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HISTORICAL REVIEW

Rethinking time-lag bias in meta-analysis: Broader definitions and conceptual frameworks

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Abstract

Meta-analysis is often viewed as a gold standard for synthesizing available evidence, but it faces challenges as evidence becomes available gradually and studies may be disseminated selectively and at different times. When publication timing is systematically related to study results, meta-analytic conclusions at any given time can be biased; for example, studies with statistically significant or larger effects may be published earlier than those with null or smaller effects. This phenomenon, commonly referred to as time-lag bias, is a key reason why early meta-analytic conclusions may later weaken, reverse, or become more heterogeneous as additional evidence accrues. To address the limitations of existing definitions and detection approaches, which are largely tied to monotone, effect-size-driven dissemination, we broaden the concept of time-lag bias beyond the traditional yet simple notion that "positive" studies are published earlier. Specifically, we view time-lag bias more generally as a manifestation of time-dependent evidence availability, whereby the timing of study dissemination can distort meta-analytic conclusions at different stages of evidence accrual. We illustrate this broader perspective through several real-world case studies, including classical time-lag bias, inverse time-lag bias, non-monotone temporal patterns, and anomalous evidence localized within specific time windows. These examples show that time-lag bias can arise through multiple dissemination mechanisms and may exaggerate, attenuate, or even reverse pooled estimates over time. They highlight the importance of explicitly accounting for the temporal dimension of evidence accumulation and motivate the routine use of diagnostic and sensitivity strategies to assess robustness to selective dissemination over time.

Highlights

What is already known?

- Time-lag bias is traditionally understood as the tendency for studies with statistically significant or favorable findings to be published earlier than studies with null or unfavorable results.
- Common approaches for assessing time-lag bias include time-based meta-regression, cumulative meta-analysis, and analyses of time-to-publication.

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- Existing definitions and detection approaches largely focus on simple, monotone, effect-size-driven dissemination patterns.

What is new?

- We broaden the concept of time-lag bias by viewing it as a manifestation of time-dependent evidence availability rather than restricting it to the earlier publication of positive findings.
- We distinguish between time-point-based and time-duration-based definitions of time-lag bias and clarify how each may capture different aspects of the research dissemination process.
- Through real-world case studies, we illustrate classical, inverse, non-monotone, and time-localized anomalous patterns that may exaggerate, attenuate, or reverse meta-analytic conclusions over time.

Potential impact for RSM readers

- The broader perspective highlights limitations of commonly used methods that assume linear or monotone temporal trends and may fail to detect more complex dissemination patterns.
- The findings encourage systematic reviewers and meta-analysts to examine the temporal dimension of evidence accumulation and to interpret early or interim meta-analytic conclusions cautiously.
- This work motivates the development and routine use of broader diagnostic and sensitivity strategies for assessing the robustness of evidence syntheses to time-dependent dissemination.

1. Introduction

Meta-analysis is often treated as a tool for providing the best quality of evidence in medical research through combining evidence from multiple clinical trials or observational studies.[1,2] However, different types of bias are pervasive in meta-analysis because the available evidence may be an incomplete and non-random subset of all studies that were truly conducted. This incompleteness can arise at multiple stages, including selective decisions to submit or publish results, differential indexing and discoverability, selective outcome reporting, and delays in dissemination.[3,4] Consequently, the set of studies included in a meta-analysis may systematically over-represent certain types of findings, leading to biased pooled estimates and inaccurate confidence intervals (CIs).[5]

Among the various types of bias, publication bias (PB) arises when studies with statistically significant or favorable results are more likely to be published and therefore more likely to be included in evidence syntheses.[6] At the same time, bias may also operate in the opposite direction. Inverse PB (IPB) describes situations in which studies with null or unfavorable results are more likely to be published (or published earlier) than studies reporting larger or more favorable effects, leading to an apparent deflation of the pooled estimate.[7–9] These mechanisms suggest that meta-analytic conclusions reflect not only the underlying scientific truth but also the selective processes that govern the visibility and timing of evidence. Therefore, methodologists have developed a wide range of approaches to detect PB or IPB, including regression-based tests, selection (weight-function) models, and Bayesian frameworks.[10–15]

However, conventional methods for PB and IPB focus on whether studies are selectively disseminated and become available to reviewers, whereas in many research areas, the evidence base does not arrive all at once. Studies appear over time, and their timing is unlikely to be random. However, meta-analyses often treat studies as if they were random samples, without accounting for temporal features. When the order of publication is systematically related to study results, a meta-analysis conducted at any given time can be biased; the studies with significant or large effect sizes could get published earlier than the studies with null or small effect,[16,17] where time is a key contributor to the potential bias in estimating the effect in meta-analysis. This phenomenon is broadly referred to as time-lag bias and is one key reason early meta-analytic conclusions may later weaken, reverse, or become more heterogeneous as additional evidence accumulates.

Although PB and time-lag bias may arise from related selective dissemination mechanisms, they concern distinct dimensions of evidence availability. Publication bias primarily concerns whether a

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study becomes available for inclusion in a meta-analysis, whereas time-lag bias concerns when it becomes available. The two biases overlap when statistically significant or favorable studies are both more likely to be published and published more rapidly. However, adjustment for PB at a single time point does not necessarily account for the temporal ordering of evidence or reconstruct how meta-analytic conclusions may have differed at earlier stages of evidence accrual. Time-lag bias therefore warrants separate consideration, particularly in early, interim, or living systematic reviews; when most studies are eventually published but with result-dependent delays; when inverse or non-monotone temporal patterns are possible; and when changes in dissemination practices cause the composition of the available evidence to vary over time. In these settings, methods developed for conventional PB may fail to capture distortions arising specifically from the timing of evidence availability.

