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Replication of Systematic Reviews: Is It to the Benefit or Detriment of Methodological Quality?

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Abstract

Objective: To perform an overview of the overlap of systematic reviews (SR) assessing direct oral anticoagulants (DOACs) and characterise these reviews in terms of bias and methodological quality (PROSPERO: CRD42022316273).

Study design and setting: A PubMed-indexed search was performed from inception to 31 January 2022 to identify SR evaluating DOACs in patients treated for an acute venous thromboembolism. The risk of bias of these SR was assessed according to the Risk Of Bias In Systematic reviews (ROBIS) tool. Redundancy was defined as overlap in terms of the type of population considered, the interventions compared and the studies included.

Results: A total of 144 SR were evaluated, of which 26 (18.1%) were classified as original, 87 (60.4%) as conceptual replications and 31 (21.5%) as excessive replications. The risk of bias was high in 19 (73.1%) of the original SR, 65 (74.7%) of the conceptual replications and 21 (67.7%) of the excessive replications. Compared to the original SR, the overall methodological quality was not improved in either conceptual or excessive replications.

Conclusion: A large number of SR were classified as replications, a fifth constituted excessive replications. The replications showed no improvement in overall methodological quality compared to the original SR.

Keywords: systematic review; bias; methodological quality; replication; redundancy

Running title: Replication and Risk of Bias In Systematic Reviews

Word count: 3293

What is new?**Key findings**

- More than 80% of the systematic reviews analysed were replications and were considered as being of poor methodological quality; a fifth of these reviews constituted excessive replications, showing overlap of population types, interventions compared and studies included.

What this adds to what is known

- Methodological quality tended to improve in excessive replications compared to original systematic reviews or conceptual replications but the differences were not statistically significant.

What is the implication and what should change now

- Systematic reviews replications of poor methodological quality represent a considerable waste of effort and resources.
- Authors, publishers and reviewers should be vigilant and carefully scrutinise already existing reviews to avoid wasteful replication.

1. Introduction

For many years now, a race to publish seems to have been underway. However, the increasing number of scientific articles published each year raises issues in terms of scientific integrity and value. Specifically, the notion of “publish or perish” [1] and the mass production of trials of poor methodological quality that ultimately fail to provide reliable results [2,3] and represent a waste of research resources [4–6], have become a harsh reality. In view of their high level of evidence, systematic reviews and meta-analyses have become a common feature of clinical research, and therefore do not escape this rush to publish [7,8]. In particular, meta-analyses of aggregate data (i.e. those based on effect estimates of studies reported in the literature) have dramatically increased due to the facility of obtaining aggregate data and the development of free and easy-to-use statistical software.

Meta-analytical methods were originally developed to quantitatively synthesise an abundance of published data and produce a readily comprehensible and concise overview of a therapeutic field to facilitate decision-making. However, the validity of meta-analyses depends mainly on the quality of their development and reporting. Many systematic reviews and meta-analyses are of poor quality, principally due to methodological weaknesses in their execution [7]. Given the mass of systematic reviews and meta-analyses published, it is difficult to distinguish the most reliable, relevant and least biased results. This is especially true when these systematic reviews and meta-analyses are redundant or show contradictory results [7,9], and when their number exceeds that of individual studies [10,11]. Overlap, replication and redundancy have already been observed in many fields of medical research [12–26]. Various arguments have been invoked to justify replication and redundancy, such as the wish to update an earlier systematic review and meta-analysis by including data from new high-quality trials not evaluated previously, reluctance to extrapolate the results obtained to all patients in the absence of subgroup analyses, the need to assess an endpoint not evaluated in other systematic reviews and meta-analyses, or a change in endpoint definition. In fact, redundancy might be acceptable if its sole aim was to produce a less biased meta-analysis. Redundancy may also be unintentional, especially when similar systematic reviews and meta-analyses are accepted for publication by different journals during the same period, but this could be avoided by pre-registration of systematic reviews. In addition, Tugwell et al. developed a checklist and guidance to aid assessment of whether or not replication of systematic reviews would be useful

[27]. Up to now, this mechanism of replication has never been described, especially with regards to the links between the authors of such successive systematic reviews.

Our study aimed in particular to investigate replication and its characteristics in terms of the biases and methodological quality of the systematic reviews concerned. With this objective in mind, and to illustrate the phenomenon of replication, we chose the example of direct oral anticoagulants (DOACs) used for the acute treatment of venous thromboembolism (VTE), in view of the recent development of these medicinal products and the large number of systematic reviews published on this topic.

2. Material and Methods

2.1. Identification and Selection of Systematic Reviews and Data Extraction

The study protocol was prospectively registered in the International prospective register of systematic reviews (PROSPERO, <https://www.crd.york.ac.uk/PROSPERO>, registration number CRD42022316273).

We sought to identify all relevant published systematic reviews including randomised controlled trials or observational studies evaluating DOACs in relation to any comparator in patients treated for VTE during the acute and/or extended phase of anticoagulation, including patients receiving acute treatment for VTE in the context of cancer. A literature search was performed on PubMed from inception to January 31, 2022 using keywords and medical subject headings (MeSH) terms with no restrictions on language or publication period. Initially, the search was not restricted to the treatment of VTE in order to include systematic reviews addressing several indications. The full electronic search equation is presented in Appendix Table 1.

