effects of author COI on target outcomes. None evaluated COI magnitude, and 3 studies (9.1%) stratified COI by disbursement type and/or reporting practices. Participation of an industry-employed author showed the most consistent effect on favorability of results across studies.

Conclusions: Substantial evidence demonstrates that industry funding and COI can bias biomedical research. Evidence-based policies are essential for mitigating the risks associated with COI. Although most policies stratify guidelines, distinguishing among COIs based on the type of relationship or monetary value, this review shows that the available research has generally not been designed to assess the differential risks of COI types or magnitudes. Targeted research is necessary to establish an evidence base that can effectively inform policy.

Strengths and limitations of this study

- We considered a broad range of available research on the effects of industry funding and COI on biomedical research.
- Our analysis of common research designs demonstrates a significant need for new approaches to research on the effects of industry funding and COI.
- We achieved high inter-rater reliability for article screening.
- This methodological review evaluates research on the relationships between industry funding or author COI and biomedical research. It does not address studies of the relationships between industry funding or COI and guidelines development, regulatory decision-making, or clinical practice.

Background

Substantial evidence indicates that industry funding of biomedical research and author financial conflicts of interest (COI) arising from financial relationships with medically-related industry can bias research results.[1–7] Associations between industry funding or COI and positive outcomes, such as results favorable to the sponsor, are the most well documented.[2–5,7] Available evidence indicates that industry-funded trials can be up to 5.4 times more likely to return positive results than trials not sponsored by industry,[8] and trials with author COI may be as much as 8.4 times more likely to return favorable results when compared to those without author COI.[6] Additional research has demonstrated that industry funding and COI may be associated with reduced drug and device safety[6,9] and can have adverse effects on the methodological quality of clinical trials.[10–12] Recent studies also suggests that industry sponsorship may be associated with premature trial termination and non-reporting of trial results.[13,14] Calls for more evidence documenting that industry funding and COI can measurably bias biomedical research persist even though these findings have been repeatedly replicated.[15]

Recognizing the risks of bias, many organizations involved in biomedical research have adopted specific policies designed to address COI. The need for such policies is clear, which in turn raises important questions about the form those policies should take. Differentiation among COI types and magnitudes is a common feature of the policies adopted by universities, academic medical centers (AMCs), government laboratories, and similar research institutions. COI policy guidelines published in the literature and by professional medical organizations also routinely differentiate among different COI types and magnitudes. That is, COI policies and guidelines routinely make distinctions based on the method of remuneration (industry employment, consultancy relationships, honoraria, travel fees, etc.), the nature of the funder (e.g., industry,

nonprofit, government agency), the recipient of remuneration (e.g., self, partner, family, collaborator), and the magnitude or monetary value of the disbursement. Table 1 describes explicit recommendations by the American Medical Student Association (AMSA),[16] the Association of Academic Medical Centers (AAMC),[17] the British Medical Association (BMA),[18] and Brennen et al.[19]

These COI policies and guidelines suggest that some types of COI should be prohibited outright, others should be subjected to specific restrictions, and some should merely require disclosure. However, different policies and guidelines do not agree on the risk presented by different types or magnitudes of COI. The recommendations typically advise a total prohibition on gifts from industry and ghostwriting, but recommendations about other COI types vary widely. For example, AMSA recommends restrictions on consulting fees, but the AAMC, BMA, and Brennen et al. do not address consultancies outside general recommendations for transparency via COI disclosure. All four guidelines disagree if industry representative access to research spaces should be restricted or prohibited outright.

Various policies also make distinctions about the magnitude or monetary value of COI to set disclosure thresholds. However, recommended thresholds vary widely within and between organizations. For example, since 1995, the US Department of Health and Human Services has required AMCs and other entities that receive federal research funding to adopt policies that require disclosure of COI over a certain threshold.[20] This value was lowered from $10,000 to $5,000 in 2011.[21] The BMA sets the declaration threshold for gifts at £500 and for equity holdings at greater than 1% of the value of the company or greater than £25,000.[18]

COI	AMSA	AAMC	BMA	Brennen et al.

Attendance at unaccredited industry-sponsored events	Prohibit			Prohibit
Consulting	Restrict			
Donations			Disclose	
Ghostwriting	Prohibit	Prohibit		Prohibit
Gifts	Prohibit	Prohibit	Prohibit	Prohibit
Grants			Disclose	
Industry access- device representatives	Restrict	Restrict		Restrict
Industry access- pharmaceutical representatives	Prohibit	Restrict	Restrict	Prohibit
Industry sponsored CME	Restrict	Restrict		Restrict
Industry sponsored scholarships		Restrict		
Meals	Prohibit			Prohibit
Pharmaceutical samples		Restrict		
Research contracts			Disclose	
Speakers bureaus	Prohibit			Prohibit
Travel funds		Restrict		
Travel for industry sponsored meetings		Prohibit		
Travel funds for trainees	Prohibit		Prohibit	Prohibit
Treatment inducements	Prohibit			

Table 1: Illustrative Recommendations for Strata-Specific COI Policies. This table shows AMSA,[16] AAMC,[17] BMA,[18] and Brennen et al.'s[19] recommendations for whether AMC COI policies should prohibit, restrict, or require disclosure of specific COI strata. Where entries are blank, the guidance provided no specific recommendations for that type of relationship.

The establishment of approaches to COI management that differentiate by type magnitude COI indicate that common guidance *assumes* that different COI types and magnitudes carry different degrees of risk for biomedical research and require different responses. This assumption even drives much of the available research on COI policies at AMCs and similar institutions. The AMSA scorecard, for example, is a well-established framework for COI policy evaluation.[16,22] It has been used to assess the extent to which COI policies at AMCs in the

United States,[16] France,[23] and Germany [24] follow AMSA recommendations for COI policy construction and stratification.

Despite the significant investments in developing and evaluating stratified COI policies, it is not clear that different types of COI do, in fact, carry different risks or levels of risk for biomedical research. If one were to assess the efficacy of COI policies (i.e., determine if COI policies have any effects on the quality of research), one must first assess whether policies stratified by COI types are grounded in evidence about the differential risks of different COI types. This study sought to assess the extent to which orthodox research designs for assessing the effects of COI on biomedical research have been designed to generate evidence relevant to the stratification of COI policies. Demonstrating the existence of differential risk profiles for different COI types would require, at minimum, research designs that stratify COI variables prior to analysis. They should further disaggregate industry research sponsorship generally from specific forms of author COI. Therefore, the goal of this methodological review is to evaluate the extent to which study designs in available industry funding and COI research can support COI policies or that policy recommendations should assume differential risk profiles for different types of COI and/or different monetary values. Put another way, the evidence for the need for mitigating the risks imposed by COI is strong, but the state of the research that can guide *how* to manage that risk is unclear. This study reviews methodological designs for 1) industry funding variable stratification and disaggregation, 2) COI variable stratification and disaggregation, and 3) diversity of outcomes assessments.

Methods

Methodological reviews are designed to provide information on the prevalence of available study designs in a body of literature. They have facilitated advances in a wide variety

of health and health policy contexts and can be used to identify and prioritize new pathways for research [25–28]. A methodological review is the ideal approach for this study, which requires identifying the extent to which assessments the effects of industry funding and COI on biomedical research were conducted in such a way that could support current COI policy stratifications. Our review proceeded in three phases. First, we replicated the search strategy and article screening protocol for a previously published Cochrane systematic review of the effects of industry funding and author COI on biomedical research.[2] The prior Cochrane review evaluated the overall strength of the evidence base regarding the association of industry funding and author COI with results favorable to the sponsor, risks of bias associated with the methodological design, and the quality of reporting of the concordance between results and conclusions, but it did not document the methodological design elements in focus in this study.[2] Our study adopted the search strategy and screening protocol of the original review, and the second phase of this review involved conducting a novel assessment of the methodological features of included articles, with particular focus on how industry funding and COI variables were operationalized in statistical analyses. Finally, we used these data to synthesize the evidence for evaluating different types of industry funding or author COI on target outcomes in biomedical research.

Search strategy and study selection

We began by replicating the search strategy in a previously published Cochrane review. The strategy was designed to identify relevant articles indexed in the Ovid database. The original review and screening protocol identified 75 studies of interest published between 1986 and 2016. We retrieved each of the original 75 studies, and in June 2021, we repeated the search strategy to collect additional relevant articles published since 2016. We also replicated the study inclusion

protocol from the previous Cochrane review. Specifically, eligible studies provided a quantitative assessment of the extent to which industry funding or author COI were associated with target outcomes of interest (i.e., results favorable to industry, methodological biases, reporting quality, and results-conclusions concordance) within research on drug and device products. All collected studies evaluated one of these outcomes on a dataset of clinical trials. Clinical trials data may come from published articles, clinical trials registries, or both. Studies of the effects of industry funding and/or COI in research areas related to smoking, nutrition, physical therapy, psychotherapy, and surgery were excluded except in cases where analyses were performed on separate identifiable drug or device data. Additionally, studies that evaluated the effects of industry funding or COI on clinical practices, guidelines development, patient organizations, and regulatory policy were excluded.

Three evaluators screened titles and abstracts. After initial norming, a random sample of 255 titles and abstracts were selected by all three raters to assess reliability across screeners. A sample size of 255 was chosen to achieve 90% assurance using the intraclass correlation coefficient (ICC).[29] Overall agreement between the three raters was 94.9% with an ICC = 0.801. A secondary analysis of the random sample indicated that the abstracts for all articles selected for further screening included at least one of the following terms: "funding," "funded," "COI," "fCOI," "conflict," or "sponsor," which allowed us to develop an automated screening tool based on those terms. Articles selected for full-text review passed both automated and manual screening. The full article text of the remaining articles was evaluated by three raters.

Data Extraction and Synthesis

The current methodological review was designed to collect data on the underlying analytic designs in selected articles. Specifically, the investigators collected data on which

independent and dependent variables had been operationalized and defined. That is, each industry funding and COI independent variable was categorized as "stratified," "unstratified," or "magnitude." Here, "stratified," refers to what is often called categorical or nominal variables. For example, a study that stratified industry funding variables might assess if funding provided by a drug manufacturer or a competing pharmaceuticals company has differential impacts on target outcomes. Similarly, a study that stratified a COI variable might evaluate the relative impact of different disclosed COI types such as "industry employed author," "receipt of consulting fees," or "receipt of travel fees." We classified independent variables as "magnitude" if they assessed industry funding or COI as a continuous or ordinal variable. This might mean assessing industry funding in terms of disbursed amounts (e.g., $5000 or £20,000) or the total number of COI per article. Relevant variables were identified as "unstratified" when they were assessed as simply present or absent (e.g., industry funded vs. non-industry funded or reported COI vs. no reported COI). We also noted if variables had been dichotomized prior to analysis. This occurs when articles present stratified variable data as part of descriptive statistics, but then perform statistical analyses on simplified, unstratified, dichotomous industry funding or COI variables.

Our analysis also assessed whether author COI was used as a proxy for industry funding. This research design choice would indicate that the article in question did not fully disaggregate general industry sponsorship from specific types of author COI. Each outcome variable was also categorized according to the primary domain of interest, including outcome favorability to sponsor, drug or device safety; quality of study design or reporting; and if results were reported at all. Finally, for all articles with stratified independent variables for industry funding or author COI, we identified clinical areas of interest, sample sizes used, each assessed stratum, outcomes

against which the stratum were assessed, significance of the results, and any reported effect sizes. A complete description of the criteria is available in Supplemental Table 1.

Patients and Public Involvement

No patients or public were involved in the study.

Results

Our replication of the previously published search strategy retrieved 3,884 unique records for articles published in 2016 and later. Automated screening removed 2,671 articles from consideration. Subsequent manual screening of titles and abstracts excluded another 926 articles. The remaining 287 articles were selected for full text review, and 92 studies were ultimately selected for inclusion. An additional 75 articles were included from the preexisting systematic review for a dataset of 167 articles. (See Figure 1.)

Industry Funding Variable Assessment

Of the 167 articles included in this study, a substantial majority (n = 164, 98.2%) evaluated the effects of industry sponsorship (See Supplemental Table 2). In most cases, industry funding was determined based on an article's acknowledgements or sponsorship declaration. However, some studies collected data from clinical trials registries like clinicaltrials.gov, which index sponsorship. Notably, thirty-five studies (21.3%) assessing industry funding used author employment in industry or other author COI as part of the inclusion criteria for a variable identified as "industry funding" or "industry sponsorship." Studies also used industry provision of drugs or devices as a criterion for industry funding. Others treated provision of supplies as its own isolated variable.

Among the articles that assessed industry funding in some form, none evaluated associations between funding magnitude and outcomes of interest. Ten studies (6.1%) collected stratified data on industry funding but dichotomized the variable prior to statistical analysis. Only seven studies (4.3%) stratified industry funding for analysis in any way. Evaluated strata included details about the nature of the sponsor (evaluated drug manufacturer vs. competitor company) or the nature of the sponsorship (full study sponsorship, collaborative sponsorship with other funders, or provision of medications). Three of the seven studies included assessed differences in favorable outcomes based on funder relationship to the product evaluated (e.g., manufacturer vs. competitor company).[30–32] Only one study found significant results:[30] This review of 542 psychiatry studies found that a greater percentage of studies sponsored by the drug manufacturer have positive outcomes than those not sponsored by a pharmaceutical company (78% vs 48%), and that research sponsored by a competitor had the lowest rate of favorable findings (28%). Pairwise comparisons between manufacturer-funded or competitor-funded and non-industry-funded studies were significantly different, but the study reported no indicators of effect size. Three studies evaluated strata related to the mode of industry involvement.[33–35] These studies assessed the relationship between favorable outcomes and industry provision of medication, report of findings in an industry publication venue, and other (unspecified) industry involvement. One study found significant results, and reported that "other" industry involvement associates with favorable outcomes for industry.[35] See Table 2 for further details. In sum, a substantial proportion of the research that might provide insight into COI policy design assesses only industry sponsorship generally. Nearly a quarter of the assessed studies conflate industry funding and COI variables making it impossible for results to shed light on potentially useful

policy differences. And, finally, studies of industry funding that do stratify variables primarily provide insight on different sponsorship modalities and not on issues related to author COI.