At a conceptual level, time-lag bias is commonly framed as an effect-size-driven delay in publication, which implicitly assumes a single, monotone dissemination mechanism, in which the probability or timing of dissemination is a monotone function of study results.[18] This framework also ignores the impact of time-dependent evidence availability arising from multiple, interacting selection processes. Thus, despite its importance, existing detection approaches for time-lag bias remain limited in scope and are often tied to specific parametric trends or to cumulative meta-analysis (CMA) and simple meta-regression frameworks.[19–22] Such approaches may have limited power to detect complex, nonlinear, or non-monotone temporal patterns, and they do not directly accommodate inverse dissemination mechanisms or heterogeneous time-dependent selection processes.[21]

This article extends and formalizes the concept of time-lag bias by reframing it as a general manifestation of time-dependent evidence availability, rather than limiting it to earlier publication of statistically significant results. This broader perspective accommodates multiple interacting dissemination mechanisms. We start by formalizing the definition of time in time-lag bias, then clarify how time-dependent dissemination can distort meta-analysis conclusions at different stages of evidence accumulation. Lastly, we illustrate various time-lag bias patterns observed in real-world case studies.

2. How to define the "time" in time-lag bias?

The concept of time-lag bias was originally articulated in the context of publication and dissemination bias, referring to the tendency for studies with statistically significant or "positive" findings to be published more rapidly than studies with null or unfavorable results.[16,17] In practice, however, the definition of "time" in time-lag bias can vary across settings. Studies may now have multiple relevant dissemination dates, including preprint posting, preprint updates, journal publication, and database indexing dates. Moreover, preprints may influence the timing of subsequent journal publication by other studies; for example, the public release of a positive preprint could prompt teams with null or unfavorable findings to publish more quickly. Thus, using only the formal journal publication date may obscure temporal dynamics that began during the prepublication period.[23]

2.1. Time-point-based bias

One commonly used approach defines time simply as the publication time point. Under this framework, studies are ordered chronologically by publication date, and temporal patterns in reported effect sizes are examined across this sequence of studies. This approach differs from duration-based definitions of time-lag bias in that it does not require information on study completion, submission, or registration dates. Instead, it relies solely on the timing of evidence availability in the published literature, which is often the only information accessible to systematic reviewers.

Common methods for detecting this type of time-lag bias include time-based meta-regression and CMA.[19,21] In the meta-regression approach, the study-specific effect size, y_i, is regressed on the study's publication time, t_i, as follows:

$$y_i = \beta_0 + \beta_1 t_i + \varepsilon_i,$$

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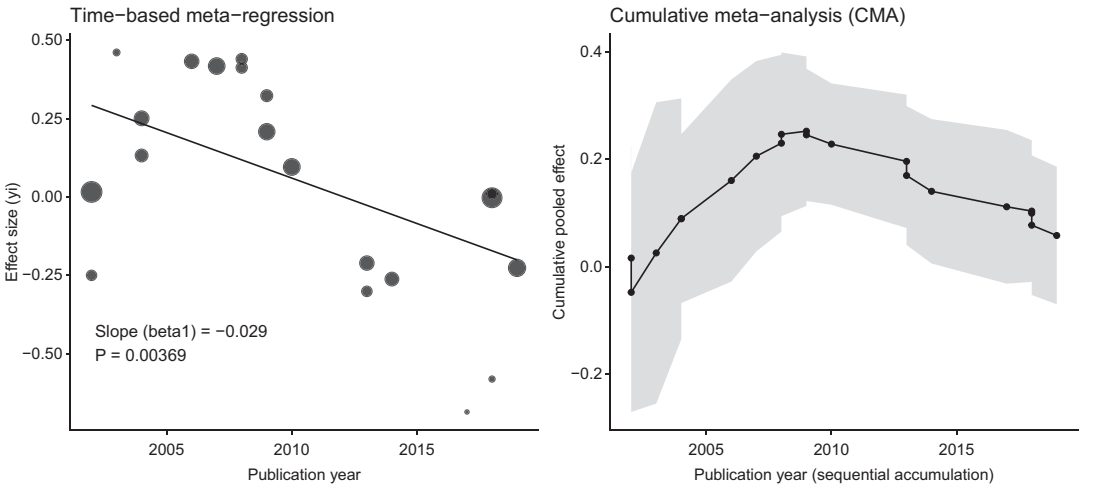


Figure 1. *A simulated meta-analysis with time-lag bias presented in chronological order.*

where β_1 represents the temporal trend in effect size over publication time. The meta-regression approach tests whether this slope differs from zero. Statistical inference for β_1 may be based on a Wald z-test or a small-sample t-based procedure. In the empirical illustrations presented in this article, the reported P-values were obtained using the default Wald z-test implemented in the `metafor` package. Rejecting the null hypothesis, $H_0 : \beta_1 = 0$ provides evidence of time-lag bias (Figure 1). A limitation of the commonly used linear meta-regression approach is that it assumes a linear association between effect size and publication time. Although nonlinear meta-regression models could, in principle, be used, meta-analyses often include too few studies to reliably detect or characterize nonlinear temporal patterns.[24,25]

On the other hand, CMA is a popular method for evaluating and monitoring temporal changes in study results.[19,26,27] The procedure starts with a single study and sequentially adds additional studies as time progresses. The cumulative effect size shows how the overall estimate changes as an additional study is added. By accumulating studies by publication year, the potential impact of time on effect sizes can be visualized, which helps to suggest whether time-lag bias might exist (Figure 1). If the cumulative effect estimates show a systematic temporal trend, this may suggest time-lag bias, as such patterns can arise when the timing of publication is associated with study results (e.g., larger or statistically significant effects). However, this approach alone cannot confirm the presence of bias and should be supplemented by formal statistical methods. Related approaches, such as trial sequential analysis (TSA), extend this idea by incorporating monitoring boundaries and required information size to assess the stability of accumulating evidence.[23] Although TSA is primarily designed to control type I error in CMA, patterns such as early crossing of significance boundaries followed by attenuation as more studies accumulate may indirectly suggest time-dependent dissemination processes.