One of the authors (CC) screened the titles and abstracts of publications for possible inclusion. Then, two of the authors (CC, PB) independently screened the full-text articles, discrepancies between reviewers being resolved by discussion. To be eligible, the systematic reviews had to meet the following criteria: 1) include randomised controlled trials or observational studies; 2) evaluate DOACs in relation to any comparator (active standard treatment: vitamin-K antagonists, aspirin, or low-molecular-weight heparin; non-active treatment: placebo or control; or other DOACs); 3) include patients treated for an acute VTE during the acute or extended

phase of anticoagulation. Pairwise (individual patient data or aggregated data) and network meta-analyses were included. Systematic reviews including only one study assessing DOACs in acute VTE patients were excluded. In order to characterise replication, only full-text articles were included in this review.

Data were independently extracted by two of the authors (CC and PB). In the event of discrepancies between reviewers, a consensus was reached by discussion. The following data were extracted from each systematic review: publication details (author names, year of publication, journal, free-access journal, impact factor of the journal), details of the meta-analysis (pairwise or network design, statistical model, registration, number of studies included, names and designs of the studies included, treatments, method used to assess the risk of bias of the included studies [tool employed and use of this tool to assess the effect of bias on the results]), and citations of previous systematic reviews in the field. A systematic review was defined as having no overlap in authorship if it shared no common author with other systematic reviews. Two systematic reviews were considered as having an overlap in authorship if they shared at least one common author.

2.2. Description of the Phenomenon of Replication

Systematic reviews are first classified according to their PICO (Population, Intervention, Comparison and Outcome) question. Each systematic review is then assigned to one of three replication categories according to the definitions used by Tugwell et al. [27]: original, conceptual replication or excessive replication. The original category comprises both original and updated systematic reviews, i.e. both the original systematic review published on a particular topic and any updates published by the same team [28]. Conceptual replication corresponds to replication in order to broaden or narrow the research question, while maintaining the same objectives as the original systematic reviews, but 1) adding new randomised studies, 2) focusing on a comparator or an intervention, 3) highlighting patient subgroups, 4) investigating other outcomes or 5) adding non-randomised studies. Finally, excessive replication is defined as overlap in terms of the type of population, the interventions compared and the studies included. If several systematic reviews are published at the same time, the first systematic review registered is considered as the original one. Two of the authors (CC, SL) assigned each systematic review to one of the three categories, discrepancies being resolved by discussion.

2.3. *Quality Assessment of the Systematic Reviews*

Two authors (CC and PB) independently assessed the risk of bias of the systematic reviews according to the Risk of Bias in Systematic Reviews (ROBIS) tool, discrepancies between reviewers being resolved by discussion. Using this tool, the assessment of the risk of bias of the systematic reviews was accomplished in two phases: 1) identification of concerns regarding the review process and 2) appraisal of the overall risk of bias [29]. Phase 1 covered four domains: study eligibility criteria, study identification and selection, data collection and study appraisal and synthesis and findings. Each of the four domains was subjectively assessed as having a low, unclear or high risk of bias, based on the questions specified in the tool. In the second phase, the overall risk of bias of the systematic reviews was assessed as low, unclear or high, based on assessment of the four domains in phase 1.

2.4. *Statistical Analysis*

The descriptive analysis was performed according to the category of replication (original, conceptual replication, other type of replication or excessive replication) using numbers and percentages for qualitative data, and means with their standard errors, as well as medians with interquartile range (IQR) for quantitative data.

Network diagrams were used to visualise the links between authors of the systematic reviews. To visualise the number of replications of systematic reviews associated with the original systematic review, we used alluvial diagrams. To analyse whether the methodological quality of the systematic reviews differed between the original, conceptual replication and excessive replication categories, a logistic regression analysis was performed, taking the replication category (original, conceptual replication or excessive replication) as the covariate and the risk of bias in each domain and overall (high vs low) as the dependent variable. The coefficient of the covariate was expressed as a ratio.

All analyses were performed using R statistical software (R Foundation for Statistical Computing). Network diagrams were plotted using igraph and network packages [30].

3. Results

3.1. Study Selection

The search procedure identified 1,258 potentially eligible systematic reviews, of which 988 were excluded after a scan of their titles and abstracts (Appendix Figure 1). After assessment of the full texts, 91 additional references were excluded. Finally, 144 systematic reviews were included in the review (references listed in the Appendix).

3.2. Description of the Systematic Reviews Included According to the Category of Replication

Among these 144 systematic reviews, 26 were classified as original, 87 as conceptual replications and 31 as excessive replications. For 19 (73.1%) of the 26 original systematic reviews we identified at least one other systematic review showing overlap, i.e., either a conceptual replication, an excessive replication or both (Figure 1). Some original systematic reviews exhibited extensive overlap with up to 15 conceptual replications and 12 excessive replications.

The characteristics of the 144 systematic reviews included are summarised in Table 1 and fully described in Appendix Table 2 and Table 3. Most of the systematic reviews had a pairwise design and had been performed in Europe and North America. The majority of the conceptual replications (54.0%) were published in a free-access format compared to 42.3% and 45.2% of the original systematic reviews and excessive replications, respectively. A protocol of the systematic review had been registered in 46.1%, 27.6% and 19.3% of the original reviews, conceptual replications and excessive replications, respectively, mainly in the PROSPERO database. A quarter of the excessive replications indicated protocol registration within 10 days prior to submission of the systematic review for publication, compared to 2 months for original systematic reviews and 3 months for conceptual replications. Twenty (64.5%) excessive replications had assessed the risk of bias of the studies included, compared with over 70% in the original systematic reviews and conceptual replications. No overlap in authorship with other systematic reviews was observed in 14 (45.2%) of the 31 excessive replications, 35 (40.2%) of the 87 conceptual replications and 7 (26.9%) of the 26 original systematic reviews. Of the 734 authors of systematic reviews, 537 (73.2%) had published an original systematic review and/or a conceptual replication (Appendix Figure 2). The remaining 197 authors (26.8%) had

published at least one excessive replication, of which 51 (25.9%) had also published at least one original systematic review or a conceptual replication.