COI Variable Assessment

Of the 167 articles evaluated, only 33 (19.8%) assessed COI as a discrete variable. Attention to COI began considerably later in the dataset, not appearing until 2005. Most studies that evaluated author COI relied on the data in the published disclosure statement. A handful of studies used the authors institutional affiliation as an indicator of industry employment, and a few studies also compared disclosure statements to data available in the Open Payments Database. Of the articles that evaluated author COI, none assessed COI magnitude, and only 3 studies (9.1%) stratified COI for analysis. Four studies (12.1%) collected stratified COI data but dichotomized it prior to analysis. The few studies that assessed COI strata independently tended to evaluate disclosure practices as opposed to COI types.[36–38] These articles report on evaluations of the relationship between favorable outcomes or methodological quality and COI disclosure, lack of funding disclosure, incomplete disclosure, lack of disclosure requirements by journal, or affirmative statements of no author COI. Disclosure of COI and "full" disclosure of COI were most strongly associated with results favorable to industry.[37,38] Here "full" disclosure meant that all payments reported to the Open Payments Database were reflected in published disclosure statements. Assessments of these different disclosure practices returned non-significant results or smaller effect sizes. Two studies evaluated the relationship between participation of industry-employed authors and results favorable to industry.[33,34] An evaluation of 215 psychiatric studies published between 1998 and 2003 found that participation of industry authors was significantly associated with favorable outcomes.[33] Similarly, an

assessment of 91 asthma product studies found that favorable outcomes were more likely for studies with industry-employed authors.[34] (See Table 2.)

Article	Area	Samp.	Outcome	Strata	Sig.	Effect Measure	Effect
Ahmer 2005	psychiatry	306	Outcome Favorability	Industry Provided Medications	0.053	-	-
				Author is Industry Employee	0.01*	OR	8.33 (1.64-50.0)
Bartels 2012	spine research	51	Outcome Favorability	Disclosed COI	<0.05*	OR	16.5 (4.7–58.1)
				Statement of No COI	-	-	-
				Disclosure Not Required by Journal	-	-	-
Bond 2012	asthma	91	Outcome Favorability	Industry Sponsorship	0.546	-	-
				Industry Publication Venue	0.191		-
				Other Industry Involvement	NR	-	-
				Author is Industry Employee	0.003*	RR	1.42 (1.10-1.82)
Jinapriya 2011	latanoprost	44	Outcome Favorability	Sponsorship by Parent Company	0.53	-	-
				Sponsorship by Competing Company	0.53	-	-
Kelly 2006	psychiatry	542	Outcome Favorability	Sponsorship by Manufacturer	0.001*	-	-
				Sponsorship by Competing Company	0.001*	-	-
Rattinger 2009	Thiazolidinediones	61	Outcome Favorability	Sponsorship by Manufacturer	0.7778	-	-
				Sponsorship by Competing Company	0.037*	OR	0(0,0.886)
				No Funding Disclosure	0.4153	-	-
				Corresponding Author COI	0.3939	-	-
				Corresponding Author is Sponsor Employee	0.5714	-	-
				Corresponding Author No Disclosure	0.4388	-	-
				Corresponding Author COI with sponsor	0.049*	OR	4.125(1.048;19.525
				First Author COI	0.1667	-	-
				First Author is Sponsor Employee	-	-	-
				First Author No Disclosure	-	-	-
				First Author COI with sponsor	0.4588	-	-
Vlad 2007	osteoarthritis	15	Outcome	Industry Sponsorship	0.05	-	-

			Favorability	Other Industry Involvement	0.02*	random effects	0.55 (0.29-0.81)
				Author COI	0.04*	random effects	0.55 (0.27-0.84)
Cherla 2018	multiple	590	Outcome Favorability	Full Disclosure	0.001*	OR	8.65 (2.46-30.44)
				Incomplete Industry Disclosure	0.003*	OR	3.61 (1.53-8.51)
				Incomplete Self-Disclosure (Partial)	0.004*	OR	4.14 (1.58-10.82)
				Incomplete Self-Disclosure (None)	0.002*	OR	0.14 (0.37-1.15)
Saa 2018	probiotics	66	Outcome Favorability	Industry sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-
			Methodological or Reporting Quality	Industry Sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-

Table 2: Industry funding and COI Strata Assessed and Associated Results. This table describes the clinical area, methodological design (sample, outcome, variable strata), and results of analysis presented in articles that evaluated identifiable industry funding and COI strata.

Target Outcomes Evaluation

Most studies in the dataset (n = 108, 64.7%) evaluated the relationship between industry funding or COI and outcomes favorability for sponsors. Sixty-six (39.5%) evaluated methodological or reporting quality. Nineteen (11.4%) assessed reporting of results, and 15 (9.0%) evaluated drug or device safety. Attention to specific outcomes appears to have changed over time. Industry favorability of study outcomes had long been the dominant focus of research on industry funding and COI. Quality, safety, and reporting grew increasingly prevalent (Figure 2). Importantly, however, studies that stratified industry funding or COI variables were less diverse in their target outcomes. Of the 10 studies that stratified relevant variables, outcomes favorability to industry was assessed in all cases. One study also assessed the relationship between disclosure practices and methodological or reporting quality.[36]

Discussion

For COI policies to make effective distinctions based on nature of relationships or amount of remuneration, these distinctions must be grounded in research that assesses differential risk profiles of COI types and magnitudes. However, a substantial majority of research assessing the effects of industry funding and author COI on biomedical research does not stratify relevant variables. Remarkably, *zero* studies included in this review conducted any assessments of the magnitude of either industry funding or author COI. Additionally, the available literature's ability to support evidence-based stratifications in COI policies is further compromised by regular conflation of industry sponsorship and author COI variables as well as the practice of dichotomizing variables prior to conducting statistical analyses. The few studies that did stratify COI variables tended to focus on disclosure practices rather than COI types, and most studies assess only if COI types associated with results favorable to industry and not if they associated with other target outcomes of interest. The results of this methodological review indicate that the available research on industry funding and COI has generally not been designed to guide COI policy stratifications or the establishment of disclosure thresholds.

Appropriate and evidence-based COI policies are essential for safeguarding the integrity of the biomedical research enterprise. Therefore, it is critical that research can meaningfully inform continued policy refinement. Clearly, guiding the design of COI policy requires additional research designed to assess the differential risks associated with various COI types and magnitudes.

Furthermore, research in this area could also be better supported by the development of standardized taxonomies of industry funding and/or author COI. Since the literature variously defines "industry funding" as sponsorship, employment, provision of medications, or any author COI, it is quite difficult to compare and aggregate findings across studies. Likewise, competing

understandings of author COI based in different disclosure practices and type definitions also indicate the strong need for robust taxonomies that can guide future research.

These taxonomies combined with evidence about the magnitude of COIs would allow for computation and aggregation of COIs essential for supporting research that could effectively guide COI policy refinement. New research on the risks of COI would also benefit from continued diversification of outcomes assessment. Recent years have seen a steady expansion of outcomes of interest (e.g., outcomes favorability giving way to more assessments of quality, safety, and reporting practices), but favorability of results is still the overwhelmingly dominant target outcome.

Finally, the results of this review also suggest that researchers and policymakers would benefit from considering COI risks beyond those manageable at the individual researcher level. It is notable that common COI policies and guidelines tend to be strict with respect to relationships of modest economic benefit to individuals (e.g., meals and travel) whereas relationships with well-documented risks but considerable economic benefit to institutions (e.g., industry grants and collaborations) are largely left out of COI policy recommendations. Furthermore, the strongest evidence relates to author employment in industry, although specific instructions about disclosing employment have been removed from the latest ICMJE disclosure guidance. Given that collaborations with industry are a common form of institutional COI, and one not addressed by individualized COI policies, these findings support recent calls for greater attention to institutional COI at institutions that conduct biomedical research.[39–42] Research conducted primarily at universities, AMCs, and other research institutions may be more prone to bias when it is supported by industry funding or industry collaboration. COI policies that focus on individual researchers alone will not mitigate against these risks.

This study has several limitations that should inform the reading of the findings. Our review evaluates the methodological design and approaches to variable stratification for studies of the relationships between industry funding or author COI and four specified outcomes of interest in biomedical research. Although we are aware of studies that evaluate COI magnitude, for example, they were not returned by our search strategy either because they treat COI magnitude in the aggregate[43] or because they assess non-target outcomes such as associations with commercial publishing practices.[44] Additionally, AMC guidelines are designed to respond to COI risks in multiple domains including research, clinical practice, and medical education. We assume that COI strata related to industry-funded continuing medical education or pharmaceutical representative access to AMCs are designed primarily to address risks of bias associated with medical education and clinical practice. Additional research not covered by this review is available that evaluates the relationships of industry funding and COI with prescription practices, guidelines development, and policy decision-making.

These limitations notwithstanding, the results suggest that policies designed to address COI risks associated with clinical practice may not effectively safeguard the integrity of biomedical research across institutional contexts because of the gap between policy and available COI research. Furthermore, it is possible that a one-size-fits-all COI policy may not be appropriate. Additional efforts should be made to ensure that COI policies are responsive to risks associated with bias in biomedical research. For example, AMCs should potentially consider differential policies based on institutional roles. Future research might, therefore, investigate the utility of separate COI policies for clinical, educational, and research staff as well as staff holding multiple roles. In such cases, it might be appropriate to require staff to adhere to the most restrictive policy. COI policies should be developed based on an understanding of the

differential effects of distinct strata and magnitudes of COI on outcomes across the multiple domains.

Conclusion

Current COI policies in research contexts devote considerable attention to distinguishing between different types and magnitudes of COI. Although substantial evidence exists that industry funding and COI have adverse effects on biomedical research, the current evidence cannot guide policy stratification by type or magnitude. Given the broad adoption of policies that distinguish between COI types and set disclosure thresholds, the shortcomings identified here are weaknesses of current research that must be addressed. Importantly, however, we are not calling for a suspension of COI policies while this research is conducted. Inaccurate claims to insufficient evidence have long served to limit the scope of COI policies and to delay adoption.[15] A precautionary approach would involve adopting more restrictive unstratified policies until such time that certain COI types are demonstrated to be of lower risk. Furthermore, our findings also suggests that these problematic claims may have adversely affected COI research itself. Unspecified calls for "more research" might partially explain why, despite the clear findings of the 2017 meta-study [2], so many studies continue to assess if COI has an effect rather than which COI have what effects and why. Instead of suggesting the need for more COI research broadly, the current methodological review points towards targeted research needs about COI types and magnitudes. If stratified policies at research institutions are to mitigate the risks of COI, they must be based on comparative assessments of differential risks.

Data Availability Statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Ethics Approval: This study did not require ethics approval as it did not involve human subjects.