Though the aforementioned methods have been widely used in practice,[21] the simplified parametric assumptions may fail to capture nonlinear or non-monotone dissemination patterns observed in practice, which helps explain the emergence of diverse and heterogeneous forms of time-lag bias beyond the classical paradigms. Complex, nonlinear, or non-monotone dissemination patterns arise because the timing of evidence availability is shaped by multiple, interacting mechanisms rather than a single effect-size-dependent process. Another important mechanism is outcome mismatch between the meta-analysis and the original trials: the outcome synthesized in a meta-analysis may differ from the primary outcome for which the included trials were designed and reported. For example, a meta-analysis may focus on mortality even when mortality was reported only as an adverse event or ancillary outcome in many trials, or on kidney outcomes in trials originally designed around primary cardiovascular outcomes.[28,29] In such cases, the timing and completeness of evidence availability for the meta-analytic outcome

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may differ from those for the original primary outcome, creating more complex temporal patterns. These mechanisms include heterogeneous time-to-publication across study designs, outcomes, and journals; selective outcome reporting that delays the release of certain endpoints; evolving incentives and editorial priorities over time; and changes in the research dissemination ecosystem, such as the emergence of trial registries, preprints, and shifts in database indexing and coverage. The increasing use of preprints further complicates the definition of publication time in time-point-based analyses. A study may have multiple relevant dissemination dates, including initial preprint posting, subsequent preprint updates, formal journal publication, and database indexing. Therefore, relying solely on the formal journal publication date may not fully capture when evidence first became publicly available.

2.2. Time-duration-based bias

An alternative approach defines time as the duration between key stages in the research dissemination process, such as the interval from study completion to publication, from manuscript submission to publication, or from trial registration to publication.[23,30,31] In these settings, time-lag bias is reflected in systematic differences in dissemination durations across studies with different characteristics or results. Several empirical investigations have directly examined the association between dissemination duration and study findings, documenting systematic delays for null or unfavorable results.[17,31,32] Moreover, when trial completion dates and publication dates are available, time-lag bias can be modeled within a survival analysis framework: "publication" is treated as the event of interest, studies that remain unpublished by the end of follow-up are treated as censored, and Kaplan–Meier estimators or Cox proportional hazards models are used to compare time-to-publication distributions or publication hazards across result types.[17,31,32] Nevertheless, these survival-based approaches do not fully eliminate modeling challenges. Similar to regression-based methods that use publication time as a covariate, they may be sensitive to nonlinear or nonproportional temporal patterns, particularly when the association between study results and publication hazard changes over follow-up.

However, several methodological challenges should be considered when applying survival analysis to investigate time-lag bias. First, accurate information on trial completion dates, submission dates, or publication dates is not always available or may be inconsistently reported across studies. Misclassification of these time points can lead to biased estimates of time-to-publication distributions. Second, unpublished studies are often unobserved rather than merely censored, which can introduce informative censoring and potentially distort hazard estimates. Third, time-to-publication may be influenced by multiple factors beyond study results, such as trial size, funding source, journal selection, or field-specific editorial practices. Finally, survival models typically assume proportional hazards or other parametric structures that may not represent complex dissemination processes.

Importantly, the presence of a longer-than-usual time interval alone does not constitute time-lag bias. Some degree of delay between study completion and publication is inevitable in the research process due to manuscript preparation, peer review, and editorial procedures. Bias arises when publication delays are systematically associated with the magnitude or direction of study effects, or with study characteristics that are themselves related to effect estimates. For example, if trials with statistically significant or favorable findings have a shorter time interval to be published than trials with null results, early evidence syntheses will disproportionately include positive studies, while null or unfavorable studies remain unpublished or appear later. As a consequence, the evidence available at a given time point may provide a distorted picture of the true intervention effect.

3. Different patterns of time-lag bias

In the following sections, we describe several distinct patterns of time-lag bias. For illustrative purposes, these patterns are presented using the time-point-based definition (i.e., publication time or publication order), which allows temporal trends in effect estimates to be more easily visualized in meta-analytic settings. Conceptually, similar patterns may also arise under duration-based definitions

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of time (e.g., completion-to-publication intervals). However, because the underlying mechanisms and interpretations are similar, we focus on the time-point-based framework for clarity and do not elaborate further on duration-based scenarios. Importantly, the empirical examples presented below are intended to illustrate possible temporal patterns in the accumulation of evidence, rather than to establish that time-lag bias is definitively present in each case. Observed temporal patterns may also reflect random variation, clinical or methodological differences across studies, changes in intervention formulation or implementation, or other sources of heterogeneity.

3.1. Classical time-lag bias: Earlier publication of positive findings

In the classical formulation of time-lag bias, studies reporting statistically significant or favorable results tend to be disseminated more rapidly than studies with null or unfavorable findings. As a result, early meta-analyses are often dominated by "positive" evidence, leading to inflated pooled effect estimates and overconfident inference. This phenomenon can arise from multiple, interacting mechanisms. Investigators may be more motivated to submit manuscripts with positive results promptly, journals may prioritize findings perceived as novel or impactful, and null or unfavorable results may undergo longer review processes or be deprioritized. In addition, selective outcome reporting can delay the availability of certain endpoints, particularly when the outcome synthesized in the meta-analysis differs from the primary outcome of the original trial, further skewing the early evidence base and complicating the definition of publication date or time lag for the meta-analytic outcome. In practice, when evidence accrues sequentially and early-appearing studies are disproportionately positive, CMAs may initially overestimate the effect size, followed by attenuation as later, less favorable studies become available. This classical pattern provides a useful baseline for understanding more complex temporal dissemination patterns discussed in Sections 3.2–3.4.

We used a meta-analysis of 14 randomized controlled trials evaluating diet and physical activity interventions versus control among children aged 6–12 years as an example.[33] The outcome was body mass index z-score (zBMI), and the meta-analytic effect size was defined as the mean difference in zBMI between the intervention and control groups, and Figure 2a displays the corresponding forest plot. When the trials are ordered by publication year, earlier studies tend to report larger and more favorable effects of the intervention relative to control, whereas later studies yield smaller or null effects.

