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ORIGINAL ARTICLE

The timing and frequency of trial inclusion in systematic reviews of type 2 diabetes drugs was associated with trial characteristics

Adam G. Dunn[a,b,*], Liat Orenstein[b], Enrico Coiera[a], Kenneth D. Mandl[b,c], Florence T. Bourgeois[b,d,e]

[a]*Centre for Health Informatics, Australian Institute of Health Innovation, Macquarie University, Sydney, NSW, Australia*
[b]*Computational Health Informatics Program, Boston Children's Hospital, Boston, MA, USA*
[c]*Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA*
[d]*Division of Emergency Medicine, Boston Children's Hospital, Boston, MA, USA*
[e]*Departments of Pediatrics and Emergency Medicine, Harvard Medical School, Boston, MA, USA*

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Abstract

Objective: To determine whether certain trial characteristics are associated with faster or more frequent inclusion in systematic reviews for drug interventions in type 2 diabetes.

Study Design and Setting: We examined trials included in systematic reviews published between January 1, 2007 and January 1, 2017. Primary outcomes were time between trial publication and first inclusion in a systematic review and frequency of inclusion in systematic reviews over the study period. Multivariable Cox proportional hazards and regression models quantified associations with funding source, number of participants, trial conclusion, and journal impact factor.

Results: Among 668 trials, the median time to inclusion was 76.1 weeks. Time to inclusion was shorter for trials with industry funding (hazard ratio [HR] 1.39; 95% confidence interval [CI] 1.13−1.71), more participants (HR 1.26; 95% CI 1.17−1.36), and published in higher impact factor journals (HR 1.28; 95% CI 1.14−1.45). The median frequency of inclusion was three. Frequency of inclusion was greater for trials with industry funding (relative risk [RR] 2.36; 95% CI 2.11−2.64), more participants (RR 1.51; 95% CI 1.47−1.55), positive conclusions (RR 1.89; 95% CI 1.68−2.13), and published in higher impact factor journals (RR 1.13; 95% CI 1.08−1.18).

Conclusion: Certain trial characteristics are associated with faster or more frequent trial inclusion in systematic reviews of type 2 diabetes.

Keywords: Type 2 diabetes; Systematic review as a topic; Randomized controlled trials; Systematic review biases; Industry funding; Clinical trial as a topic

1. Background

Systematic reviews play a critical role in evidence-based medicine—at their best, they provide a comprehensive, up-to-date, and unbiased assessment of what is and what is not known about a clinical intervention. Where it is impossible for clinicians to keep up with the volume of studies being published every day [1,2], systematic reviews represent a readily accessible synthesis of the available clinical evidence as it accrues and changes over time.

Systematic reviews address the variability between primary studies and account for a range of biases that might otherwise lead to incomplete or incorrect assessments of the evidence base. For example, careful consideration is given to the methods for treatment allocation in randomized trials, investigator and participant blinding, and the impact of incomplete outcome data due to participant attrition [3]. Reviewers also consider selective reporting of outcomes and search for trial data beyond published scientific articles to account for biases arising from the nonpublication or delayed publication of trials [4,5], which disproportionately affect certain studies, such as those with negative findings [6,7].

However, the methods and motivations underlying the production of systematic reviews may still result in inaccurate or misleading findings [8,9]. For example, reviews covering the same topic and with access to the same evidence base have reached different and at times even contradictory conclusions [10]. Such discrepancies have been attributed in part to differences in how a clinical question is framed, the evidence selected for analysis, the methods

Conflict of interest: The authors declare that they have no competing interests.

* Corresponding author. Tel.: +612 9850 2413.
E-mail address: adam.dunn@mq.edu.au (A.G. Dunn).

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What is new?

Key findings

- Trials of type 2 diabetes drugs are included in systematic reviews faster if they are funded by industry, irrespective of sample size, trial conclusion, and journal in which the trial is published.
- Trials of type 2 diabetes without full industry funding or with negative conclusions are included in fewer systematic reviews than those with industry funding or positive conclusions.

What this adds to what was known?

- Trial characteristics, including funding, design, and conclusions are known to be associated with the likelihood and timing of trial results reporting.
- Our results indicate that the time and frequency of subsequent inclusion of trials in systematic reviews is associated with similar factors.

What is the implication and what should change now?