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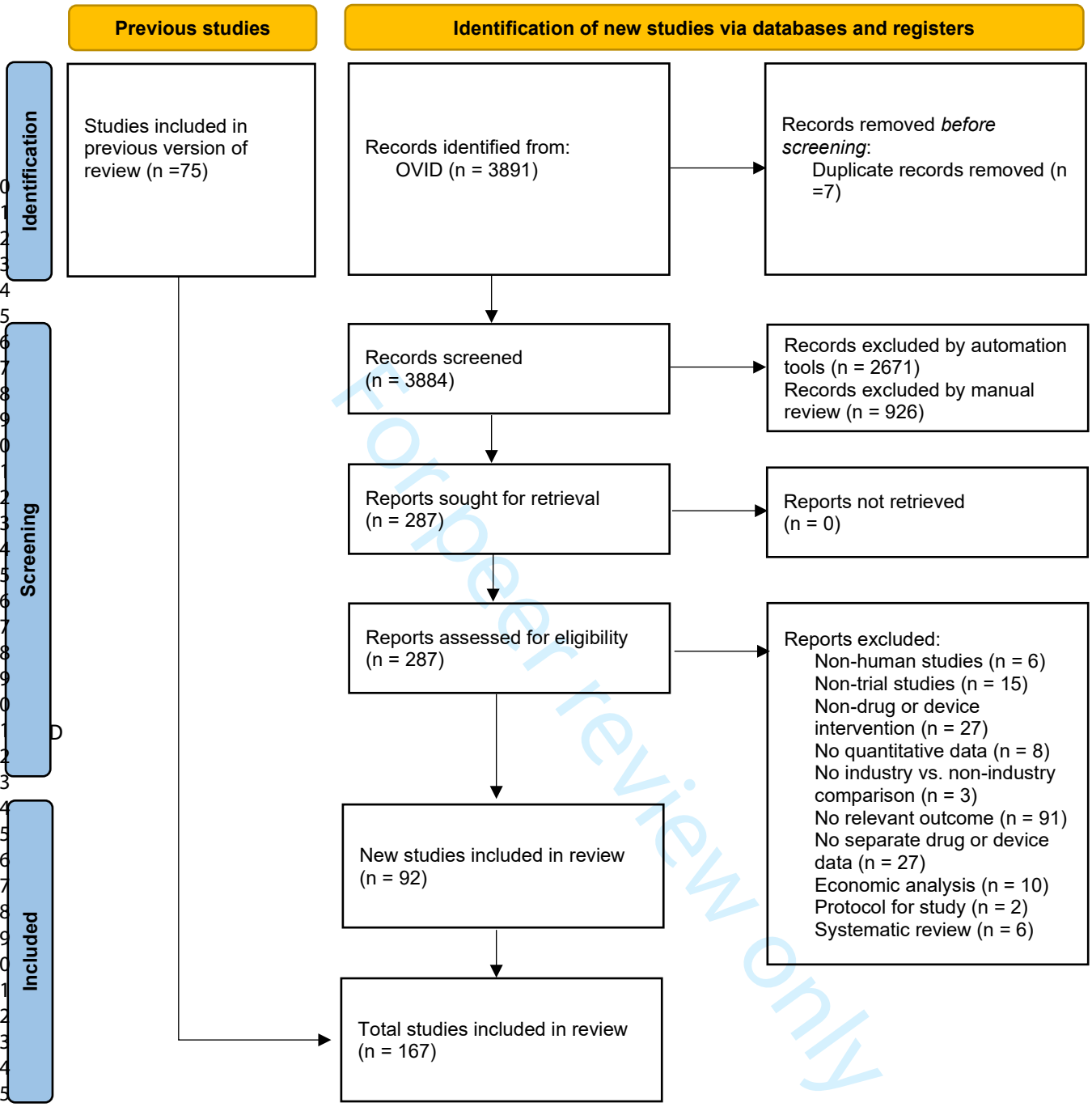
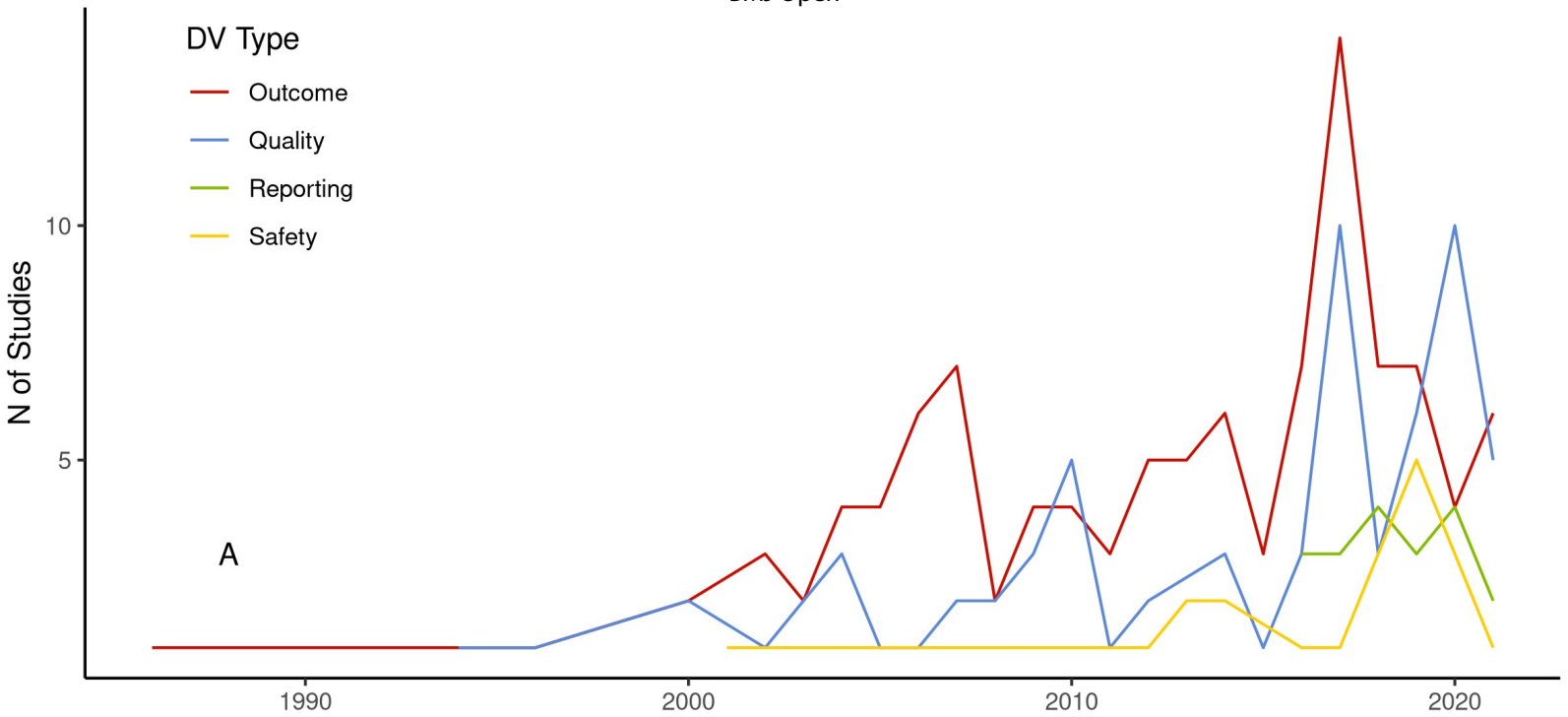
Figure Legends

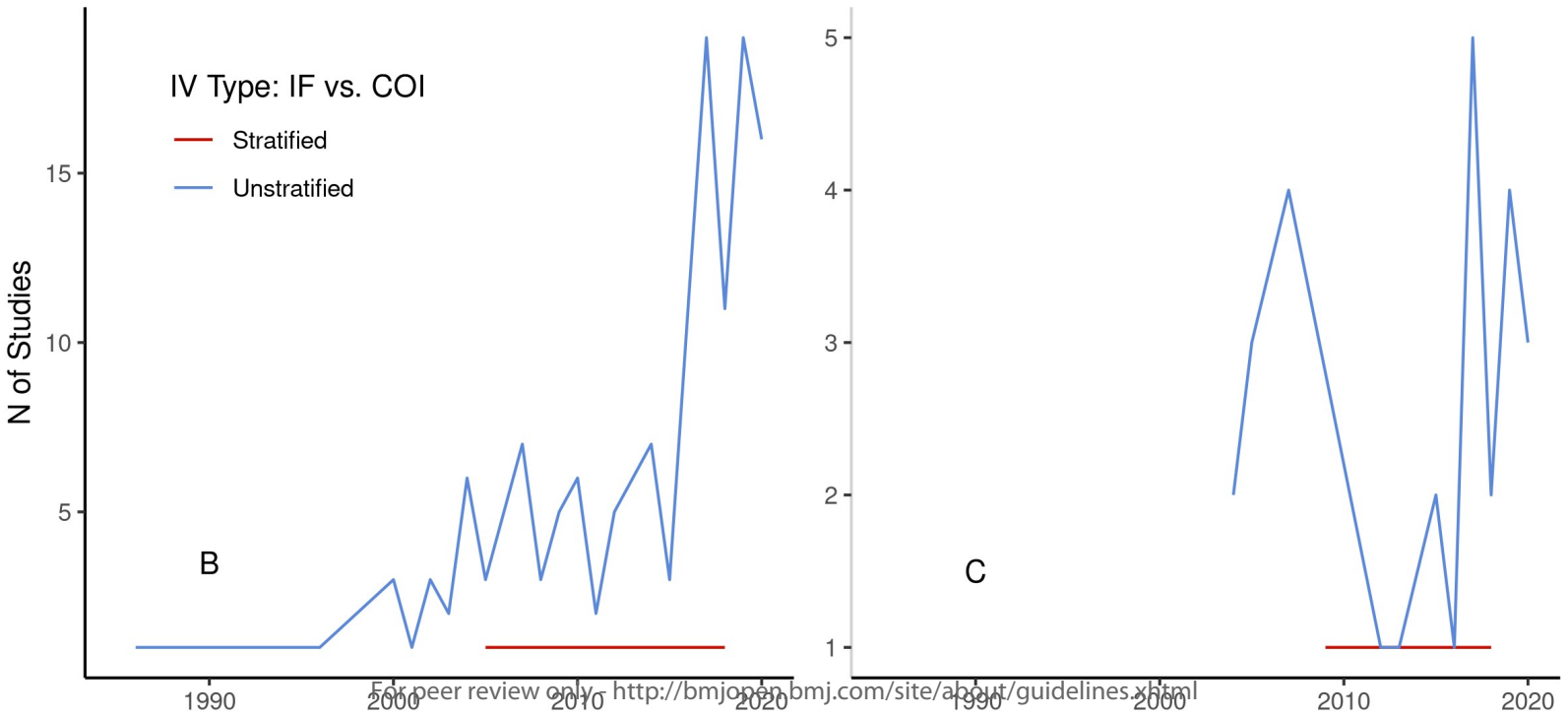
Figure 1. PRISMA Flow Diagram

Figure 2: Variable Types By Year Number (1986-2021). Figure includes number of studies per year by dependent variable (DV) type (A), number of studies by independent variable (IV) type for studies assessing industry funding (B) and number of studies by IV type for studies evaluating COI (C).

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only







Supplementary Online Materials

Industry Funding Independent Variable (IV) Type.	
Stratified	Study provides a quantitative assessment of the relationship between different types of industry funding and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of industry funding categories. Funder stratifications may include level of involvement (primary, secondary), relationship to drug or device under study (manufacturer, competitor), or mode of sponsorship (study sponsor, medication provider, author employer).
Unstratified	Industry funding is analyzed as a dichotomous variable or as one category in a categorical variable, e.g. funder types might include industry, government, nonprofit.
Magnitude	Industry funding is a continuous variable representing either the total number of industry funders per study or total dollar value of contributions.
Author COI IV Type	
Stratified	Study provides a quantitative assessment of the relationship between different types of COI and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of COI categories. COI stratifications may include type of disbursement (employment, speaker fees, etc) and affiliation (trial sponsor vs. non-sponsor funder).
Unstratified	COI is analyzed as a dichotomous variable or as one category in a categorical variable, e.g., Industry funding, Author COI, Government Funding.
Magnitude	COI is a continuous variable representing either the total number of relationships or the total dollar value of contributions.
COI as Proxy for Industry Funding Study	
Yes	Disclosed author COI are used as inclusion criteria for industry funding.
No	Disclosed COI are not used as inclusion criteria for industry funding or industry funding is not measured.
IV Dichotomization	
NA	The IV used in the statistical analysis was stratified or an assessment of magnitude.
Yes	The categorical schema was converted to dichotomous variables that were used for analysis.
No	The IV was consistently treated as dichotomous throughout the article.
Dependent Variable Type (DV Type)	
Outcome	The analysis evaluates if chosen IVs are associated with results indicating the success of the intervention (drug, device, etc) or are otherwise favorable to trial sponsors. Includes drug efficacy, response rate, positive interpretation of findings, etc.
Safety	The analysis evaluates if chosen IVs associate with results related to drug safety.
Quality	The analysis evaluates if chosen IVs are associated with results related to methodological or reporting quality. Includes issues of statistical power, risk of bias, presence of hype or spin.
Reporting	The analysis evaluates whether or not trial results were reported at all. May include reporting to ClinicalTirals.Gov or publication of findings.

Supplemental Table 1. Methodological Design Feature Schema for Analyzed Studies. Definition and details for industry funding IV type, author COI IV type, COI as proxy for industry funding, dichotomization, and DV type analyses.

Article	*Year*	*IF IV Type*	*COI IV Type*	*DV Type*	*COI Proxy*	*IF Dichotomize*	*COI Dichotomize*
Abildgaard et al. (1)	2019	Unstratified	None	Outcome	yes	yes	NA
Addeo et al. (2)	2019	Unstratified	None	Outcome, Safety	no	no	NA
Ahmer et al. (3)	2005	Stratified	Unstratified	Outcome	no	NA	no
Ahn et al. (4)	2016	Unstratified	Unstratified	Outcome	no	no	yes
Alasbali et al. (5)	2009	Unstratified	None	Outcome, Quality	no	no	NA
Als-Nielsen et al. (6)	2003	Unstratified	None	Outcome	yes	NA	NA
Avni et al. (7)	2004	Unstratified	None	Quality	no	no	NA
Azad et al. (8)	2019	Unstratified	None	Quality	no	NA	NA
Azharuddin et al. (9)	2020	Unstratified	None	Quality	no	no	NA
Barden et al. (10)	2005	Unstratified	None	Outcome	yes	no	NA
Bariani et al. (11)	2013	Unstratified	Unstratified	Outcome	no	yes	yes
Bartels et al. (12)	2012	Unstratified	Stratified	Outcome	yes	no	NA
Bero et al. (13)	2007	Unstratified	Unstratified	Outcome	no	NA	no
Bhandari et al. (14)	2004	Unstratified	None	Outcome	no	yes	no
Bighelli et al. (15)	2020	Unstratified	Unstratified	Quality	no	no	NA
Bond et al. (16)	2012	Stratified	Unstratified	Outcome	yes	NA	no
Booth et al. (17)	2008	Unstratified	None	Outcome, Quality	no	NA	NA
Bourgeois et al. (18)	2010	Unstratified	None	Outcome, Quality	no	NA	NA
Brown et al. (19)	2006	Unstratified	None	Outcome, Quality	no	no	NA
Buchkowsky and Jewesson (20)	2004	Unstratified	Unstratified	Outcome	no	NA	no
Budhiraja et al. (21)	2021	Unstratified	None	Outcome	no	NA	NA
Bugano et al et al. (22)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Catillon (23)	2019	Unstratified	Unstratified	Quality	no	no	NA
Chang et al. (24)	2021	Unstratified	None	Quality	no	NA	NA
Chard et al. (25)	2000	Unstratified	None	Outcome, Quality	no	NA	NA
Chen et al. (26)	2016	Unstratified	None	Reporting	no	NA	NA
Cherla et al. (27)	2018	None	Stratified	Outcome	no	NA	NA
Cho and Bera (28)	1996	Unstratified	None	Outcome, Quality	yes	no	NA
Clark et al. (29)	2002	Unstratified	None	Outcome	no	no	NA
Clifford et al. (30)	2002	Unstratified	None	Outcome, Quality	no	NA	NA
Corona et al. (31)	2014a	Unstratified	None	Quality, Safety	yes	no	NA
Corona et al. (32)	2014b	Unstratified	None	Outcome, Quality	yes	no	NA
Cristea et al. (33)	2017	None	Unstratified	Outcome	no	NA	no
Crocetti et al. (34)	2010	Unstratified	None	Quality	no	NA	NA
Davidović et al. (35)	2021	Unstratified	None	Outcome, Reporting	no	no	NA
Davidson (36)	1986	Unstratified	None	Outcome	yes	no	NA