This temporal pattern is consistent with the classical formulation of time-lag bias, in which studies with statistically significant or favorable findings are disseminated earlier and therefore disproportionately influence early meta-analytic summaries. As less favorable evidence accumulates over time, the pooled estimate attenuates toward the null, illustrating how meta-analytic conclusions can be inflated early on and subsequently weakened as the evidence base matures (Figures 2b and 2c). Panels b and c provide complementary information about temporal patterns in the accumulated evidence. In panel b, the bubble sizes are proportional to the inverse-variance weights of the individual studies, the solid line represents the fitted linear association between effect size and publication time, and the gray shaded area represents the 95% CIs around the fitted line. The reported *P*-value tests whether the linear meta-regression slope differs from zero. However, a nonsignificant slope does not exclude nonlinear, non-monotone, or time-localized temporal patterns. In panel c, the black points and connecting line represent the cumulative pooled estimates obtained as studies are added sequentially according to publication time, and the gray shaded area represents the corresponding 95% CIs. The intervals are generally wider during the early stages because fewer studies are available and tend to narrow as evidence accumulates. Cumulative meta-analysis is primarily a descriptive diagnostic: changes in the magnitude, direction, or statistical significance of the cumulative estimate may indicate temporal instability, but no universally accepted objective threshold based on panel c alone establishes the presence of time-lag bias. Such changes may also reflect random variation or genuine clinical or methodological differences among studies. Panel c should therefore be interpreted together with panel b, study characteristics, and contextual information about the dissemination process. In this example, the outcome was zBMI. Because lower zBMI generally indicates a more favorable weight-related outcome in childhood obesity

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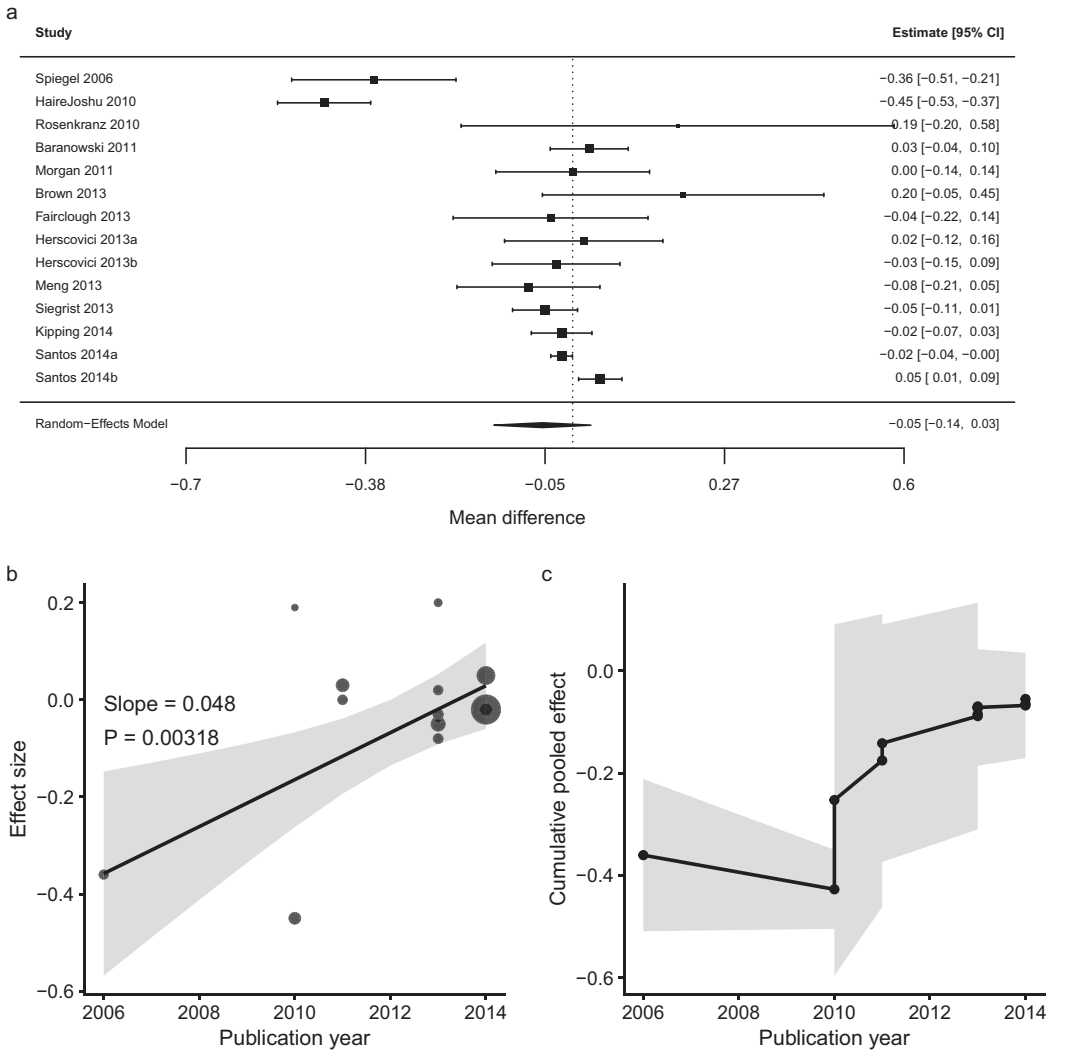


Figure 2. *Plots from a real-world meta-analysis illustrating classical time-lag bias: (a) forest plot; (b) time-based meta-regression bubble plot; and (c) cumulative meta-analysis plot. In panel b, bubble sizes are proportional to the inverse-variance weights of the individual studies, the solid line represents the fitted linear association between effect size and publication time, and the gray shaded area represents the corresponding 95% CIs. In panel c, the black points and connecting line represent the cumulative pooled estimates obtained as studies are added sequentially according to publication time, and the gray shaded area represents the corresponding 95% CIs.*

prevention, negative values indicate lower zBMI in the intervention group and therefore favor the intervention, whereas positive values favor the control group. In the context of time-lag bias, this pattern suggests that the later studies yielded smaller or null effects.