- It may be useful to check the relative timing and frequency with which trials with industry funding and positive conclusions are included in systematic reviews to identify the potential for over representation of certain evidence.

for data extraction, and the interpretation of the results [11−15]. Conflicts of interest, stemming from both financial and nonfinancial interests [16], may play a part in guiding subjective decisions and a number of studies have documented the association between industry sponsorship and favorable conclusions in systematic reviews [17,18].

Among clinical trials, reporting policies, funding source, design, and conclusions are known to influence the time to publication of trial results [10,19−23]. Incomplete or delayed reporting of results may distort the primary scientific evidence available on a clinical topic and impact the timely identification of safety issues associated with an intervention [24,25]. Similarly, the time to incorporation of trial results into systematic reviews may influence the integrity of evidence and assessments of risks and benefits in clinical decision-making. Little is known on how long it takes for trials to be incorporated into systematic reviews and whether certain types of trials are included faster or more often.

Focusing on clinical trials included in systematic reviews of drug interventions for type 2 diabetes, we aimed to assess whether specific trial characteristics are associated with faster or more frequent inclusion in systematic reviews.

2. Methods

The study design was a time-to-event analysis applied to the set of all trials included in one or more systematic reviews of drugs used in the treatment of type 2 diabetes identified through a comprehensive search. We constructed models to determine whether funding, conclusions, size, or prominence were associated with the time to inclusion or the frequency of inclusion in systematic reviews.

2.1. Eligible trials

We searched for systematic reviews of drug treatments for type 2 diabetes, indexed in PubMed or Embase and published between 1 January 2007 and 1 January 2017 (search strategy in Appendix Table 1). Drug classes included dipeptidyl-peptidase IV inhibitors, glucagon-like peptide-1 receptor agonists, sodium glucose transporter 2 inhibitors, alpha-glucosidase inhibitors, sulfonylureas, and biguanides. Systematic reviews were selected for inclusion if they were written in English, reported a search strategy that we judged to be replicable based on the description of keywords and terms, specified the bibliographic databases and other sources of trial reports that were searched, included trials of patients with type 2 diabetes, and reported at least one meta-analysis for a safety or efficacy outcome. We limited to systematic reviews that included a meta-analysis or network meta-analysis to define a cohort of reviews that synthesized the results of efficacy and safety trials. Reviews that also included trials of healthy volunteers or patients at risk of type 2 diabetes were excluded, as were umbrella reviews that did not conduct their own comprehensive searches of trials. The publication date of a systematic review was the first publication date available via PubMed, which typically corresponded to the online publication.

All trials included in the systematic reviews were identified from the references provided in the reviews. To collect information on when the trials were conducted and when their results were first made available for use in systematic reviews, we linked all identified trials to bibliographic databases and, whenever available, ClinicalTrials.gov and trial reports on company websites. Links to trials in ClinicalTrials.gov were identified from information provided in the primary trial publication or, when this was not available, through searches in the registry based on investigator names, study sponsors, drug name, design features (e.g., randomization, comparators, study population), and study years. Where available, a modified version of this search was performed in databases on company websites to identify trial reports. Published articles, registry entries, and company reports were used to extract all information on trial completion and publication dates. Where there were multiple publications describing the results of a trial or where trial results were provided in multiple reports (e.g., summary results in ClinicalTrials.gov and publication in a journal), we selected the earliest report

providing results for a primary outcome of the trial. Trial publication dates were assigned using the same approach applied to systematic reviews.

The set of eligible trials were all included in at least one systematic review. As a result, there may be additional trials evaluating the safety or efficacy of these drug classes that were not included in the analysis because they were not deemed eligible for inclusion in any of the systematic reviews or because the results of the trial were otherwise inaccessible.

2.2. Outcomes and trial characteristics

Our two primary outcomes were the time between trial publication date and publication date of the first systematic review including the trial and the frequency with which the trial was included in systematic reviews over the study period. We selected a priori a set of factors that might influence the timing and frequency of trial inclusion in systematic reviews. Where information for these variables was available in multiple trial records, we preferentially selected the value provided in the first published article reporting on a primary outcome or a company report if no publication was available.