Davis et al. (37)	2008	Unstratified	None	Outcome	yes	no	NA
de Souza Gutierres et al. (38)	2020	Unstratified	None	Quality	no	no	NA
DeFrance et al. (39)	2021	None	Unstratified	Outcome	no	NA	no
DeGeorge et al. (40)	2015	Unstratified	Unstratified	Outcome	no	NA	no
Del Paggio et al. (41)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Falk Delgado and Falk Delgaddo (42)	2017a	Unstratified	None	Outcome	no	NA	NA
Falk Delgado and Falk Delgaddo (43)	2017b	Unstratified	Unstratified	Reporting	no	NA	no
DePasse et al. (44)	2018	Unstratified	None	Reporting	no	NA	NA
DeVito et al. (45)	2020	Unstratified	None	Reporting	no	NA	NA
Djulbegovic et al. (46)	2013	Unstratified	None	Outcome	no	no	NA
Djulbegovic et al. (47)	2000	Unstratified	None	Quality	yes	no	NA
Etter et al. (48)	2007	Unstratified	None	Outcome	yes	no	NA
Finucane and Boult (49)	2004	Unstratified	None	Outcome	yes	no	NA
Flacco et al. (50)	2015	Unstratified	Unstratified	Outcome, Quality	yes	yes	no
Fraguas et al. (51)	2018	Unstratified	None	Quality	no	no	NA
Freemantle et al. (52)	2000	Unstratified	None	Outcome	no	no	NA
Fung et al. (53)	2017	Unstratified	None	Quality, Reporting	no	no	NA
Gabler et al. (54)	2016	Unstratified	None	Reporting, Quality	no	no	NA
Gan et al. (55)	2012	Unstratified	None	Quality	no	no	NA
Gao et al. (56)	2019	Unstratified	None	Quality	no	NA	NA
Gartlehner et al. (57)	2010	Unstratified	None	Outcome, Quality	yes	no	NA
Gaudino et al. (58)	2020	Unstratified	Unstratified	Outcome, Quality	yes	no	yes
Gonzalez et al. (59)	2019	Unstratified	None	Quality	no	NA	NA
Grey et al. (60)	2018	Unstratified	None	Outcome	no	no	NA
Gyawali et al. (61)	2019	Unstratified	None	Safety	no	NA	NA
Hajibandeh et al. (62)	2017	Unstratified	Unstratified	Outcome	no	no	no
Halpern et al. (63)	2004	Unstratified	None	Quality	no	NA	NA
Hanna et al. (64)	2016	Unstratified	None	Outcome	no	NA	NA
Hashemipour et al. (65)	2019	Unstratified	Unstratified	Outcome	no	no	no
Hengartner et al. (66)	2021	Unstratified	None	Safety	yes	no	NA
Heres et al. (67)	2006	Unstratified	None	Outcome	no	no	NA
Janiaud et al. (68)	2018	Unstratified	None	Outcome	no	yes	NA
Jefferson et al. (69)	2009	Unstratified	None	Quality	no	no	NA
Jellison et al. (70)	2020	Unstratified	None	Quality	no	yes	NA
Jinapriya et al. (71)	2011	Stratified	None	Outcome	no	NA	NA
Johnson et al. (72)	2020	Unstratified	None	Reporting	no	NA	NA

Jones et al. (73)	2010	Unstratified	None	Quality	no	NA	NA
Kakkar et al. (74)	2019	Unstratified	None	Quality	no	no	NA
Kapelios et al. (75)	2020	Unstratified	None	Outcome, Quality	no	no	NA
Kelly et al. (76)	2006	Stratified	None	Outcome	yes	NA	NA
Kemmeren et al. (77)	2001	Unstratified	None	Safety	no	no	NA
Khan et al. (78)	2012	Unstratified	None	Outcome, Quality	no	NA	NA
Killin et al. (79)	2014	Unstratified	None	Outcome	yes	no	NA
Kjaergard and Als-Nielson (80)	2002	Unstratified	None	Outcome	no	NA	NA
Lee et al. (81)	2012	Unstratified	None	COI, Outcome	no	no	NA
Lee et al. (82)	2020	Unstratified	None	Reporting	no	no	NA
Leite et al. (83)	2017	Unstratified	Unstratified	Outcome	no	no	no
Leucht et al. (84)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Leucht et al. (85)	2019	Unstratified	None	Outcome	no	no	NA
Linker et al. (86)	2017	Unstratified	None	Outcome, Quality	no	NA	NA
Liss (87)	2006	Unstratified	None	Outcome	yes	no	NA
Liu et al. (88)	2018	Unstratified	None	Outcome	no	NA	NA
Lubowitz et al. (89)	2007	Unstratified	None	Outcome	no	no	NA
Lynch et al. (90)	2007	Unstratified	None	Outcome, Quality	yes	NA	NA
Ma et al. (91)	2014	Unstratified	None	Outcome, Safety	no	no	NA
Magnani et al. (92)	2021	Unstratified	None	Reporting, Outcome	no	NA	NA
Maillet et al. (93)	2015	Unstratified	None	Outcome	no	no	NA
Malek et al. (94)	2017	Unstratified	None	Outcome	no	no	NA
Mian et al. (95)	2020	Unstratified	None	Quality	no	NA	NA
Mitchell and Patterson (96)	2020	Unstratified	None	Quality	no	NA	NA
Momeni et al. (97)	2009	Unstratified	None	Outcome	no	NA	NA
Moncrieff (98)	2003	Unstratified	None	Outcome	no	no	NA
Montgomery et al. (99)	2004	Unstratified	Unstratified	Outcome, Quality	no	no	no
Moraes et al. (100)	2017	Unstratified	Unstratified	Outcome	no	NA	no
Mossman et al. (101)	2021	Unstratified	None	Outcome	no	no	NA
Naci et al. (102)	2014	Unstratified	None	Outcome, Quality	no	no	NA
Ng et al. (103)	2016	Unstratified	None	Quality	no	no	NA
Nieto et al. (104)	2007	Unstratified	None	Safety	no	no	NA
Nithianandan et al. (105)	2020	Unstratified	Unstratified	Outcome	no	no	no
Odutayo et al. (106)	2017	Unstratified	None	Outcome	no	no	NA
Paggio et al. (107)	2021	Unstratified	None	Quality	no	no	NA
Pasalic et al. (108)	2020	Unstratified	None	Quality	no	no	NA
Pengel et al. (109)	2009	Unstratified	None	Quality	yes	NA	NA

Pepper et al. (110)	2019	Unstratified	None	Safety	no	no	NA
Peppercorn et al. (111)	2007	Unstratified	Unstratified	Outcome	yes	no	no
Perlis et al. (112)	2005a	Unstratified	Unstratified	Outcome, Quality	yes	no	no
Perlis et al. (113)	2005b	Unstratified	Unstratified	Outcome	yes	no	no
Popelut et al. (114)	2010	Unstratified	None	Outcome	no	NA	no
Pouwels et al. (115)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Prakash et al. (116)	2018	Unstratified	None	Quality	no	NA	NA
Price-Haywood et al. (117)	2019	Unstratified	None	Safety	no	NA	NA
Printz et al. (118)	2013	Unstratified	None	Outcome	yes	no	NA
Probst et al. (119)	2016	Unstratified	None	Outcome	no	no	NA
Punja et al. (120)	2016	Unstratified	None	Outcome, Safety	no	no	NA
Putman et al. (121)	2021	Unstratified	None	Quality	yes	no	NA
Raman et al. (122)	2018	Unstratified	Unstratified	Outcome	no	NA	no
Rasmussen et al. (123)	2009	Unstratified	None	Outcome	yes	yes	NA
Rattinger and Bero (124)	2009	Stratified	Stratified	Outcome	yes	NA	NA
Reda et al. (125)	2016	Unstratified	None	Outcome, Quality	no	yes	NA
Rees et al. (126)	2019	Unstratified	None	Reporting	no	NA	NA
Ridker and Torres (127)	2006	Unstratified	None	Outcome	no	NA	NA
Rios et al. (128)	2008	Unstratified	None	Quality	no	NA	NA
Rochon et al. (129)	1994	Unstratified	None	Outcome, Quality	yes	no	NA
Roddick et al. (130)	2017	Unstratified	None	Outcome	no	NA	NA
Roper et al. (131)	2014	Unstratified	None	Limitations, Outcome	no	NA	NA
Rosner et al. (132)	2010	Unstratified	None	Outcome, Quality	no	no	NA
Rosner et al. (133)	2011	Unstratified	None	Outcome	no	NA	no
Saa et al. (134)	2018	Stratified	None	Outcome, Quality	yes	NA	NA
Saleh et al. (135)	2020	Unstratified	None	Outcome	no	no	NA
Sendyk et al. (136)	2019	Unstratified	None	Quality, Reporting	no	no	NA
Shepard et al. (137)	2021	Unstratified	None	Quality	no	NA	NA
Silva et al. (138)	2017	Unstratified	None	Safety, Quality	no	no	NA
Simonetti et al. (139)	2019	Unstratified	None	Safety	no	no	NA
Sinyor et al. (140)	2012	Unstratified	None	Outcome, Safety	yes	no	NA
Son et al. (141)	2016	Unstratified	None	Outcome	no	no	NA
Spanemberg et al. (142)	2011	Unstratified	None	Outcome, Quality	no	no	NA
Sriganesh et al. (143)	2017	Unstratified	None	Quality	no	no	NA
Stefaniak et al. (144)	2017	Unstratified	None	Reporting, Quality	no	NA	NA
Steffens et al. (145)	2021	Unstratified	None	Quality	yes	no	NA

Sung et al. (146)	2013	Unstratified	None	Outcome	yes	no	NA
Tiabau et al. (147)	2018	Unstratified	None	Outcome	no	NA	NA
Trinquart et al. (148)	2018	Unstratified	None	Reporting	no	no	NA
Tulikangas et al. (149)	2006	Unstratified	None	Outcome	no	no	NA
Tungaraza and Poole (150)	2007	Unstratified	Unstratified	Outcome	no	no	no
Urrutia et al. (151)	2016	Unstratified	None	Reporting	no	no	NA
van den Bogert et al. (152)	2017	Unstratified	None	Quality	no	yes	NA
van Heteren et al. (153)	2019	Unstratified	None	Reporting	no	NA	NA
Van Lent et al. (154)	2014	Unstratified	None	Outcome	yes	NA	NA
Venincasa et al. (155)	2019	Unstratified	Unstratified	Outcome	no	no	no
Vlad et al. (156)	2007	Stratified	Unstratified	Outcome, Quality	no	NA	no
Walkup et al. (157)	2017	Unstratified	None	Outcome	no	no	NA
Walter et al. (158)	2020	Unstratified	None	Reporting	no	no	NA
Waqas et al. (159)	2019	Unstratified	Unstratified	Outcome	no	no	no
Welsh et al. (160)	2018	Unstratified	Unstratified	Reporting	no	NA	no
Wise et al. (161)	2021	Unstratified	Unstratified	Outcome	no	yes	yes
Wong et al. (162)	2019	Unstratified	None	Outcome	no	no	NA
Wortzel et al. (163)	2020	Unstratified	None	Quality	no	NA	NA
Xu et al. (164)	2013	Unstratified	None	Safety	no	no	NA
Yilmaz et al. (165)	2018	Unstratified	None	Reporting	no	no	NA
Youssef et al. (166)	2016	Unstratified	None	Outcome	no	no	NA
Zhang et al. (167)	2013	Unstratified	None	Outcome, Safety	no	no	NA

Supplemental Table 2. Methodological Design Analysis for All Collected Articles. Includes industry funding IV type, author COI IV type, DV type(s), COI as proxy, and dichotomization data.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review. (Methodological review)	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-7
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6-7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	8; supp
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8-9
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9-10
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9-10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	10
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	10-15; supp
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	10-15
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10-15
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	15-18
Limitations	20	Discuss the limitations of the scoping review process.	17
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	22

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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Evidence for Stratified Conflicts of Interest Policies in Research Contexts: A Methodological Review

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Abstract

Objectives: The purpose of this study was to conduct a methodological review of research on the effects of conflicts of interest (COI) in research contexts.

Design: Methodological review.

Data Sources: Ovid.

Eligibility Criteria: Studies published between 1986 and 2021 conducting quantitative assessments of relationships between industry funding or COI and four target outcomes: positive study results, methodological biases, reporting quality, and results-conclusions concordance.

Data Extraction and Synthesis: We assessed key facets of study design: Our primary analysis identified whether studies stratified industry funding or COI variables by magnitude (i.e., number of COI or disbursement amount), type (employment, travel fees, speaking fees) or if they assessed dichotomous variables (i.e., conflict present or absent). Secondary analyses focused on target outcomes and available effects measures.

Results: Of the 167 articles included in this study, a substantial majority (98.2%) evaluated the effects of industry sponsorship. None evaluated associations between funding magnitude and outcomes of interest. Seven studies (4.3%) stratified industry funding based on the mechanism of disbursement or funder relationship to product (manufacturer or competitor). A fifth of the articles (19.8%) assessed the effects of author COI on target outcomes. None evaluated COI magnitude, and 3 studies (9.1%) stratified COI by disbursement type and/or reporting practices. Participation of an industry-employed author showed the most consistent effect on favorability of results across studies.

Conclusions: Substantial evidence demonstrates that industry funding and COI can bias biomedical research. Evidence-based policies are essential for mitigating the risks associated with COI. Although most policies stratify guidelines for managing COI, differentiating COIs based on the type of relationship or monetary value, this review shows that the available research

has generally not been designed to assess the differential risks of COI types or magnitudes. Targeted research is necessary to establish an evidence base that can effectively inform policy to manage COI.