3.2. Inverse time-lag bias: Earlier availability of null or unfavorable findings

Inverse time-lag bias arises when null, negative, or unfavorable findings become available earlier than more favorable results, leading to an apparent deflation of early pooled estimates. Although

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this pattern may seem counterintuitive under the conventional view that favorable or statistically significant findings are disseminated more rapidly, several settings may favor earlier dissemination of null or negative results. As discussed by Ioannidis[9], inverse publication or reporting bias may occur when null or negative findings are themselves considered informative or desirable, including non-inferiority studies, adverse-event or drug-toxicity studies, and other reassurance-oriented research settings in which evidence of no difference, no harm, or lack of a safety signal may be more publishable or more rapidly reported.[34,35] In post-marketing or regulatory settings, for example, findings suggesting lack of benefit, potential harm, or reassuring safety profiles may be prioritized for rapid dissemination. Similarly, in non-inferiority or equivalence settings, studies showing no clinically meaningful disadvantage may be viewed as favorable, even though they are statistically "null" in the conventional superiority-testing framework.[36] In evidence synthesis, this mechanism can produce temporal patterns in which early cumulative pooled estimates lie closer to the null or suggest harm, whereas later studies shift the pooled estimate toward benefit. In time-based meta-regression, this may appear as an increasing treatment benefit over publication time, reversing the direction expected under classical time-lag bias. Therefore, time-lag bias should not be viewed as inherently monotone or necessarily favoring early exaggerated benefit. Depending on the clinical context, study design, outcome type, and dissemination incentives, early meta-analytic conclusions may be biased either toward or away from benefit.

In a meta-analysis of epidural versus systemic analgesia, the outcome pain on movement/coughing at 24 hours was reported as a continuous measure, with data available as mean and standard deviation, enabling synthesis using mean difference.[37] Figure 3a illustrates how early estimates can cluster around null or modest effects, with later studies showing increasingly favorable effects, producing a downward temporal drift of the effect size away from 0, and yielding an overall pooled estimate that is substantially more favorable than early impressions. Although these issues may also be relevant to classical time-lag bias, our focus here is on the inverse setting, in which later, more favorable results are slower to emerge. This may occur because beneficial outcomes require longer follow-up, more complex ascertainment, or delayed dissemination (Figure 3b). Regardless of the underlying drivers, the meta-analytic implication is the same: early CMAs may underestimate benefit (Figure 3c), and conclusions based on the early evidence base can be systematically conservative.

3.3. Non-monotone time-lag bias: Cyclical dissemination patterns

In some research areas, the availability of evidence over time exhibits cyclical or oscillatory patterns rather than monotone trends. Under non-monotone time-lag bias, early meta-analytic estimates may be inflated, attenuated in intermediate stages, and subsequently re-inflated or even reversed as different waves of studies become available. Such patterns can arise from shifting research agendas, funding cycles, and periodic bursts of interest following landmark trials, regulatory actions, or guideline updates.[38,39] For example, initial enthusiasm surrounding a novel intervention may trigger a wave of small, early-phase studies reporting favorable results, followed by larger confirmatory trials with more modest or null effects, and later by targeted subgroup analyses or implementation studies that again yield heterogeneous or directionally different findings. Additional drivers include changes in editorial priorities, methodological standards, and dissemination channels over time, such as the rise of preprints or registry-based reporting. These dynamics can generate oscillatory trajectories in pooled estimates and apparent "reversals" at different stages of evidence accrual. Under this scenario, CMA may exhibit sign reversals or alternating inflation and attenuation, while linear time-based meta-regression may fail to detect any temporal association despite pronounced non-monotone distortions.

The case study focused on the subgroup of participants not selected for higher risk of falling from Sherrington et al.,[40] which evaluated whether balance and functional exercise interventions reduce the rate of falls among community-dwelling older adults. A total of 19 trials were included, and the effect size was measured as the log rate ratio, with negative values favoring exercise and positive values favoring control. When trials were ordered by publication year, the pooled trajectory exhibited a

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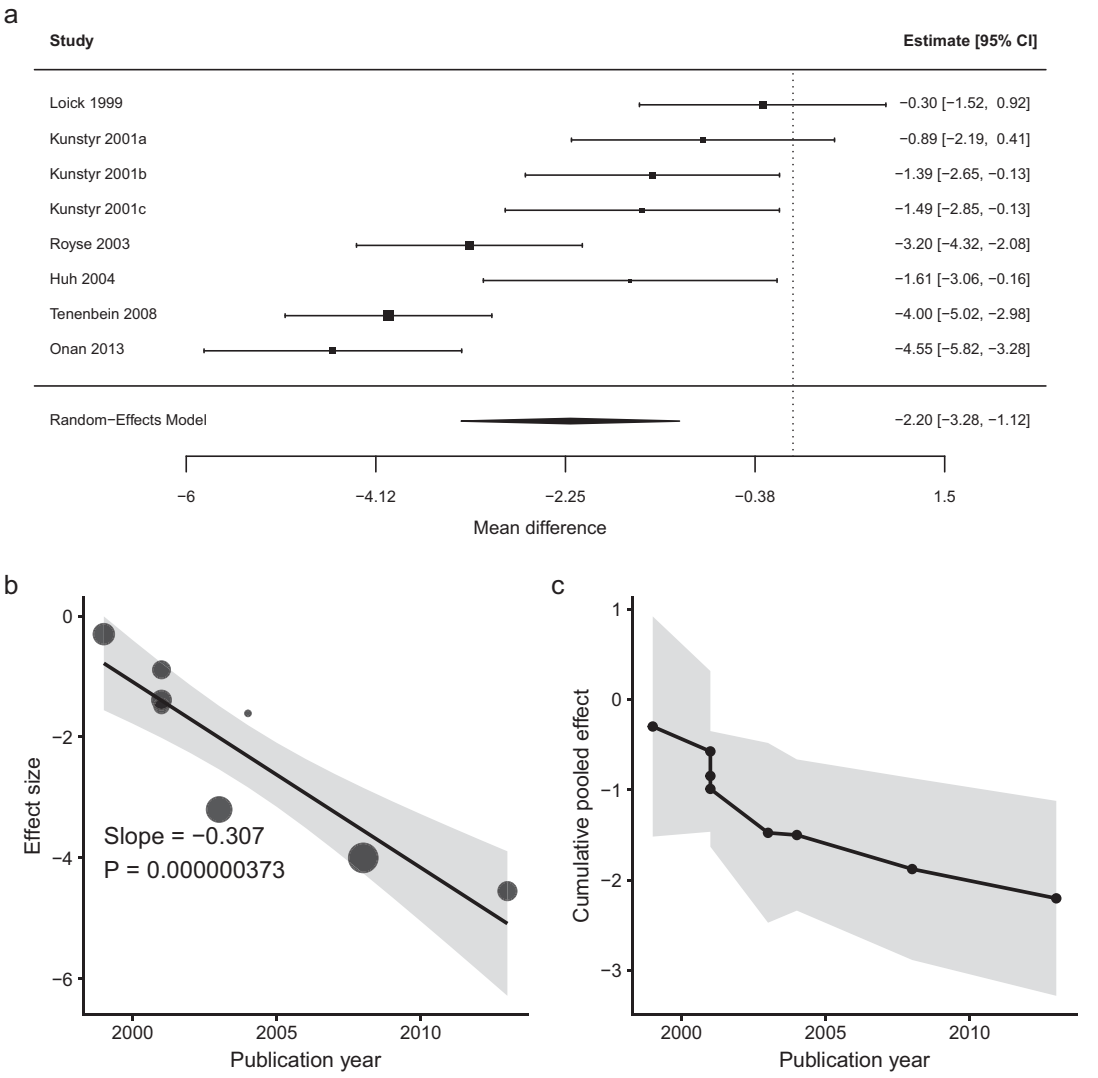