The first factor was trial funding, with trials classified as entirely industry funded, partially industry funded, or non−industry funded. The rationale for including this variable was that extensive prior studies demonstrate the role of industry funding on trial design, conduct, and reporting, as well as on a trial's dissemination and impact [26−28]. The second characteristic was the number of participants enrolled in the trial. For the third variable, two investigators (L.O. and A.G.D.) reviewed the published articles, registry entries, and company reports for every trial and labeled the trial conclusions as ''positive'' or ''negative'' depending on whether the conclusion reported a significant favorable finding for the primary outcome. For noninferiority trials, conclusions were labeled as positive if the trial concluded that the drug was noninferior. If no trial publication was available, we evaluated the results provided in the company report or checked for statistical significance for the primary outcome in the results data in ClinicalTrials.gov. Disagreements were resolved by discussion with a third investigator (F.T.B.). Finally, we recorded journal impact factors reported in the 2017 Journal Citation Reports (Clarivate Analytics) for the subset of trials that were first reported in a journal article. Although journal impact factors are imperfect indicators of the importance of individual trials and vary over time, this variable was used as a proxy for the greater visibility and accessibility of articles published in high-impact journals. We assigned a value of zero to trials reported in journals that were not indexed in the 2017 Journal Citation Reports.

2.3. Statistical analysis

Univariable and multivariable Cox proportional hazards regression models were used to examine factors associated with the time from reporting to inclusion in a systematic review. In both cases, we reported hazard ratios (HRs) with 95% confidence intervals (CIs).

We used univariable models to examine individual associations with funding (as industry, mixed, and nonindustry), number of participants (dichotomized by the median value), conclusions (positive or negative), and journal impact factors (dichotomized by the median value). To visualize differences in how quickly trials were taken up by systematic reviews relative to their characteristics, we produced cumulative incidence plots to examine the time from first publication of trial results to inclusion in a published systematic review. We used the dichotomized variables for ease of interpretation in the univariable models.

In a multivariable model, we included funding, number of participants (as a continuous variable), and conclusions, as well as adjusting for the date the trial was first reported. We adjusted for the reporting date by including the number of days since the first reported trial because changes in reporting as well as searching and screening technologies may have led to faster incorporation of more recent trials. For the subset of trials first reported in journal articles, we created a second multivariable model with the addition of journal impact factor (as a continuous variable).

In a similar manner, we used univariable and multivariable Poisson regression models to examine factors associated with the number of times a trial was included in a systematic review, reporting relative risk (RR; also defined as incidence rate ratios) with 95% CIs. We parameterized the model as before and constructed a separate model to identify associations with journal impact factor among trials that were first reported in journal articles. Data preprocessing was performed using MATLAB (9.2 R2017a), and all analyses were conducted in SAS (9.4).

3. Results

We identified 228 systematic reviews that included results from 668 unique trials (Fig. 1), of which 126 were noninferiority trials. The median time from first reporting of a trial to inclusion in a systematic review was 76.1 weeks (interquartile range [IQR] 49.7−117.8). In the first year after reporting, 21.4% (143 of 668) of trials were incorporated into a systematic review, increasing to 56.4% (377 of 668) during the second year. Trials were included in a median of three systematic reviews (IQR 1−9), with one trial included in 68 systematic reviews. Overall, 29.2% (195 of 668) of trials were included in only one systematic review, 15.3% (102 of 668) in two, and 55.5% (371 of 668) in three or more.

Most trials were either entirely (70.2%; 469 of 668) or partially (8.4%; 56 of 668) funded by industry (Table 1). Trials enrolled a median of 282 participants (IQR 94−543). Most trials presented positive conclusions (89.4%; 597 of 668). In the set of 501 trials first reporting

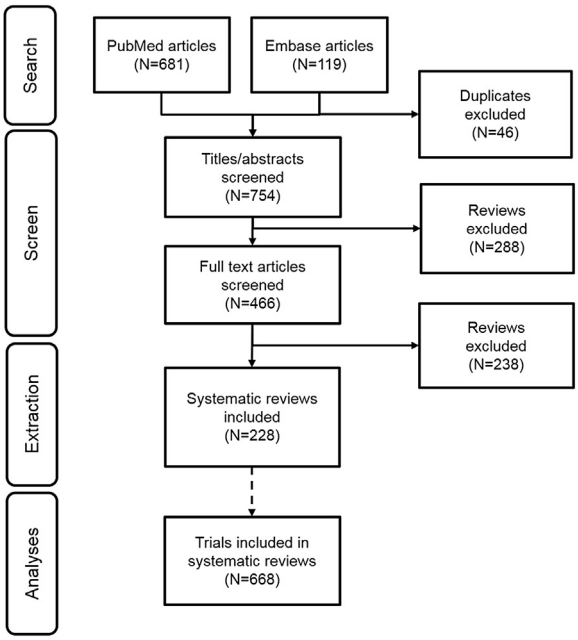

Fig. 1. There were 668 trials included in 228 systematic reviews of drug interventions for type 2 diabetes.