Strengths and limitations of this study

- We considered a broad range of available research on the effects of industry funding and COI on biomedical research.
- This methodological review evaluates research designs assessing the relationships between industry funding or author COI and biomedical research.
- We achieved high inter-rater reliability for article screening.
- This review does not address studies of the relationships between industry funding or COI and guidelines development, regulatory decision-making, or clinical practice.

Background

Substantial evidence indicates that industry funding of biomedical research and author financial conflicts of interest (COI) arising from financial relationships with medically-related industry can bias research results.[1–7] Associations between industry funding or COI and positive outcomes, such as results favorable to the sponsor, are the most well documented.[2–5,7] Available evidence indicates that industry-funded trials can be up to 5.4 times more likely to return positive results than trials not sponsored by industry,[8] and trials with author COI may be as much as 8.4 times more likely to return favorable results when compared to those without author COI.[6] Additional research has demonstrated that industry funding and COI may be associated with reduced drug and device safety[6,9] and can have adverse effects on the methodological quality of clinical trials.[10–12] Recent studies also suggests that industry sponsorship may be associated with premature trial termination and non-reporting of trial results.[13,14] Calls for more evidence documenting that industry funding and COI can measurably bias biomedical research persist even though these findings have been repeatedly replicated.[15]

Recognizing the risks of bias, many organizations involved in biomedical research have adopted specific policies designed to address industry funding and COI. These include both policies designed to manage the risks associated with individual researcher COIs and guidelines addressing potential institutional COI resulting from industry gifts and research sponsorship. The need for such policies is clear, which in turn raises important questions about the form those policies should take. Differentiation among COI types and magnitudes is a common feature of the policies adopted by universities, academic medical centers (AMCs), government laboratories, and similar research institutions. COI policy guidelines published in the literature and by professional medical organizations also routinely differentiate among different COI types and

magnitudes. That is, COI policies and guidelines routinely make distinctions based on the method of remuneration (industry employment, consultancy relationships, honoraria, travel fees, etc.), the nature of the funder (e.g., industry, nonprofit, government agency), the recipient of remuneration (e.g., self, partner, family, collaborator), and the magnitude or monetary value of the disbursement. Table 1 describes explicit recommendations by the American Medical Student Association (AMSA),[16] the Association of Academic Medical Centers (AAMC),[17] the British Medical Association (BMA),[18] and Brennen et al.[19]

These COI policies and guidelines suggest that some types of COI should be prohibited outright, others should be subjected to specific restrictions, and some should merely require disclosure. However, different policies and guidelines do not agree on the risk presented by different types or magnitudes of COI. The recommendations typically advise a total prohibition on gifts from industry and ghostwriting, but recommendations about other COI types vary widely. For example, AMSA recommends restrictions on consulting fees, but the AAMC, BMA, and Brennen et al. do not address consultancies outside general recommendations for transparency via COI disclosure. All four guidelines disagree if industry representative access to research spaces should be restricted or prohibited outright.

Various policies also make distinctions about the magnitude or monetary value of COI to set disclosure thresholds. However, recommended thresholds vary widely within and between organizations. For example, since 1995, the US Department of Health and Human Services has required AMCs and other entities that receive federal research funding to adopt policies that require disclosure of COI over a certain threshold.[20] This value was lowered from $10,000 to $5,000 in 2011.[21] The BMA sets the declaration threshold for gifts at £500 and for equity holdings at greater than 1% of the value of the company or greater than £25,000.[18]

COI	AMSA	AAMC	BMA	Brennen et al.
Attendance at unaccredited industry-sponsored events	Prohibit			Prohibit
Consulting	Restrict			
Donations			Disclose	
Ghostwriting	Prohibit	Prohibit		Prohibit
Gifts	Prohibit	Prohibit	Prohibit	Prohibit
Grants			Disclose	
Industry access- device representatives	Restrict	Restrict		Restrict
Industry access- pharmaceutical representatives	Prohibit	Restrict	Restrict	Prohibit
Industry sponsored CME	Restrict	Restrict		Restrict
Industry sponsored scholarships		Restrict		
Meals	Prohibit			Prohibit
Pharmaceutical samples		Restrict		
Research contracts			Disclose	
Speakers bureaus	Prohibit			Prohibit
Travel funds		Restrict		
Travel for industry sponsored meetings		Prohibit		
Travel funds for trainees	Prohibit		Prohibit	Prohibit
Treatment inducements	Prohibit			

Table 1: Illustrative Recommendations for Strata-Specific COI Policies. This table shows AMSA,[16] AAMC,[17] BMA,[18] and Brennen et al.'s[19] recommendations for whether AMC COI policies should prohibit, restrict, or require disclosure of specific COI strata. Where entries are blank, the guidance provided no specific recommendations for that type of relationship.

The establishment of approaches to COI management that differentiate by type and magnitude indicate that common guidance *assumes* that different COI types and magnitudes carry different degrees of risk for biomedical research and require different responses. This assumption even drives much of the available research on COI policies at AMCs and similar

institutions. The AMSA scorecard, for example, is a well-established framework for COI policy evaluation.[16,22] It has been used to assess the extent to which COI policies at AMCs in the United States,[16] France,[23] and Germany [24] follow AMSA recommendations for COI policy construction and stratification.

Despite the significant investments in developing and evaluating stratified COI policies, it is not clear that different types of COI do, in fact, carry different risks or levels of risk for biomedical research. If one were to assess the efficacy of COI policies (i.e., determine if COI policies have any effects on the quality of research), one must first assess whether policies stratified by COI types are grounded in evidence about the differential risks of different COI types. This study sought to assess the extent to which orthodox research designs for assessing the effects of COI on biomedical research have been designed to generate evidence relevant to the stratification of COI policies. Demonstrating the existence of differential risk profiles for different COI types would require, at minimum, research designs that stratify COI variables prior to analysis. They should further disaggregate industry research sponsorship generally from specific forms of author COI. Therefore, the goal of this methodological review is to evaluate the extent to which study designs in available industry funding and COI research can support COI policies or that policy recommendations should assume differential risk profiles for different types of COI and/or different monetary values. Put another way, the evidence for the need for mitigating the risks imposed by COI is strong, but the state of the research that can guide *how* to manage that risk is unclear. This study reviews methodological designs for 1) industry funding variable stratification and disaggregation, 2) COI variable stratification and disaggregation, and 3) diversity of outcomes assessments.

Methods

Methodological reviews are designed to provide information on the prevalence of available study designs in a body of literature. They have facilitated advances in a wide variety of health and health policy contexts and can be used to identify and prioritize new pathways for research [25–28]. A methodological review is the ideal approach for this study, which requires identifying if research on the effects of industry funding and COI has been conducted in ways that could support current COI policy stratifications. Our review proceeded in three phases. First, we replicated the search strategy and article screening protocol for a previously published Cochrane systematic review of the effects of industry funding on biomedical research.[2] The prior Cochrane review evaluated the overall strength of the evidence base regarding the association of industry funding with results favorable to the sponsor, risks of bias associated with the methodological design, and the quality of reporting of the concordance between results and conclusions, but it did not document the methodological design elements in focus in this study.[2] While the meta-analysis did not expressly evaluate author COI as an isolated variable "conflicts of interest" was a key term in the search strategy, and many articles included in the Cochrane review used COI as proxy for industry funding. Our study adopted the search strategy and screening protocol of the original review, and the second phase of this review involved conducting a novel assessment of the methodological features of included articles, with particular focus on how industry funding and COI variables were operationalized in statistical analyses. Finally, we used these data to synthesize the evidence for evaluating different types of industry funding or author COI on target outcomes in biomedical research.

Search strategy and study selection

We began by replicating the search strategy in a previously published Cochrane review. The strategy was designed to identify relevant articles indexed in the Ovid database. (See the supplementary materials for complete details.) The original review and screening protocol identified 75 studies of interest published between 1986 and 2016. We retrieved each of the original 75 studies, and in June 2021, we repeated the search strategy to collect additional relevant articles published since 2016. We also replicated the study inclusion protocol from the previous Cochrane review. Specifically, eligible studies provided a quantitative assessment of the extent to which industry funding or author COI were associated with target outcomes of interest (i.e., results favorable to industry, methodological biases, reporting quality, and results-conclusions concordance) within research on drug and device products. All collected studies evaluated one of these outcomes on a dataset of clinical trials. Clinical trials data may come from published articles, clinical trials registries, or both. Studies of the effects of industry funding and/or COI in research areas related to smoking, nutrition, physical therapy, psychotherapy, and surgery were excluded except in cases where analyses were performed on separate identifiable drug or device data. Additionally, studies that evaluated the effects of industry funding or COI on clinical practices, guidelines development, patient organizations, and regulatory policy were excluded.

Three evaluators screened titles and abstracts. After initial norming, a random sample of 255 titles and abstracts were selected by all three raters to assess reliability across screeners. A sample size of 255 was chosen to achieve 90% assurance using the intraclass correlation coefficient (ICC).[29] Overall agreement between the three raters was 94.9% with an ICC = 0.801. A secondary analysis of the random sample indicated that the abstracts for all articles selected for further screening included at least one of the following terms: “funding,” “funded,”

"COI," "fCOI," "conflict," or "sponsor," which allowed us to develop an automated screening tool based on those terms. Articles selected for full-text review passed both automated and manual screening. The full article text of the remaining articles was evaluated by three raters.

Data Extraction and Synthesis

The current methodological review was designed to collect data on the underlying analytic designs in selected articles. Specifically, the investigators collected data on which independent and dependent variables had been operationalized and defined. That is, each industry funding and COI independent variable was categorized as "stratified," "unstratified," or "magnitude." Here, "stratified," refers to what is often called categorical or nominal variables. For example, a study that stratified industry funding variables might assess if funding provided by a drug manufacturer or a competing pharmaceuticals company has differential impacts on target outcomes. Similarly, a study that stratified a COI variable might evaluate the relative impact of different disclosed COI types such as "industry employed author," "receipt of consulting fees," or "receipt of travel fees." We classified independent variables as "magnitude" if they assessed industry funding or COI as a continuous or ordinal variable. This might mean assessing industry funding in terms of disbursed amounts (e.g., $5000 or £20,000) or the total number of COI per article. Relevant variables were identified as "unstratified" when they were assessed as simply present or absent (e.g., industry funded vs. non-industry funded or reported COI vs. no reported COI). We also noted if variables had been dichotomized prior to analysis. This occurs when articles present stratified variable data as part of descriptive statistics, but then perform statistical analyses on simplified, unstratified, dichotomous industry funding or COI variables.

Our analysis also assessed whether author COI was used as a proxy for industry funding. This research design choice would indicate that the article in question did not fully disaggregate general industry sponsorship from specific types of author COI. Each outcome variable was also categorized according to the primary domain of interest, including outcome favorability to sponsor, drug or device safety; quality of study design or reporting; and if results were reported at all. Finally, for all articles with stratified independent variables for industry funding or author COI, we identified clinical areas of interest, sample sizes used, each assessed stratum, outcomes against which the stratum were assessed, significance of the results, and any reported effect sizes. A complete description of the criteria is available in Supplemental Table 1.

Patients and Public Involvement

No patients or public were involved in the study.

Results

Our replication of the previously published search strategy retrieved 3,884 unique records for articles published in 2016 and later. Automated screening removed 2,671 articles from consideration. Subsequent manual screening of titles and abstracts excluded another 926 articles. The remaining 287 articles were selected for full text review, and 92 studies were ultimately selected for inclusion. An additional 75 articles were included from the preexisting systematic review for a dataset of 167 articles. (See Figure 1.)

Industry Funding Variable Assessment

Of the 167 articles included in this study, a substantial majority (n = 164, 98.2%) evaluated the effects of industry sponsorship (See Supplemental Table 2). In most cases, industry funding was determined based on an article's acknowledgements or sponsorship declaration.

However, some studies collected data from clinical trials registries like clinicaltrials.gov, which index sponsorship. Notably, thirty-five studies (21.3%) assessing industry funding used author employment in industry or other author COI as part of the inclusion criteria for a variable identified as "industry funding" or "industry sponsorship." Studies also used industry provision of drugs or devices as a criterion for industry funding. Others treated provision of supplies as its own isolated variable.

Among the articles that assessed industry funding in some form, none evaluated associations between funding magnitude and outcomes of interest. Ten studies (6.1%) collected stratified data on industry funding but dichotomized the variable prior to statistical analysis. Only seven studies (4.3%) stratified industry funding for analysis in any way. Evaluated strata included details about the nature of the sponsor (evaluated drug manufacturer vs. competitor company) or the nature of the sponsorship (full study sponsorship, collaborative sponsorship with other funders, or provision of medications). Three of the seven studies included assessed differences in favorable outcomes based on funder relationship to the product evaluated (e.g., manufacturer vs. competitor company).[30–32] Only one study found significant results:[30] This review of 542 psychiatry studies found that a greater percentage of studies sponsored by the drug manufacturer have positive outcomes than those not sponsored by a pharmaceutical company (78% vs 48%), and that research sponsored by a competitor had the lowest rate of favorable findings (28%). Pairwise comparisons between manufacturer-funded or competitor-funded and non-industry-funded studies were significantly different, but the study reported no indicators of effect size. Three studies evaluated strata related to the mode of industry involvement.[33–35] These studies assessed the relationship between favorable outcomes and industry provision of medication, report of findings in an industry publication venue, and other (unspecified) industry

involvement. One study found significant results, and reported that "other" industry involvement associates with favorable outcomes for industry.[35] See Table 2 for further details. In sum, a substantial proportion of the research that might provide insight into COI policy design assesses only industry sponsorship generally. Nearly a quarter of the assessed studies conflate industry funding and COI variables making it impossible for results to shed light on potentially useful policy differences. And, finally, studies of industry funding that do stratify variables primarily provide insight on different sponsorship modalities and not on issues related to author COI.