Figure 3. *Plots from a real-world meta-analysis illustrating inverse time-lag bias: (a) forest plot; (b) time-based meta-regression bubble plot; and (c) cumulative meta-analysis plot.*

non-monotone pattern: early studies suggested modest benefits, mid-period trials attenuated toward the null, and later studies showed renewed evidence of benefit or heterogeneity (Figure 4a). This oscillatory pattern may reflect successive waves of evidence corresponding to shifts in research emphasis, trial design, or intervention implementation.[41] Despite these temporal distortions in the pooled estimates, conventional time-based meta-regression did not detect a clear association between effect size and publication time (slope = −0.004, $P = 0.351$) (Figures 4b and 4c). This case illustrates the limitations of diagnostics that assume simple monotone temporal trends and motivates methods that remain informative under more general, non-monotone dissemination processes.

Importantly, this oscillatory trajectory should not be interpreted as definitive evidence that time-lag bias occurred in this meta-analysis. The observed pattern is potentially consistent with time-dependent selective dissemination, but it may also reflect random variation, differences in study populations or methodological quality, changes in intervention implementation, or successive waves of research conducted in different clinical settings. Confirmation of time-lag bias would require additional evidence

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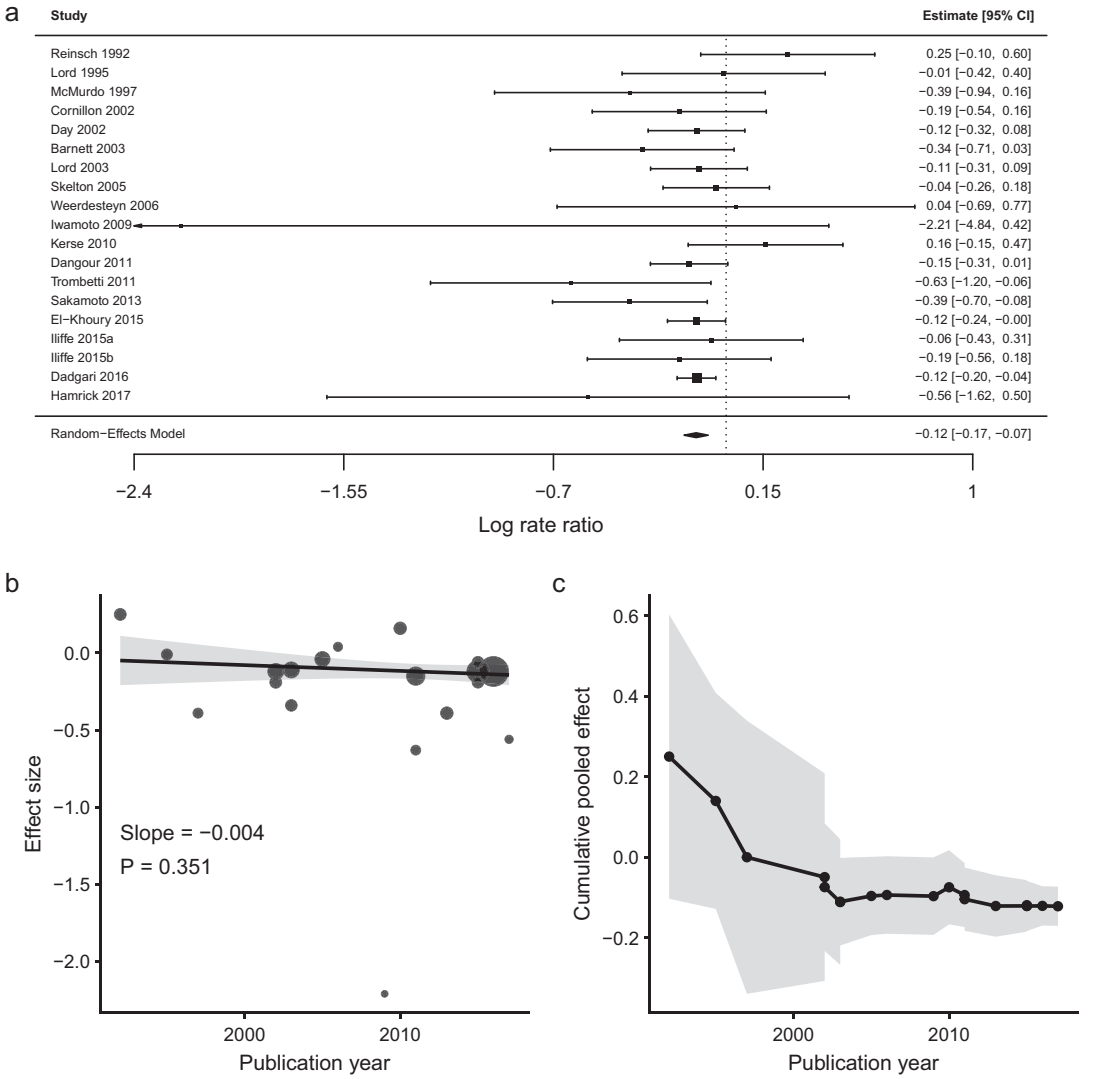