Table 1. Characteristics of trials included in systematic reviews of drug interventions for type 2 diabetes

Characteristic	All trials (*N* = 668)
Funding — no. (%)	
Nonindustry	143 (21.4)
Partially industry	56 (8.4)
Industry	469 (70.2)
Number of participants — no. (%)	
Fewer than 100	177 (26.5)
100 to fewer than 500	304 (45.5)
500 or more	187 (28.0)
Conclusion — no. (%)	
Positive	597 (89.4)
Negative	71 (10.6)
Journal impact factor — no. (%)[a]	
Less than 5	245 (48.9)
5 to less than 10	138 (27.5)
10 or greater	118 (23.6)

[a] Journal impact factor was analyzed in a model using the subset of 501 trials first published in journal articles.

results in a journal article, the median journal impact factor was 5.46 (IQR 2.76−6.72).

Among the 866 unique systematic review authors, 193 authored more than one of the reviews, 20 were authors on 5 or more reviews, and one author was included on 25 of the 228 systematic reviews (Appendix Fig. 1).

3.1. Time from trial reporting to inclusion in a systematic review

In univariable analyses, trials funded entirely by industry were incorporated into systematic reviews faster than trials without industry funding (unadjusted HR 1.88; 95% CI 1.55−2.27) (Fig. 2). There was no difference in the timing for trials without industry funding compared with those with partial industry funding (unadjusted HR 1.06; 95% 0.78−1.45). The median time to inclusion for industry-funded trials was 77.6 (IQR 50.9−119.4) weeks compared with 119.1 (63.4−225.3) weeks and 152.6 (IQR 96.2−221.0) weeks for trials with partial or no industry funding, respectively.

Trials with at least 282 participants (the median) were included in systematic reviews faster (unadjusted HR 2.10; 95% CI 1.80−2.46). Trials with fewer than 282 participants were incorporated into systematic reviews after a median of 118.6 (IQR 73.8−207.6) weeks, and trials with at least 282 participants were incorporated into reviews after a median of 70.1 (IQR 46.9−108.7) weeks.

There was no observable difference in timing for trials with positive conclusions vs. those with negative conclusions (unadjusted HR 0.92; 95% CI 0.72−1.17). Trials with positive conclusions were first included in a systematic review after a median of 91.1 (IQR 57.0−155.9) weeks compared with 95.1 (IQR 49.0−147.5) weeks in trials with negative conclusions.

Among the trials first reported in journal articles, those published in journals with impact factors of at least 5.46 (the median) were incorporated into systematic reviews faster (unadjusted HR 1.65; 95% CI 1.42−1.93). Trials published in journals with an impact factor of at least 5.46 were first included in systematic reviews after a median of 76.1 weeks (IQR 44.6−124.0) compared with 133.3 (IQR 79.3−209.9) weeks for trials published in journals with an impact factor less than 5.46.

Results were consistent in a multivariable model that accounted for funding source, number of participants, conclusion, journal impact factor, and reporting date (Table 2). Trials that were industry funded or had a greater number of participants were incorporated into systematic reviews faster, as were trials that were reported in journals with higher impact factors. There was no association between conclusion and time to inclusion.

3.2. Frequency of inclusion in systematic reviews

In univariable analyses examining the factors associated with the number of times a trial was included in a systematic review, industry-funded trials were included in a greater number of systematic reviews relative to non−industry funded trials (unadjusted RR 3.75; 95% CI 3.36−4.18); there was no observable difference between trials that were partially funded by industry and those without any industry funding (unadjusted RR 1.12; 95% CI 0.93−1.35). Trials with industry funding were included in a median of 5 (IQR 2−13) systematic reviews, and trials