COI Variable Assessment

Of the 167 articles evaluated, only 33 (19.8%) assessed COI as a discrete variable. Attention to COI began considerably later in the dataset, not appearing until 2005. Most studies that evaluated author COI relied on the data in the published disclosure statement. A handful of studies used the authors institutional affiliation as an indicator of industry employment, and a few studies also compared disclosure statements to data available in the Open Payments Database. Of the articles that evaluated author COI, none assessed COI magnitude, and only 3 studies (9.1%) stratified COI for analysis. Four studies (12.1%) collected stratified COI data but dichotomized it prior to analysis. The few studies that assessed COI strata independently tended to evaluate disclosure practices as opposed to COI types.[36–38] These articles report on evaluations of the relationship between favorable outcomes or methodological quality and COI disclosure, lack of funding disclosure, incomplete disclosure, lack of disclosure requirements by journal, or affirmative statements of no author COI. Disclosure of COI and "full" disclosure of COI were most strongly associated with results favorable to industry.[37,38] Here "full" disclosure meant that all payments reported to the Open Payments Database were reflected in published disclosure statements. Assessments of these different disclosure practices returned

non-significant results or smaller effect sizes. Two studies evaluated the relationship between participation of industry-employed authors and results favorable to industry.[33,34] An evaluation of 215 psychiatric studies published between 1998 and 2003 found that participation of industry authors was significantly associated with favorable outcomes.[33] Similarly, an assessment of 91 asthma product studies found that favorable outcomes were more likely for studies with industry-employed authors.[34] (See Table 2.)

Article	Area	Samp.	Outcome	Strata	Sig.	Effect Measure	Effect
Ahmer 2005	psychiatry	306	Outcome Favorability	Industry Provided Medications	0.053	-	-
				Author is Industry Employee	0.01*	OR	8.33 (1.64-50.0)
Bartels 2012	spine research	51	Outcome Favorability	Disclosed COI	<0.05*	OR	16.5 (4.7–58.1)
				Statement of No COI	-	-	-
				Disclosure Not Required by Journal	-	-	-
Bond 2012	asthma	91	Outcome Favorability	Industry Sponsorship	0.546	-	-
				Industry Publication Venue	0.191		-
				Other Industry Involvement	NR	-	-
				Author is Industry Employee	0.003*	RR	1.42 (1.10-1.82)
Jinapriya 2011	latanoprost	44	Outcome Favorability	Sponsorship by Parent Company	0.53	-	-
				Sponsorship by Competing Company	0.53	-	-
Kelly 2006	psychiatry	542	Outcome Favorability	Sponsorship by Manufacturer	0.001*	-	-
				Sponsorship by Competing Company	0.001*	-	-
Rattinger 2009	Thiazolidinediones	61	Outcome Favorability	Sponsorship by Manufacturer	0.7778	-	-
				Sponsorship by Competing Company	0.037*	OR	0(0,0.886)
				No Funding Disclosure	0.4153	-	-
				Corresponding Author COI	0.3939	-	-
				Corresponding Author is Sponsor Employee	0.5714	-	-
				Corresponding Author No Disclosure	0.4388	-	-

				Corresponding Author COI with sponsor	0.049*	OR	4.125(1.048;19.525
				First Author COI	0.1667	-	-
				First Author is Sponsor Employee	-	-	-
				First Author No Disclosure	-	-	-
				First Author COI with sponsor	0.4588	-	-
Vlad 2007	osteoarthritis	15	Outcome Favorability	Industry Sponsorship	0.05	-	-
				Other Industry Involvement	0.02*	random effects	0.55 (0.29-0.81)
				Author COI	0.04*	random effects	0.55 (0.27-0.84)
Cherla 2018	multiple	590	Outcome Favorability	Full Disclosure	0.001*	OR	8.65 (2.46-30.44)
				Incomplete Industry Disclosure	0.003*	OR	3.61 (1.53-8.51)
				Incomplete Self-Disclosure (Partial)	0.004*	OR	4.14 (1.58-10.82)
				Incomplete Self-Disclosure (None)	0.002*	OR	0.14 (0.37-1.15)
Saa 2018	probiotics	66	Outcome Favorability	Industry sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-
			Methodological or Reporting Quality	Industry Sponsorship	0.491	-	-
				Non-Disclosure of Sponsorship	0.491	-	-

Table 2: Industry funding and COI Strata Assessed and Associated Results. This table describes the clinical area, methodological design (sample, outcome, variable strata), and results of analysis presented in articles that evaluated identifiable industry funding and COI strata.

Target Outcomes Evaluation

Most studies in the dataset (n = 108, 64.7%) evaluated the relationship between industry funding or COI and outcomes favorability for sponsors. Sixty-six (39.5%) evaluated methodological or reporting quality. Nineteen (11.4%) assessed reporting of results, and 15 (9.0%) evaluated drug or device safety. Attention to specific outcomes appears to have changed over time. Industry favorability of study outcomes had long been the dominant focus of research on industry funding and COI. Quality, safety, and reporting grew increasingly prevalent (Figure

2). Importantly, however, studies that stratified industry funding or COI variables were less diverse in their target outcomes. Of the 10 studies that stratified relevant variables, outcomes favorability to industry was assessed in all cases. One study also assessed the relationship between disclosure practices and methodological or reporting quality.[36]

Discussion

For COI policies to make effective distinctions based on nature of relationships or amount of remuneration, these distinctions must be grounded in research that assesses differential risk profiles of COI types and magnitudes. However, a substantial majority of research assessing the effects of industry funding and author COI on biomedical research does not stratify relevant variables. Remarkably, *zero* studies included in this review conducted any assessments of the magnitude of either industry funding or author COI. Additionally, the available literature's ability to support evidence-based stratifications in COI policies is further compromised by regular conflation of industry sponsorship and author COI variables as well as the practice of dichotomizing variables prior to conducting statistical analyses. The few studies that did stratify COI variables tended to focus on disclosure practices rather than COI types, and most studies assess only if COI types associated with results favorable to industry and not if they associated with other target outcomes of interest. These findings point to limitations in current disclosure practices that allow authors a great deal of latitude in reporting and describing COI. The variability of disclosure statements limits the extent to which research on COI can evaluate differential effects. Nevertheless, the results of this methodological review indicate that the available research on industry funding and COI has generally not been designed to guide COI policy stratifications or the establishment of disclosure thresholds.

Appropriate and evidence-based COI policies are essential for safeguarding the integrity of the biomedical research enterprise. Therefore, it is critical that research can meaningfully inform continued policy refinement. Clearly, guiding the design of COI policy requires additional research designed to assess the differential risks associated with various COI types and magnitudes.

Furthermore, research in this area could also be better supported by the development of standardized taxonomies of industry funding and/or author COI. Since the literature variously defines "industry funding" as sponsorship, employment, provision of medications, or any author COI, it is quite difficult to compare and aggregate findings across studies. Likewise, competing understandings of author COI based in different disclosure practices and type definitions also indicate the strong need for robust taxonomies that can guide future research. Empirically validated taxonomies could also support more consistent disclosure practices, which would aid future research evaluating the differential effects of COIs by type or magnitude.

These taxonomies combined with evidence about the magnitude of COIs would allow for computation and aggregation of COIs essential for supporting research that could effectively guide COI policy refinement. New research on the risks of COI would also benefit from continued diversification of outcomes assessment. Recent years have seen a steady expansion of outcomes of interest (e.g., outcomes favorability giving way to more assessments of quality, safety, and reporting practices), but favorability of results is still the overwhelmingly dominant target outcome.

Finally, the results of this review also suggest that researchers and policymakers would benefit from considering COI risks beyond those manageable at the individual researcher level. It is notable that common COI policies and guidelines tend to be strict with respect to relationships

of modest economic benefit to individuals (e.g., meals and travel) whereas relationships with well-documented risks but considerable economic benefit to institutions (e.g., industry grants and collaborations) are largely left out of COI policy recommendations. Furthermore, the strongest evidence relates to author employment in industry, although specific instructions about disclosing employment have been removed from the latest ICMJE disclosure guidance. Given that collaborations with industry are a common form of institutional COI, and one not addressed by individualized COI policies, these findings support recent calls for greater attention to institutional COI at institutions that conduct biomedical research.[39–42] Research conducted primarily at universities, AMCs, and other research institutions may be more prone to bias when it is supported by industry funding or industry collaboration. COI policies that focus on individual researchers alone will not mitigate against these risks.

This study has several limitations that should inform the reading of the findings. Our review evaluates the methodological design and approaches to variable stratification for studies of the relationships between industry funding or author COI and four specified outcomes of interest in biomedical research. Although we are aware of studies that evaluate COI magnitude, for example, they were not returned by our search strategy either because they treat COI magnitude in the aggregate[43] or because they assess non-target outcomes such as associations with commercial publishing practices.[44] Additionally, AMC guidelines are designed to respond to COI risks in multiple domains including research, clinical practice, and medical education. We assume that COI strata related to industry-funded continuing medical education or pharmaceutical representative access to AMCs are designed primarily to address risks of bias associated with medical education and clinical practice. Additional research not covered by this

review is available that evaluates the relationships of industry funding and COI with prescription practices, guidelines development, and policy decision-making.

These limitations notwithstanding, the results suggest that policies designed to address COI risks associated with clinical practice may not effectively safeguard the integrity of biomedical research across institutional contexts because of the gap between policy and available COI research. Furthermore, it is possible that a one-size-fits-all COI policy may not be appropriate. Additional efforts should be made to ensure that COI policies are responsive to risks associated with bias in biomedical research. For example, AMCs should potentially consider differential policies based on institutional roles. Future research might, therefore, investigate the utility of separate COI policies for clinical, educational, and research staff as well as staff holding multiple roles. In such cases, it might be appropriate to require staff to adhere to the most restrictive policy. COI policies should be developed based on an understanding of the differential effects of distinct strata and magnitudes of COI on outcomes across the multiple domains.

Conclusion

Current COI policies in research contexts devote considerable attention to distinguishing between different types and magnitudes of COI. Although substantial evidence exists that industry funding and COI have adverse effects on biomedical research, the current evidence cannot guide policy stratification by type or magnitude. Given the broad adoption of policies that distinguish between COI types and set disclosure thresholds, the shortcomings identified here are weaknesses of current research that must be addressed. Importantly, however, we are not calling for a suspension of COI policies while this research is conducted. Inaccurate claims to insufficient evidence have long served to limit the scope of COI policies and to delay

adoption.[15] A precautionary approach would involve adopting more restrictive unstratified policies until such time that certain COI types are demonstrated to be of lower risk. Furthermore, our findings also suggests that these problematic claims may have adversely affected COI research itself. Unspecified calls for "more research" might partially explain why, despite the clear findings of the 2017 meta-study [2], so many studies continue to assess if COI has an effect rather than which COI have what effects and why. Instead of suggesting the need for more COI research broadly, the current methodological review points towards targeted research needs about COI types and magnitudes. If stratified policies at research institutions are to mitigate the risks of COI, they must be based on comparative assessments of differential risks.

Data Availability Statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Ethics Approval: This study did not require ethics approval as it did not involve human subjects.

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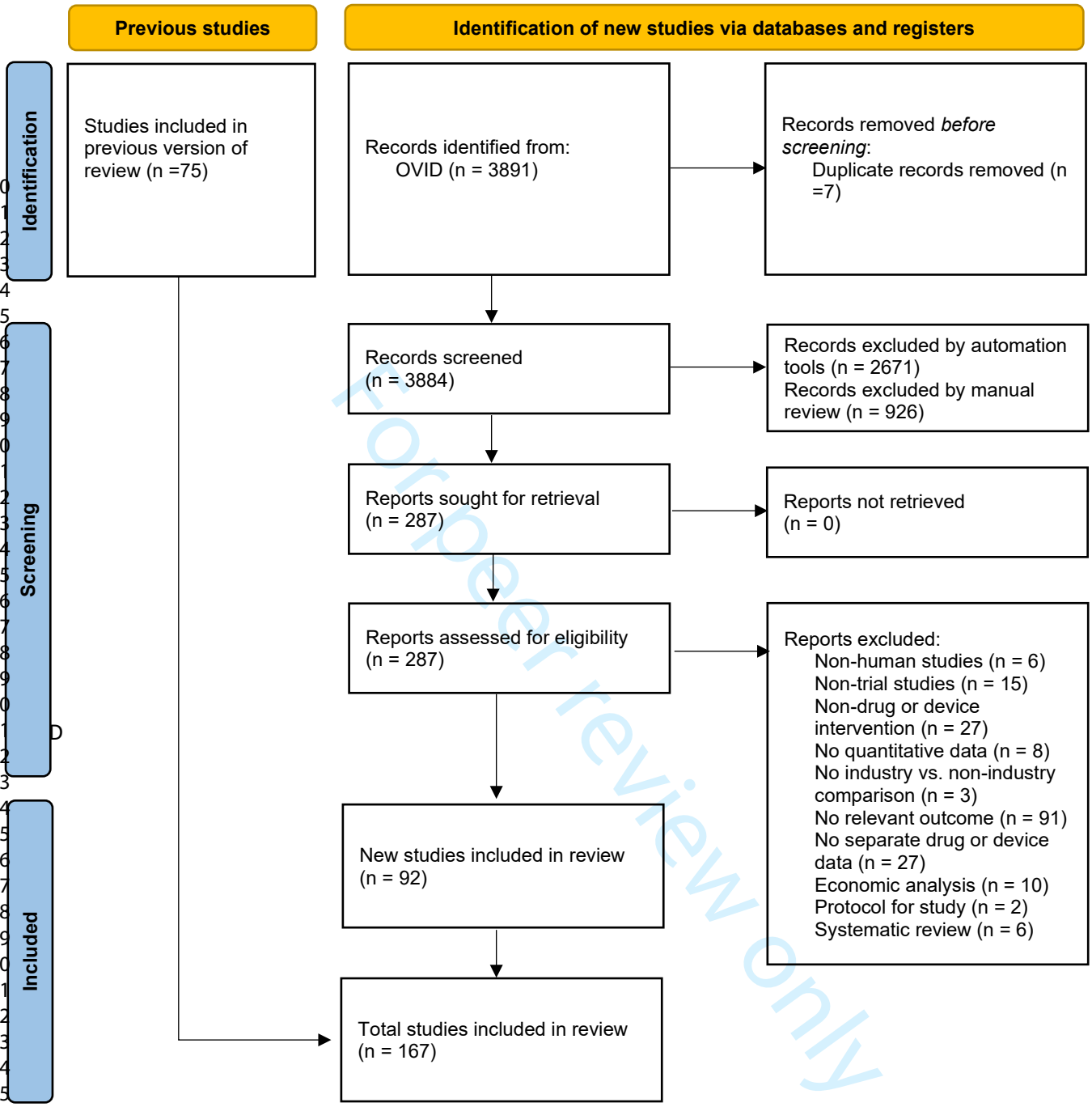
Figure Legends