Figure 4. *Plots from a real-world meta-analysis illustrating non-monotone time-lag bias: (a) forest plot; (b) time-based meta-regression bubble plot; and (c) cumulative meta-analysis plot.*

that the timing of study availability was systematically associated with study findings or related characteristics. Nevertheless, the pattern illustrates a potential limitation of conventional analyses: opposing changes across different periods may produce a linear meta-regression slope close to zero even when the cumulative pooled estimate changes meaningfully in magnitude, direction, or statistical significance over time.

3.4. "Anomalous evidence" concentrated in a specific time window

In practice, apparent time trends in meta-analytic effect estimates do not always reflect a genuine time-lag dissemination process. A common alternative is a localized shock: one or a few outlying or otherwise anomalous studies appearing in a particular period, producing a sharp jump or dip in the time-ordered series. The signature of this scenario is a non-smooth evolution; rather than a gradual

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monotone drift, the trajectory exhibits an abrupt change within a specific time window, and the pooled estimate may remain distorted thereafter or return toward earlier levels once additional studies accrue.

Such time-localized outliers can arise through several real-world mechanisms.[42,43] Changes in clinical practice or study design during a particular era (e.g., adoption of new surgical techniques, perioperative management protocols, anticoagulation strategies, monitoring practices, or revised outcome definitions) may complicate comparisons with earlier or later studies. Measurement and reporting conventions can also shift over time, including changes in scales, follow-up windows, analysis definitions, or endpoint adjudication procedures, creating an artificial "period effect." Alternatively, the affected period may contain studies with a high risk of bias or data anomalies, generating extreme estimates without any systematic dissemination ordering. Localized outliers can be misleading because they may trigger sudden changes in direction or statistical significance in CMA; a few high-leverage studies can drive time-based meta-regression slopes, creating spurious evidence of time-lag bias.

To illustrate a time-localized anomalous pattern in evidence accumulation, we reanalyzed the pain outcome from a Cochrane review comparing glucosamine versus placebo for osteoarthritis.[44] The outcome was pain severity, and the effect size was defined as the standardized mean difference in pain scores between the glucosamine and placebo groups. Because lower pain scores indicate greater symptom improvement, negative effect estimates favor glucosamine, whereas positive estimates favor placebo. The apparent temporal pattern is dominated by a localized cluster of extreme effects in the early window around 1980–1981 rather than by a smooth dissemination-driven drift. Several early trials show large negative effect sizes favoring glucosamine, including one highly extreme estimate, while the later evidence base from the late 1990s through 2008 contains many trials with estimates close to the null and CIs frequently overlapping 0 (Figure 5a). This visual step change is consistent with time-localized anomalous or outlier influence. In CMA, these early studies induce abrupt level shifts, while in meta-regression, they can drive the estimated temporal slope away from zero, creating apparent evidence of time-lag bias even in the absence of a genuine dissemination-driven temporal process (Figures 5b and 5c).

4. Discussion

This article has clarified and broadened the time-lag bias concept by reframing it as a general manifestation of time-dependent evidence availability, rather than restricting it to the conventional notion that studies with statistically significant results are published earlier. Specifically, the key contributions of this manuscript are threefold. First, we distinguish between the conventional definition of time-lag bias, typically framed as earlier publication of "positive" studies, and a broader, more general definition that encompasses multiple, potentially interacting time-dependent dissemination mechanisms, including inverse and non-monotone temporal patterns. Second, we provide a series of real-world case studies to illustrate diverse forms of time-lag bias, demonstrating that the temporal dynamics of evidence accrual can lead to exaggerated, attenuated, or even reversed meta-analytic conclusions at different stages of evidence accumulation. Third, we highlight the limitations of existing detection approaches, including parametric time-trend models, CMA frameworks, and survival-based approaches to time-to-publication, and motivate the need for diagnostic and sensitivity strategies that explicitly account for time-dependent evidence availability.

These findings have important implications for the interpretation of early and interim meta-analyses. When evidence accrues sequentially, pooled estimates at any given time point reflect not only the underlying treatment effects but also the prevailing dissemination processes that govern which studies are available and when. As illustrated by our case studies, early conclusions may be inflated, attenuated, or even reversed as additional waves of evidence become available. This temporal instability cautions against overinterpretation of early meta-analytic summaries and underscores the value of reporting the sensitivity of conclusions to the timing of evidence accrual.

Several statistical approaches may help assess the influence of time-lag bias, although no universally accepted method is currently available to fully adjust for it. As discussed above, cumulative and