Forty-one (47.1%) of the 87 conceptual replications cited a previous systematic review, of which 17 included a justification for the replication, and 27 cited another conceptual replication (Table 2). Twenty-one (67.7%) of the 31 excessive replications cited a previous systematic review, of which 14 included a justification for the replication, and 15 cited the original systematic review. Eight of the 31 excessive replications cited the systematic review they duplicated.

The reasons for conceptual replication were to add new randomised studies (26.4%), to highlight particular patient subgroups (20.7%), to investigate other outcomes (19.5%), to focus on a comparator or an intervention (17.2%) and to add non-randomised studies (16.1%). The characteristics of the 87 conceptual replications are summarised in Appendix Table 4.

3.3. Risk of Bias of the Systematic Reviews

Overall, the risk of bias was assessed as high in 99 (68.7%) systematic reviews and low in 39 (27.1%) systematic reviews (Table 1). A high risk of bias was observed in almost 70% of the original and conceptual replications but in 61.3% of the excessive replications. The high overall risk of bias of the systematic reviews was mainly due to the high risk of bias in domain 4 of the ROBIS tool regarding study synthesis and findings (Figure 2, Appendix Table 5).

3.4. Comparison of Risk of Bias

Compared to original systematic reviews, the overall methodological quality was not improved in replications (Figure 3).

Comparison of conceptual replications versus original systematic reviews revealed no difference in either overall methodological quality (OR 1.09, 95% CI [0.38-2.85]) or the risk of bias in each domain (Figure 3A). The risk of bias of the individual items within each domain are presented in Appendix Figure 3.

Comparison of excessive replications versus original systematic reviews suggested a better overall methodological quality (OR 0.77, 95% CI [0.24-2.42]), although the difference was not statistically significant (Figure 3B). The risk of bias of individual items within each of these domains are presented in Appendix Figure 4.

Comparison of excessive replications versus conceptual replications suggested a better overall methodological quality of excessive replication, although the difference was not statistically significant (Figure 3C). The risk of bias of individual items within each domain are presented in Appendix Figure 5.

4. Discussion

This systematic overview included 144 systematic reviews evaluating DOACs versus any comparator in patients treated for VTE, of which 87 (60.4%) were conceptual replications and 31 (21.5%) were excessive replications. Compared with other systematic reviews, excessive replications assessed the risk of bias of the included studies to a lesser extent and barely 20% registered the protocol of the systematic review (19.3%). However, excessive replications showed a trend towards a lower risk of bias than the other types of systematic review.

To the best of our knowledge, this is the first study analysing replications among systematic reviews assessing DOACs in the acute treatment of VTE and evaluating the methodological quality of excessive replications compared to original systematic reviews. Overlap of systematic reviews assessing DOACs has previously been evaluated only with regard to stroke prevention in atrial fibrillation [23]. In that context, the extent of overlap was substantial, possibly owing to the small number of trials compared to the number of systematic reviews. Several other studies have also observed overlap and redundancy of systematic reviews in many fields of medical research [10,13–22,24–26]. A quarter of the excessive replications included in the present review cited the systematic review they duplicated, indicating that these systematic reviews were performed despite awareness of other systematic reviews with a similar PICO question, suggesting deliberate redundancy. The justifications for replication advanced by the authors of systematic reviews included, for example, the assessment of an outcome not previously evaluated or of the separate components of composite outcomes, the need for subgroup analyses, the availability of new data or the inclusion of a larger number of studies and patients. Other non-valid justifications were also advanced, such as to “have a clear presentation and summarization of the study and sensitivity analysis”. Ioannidis [7] and Siontis and colleagues [12] also noted that the authors of redundant systematic reviews and meta-analyses did not systematically cite previous systematic reviews and meta-analyses concerning

the same topic. They found that only 3% of these prior meta-analyses “were cited by subsequent studies claiming to be replications addressing the same question”.

Based on the ROBIS quality assessment tool, more than 70% of the systematic reviews included in this overview were considered to be at high risk of bias. For this reason, despite the level of evidence of these systematic reviews and meta-analyses, they were not always synonymous with high-quality research. Even assuming that when a systematic review is replicated, the methodological quality might be improved, this was not the case and these replications retained a high overall risk of bias. Most of the systematic reviews evaluated were therefore of low methodological quality, replications decreasing their quality still further. The quality of systematic reviews needs to be improved through prospective registration of the protocol, an exhaustive search strategy, reporting of the methods and results of additional analyses, and assessment of the potential impact of the risk of bias of the studies included in the meta-analysis of the results obtained. This conclusion is consistent with those of studies evaluating the methodological quality of systematic reviews and meta-analyses concerning many other clinical issues and finding this to be generally poor [26,31–41]. As we have seen, some authors registered their systematic reviews only a few weeks prior to publication, which does not comply with PROSPERO requirements and suggests retrospective rather than prospective registration. The prospective registration of a systematic review protocol has two objectives. The first is to avoid excessive replication and therefore redundancy. The second is to avoid any inductive approach and thus to declare the research objective once the results have been obtained. Registration does not imply a prospective evaluation process if it precedes publication by only a few weeks. Nowadays, it is not only registration that is important, but also the date of this registration.