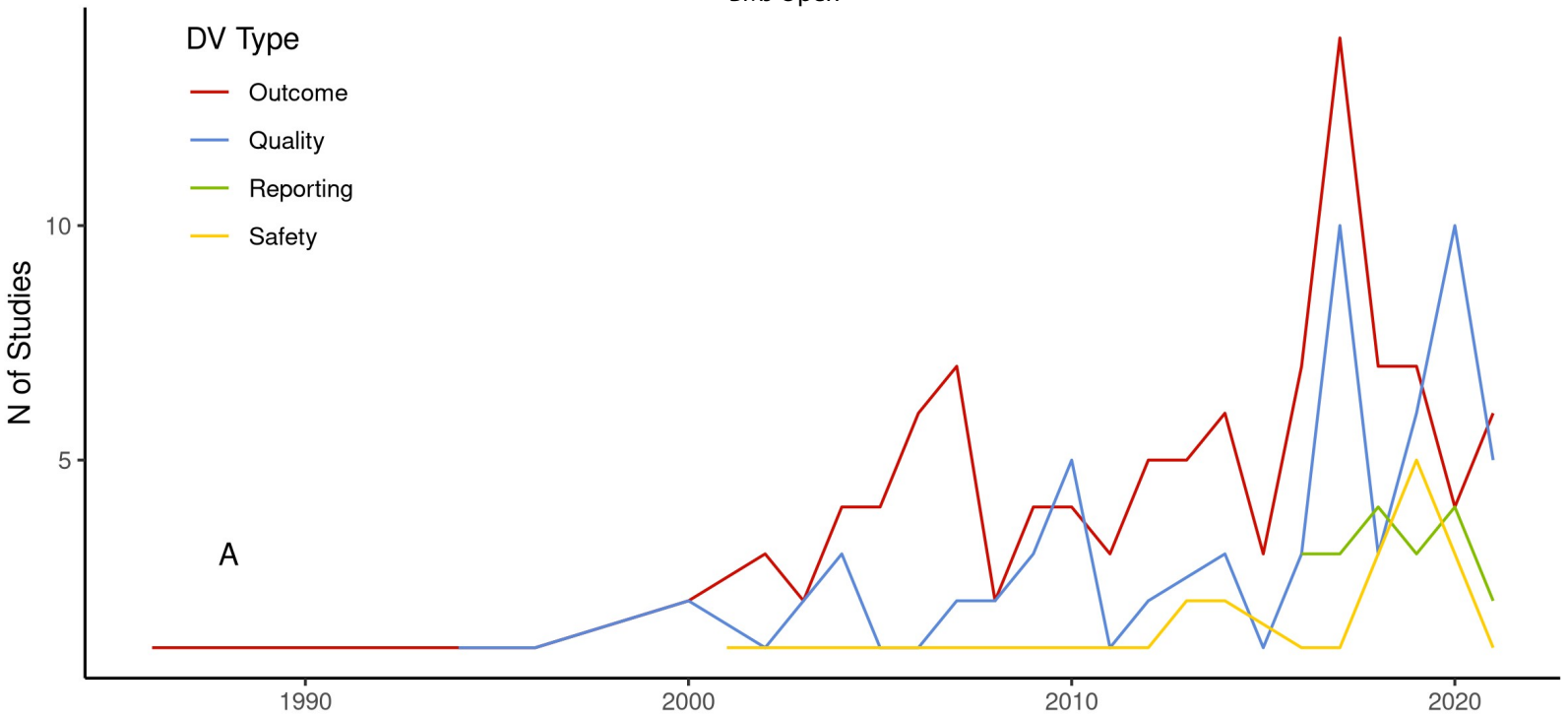
Figure 1. PRISMA Flow Diagram

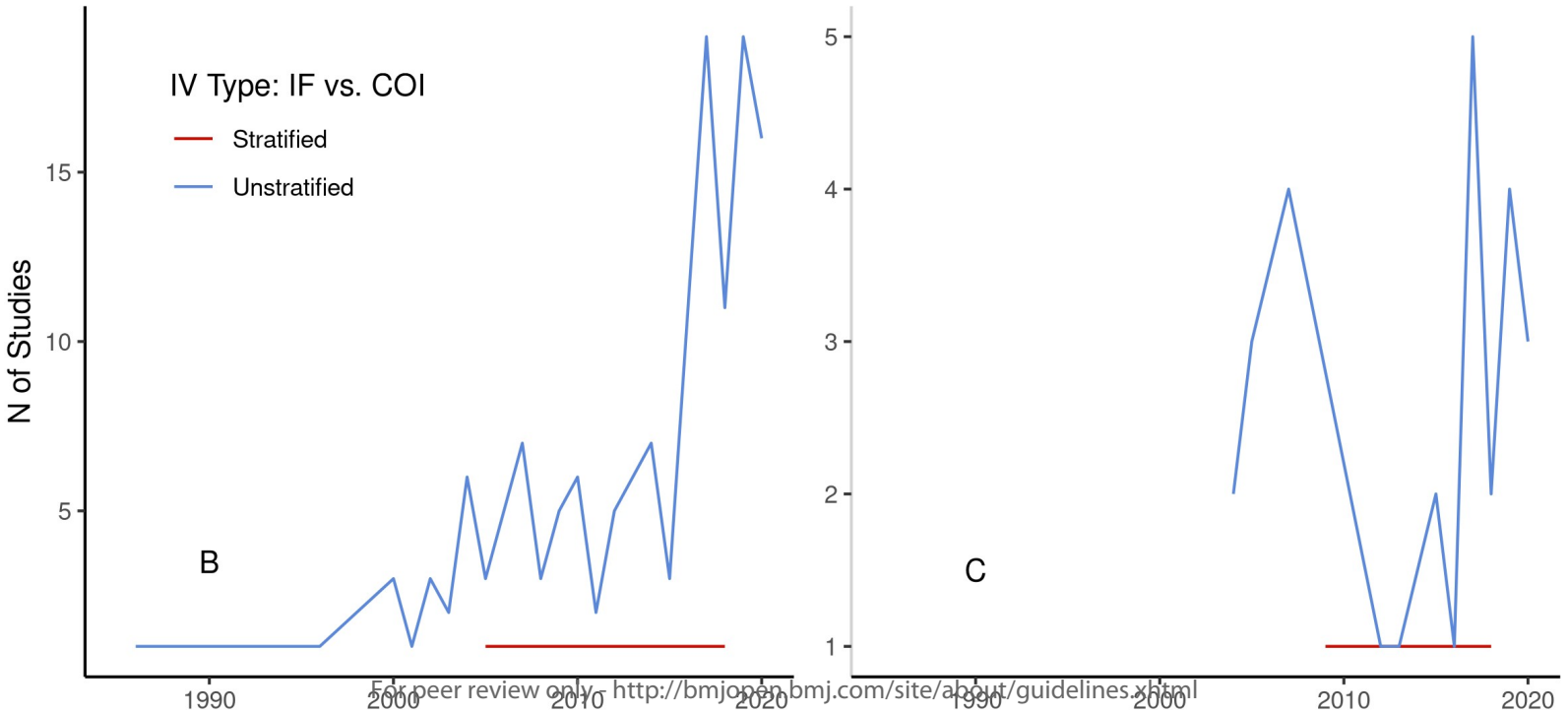
Figure 2: Variable Types By Year Number (1986-2021). Figure includes number of studies per year by dependent variable (DV) type (A), number of studies by independent variable (IV) type

for studies assessing industry funding (B) and number of studies by IV type for studies evaluating COI (C).

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases and registers only







Search strategy

MEDLINE via OvidSP (2015 – June 2021)

1. Drug Industry/

2. ((drug$ or pharmaceutical or device$ or for-profit or commercial$) adj2 (industr$ or company or companies or manufacturer$ or organi#ation$ or agency or agencies or source$ or party or parties)).ti,ab.

3. private industr$.ti,ab.

4. (industr$ or nonindustr$ or non-industr$).ti,ab.

5. or/1-4

6. "Conflict of Interest"/

7. Financial Support/

8. Research Support as Topic/

9. (influenc$ or funded or funding or sponsor$ or support$ or financ$ or involvement).ti,ab.

10. competing interest$.ti,ab.

11. or/6-10

12. and/5,11

13. Publication Bias/

14. "bias (epidemiology)"/

15. bias$.ti,ab.

16. or/13-15

17. and/12,16

18. Treatment Outcome/

19. "Outcome Assessment (Health Care)"/

20. (outcome$ or finding$).ti,ab.

21. or/18-20

22. (favo?r$ or positive or significan$ or beneficial or benefit$ or effective or effectual or efficacious).ti,ab.

23. (insignifican$ or nonsignifican$ or negative or adverse or ineffectiv$ or ineffectual or unfavo?rabl$ or detrimental).ti,ab.

24. or/22-23

25. and/21,24

26. and/12,25

27. ((favo?r$ or positive or significan$ or insignifican$ or nonsignifican$ or negative or unfavo?rabl$ or detrimental) adj2 (event$ or result$ or outcome$ or conclusion$)).ti,ab.

28. and/12,27

29. or/17,26,28

Supplementary Online Materials

Industry Funding Independent Variable (IV) Type.	
Stratified	Study provides a quantitative assessment of the relationship between different types of industry funding and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of industry funding categories. Funder stratifications may include level of involvement (primary, secondary), relationship to drug or device under study (manufacturer, competitor), or mode of sponsorship (study sponsor, medication provider, author employer).
Unstratified	Industry funding is analyzed as a dichotomous variable or as one category in a categorical variable, e.g. funder types might include industry, government, nonprofit.
Magnitude	Industry funding is a continuous variable representing either the total number of industry funders per study or total dollar value of contributions.
Author COI IV Type	
Stratified	Study provides a quantitative assessment of the relationship between different types of COI and one or more outcomes of interest. Industry funding may be analyzed as a categorical variable or as a series of dichotomous variables representing a range of COI categories. COI stratifications may include type of disbursement (employment, speaker fees, etc) and affiliation (trial sponsor vs. non-sponsor funder).
Unstratified	COI is analyzed as a dichotomous variable or as one category in a categorical variable, e.g., Industry funding, Author COI, Government Funding.
Magnitude	COI is a continuous variable representing either the total number of relationships or the total dollar value of contributions.
COI as Proxy for Industry Funding Study	
Yes	Disclosed author COI are used as inclusion criteria for industry funding.
No	Disclosed COI are not used as inclusion criteria for industry funding or industry funding is not measured.
IV Dichotomization	
NA	The IV used in the statistical analysis was stratified or an assessment of magnitude.
Yes	The categorical schema was converted to dichotomous variables that were used for analysis.
No	The IV was consistently treated as dichotomous throughout the article.
Dependent Variable Type (DV Type)	
Outcome	The analysis evaluates if chosen IVs are associated with results indicating the success of the intervention (drug, device, etc) or are otherwise favorable to trial sponsors. Includes drug efficacy, response rate, positive interpretation of findings, etc.
Safety	The analysis evaluates if chosen IVs associate with results related to drug safety.
Quality	The analysis evaluates if chosen IVs are associated with results related to methodological or reporting quality. Includes issues of statistical power, risk of bias, presence of hype or spin.
Reporting	The analysis evaluates whether or not trial results were reported at all. May include reporting to ClinicalTirals.Gov or publication of findings.

Supplemental Table 1. Methodological Design Feature Schema for Analyzed Studies. Definition and details for industry funding IV type, author COI IV type, COI as proxy for industry funding, dichotomization, and DV type analyses.