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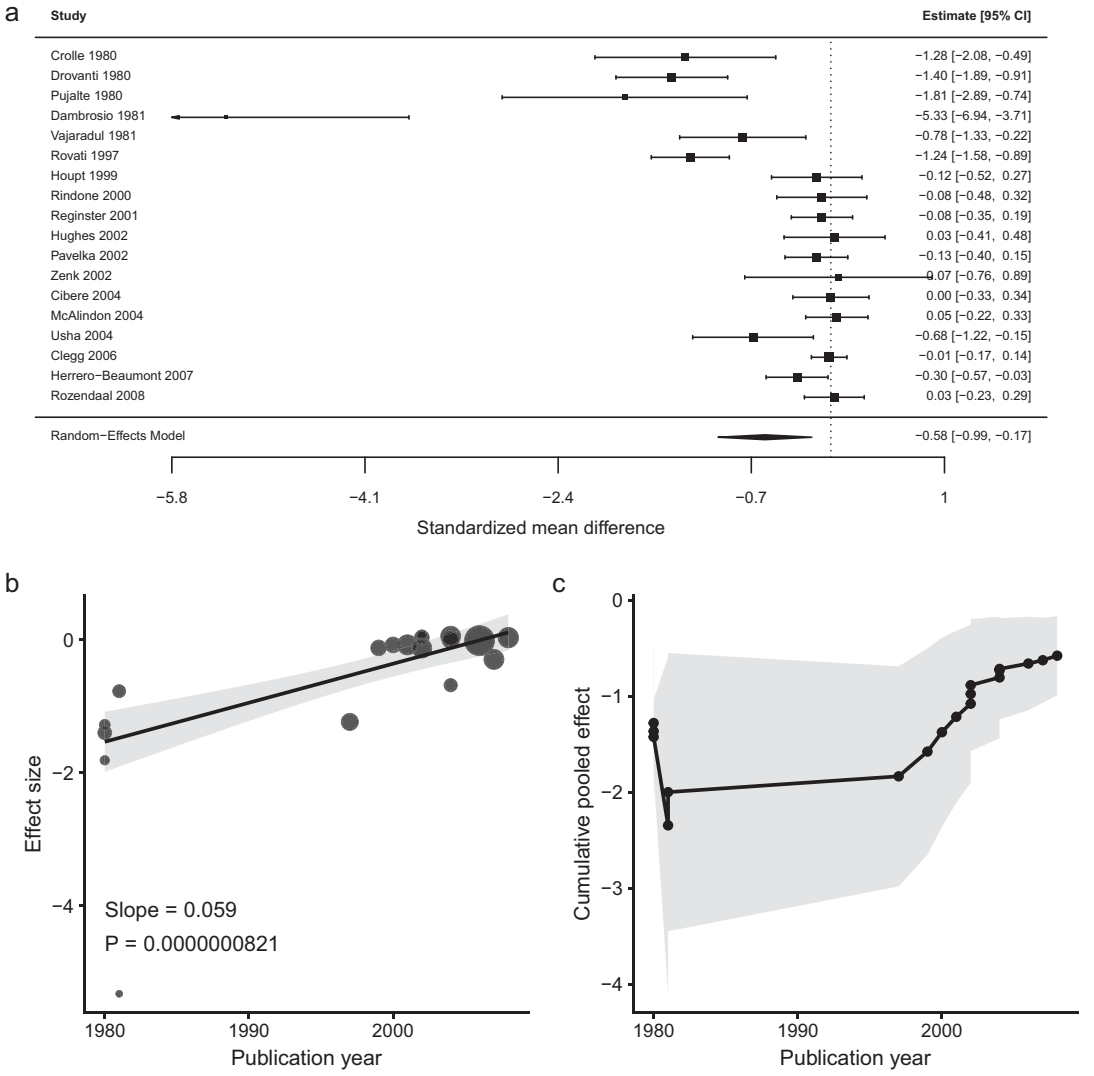


Figure 5. *Plots from a real-world meta-analysis illustrating time-lag bias with anomalies concentrated within a specific time window: (a) forest plot; (b) time-based meta-regression bubble plot; and (c) cumulative meta-analysis plot.*

recursive cumulative meta-analyses can characterize changes in pooled estimates as evidence accrues, while meta-regression using publication time as a moderator can quantify prespecified temporal trends. For duration-based time-lag bias, survival models can assess whether time to publication is associated with study findings. When selective or delayed dissemination is suspected, selection models or sensitivity analyses based on assumed dissemination mechanisms may also be informative. However, these approaches generally rely on assumptions that are difficult to verify and cannot reliably distinguish selective dissemination from genuine temporal changes in study populations, interventions, methodological quality, or clinical practice. They should therefore be viewed primarily as diagnostic and sensitivity-analysis tools rather than as definitive methods for eliminating time-lag bias. Developing formal adjustment methods that accommodate complex and non-monotone temporal patterns remains an important direction for future research.

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Several limitations exist. First, publication time is an imperfect proxy for evidence availability, as dissemination can also occur through preprints, registries, and other channels that are not uniformly captured. Second, our analyses are descriptive in nature and do not establish causal mechanisms underlying dissemination dynamics. Third, the emergence of preprints has introduced additional challenges for assessing time-lag bias by complicating the definition of time. Although recent work has proposed data-driven confidence-score methods to evaluate or weight unpublished preprints when incorporating them into evidence synthesis,[45] further consideration is needed regarding which dissemination time point or interval should be used when assessing time-lag bias. Fourth, an important practical limitation is that meaningful and reliable temporal trends may become discernible only after evidence has accumulated over a sufficiently long period. Many of the empirical patterns illustrated in this review span one or even two decades of publications. Accordingly, the assessment of temporal instability may be challenging in emerging research areas with relatively short publication histories or few available studies. In such settings, the absence of an apparent temporal trend should not be interpreted as conclusive evidence of temporal stability, as it may simply reflect an insufficient duration of evidence accumulation. Last, a limitation arises when multiple effect estimates come from the same study. Although similar entries may be combined, this may be inappropriate for clinically distinct subgroups. In such cases, tied publication times and within-study dependence are not well addressed by existing methods for time-lag bias, and further methodological work is needed. Future work could formalize generative models for the time-dependent evidence availability process, develop formal tests with calibrated operating characteristics under non-monotone patterns, and integrate time-lag diagnostics into living systematic reviews and sequential evidence monitoring frameworks.

5. Conclusion

Time-lag bias should be viewed as a general, dynamic process of time-dependent evidence availability that can distort meta-analytic conclusions through multiple, interacting dissemination mechanisms. Explicitly accounting for the temporal dimension of dissemination is essential for robust interpretation of meta-analytic findings and for the development of diagnostics and sensitivity analyses that remain valid as evidence accrues over time.

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Competing interests. The authors declare that no competing interests exist.

Data availability statement. All code and data associated with this study can be accessed via the Open Science Framework at https://osf.io/equn8.

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