The reporting of systematic reviews and meta-analyses should be further regulated and authors should follow the guidelines issued. In particular, the consistency of the publication with the protocol should be carefully assessed and reported in order to enable identification of any sources of bias and explanation of disparities between the results of different meta-analyses. Bolland and Grey reviewed meta-analyses evaluating the effects of vitamin D supplementation on bone fractures and found their results to be discordant owing to substantial disparities in trial selection, outcome definition and statistical methodology [14]. Among the seven meta-analyses included in their review, only four included all eligible trials and two even included trials that did not meet their eligibility criteria. Finally, assessment of the quality of the methodology and results of redundant systematic reviews and meta-analyses is crucial to ensure that these do not convey misleading, inaccurate, or biased information.

Our overview has some limitations. First, we performed an umbrella review and restricted our search to a single database. Even though the list of systematic reviews indexed by PubMed is comprehensive, we may have missed some additional published and unpublished systematic reviews. The extent of replication is therefore potentially even greater than that we describe here. A second limitation is that we based our analysis of replication on the date of registration of the protocol whenever possible, but otherwise on the date of publication of the systematic reviews (online or in printed issues) without considering the delay in editorial and publication procedures. The third limitation concerns evaluation of the level of bias present within a systematic review. We chose to use the ROBIS tool which requires substantial reflection to complete, an issue that could become problematic in the context of a larger review. Furthermore, the assessment of each risk of bias domain requires careful analysis of the systematic review concerned in order to correctly rate the risk of bias, adding to the difficulty of using this tool. Finally, even when used by experienced methodologists, the ROBIS tool remains subjective.

5. Conclusion

The massive production of systematic reviews has led to a considerable waste in the form of excessive replicated publications of poor methodological quality. This waste could be avoidable in most cases if authors, publishers and reviewers were sufficiently vigilant. Authors have a role to play before starting their review, first by systematically checking the evidence already existing or likely to be published soon and then, if a further systematic review and meta-analysis is considered necessary, by systematically registering its protocol, assuming that excessive replication is not deliberate. In that case, publishers and reviewers should scrutinise the existing evidence to avoid wasteful excessive replication and should ensure that the recommendations of well-established guidelines for the reporting of systematic reviews and meta-analyses are fully respected in order to improve the publication quality.

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Declaration of interest

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Study protocol: Registered in PROSPERO (registration no. CRD42022316273)
(https://www.crd.york.ac.uk/prospERO/display_record.php?RecordID=316273)

Statistical code and data set: The analysis scripts and data set may be requested from Céline Chapelle (e-mail address: celine.chapelle@chu-st-etienne.fr).

CRediT author statement

Céline Chapelle: Conceptualization, Methodology, Data curation, Formal analysis, Software, Writing - Original Draft, Writing - Review & Editing. **Edouard Ollier:** Conceptualization, Methodology, Formal analysis, Software, Supervision, Validation, Writing - Original Draft, Writing - Review & Editing. **Paul Bonjean:** Data curation, Writing - Review & Editing. **Clara Locher:** Conceptualization, Writing - Review & Editing. **Paul Jacques Zufferey:** Conceptualization, Writing - Review & Editing. **Michel Cucherat:** Conceptualization, Writing - Review & Editing. **Silvy Laporte:** Conceptualization, Methodology, Supervision, Writing - Original Draft, Writing - Review & Editing.
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References

1. Rawat S, Meena S. Publish or perish: Where are we heading? *J Res Med Sci Off J Isfahan Univ Med Sci*. 2014;19(2):87-89.
2. Alexander PE, Debono VB, Mammen MJ, et al. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. *J Clin Epidemiol*. 2020;123:120-126. doi:10.1016/j.jclinepi.2020.04.016
3. Kudhail K, Thompson J, Mathews V, Morrison B, Hemming K. Randomized controlled trials in patients with COVID-19: a systematic review and critical appraisal. *Int J Infect Dis*. 2022;122:72-80. doi:10.1016/j.ijid.2022.05.034
4. Zarin DA, Goodman SN, Kimmelman J. Harms From Uninformative Clinical Trials. *JAMA*. 2019;322(9):813-814. doi:10.1001/jama.2019.9892
5. Glasziou P, Chalmers I. Research waste is still a scandal—an essay by Paul Glasziou and Iain Chalmers. *BMJ*. 2018;363:k4645. doi:10.1136/bmj.k4645
6. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet Lond Engl*. 2009;374(9683):86-89. doi:10.1016/S0140-6736(09)60329-9
7. Ioannidis JPA. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *Milbank Q*. 2016;94(3):485-514. doi:10.1111/1468-0009.12210
8. Siontis KC, Ioannidis JPA. Replication, Duplication, and Waste in a Quarter Million Systematic Reviews and Meta-Analyses. *Circ Cardiovasc Qual Outcomes*. 2018;11(12):e005212. doi:10.1161/CIRCOUTCOMES.118.005212
9. Hacke C, Nunan D. Discrepancies in meta-analyses answering the same clinical question were hard to explain: a meta-epidemiological study. *J Clin Epidemiol*. 2020;119:47-56. doi:10.1016/j.jclinepi.2019.11.015
10. Chapelle C, Ollier E, Girard P, et al. An epidemic of redundant meta-analyses. *J Thromb Haemost*. 2021;19(5):1299-1306. doi:10.1111/jth.15280
11. Husaini M, Esmaceli A, Thangam M, Doering M, Brown DL. Synthesis of systematic reviews of percutaneous device closure of patent foramen ovale (PFO) for prevention of recurrent cryptogenic stroke: Redundant publications and methodological deficiencies. *Am Heart J*. 2021;232:57-60. doi:10.1016/j.ahj.2020.10.051
12. Siontis KC, Hernandez-Boussard T, Ioannidis JPA. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ*. 2013;347:f4501. doi:10.1136/bmj.f4501
13. Riaz IB, Khan MS, Riaz H, Goldberg RJ. Disorganized Systematic Reviews and Meta-analyses: Time to Systematize the Conduct and Publication of These Study Overviews? *Am J Med*. 2016;129(3):339.e11-339.e18. doi:10.1016/j.amjmed.2015.10.009