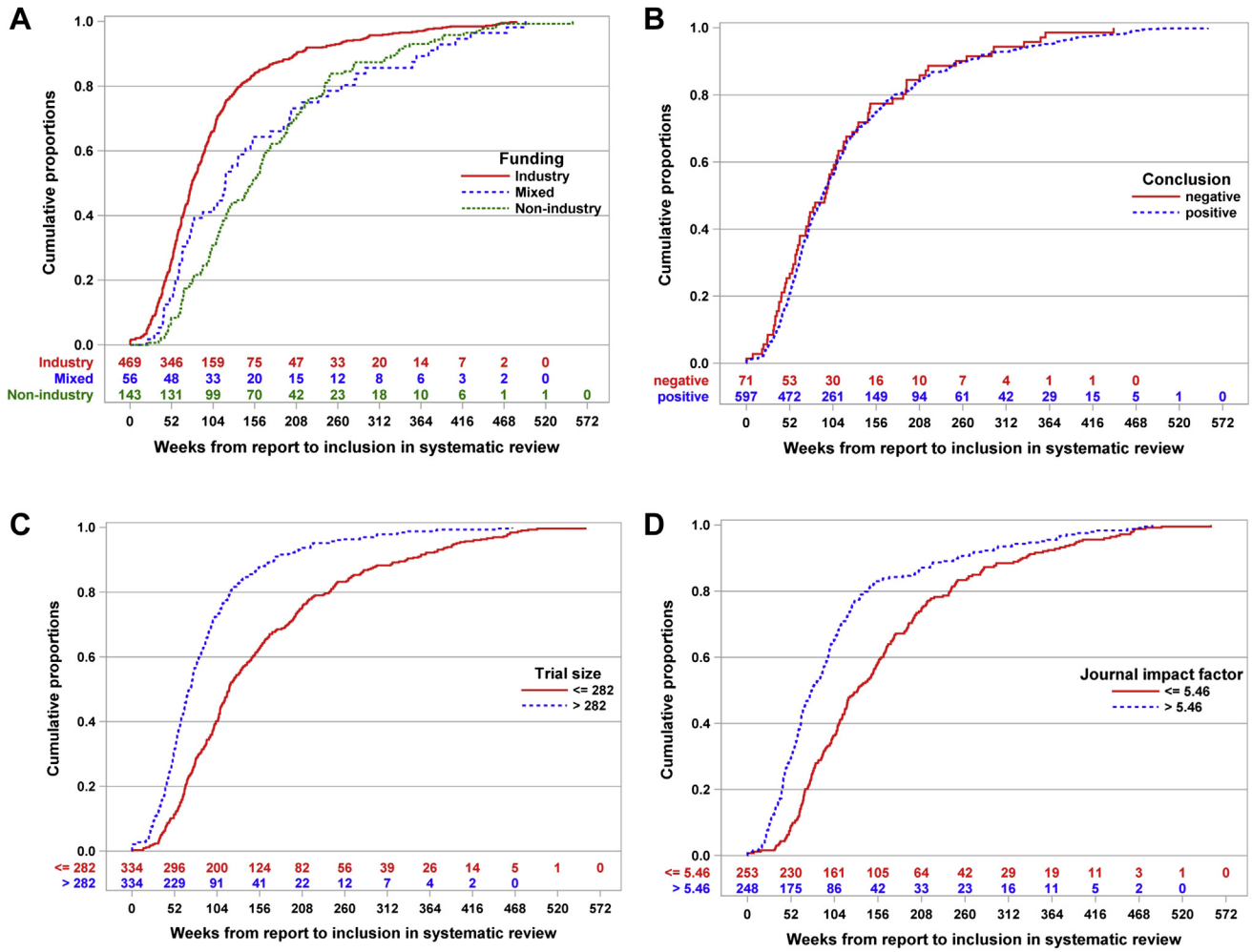

Fig. 2. Time to event is the number of weeks from first public reporting to first inclusion in 668 trials for (A) trial funding; (B) number of trial participants; (C) presence of a positive conclusion; and (D) journal impact factor (in a subset of 501 trials). Continuous variables were dichotomized using the median value for illustration purposes. Of note, values reported here are raw and unadjusted and therefore do not correspond to the multivariable analyses.

with partial or no industry funding were included in 2 (IQR 1–3) and 3 (IQR 1–9) systematic reviews, respectively. Among the 469 trials with industry funding, 157 (33.5%) were included in at least 10 systematic reviews and 29 (6.2%) were included in 30 or more systematic reviews. Among the 143 trials with no industry funding, 4 (2.8%) were included in at least 10 systematic reviews and none were included in 30 or more systematic reviews.