Article	*Year*	*IF IV Type*	*COI IV Type*	*DV Type*	*COI Proxy*	*IF Dichotomize*	*COI Dichotomize*
Abildgaard et al. (1)	2019	Unstratified	None	Outcome	yes	yes	NA
Addeo et al. (2)	2019	Unstratified	None	Outcome, Safety	no	no	NA
Ahmer et al. (3)	2005	Stratified	Unstratified	Outcome	no	NA	no
Ahn et al. (4)	2016	Unstratified	Unstratified	Outcome	no	no	yes
Alasbali et al. (5)	2009	Unstratified	None	Outcome, Quality	no	no	NA
Als-Nielsen et al. (6)	2003	Unstratified	None	Outcome	yes	NA	NA
Avni et al. (7)	2004	Unstratified	None	Quality	no	no	NA
Azad et al. (8)	2019	Unstratified	None	Quality	no	NA	NA
Azharuddin et al. (9)	2020	Unstratified	None	Quality	no	no	NA
Barden et al. (10)	2005	Unstratified	None	Outcome	yes	no	NA
Bariani et al. (11)	2013	Unstratified	Unstratified	Outcome	no	yes	yes
Bartels et al. (12)	2012	Unstratified	Stratified	Outcome	yes	no	NA
Bero et al. (13)	2007	Unstratified	Unstratified	Outcome	no	NA	no
Bhandari et al. (14)	2004	Unstratified	None	Outcome	no	yes	no
Bighelli et al. (15)	2020	Unstratified	Unstratified	Quality	no	no	NA
Bond et al. (16)	2012	Stratified	Unstratified	Outcome	yes	NA	no
Booth et al. (17)	2008	Unstratified	None	Outcome, Quality	no	NA	NA
Bourgeois et al. (18)	2010	Unstratified	None	Outcome, Quality	no	NA	NA
Brown et al. (19)	2006	Unstratified	None	Outcome, Quality	no	no	NA
Buchkowsky and Jewesson (20)	2004	Unstratified	Unstratified	Outcome	no	NA	no
Budhiraja et al. (21)	2021	Unstratified	None	Outcome	no	NA	NA
Bugano et al et al. (22)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Catillon (23)	2019	Unstratified	Unstratified	Quality	no	no	NA
Chang et al. (24)	2021	Unstratified	None	Quality	no	NA	NA
Chard et al. (25)	2000	Unstratified	None	Outcome, Quality	no	NA	NA
Chen et al. (26)	2016	Unstratified	None	Reporting	no	NA	NA
Cherla et al. (27)	2018	None	Stratified	Outcome	no	NA	NA
Cho and Bera (28)	1996	Unstratified	None	Outcome, Quality	yes	no	NA
Clark et al. (29)	2002	Unstratified	None	Outcome	no	no	NA
Clifford et al. (30)	2002	Unstratified	None	Outcome, Quality	no	NA	NA
Corona et al. (31)	2014a	Unstratified	None	Quality, Safety	yes	no	NA
Corona et al. (32)	2014b	Unstratified	None	Outcome, Quality	yes	no	NA
Cristea et al. (33)	2017	None	Unstratified	Outcome	no	NA	no
Crocetti et al. (34)	2010	Unstratified	None	Quality	no	NA	NA
Davidović et al. (35)	2021	Unstratified	None	Outcome, Reporting	no	no	NA
Davidson (36)	1986	Unstratified	None	Outcome	yes	no	NA

Davis et al. (37)	2008	Unstratified	None	Outcome	yes	no	NA
de Souza Gutierres et al. (38)	2020	Unstratified	None	Quality	no	no	NA
DeFrance et al. (39)	2021	None	Unstratified	Outcome	no	NA	no
DeGeorge et al. (40)	2015	Unstratified	Unstratified	Outcome	no	NA	no
Del Paggio et al. (41)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Falk Delgado and Falk Delgaddo (42)	2017a	Unstratified	None	Outcome	no	NA	NA
Falk Delgado and Falk Delgaddo (43)	2017b	Unstratified	Unstratified	Reporting	no	NA	no
DePasse et al. (44)	2018	Unstratified	None	Reporting	no	NA	NA
DeVito et al. (45)	2020	Unstratified	None	Reporting	no	NA	NA
Djulbegovic et al. (46)	2013	Unstratified	None	Outcome	no	no	NA
Djulbegovic et al. (47)	2000	Unstratified	None	Quality	yes	no	NA
Etter et al. (48)	2007	Unstratified	None	Outcome	yes	no	NA
Finucane and Boult (49)	2004	Unstratified	None	Outcome	yes	no	NA
Flacco et al. (50)	2015	Unstratified	Unstratified	Outcome, Quality	yes	yes	no
Fraguas et al. (51)	2018	Unstratified	None	Quality	no	no	NA
Freemantle et al. (52)	2000	Unstratified	None	Outcome	no	no	NA
Fung et al. (53)	2017	Unstratified	None	Quality, Reporting	no	no	NA
Gabler et al. (54)	2016	Unstratified	None	Reporting, Quality	no	no	NA
Gan et al. (55)	2012	Unstratified	None	Quality	no	no	NA
Gao et al. (56)	2019	Unstratified	None	Quality	no	NA	NA
Gartlehner et al. (57)	2010	Unstratified	None	Outcome, Quality	yes	no	NA
Gaudino et al. (58)	2020	Unstratified	Unstratified	Outcome, Quality	yes	no	yes
Gonzalez et al. (59)	2019	Unstratified	None	Quality	no	NA	NA
Grey et al. (60)	2018	Unstratified	None	Outcome	no	no	NA
Gyawali et al. (61)	2019	Unstratified	None	Safety	no	NA	NA
Hajibandeh et al. (62)	2017	Unstratified	Unstratified	Outcome	no	no	no
Halpern et al. (63)	2004	Unstratified	None	Quality	no	NA	NA
Hanna et al. (64)	2016	Unstratified	None	Outcome	no	NA	NA
Hashemipour et al. (65)	2019	Unstratified	Unstratified	Outcome	no	no	no
Hengartner et al. (66)	2021	Unstratified	None	Safety	yes	no	NA
Heres et al. (67)	2006	Unstratified	None	Outcome	no	no	NA
Janiaud et al. (68)	2018	Unstratified	None	Outcome	no	yes	NA
Jefferson et al. (69)	2009	Unstratified	None	Quality	no	no	NA
Jellison et al. (70)	2020	Unstratified	None	Quality	no	yes	NA
Jinapriya et al. (71)	2011	Stratified	None	Outcome	no	NA	NA
Johnson et al. (72)	2020	Unstratified	None	Reporting	no	NA	NA

Jones et al. (73)	2010	Unstratified	None	Quality	no	NA	NA
Kakkar et al. (74)	2019	Unstratified	None	Quality	no	no	NA
Kapelios et al. (75)	2020	Unstratified	None	Outcome, Quality	no	no	NA
Kelly et al. (76)	2006	Stratified	None	Outcome	yes	NA	NA
Kemmeren et al. (77)	2001	Unstratified	None	Safety	no	no	NA
Khan et al. (78)	2012	Unstratified	None	Outcome, Quality	no	NA	NA
Killin et al. (79)	2014	Unstratified	None	Outcome	yes	no	NA
Kjaergard and Als-Nielson (80)	2002	Unstratified	None	Outcome	no	NA	NA
Lee et al. (81)	2012	Unstratified	None	COI, Outcome	no	no	NA
Lee et al. (82)	2020	Unstratified	None	Reporting	no	no	NA
Leite et al. (83)	2017	Unstratified	Unstratified	Outcome	no	no	no
Leucht et al. (84)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Leucht et al. (85)	2019	Unstratified	None	Outcome	no	no	NA
Linker et al. (86)	2017	Unstratified	None	Outcome, Quality	no	NA	NA
Liss (87)	2006	Unstratified	None	Outcome	yes	no	NA
Liu et al. (88)	2018	Unstratified	None	Outcome	no	NA	NA
Lubowitz et al. (89)	2007	Unstratified	None	Outcome	no	no	NA
Lynch et al. (90)	2007	Unstratified	None	Outcome, Quality	yes	NA	NA
Ma et al. (91)	2014	Unstratified	None	Outcome, Safety	no	no	NA
Magnani et al. (92)	2021	Unstratified	None	Reporting, Outcome	no	NA	NA
Maillet et al. (93)	2015	Unstratified	None	Outcome	no	no	NA
Malek et al. (94)	2017	Unstratified	None	Outcome	no	no	NA
Mian et al. (95)	2020	Unstratified	None	Quality	no	NA	NA
Mitchell and Patterson (96)	2020	Unstratified	None	Quality	no	NA	NA
Momeni et al. (97)	2009	Unstratified	None	Outcome	no	NA	NA
Moncrieff (98)	2003	Unstratified	None	Outcome	no	no	NA
Montgomery et al. (99)	2004	Unstratified	Unstratified	Outcome, Quality	no	no	no
Moraes et al. (100)	2017	Unstratified	Unstratified	Outcome	no	NA	no
Mossman et al. (101)	2021	Unstratified	None	Outcome	no	no	NA
Naci et al. (102)	2014	Unstratified	None	Outcome, Quality	no	no	NA
Ng et al. (103)	2016	Unstratified	None	Quality	no	no	NA
Nieto et al. (104)	2007	Unstratified	None	Safety	no	no	NA
Nithianandan et al. (105)	2020	Unstratified	Unstratified	Outcome	no	no	no
Odutayo et al. (106)	2017	Unstratified	None	Outcome	no	no	NA
Paggio et al. (107)	2021	Unstratified	None	Quality	no	no	NA
Pasalic et al. (108)	2020	Unstratified	None	Quality	no	no	NA
Pengel et al. (109)	2009	Unstratified	None	Quality	yes	NA	NA

Pepper et al. (110)	2019	Unstratified	None	Safety	no	no	NA
Peppercorn et al. (111)	2007	Unstratified	Unstratified	Outcome	yes	no	no
Perlis et al. (112)	2005a	Unstratified	Unstratified	Outcome, Quality	yes	no	no
Perlis et al. (113)	2005b	Unstratified	Unstratified	Outcome	yes	no	no
Popelut et al. (114)	2010	Unstratified	None	Outcome	no	NA	no
Pouwels et al. (115)	2017	Unstratified	None	Outcome, Quality	no	no	NA
Prakash et al. (116)	2018	Unstratified	None	Quality	no	NA	NA
Price-Haywood et al. (117)	2019	Unstratified	None	Safety	no	NA	NA
Printz et al. (118)	2013	Unstratified	None	Outcome	yes	no	NA
Probst et al. (119)	2016	Unstratified	None	Outcome	no	no	NA
Punja et al. (120)	2016	Unstratified	None	Outcome, Safety	no	no	NA
Putman et al. (121)	2021	Unstratified	None	Quality	yes	no	NA
Raman et al. (122)	2018	Unstratified	Unstratified	Outcome	no	NA	no
Rasmussen et al. (123)	2009	Unstratified	None	Outcome	yes	yes	NA
Rattinger and Bero (124)	2009	Stratified	Stratified	Outcome	yes	NA	NA
Reda et al. (125)	2016	Unstratified	None	Outcome, Quality	no	yes	NA
Rees et al. (126)	2019	Unstratified	None	Reporting	no	NA	NA
Ridker and Torres (127)	2006	Unstratified	None	Outcome	no	NA	NA
Rios et al. (128)	2008	Unstratified	None	Quality	no	NA	NA
Rochon et al. (129)	1994	Unstratified	None	Outcome, Quality	yes	no	NA
Roddick et al. (130)	2017	Unstratified	None	Outcome	no	NA	NA
Roper et al. (131)	2014	Unstratified	None	Limitations, Outcome	no	NA	NA
Rosner et al. (132)	2010	Unstratified	None	Outcome, Quality	no	no	NA
Rosner et al. (133)	2011	Unstratified	None	Outcome	no	NA	no
Saa et al. (134)	2018	Stratified	None	Outcome, Quality	yes	NA	NA
Saleh et al. (135)	2020	Unstratified	None	Outcome	no	no	NA
Sendyk et al. (136)	2019	Unstratified	None	Quality, Reporting	no	no	NA
Shepard et al. (137)	2021	Unstratified	None	Quality	no	NA	NA
Silva et al. (138)	2017	Unstratified	None	Safety, Quality	no	no	NA
Simonetti et al. (139)	2019	Unstratified	None	Safety	no	no	NA
Sinyor et al. (140)	2012	Unstratified	None	Outcome, Safety	yes	no	NA
Son et al. (141)	2016	Unstratified	None	Outcome	no	no	NA
Spanemberg et al. (142)	2011	Unstratified	None	Outcome, Quality	no	no	NA
Sriganesh et al. (143)	2017	Unstratified	None	Quality	no	no	NA
Stefaniak et al. (144)	2017	Unstratified	None	Reporting, Quality	no	NA	NA
Steffens et al. (145)	2021	Unstratified	None	Quality	yes	no	NA

Sung et al. (146)	2013	Unstratified	None	Outcome	yes	no	NA
Tiabau et al. (147)	2018	Unstratified	None	Outcome	no	NA	NA
Trinquart et al. (148)	2018	Unstratified	None	Reporting	no	no	NA
Tulikangas et al. (149)	2006	Unstratified	None	Outcome	no	no	NA
Tungaraza and Poole (150)	2007	Unstratified	Unstratified	Outcome	no	no	no
Urrutia et al. (151)	2016	Unstratified	None	Reporting	no	no	NA
van den Bogert et al. (152)	2017	Unstratified	None	Quality	no	yes	NA
van Heteren et al. (153)	2019	Unstratified	None	Reporting	no	NA	NA
Van Lent et al. (154)	2014	Unstratified	None	Outcome	yes	NA	NA
Venincasa et al. (155)	2019	Unstratified	Unstratified	Outcome	no	no	no
Vlad et al. (156)	2007	Stratified	Unstratified	Outcome, Quality	no	NA	no
Walkup et al. (157)	2017	Unstratified	None	Outcome	no	no	NA
Walter et al. (158)	2020	Unstratified	None	Reporting	no	no	NA
Waqas et al. (159)	2019	Unstratified	Unstratified	Outcome	no	no	no
Welsh et al. (160)	2018	Unstratified	Unstratified	Reporting	no	NA	no
Wise et al. (161)	2021	Unstratified	Unstratified	Outcome	no	yes	yes
Wong et al. (162)	2019	Unstratified	None	Outcome	no	no	NA
Wortzel et al. (163)	2020	Unstratified	None	Quality	no	NA	NA
Xu et al. (164)	2013	Unstratified	None	Safety	no	no	NA
Yilmaz et al. (165)	2018	Unstratified	None	Reporting	no	no	NA
Youssef et al. (166)	2016	Unstratified	None	Outcome	no	no	NA
Zhang et al. (167)	2013	Unstratified	None	Outcome, Safety	no	no	NA

Supplemental Table 2. Methodological Design Analysis for All Collected Articles. Includes industry funding IV type, author COI IV type, DV type(s), COI as proxy, and dichotomization data.

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Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review. (Methodological review)	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5-6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	8; supp
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	8-9
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	9-10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	9-10
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	9-10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	10
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	10-15; supp
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	10-15
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10-15
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	15-19
Limitations	20	Discuss the limitations of the scoping review process.	17
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18-19
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	19

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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