14. Bolland MJ, Grey A. A Case Study of Discordant Overlapping Meta-Analyses: Vitamin D Supplements and Fracture. Devaney J, ed. *PLoS ONE*. 2014;9(12):e115934. doi:10.1371/journal.pone.0115934
15. Ker K, Roberts I. Exploring redundant research into the effect of tranexamic acid on surgical bleeding: further analysis of a systematic review of randomised controlled trials. *BMJ Open*. 2015;5(8):e009460. doi:10.1136/bmjopen-2015-009460
16. Sigurdson MK, Khoury MJ, Ioannidis JPA. Redundant meta-analyses are common in genetic epidemiology. *J Clin Epidemiol*. 2020;127:40-48. doi:10.1016/j.jclinepi.2020.05.035
17. Zhang H, Tang H, He Q, et al. Surgical Versus Conservative Intervention for Acute Achilles Tendon Rupture: A PRISMA-Compliant Systematic Review of Overlapping Meta-Analyses. *Medicine (Baltimore)*. 2015;94(45):e1951. doi:10.1097/MD.0000000000001951
18. McDonald S, Turner S, Page MJ, Turner T. Most published systematic reviews of remdesivir for COVID-19 were redundant and lacked currency. *J Clin Epidemiol*. 2022;146:22-31. doi:10.1016/j.jclinepi.2022.02.006
19. Bolland MJ, Grey A, Reid IR. Differences in Overlapping Meta-Analyses of Vitamin D Supplements and Falls. *J Clin Endocrinol Metab*. 2014;99(11):4265-4272. doi:10.1210/jc.2014-2562
20. Campbell KA, Erickson BJ, Saltzman BM, et al. Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses. *Arthrosc J Arthrosc Relat Surg*. 2015;31(10):2036-2045.e14. doi:10.1016/j.arthro.2015.03.030
21. Capodanno D. Overlapping meta-analyses of bioresorbable vascular scaffolds versus everolimus-eluting stents: bringing clarity or confusion? *J Thorac Dis*. 2016;8(7):1366-1370. doi:10.21037/jtd.2016.05.14
22. Naudet F, Schuit E, Ioannidis JPA. Overlapping network meta-analyses on the same topic: survey of published studies. *Int J Epidemiol*. 2017;46(6):1999-2008. doi:10.1093/ije/dyx138
23. Doundoulakis I, Antza C, Apostolidou-Kiouti F, et al. Overview of Systematic Reviews of Non-Vitamin K Oral Anticoagulants in Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes*. 2018;11(12):e004769. doi:10.1161/CIRCOUTCOMES.118.004769
24. Ioannidis JPA. Meta-analyses in environmental and occupational health. *Occup Environ Med*. 2018;75(6):443-445. doi:10.1136/oemed-2016-104128
25. Guelimi R, Afach S, Régnaux JP, et al. Overlapping network meta-analyses on psoriasis systemic treatments: an overview, quantity does not make quality. *Br J Dermatol*. 2021;187(1):29-41. doi:10.1111/bjd.20908
26. Mendoza JFW, Latorraca C de OC, Oliveira R de Á, et al. Methodological quality and redundancy of systematic reviews that compare endarterectomy versus stenting for

- carotid stenosis. *BMJ Evid-Based Med*. 2021;26(1):14-18. doi:10.1136/bmjebm-2018-111151
27. Tugwell P, Welch VA, Karunanathan S, et al. When to replicate systematic reviews of interventions: consensus checklist. *BMJ*. 2020;370:m2864. doi:10.1136/bmj.m2864
 28. Runjic R, Jelicic Kadic A, Runjic E, et al. Most systematic reviews that used the term “update” in title/abstract were not an updated version. *J Clin Epidemiol*. 2023;154:1-7. doi:10.1016/j.jclinepi.2022.11.014
 29. Whiting P, Savović J, Higgins JPT, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. 2016;69:225-234. doi:10.1016/j.jclinepi.2015.06.005
 30. Kolaczyk ED, Csárdi G. *Statistical Analysis of Network Data with R*. 2nd ed. Springer; 2020.
 31. Delaney A, Bagshaw SM, Ferland A, Manns B, Laupland KB, Doig CJ. A systematic evaluation of the quality of meta-analyses in the critical care literature. *Crit Care*. 2005;9(5):R575. doi:10.1186/cc3803
 32. Lu T ting, Lu C cun, Li M xuan, Ke L xin, Cai H, Yang K hu. Reporting and methodological quality of meta-analyses of acupuncture for patients with migraine: A methodological investigation with evidence map. *J Integr Med*. 2022;20(3):213-220. doi:10.1016/j.joim.2022.02.003
 33. Bonetti AF, Tonin FS, Della Rocca AM, Lucchetta RC, Fernandez-Llimos F, Pontarolo R. Methodological quality and risk of bias of meta-analyses of pharmacy services: A systematic review. *Res Soc Adm Pharm*. 2022;18(3):2403-2409. doi:10.1016/j.sapharm.2020.12.011
 34. Sandau N, Buxbom P, Hróbjartsson A, Harris IA, Brorson S. The methodological quality was low and conclusions discordant for meta-analyses comparing proximal humerus fracture treatments: a meta-epidemiological study. *J Clin Epidemiol*. 2022;142:100-109. doi:10.1016/j.jclinepi.2021.10.014
 35. Katsura M, Kuriyama A, Tada M, et al. High variability in results and methodological quality among overlapping systematic reviews on the same topics in surgery: a meta-epidemiological study. *Br J Surg*. 2021;108(12):1521-1529. doi:10.1093/bjs/znab328
 36. Siemens W, Schwarzer G, Rohe MS, Buroh S, Meerpohl JJ, Becker G. Methodological quality was critically low in 9/10 systematic reviews in advanced cancer patients-A methodological study. *J Clin Epidemiol*. 2021;136:84-95. doi:10.1016/j.jclinepi.2021.03.010
 37. Wei H, Zhang YJ, Yu T, Yan XY, Jiang Q. Methodological quality evaluation of systematic reviews or meta-analysis of trastuzumab-based therapy for breast cancer: A systematic review. *Medicine (Baltimore)*. 2021;100(4):e24389. doi:10.1097/MD.00000000000024389