Trials with at least 282 participants (the median) were included more frequently in systematic reviews (unadjusted RR 2.63; 95% CI 2.47–2.80). Trials with fewer than 282 participants were included in a median of 2 (IQR 1–4) systematic reviews, and trials with at least 282 participants were included in a median of 6 (IQR 2–15) systematic reviews.

Trials with positive conclusions were also included in more systematic reviews than trials with negative conclusions (unadjusted RR 1.87; 95% CI 1.66–2.10). Trials with positive conclusions were included in a median of 3 (IQR 1–10) systematic reviews and trials with negative conclusions were included in a median of 3 (IQR 1–5) systematic reviews. Although the medians were equal, among the 597 trials with positive conclusions, a quarter were included in ten or more systematic reviews, whereas among the 71

Table 2. Trial characteristics associated with time from first reporting to inclusion in a systematic review in multivariable analyses

Trial characteristic	Hazard ratio (95% CI)	*P*-value
Funding		
Nonindustry	reference	-
Partially industry	1.04 (0.76–1.41)	0.83
Industry	1.39 (1.13–1.71)	0.002
Number of participants	1.26 (1.17–1.36)	<0.0001
Conclusion		
Negative	Reference	-
Positive	0.84 (0.65–1.08)	0.17
Journal impact factor[a]	1.28 (1.14–1.45)	<0.0001

[a] Journal impact factor was analyzed in a model using the subset of 501 trials first published in journal articles.

Table 3. Trial characteristics associated with frequency of inclusion in a systematic review in multivariable analyses

Trial characteristic	Relative risk (95% CI)	*P*-value
Funding		
Nonindustry	reference	-
Partially industry	1.09 (0.90–1.31)	0.38
Industry	2.36 (2.11–2.64)	<0.0001
Number of participants	1.51 (1.47–1.55)	<0.0001
Conclusion		
Negative (N = 71)	reference	-
Positive (N = 597)	1.89 (1.68–2.13)	<0.0001
Journal impact factor[a]	1.13 (1.08–1.18)	<0.0001

[a] Journal impact factor was analyzed in a model using the subset of 501 trials first published in journal articles.

trials with negative conclusions, a quarter were included in only five or more systematic reviews.

Among the subset of trials first reported in journal articles, trials reported in journals with an impact factor of at least 5.46 (the median) were included in a greater number of systematic reviews (unadjusted RR 1.64; 1.55–1.74). Trials published in journals with impact factors less than 5.46 were included in a median of 2 (IQR 1–4) systematic reviews and trials published in journals with impact factors of at least 5.46 were included in a median of 4 (IQR 2–11) systematic reviews. Among the 255 trials that were published in higher impact journals, 78 (30.6%) were included in at least 10 systematic reviews and 21 (8.2%) were included in 30 or more systematic reviews. Among the 246 trials published in lower impact journals, 30 (11.8%) were included in at least 10 systematic reviews, and 4 (1.6%) were included in 30 or more systematic reviews.

In a multivariable model accounting for funding, number of participants, conclusion, journal impact factor, and the date the trial was first reported, the results were consistent with the univariable analyses (Table 3). Trials that were entirely industry funded, that enrolled a greater number of participants, that had positive conclusions, and that reported in journals with higher impact factors were included more frequently in systematic reviews.

4. Discussion

Among clinical trials of drug interventions for type 2 diabetes, certain factors influence the timing and frequency of trial inclusion in systematic reviews. Trials are incorporated into systematic reviews faster if they are industry funded, are larger, or are published in journals with higher impact factors. Trials are also included in systematic reviews more frequently if they are funded by industry, are larger, have positive conclusions, or are published in journals with higher impact factors. In multivariable models, the presence of industry funding appears to be the most important factor associated with shorter time to inclusion, followed by trial size. For frequency of inclusion in systematic reviews, industry funding followed by a positive conclusion were the most important factors associated with inclusion in more systematic reviews. The results suggest that certain trial characteristics may influence how trials are selected and included by reviewers, potentially leading to overrepresentation or underrepresentation of certain trials in systematic reviews and eventually in clinical guidelines and consensus statements.