38. Tonin FS, Borba HH, Leonart LP, et al. Methodological quality assessment of network meta-analysis of drug interventions: implications from a systematic review. *Int J Epidemiol.* 2019;48(2):620-632. doi:10.1093/ije/dyy197
39. Chambers JD, Naci H, Wouters OJ, et al. An Assessment of the Methodological Quality of Published Network Meta-Analyses: A Systematic Review. Krieg A, ed. *PLOS ONE.* 2015;10(4):e0121715. doi:10.1371/journal.pone.0121715
40. Delaney A, Bagshaw SM, Ferland A, Laupland K, Manns B, Doig C. The quality of reports of critical care meta-analyses in the Cochrane Database of Systematic Reviews: An independent appraisal. *Crit Care Med.* 2007;35(2):589-594. doi:10.1097/01.CCM.0000253394.15628.FD
41. Page MJ, Shamseer L, Altman DG, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. Low N, ed. *PLOS Med.* 2016;13(5):e1002028. doi:10.1371/journal.pmed.1002028

Table 1. Summary of the characteristics of the systematic reviews included according to the replication category. Values are numbers (percentages) unless stated otherwise.

	Original (N = 26)	Conceptual replication (N = 87)	Excessive replication (N = 31)
Type of meta-analysis			
Individual patient data meta-analysis	3 (11.5)	3 (3.4)	0 (0.0)
Pairwise meta-analysis	18 (69.2)	62 (71.3)	23 (74.2)
Network meta-analysis	5 (19.2)	22 (25.3)	8 (25.8)
Median (IQR) number of authors of the publication	6 (4-9)	6 (5-8)	6 (4-8)
Free-access publication	11 (42.3)	47 (54.0)	14 (45.2)
Journal not indexed for MEDLINE*	0 (0.0)	4 (4.6)	4 (12.9)
Median (IQR) impact factor of the journal	5.24 (3.06-7.66)	3.50 (2.77-5.72)	3.00 (2.32-5.33)
Geographic location of the first author			
Europe	10 (38.5)	34 (39.1)	16 (51.6)
North America	10 (38.5)	28 (32.2)	11 (35.5)
Asia	5 (19.2)	22 (25.3)	2 (6.4)
Other	1 (3.8)	3 (3.4)	2 (6.4)
Design of the included studies			
RCTs only	23 (88.5)	72 (82.8)	30 (96.8)
Observational studies only	0 (0.0)	3 (3.4)	1 (3.2)
RCTs and observational studies	3 (11.5)	12 (13.8)	0 (0.0)
Assessment of the risk of bias of the included studies	20 (76.9)	65 (74.7)	20 (64.5)
Descriptive (table/figure)	16	52	16
Analysis according to risk of bias	4	13	4
Registration of the protocol	12 (46.1)	24 (27.6)	6 (19.3)
PROSPERO	10	22	5
Cochrane database	2	1	0
Open Science Framework	0	1	1
Median time (IQR) from registration to submission of the publication (months)	2.6 (2.2-3.2)	5.8 (3.1-8.7)	0.4 (0.3-12.7)

No overlap in authorship	7 (26.9)	35 (40.2)	14 (45.2)
Risk of bias of the systematic reviews (ROBIS tool)			
Low	7 (26.9)	22 (25.3)	10 (32.3)
Unclear	1 (3.9)	3 (3.4)	2 (6.4)
High	18 (69.2)	62 (71.3)	19 (61.3)

* At the time of the publication.

IQR = interquartile range; RCT = randomised controlled trial.

Table 2. Citations of the systematic reviews included according to the replication category. Values are numbers (percentages) unless stated otherwise.

	Conceptual replication (N = 87)	Excessive replication (N = 31)
Citations of previous systematic reviews	41 (47.1)	21 (67.7)
Inclusion of a justification	17	14
Citations of the original systematic review	10 (24.4)	15 (71.4)
Inclusion of a justification	2	9
Citations of a conceptual replication	27 (65.8)	10 (47.6)
Inclusion of a justification	13	7
Citations of an excessive replication	11 (26.8)	8 (38.1)
Inclusion of a justification	4	5

Figure 1. Alluvial diagram of the number of replications associated with the corresponding original systematic review. Yellow: no associated conceptual or excessive replication; green: at least one conceptual and no excessive replication associated; blue: at least one excessive and no conceptual replication associated; purple: at least one conceptual and one excessive replication associated.

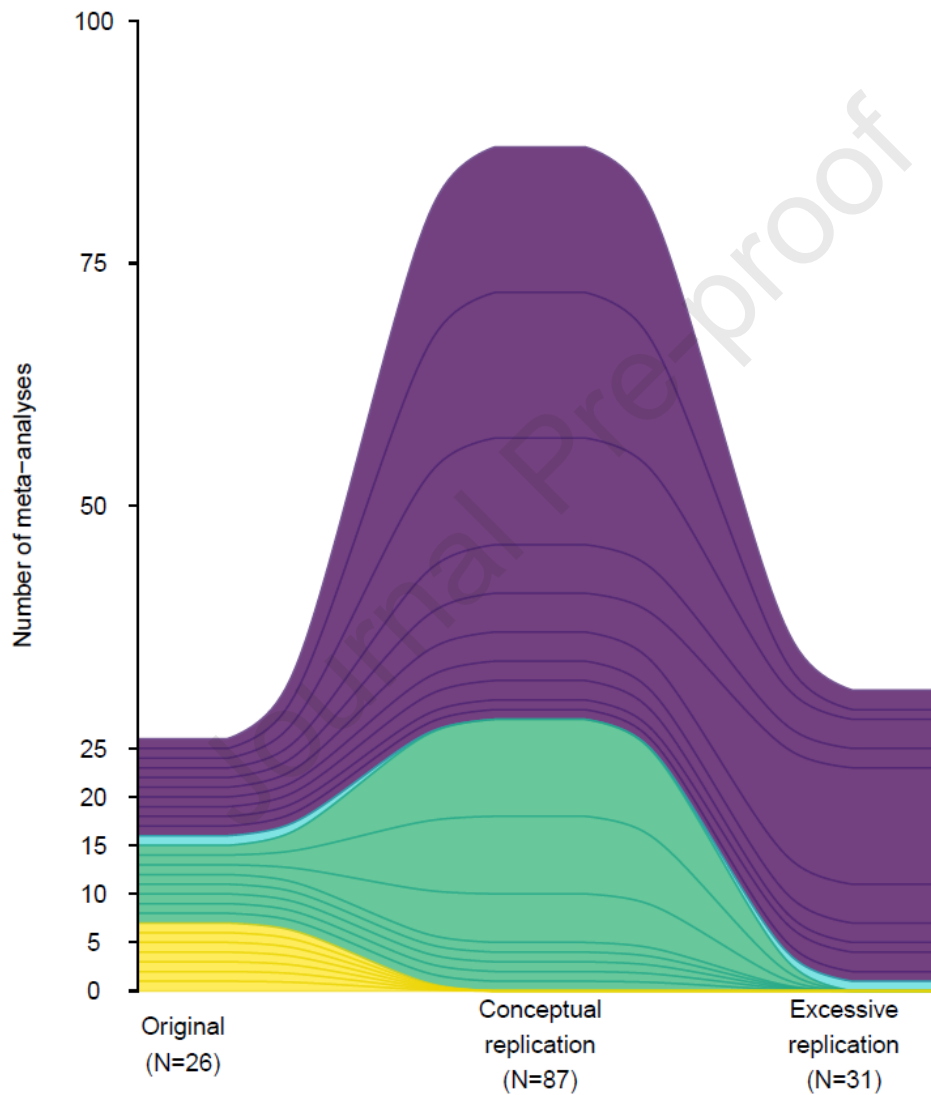


Figure 2. Risk of bias of the systematic reviews for each ROBIS tool domain according to the replication category (original, conceptual replication or excessive replication) presented as percentages across all systematic reviews included. Green: low risk of bias; orange: unclear risk of bias; red: high risk of bias.