Our research builds on a growing area of investigation examining potential biases in how clinical trial results are reported and synthesized in systematic reviews. Studies examining factors that might affect the conclusions of systematic reviews have shown an association between funding and conflicts of interest and positive conclusions in systematic reviews [17,29]. Other studies have examined how study selection is associated with contradictory conclusions [15], and whether the availability of results data in trial registries and sources other than journal articles have the potential to influence the results or conclusions in metaanalyses, with mixed results [12,30]. Here, we examined two novel outcomes—time to inclusion and frequency of inclusion of trials in systematic reviews—revealing that funding is not only associated with the conclusions of systematic reviews but also that trials with industry funding are also incorporated into systematic review faster and more often.

The time to reporting of trial results and the implications of selective delays on the evidence available for clinical decision-making and policy have been assessed in a number of studies. Trials with negative or nonsignificant results have been found to be less likely to be published within approximately 2 years [31–33]. Positive results [10,20,21], industry funding [34], and more costly trials [35] were found to be associated with shorter time to publication. Time lags for certain types of trials are believed to bias the scientific evidence available at any given point in time. For example, if trials with positive conclusions accumulate in the scientific literature faster than those with negative findings, the treatment effect or safety of an intervention may be misrepresented and subsequently disproportionately incorporated into meta-analyses [21]. Similarly, if trials with positive conclusions are included in systematic reviews more frequently than those with negative findings, the treatment effects across reviews may be overestimated [36]. Overall, some of the factors leading to faster reporting of trial results (e.g., industry funding and positive findings) are also associated with faster and more frequent inclusion in systematic reviews for type 2 diabetes, suggesting that the biases impacting the integrity of trial reporting may be further amplifying certain trials and trial findings at the level of evidence synthesis.

Policies have been implemented to improve the integrity of trial reporting (such as mandatory prospective trial registration and result reporting) but less policy-level attention has been given to ensuring the quality and currency of systematic reviews. Concerns have been raised around the

production and quality of systematic reviews, including the rapid increase in the rate at which redundant or misleading systematic reviews are published, frequent contradictory findings, lack of prespecified protocols, incomplete evidence synthesis (i.e., selective trial inclusion), and the role of industry sponsors in exacerbating these issues [10]. Prospective publication of systematic review protocols, including full details of the literature searches and selection criteria for clinical trials, may in part address the selective inclusion and overrepresentation of certain clinical trials in systematic reviews [9].

There were limitations to this study. First, we did not identify trials that were not included in any systematic reviews and therefore cannot draw conclusions about the reasons why certain trials are not included in any systematic reviews. Second, due to the wide variation in the drugs and drug combinations studied in the intervention arms of trials, we were not able to uniquely separate drug classes across the set of trials to examine whether there were differences in the timing and frequency of inclusion of trials in systematic reviews related to the drugs evaluated. Third, the set of trial characteristics we included as factors in the model were limited, and other factors could be included in future research on this topic. For example, we did not include composite indicators such as trial quality nor did we include other trial design factors (e.g., length of follow-up [7], risk of bias, the specific roles of funding sources, or other experimental design characteristics). Because these may also be associated with factors such as funding, the number of participants, and journal impact factor, we are unable to speculate on whether systematic reviewers preferentially incorporated industry funded, larger trials because of these factors or because of differences in trial design. Fourth, we did not consider characteristics of the systematic reviews. For example, systematic reviewers who were involved in relevant trials as an investigator or who hold industry funding or conflicts of interest may have better access to or awareness of results of certain trials, and this could reduce the time to inclusion or increase the frequency of inclusion. Fifth, we found that a disproportionate number of trials were funded by industry and produced positive conclusions and the unbalanced nature of the data may have affected our ability to identify associations. Finally, we did not further evaluate the types or levels of industry funding among the trials due to the heterogeneity with which funding and conflicts of interest are reported [26].

5. Conclusions

Industry funding, larger trial size, positive trial conclusions, and publication in higher impact factor journals were associated with faster or more frequent inclusion of trial results in systematic reviews for type 2 diabetes interventions. The overrepresentation of certain types of clinical trials in systematic reviews may increase the influence of these trials in health care policies and clinical care.

CRediT authorship contribution statement

Adam G. Dunn: Conceptualization, Methodology, Data curation, Writing - review & editing. **Liat Orenstein:** Methodology, Data curation. **Enrico Coiera:** Methodology, Writing - review & editing. **Kenneth D. Mandl:** Methodology, Writing - review & editing. **Florence T. Bourgeois:** Conceptualization, Methodology, Investigation, Writing - review & editing.

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Supplementary data

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