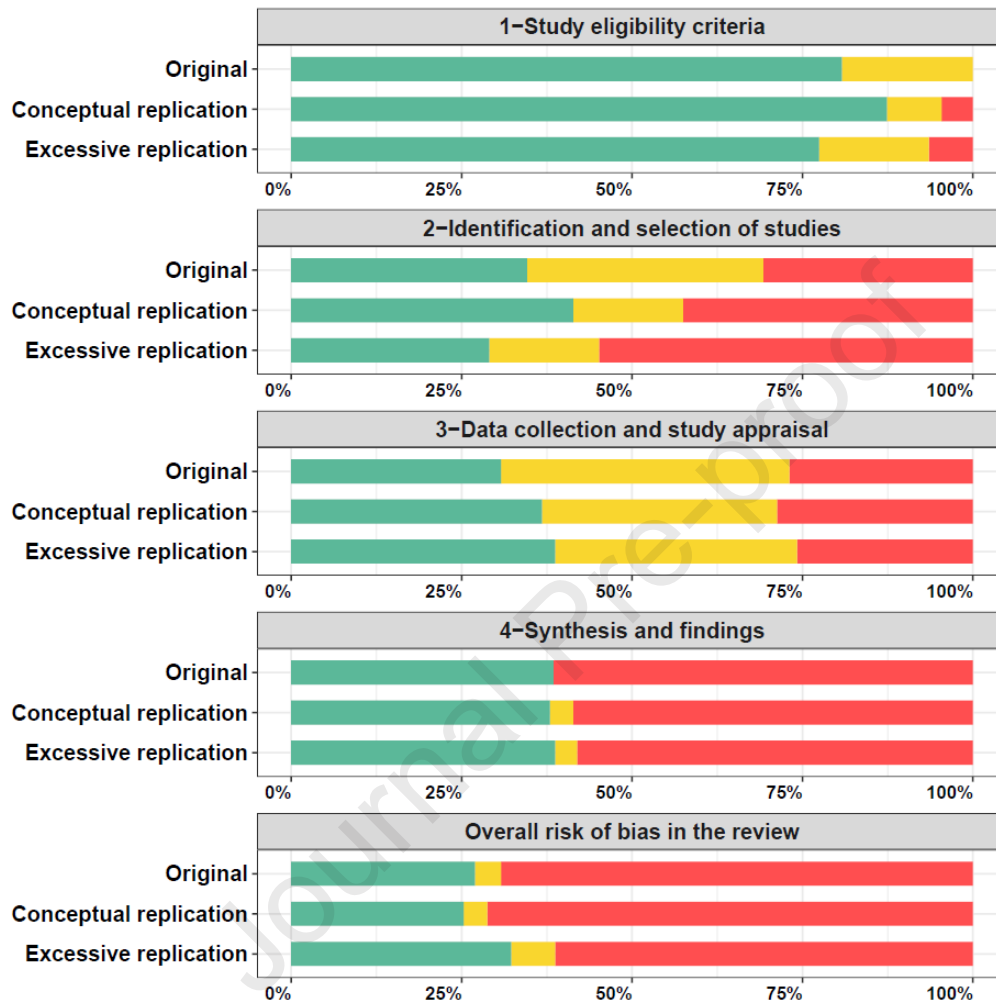
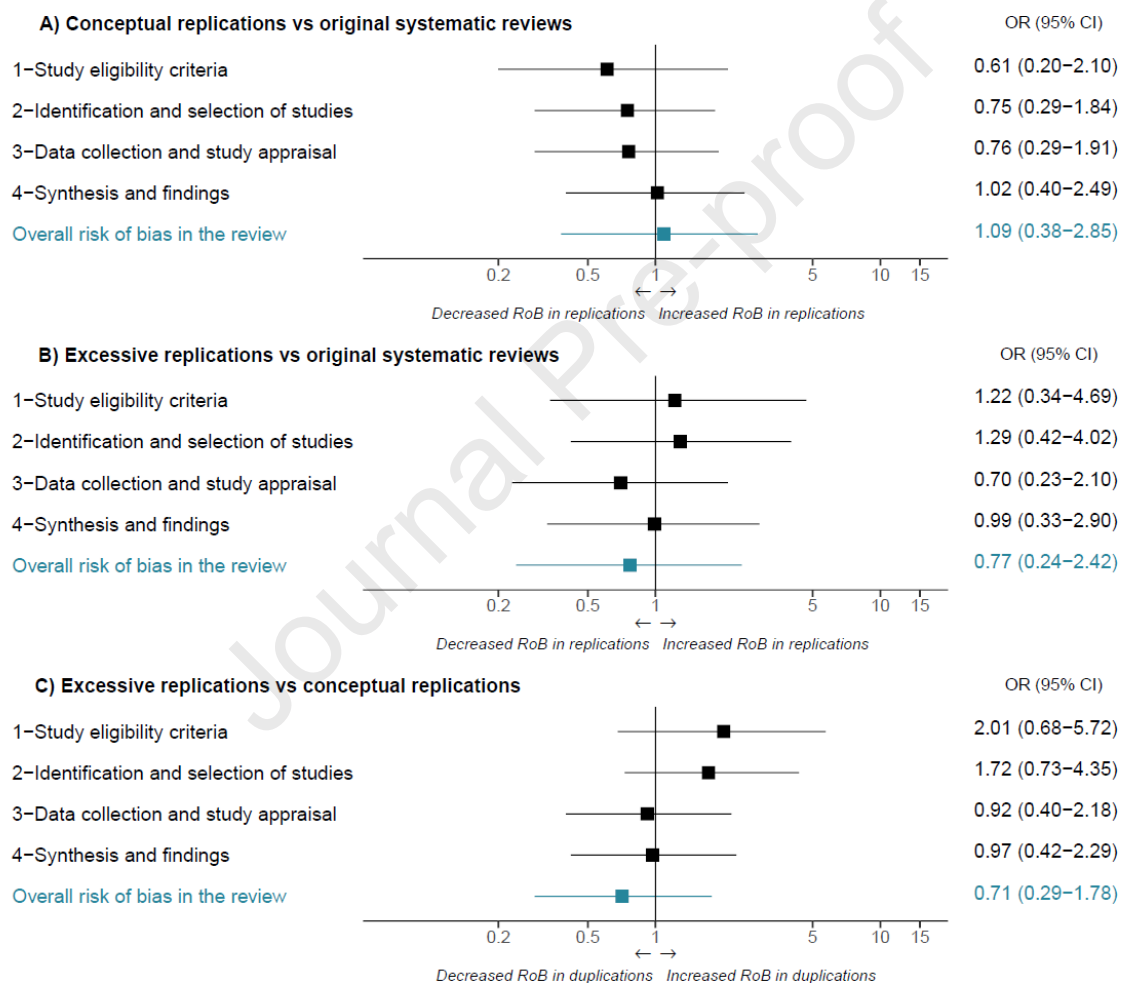


Figure 3. Comparison of the risk of bias for each ROBIS tool domain between A) conceptual replications and original systematic reviews (reference: original systematic reviews); B) excessive replications and original systematic reviews (reference: original systematic reviews); C) excessive replications and conceptual replications (reference: conceptual replications). An OR < 1 denotes a lower risk of bias compared to the reference, an OR of 1 denotes no difference, and an OR > 1 denotes a higher risk of bias compared to the reference.



95% CI = 95% confidence interval; OR = odds ratio; RoB = risk of bias.

What is new?**Key findings**

- More than 80% of the systematic reviews analysed were replications and were considered as being of poor methodological quality; a fifth of these reviews constituted excessive replications, showing overlap of population types, interventions compared and studies included.

What this adds to what is known

- Methodological quality tended to improve in excessive replications compared to original systematic reviews or conceptual replications but the differences were not statistically significant.

What is the implication and what should change now

- Systematic reviews replications of poor methodological quality represent a considerable waste of effort and resources.
- Authors, publishers and reviewers should be vigilant and carefully scrutinise already existing reviews to avoid wasteful replication.

Declaration of interest

Céline Chapelle: none

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