Original Investigation

The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

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Policy Points:

- Currently, there is massive production of unnecessary, misleading, and conflicted systematic reviews and meta-analyses. Instead of promoting evidence-based medicine and health care, these instruments often serve mostly as easily produced publishable units or marketing tools.
- Suboptimal systematic reviews and meta-analyses can be harmful given the major prestige and influence these types of studies have acquired.
- The publication of systematic reviews and meta-analyses should be realigned to remove biases and vested interests and to integrate them better with the primary production of evidence.

Context: Currently, most systematic reviews and meta-analyses are done retrospectively with fragmented published information. This article aims to explore the growth of published systematic reviews and meta-analyses and to estimate how often they are redundant, misleading, or serving conflicted interests.

Methods: Data included information from PubMed surveys and from empirical evaluations of meta-analyses.

Findings: Publication of systematic reviews and meta-analyses has increased rapidly. In the period January 1, 1986, to December 4, 2015, PubMed tags 266,782 items as "systematic reviews" and 58,611 as "meta-analyses." Annual publications between 1991 and 2014 increased 2,728% for systematic reviews and 2,635% for meta-analyses versus only 153% for all PubMed-indexed items. Currently, probably more systematic reviews of trials than new

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randomized trials are published annually. Most topics addressed by meta-analyses of randomized trials have overlapping, redundant meta-analyses; same-topic meta-analyses may exceed 20 sometimes. Some fields produce massive numbers of meta-analyses; for example, 185 meta-analyses of antidepressants for depression were published between 2007 and 2014. These meta-analyses are often produced either by industry employees or by authors with industry ties and results are aligned with sponsor interests. China has rapidly become the most prolific producer of English-language, PubMed-indexed meta-analyses. The most massive presence of Chinese meta-analyses is on genetic associations (63% of global production in 2014), where almost all results are misleading since they combine fragmented information from mostly abandoned era of candidate genes. Furthermore, many contracting companies working on evidence synthesis receive industry contracts to produce meta-analyses, many of which probably remain unpublished. Many other meta-analyses have serious flaws. Of the remaining, most have weak or insufficient evidence to inform decision making. Few systematic reviews and meta-analyses are both non-misleading and useful.

Conclusions: The production of systematic reviews and meta-analyses has reached epidemic proportions. Possibly, the large majority of produced systematic reviews and meta-analyses are unnecessary, misleading, and/or conflicted.

Keywords: systematic reviews, meta-analyses, bias, conflicts of interest, China, evidence-based medicine, industry.

Systematic reviews and meta-analyses are indispensable components in the chain of scientific information and key tools for evidence-based medicine. Evidence-based medicine and these key reviewing tools have become very popular but have also attracted criticism, even from their proponents.[1-4] Information from multiple studies can be synthesized either prospectively or retrospectively. Ideally, meta-analyses should be primary research efforts where investigators collaborate preemptively in consortia with embedded replication across teams and joint analyses. This paradigm has already been successful in some fields; for example, large consortia conduct prospective meta-analyses of genome data.[5] However, teamwork, collaboration, and replication are uncommon in most fields due to lack of incentives. The preference to fund single investigators has not allowed these paradigms to thrive. For randomized trials, examples of collaborative, prospective meta-analyses are rare.[6,7] In most fields in biomedicine and beyond, systematic reviews and meta-analyses remain retrospective exercises that try to piece

together fragmented and selectively reported published information. Even so, these efforts can have value for assessing existing evidence and for informing new research. In other words, it is irrational not to systematically review what is already known before deciding to perform any new study.[8] Moreover, once a new study is completed, it is useful to update the cumulative evidence.[9] Therefore, meta-analyses can be useful either as primary or as secondary research.

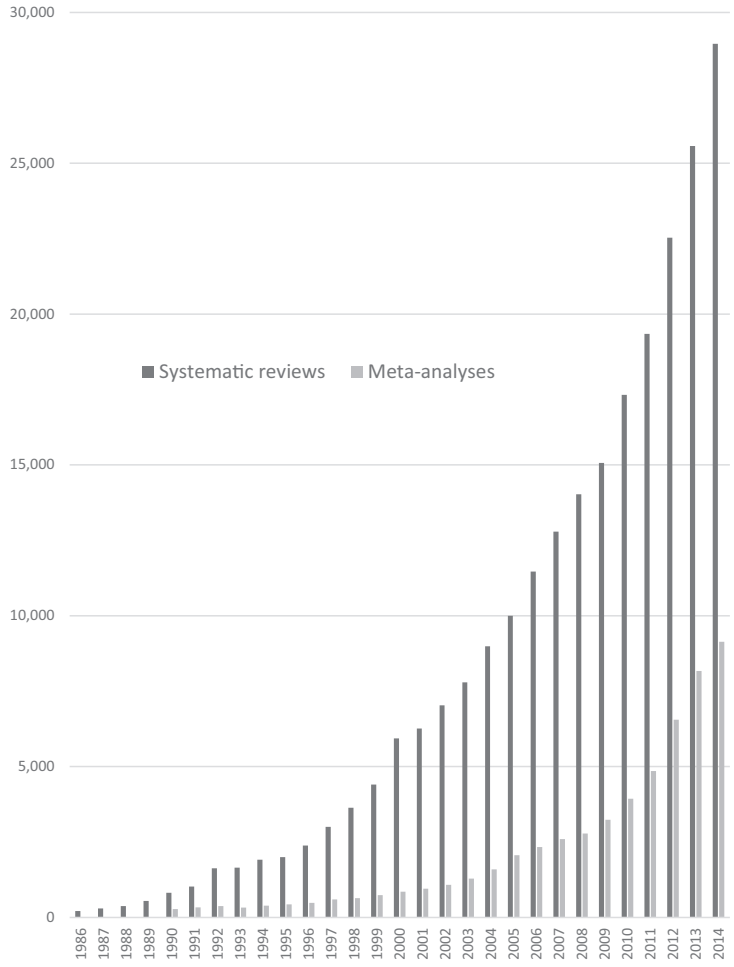
This article will argue that a large number—possibly the large majority—of systematic reviews and meta-analyses produced to date are not useful. The aim of this article is to demonstrate with empirical data that, currently, on many (not all) topics, systematic reviews and meta-analyses are overproduced and that, instead of clarifying the evidence, too many of these reviews often suffer from extensive redundancy, little value, misleading claims, and/or vested interests.

Increase in Published Systematic Reviews and Meta-analyses

An examination of PubMed-indexed articles between January 1, 1986, and December 4, 2015, shows 266,782 items tagged as "systematic reviews" and 58,611 items tagged as "meta-analyses" (Figure 1). The ascribed PubMed tags for type of publication are not fully accurate and some articles may be misclassified. The problem of poor classification in PubMed tags is relatively more prominent before 1990. However, these tags are accurate enough to show the extensive growth in the publication of these types of articles. Only 1,024 and 334 articles published in 1991 were classified as systematic reviews and meta-analyses, respectively. For articles published in 2014, the respective numbers were 28,959 systematic reviews and 9,135 meta-analyses. This corresponds to an increase in the publication rate of 2,728% for systematic reviews and 2,635% for meta-analyses. When all PubMed-indexed items are considered, 410,093 were published in 1991 and 1,039,145 in 2014, amounting to an increase of only 153% in the publication rate.

One may argue that this pattern reflects the effort of systematic reviewers to catch up with reviewing the existing published literature that had accumulated over time. Systematic reviews only started becoming popular in the late 1980s after a pivotal article by Cynthia Mulrow showed that among 50 review articles published in 1985–1986 in 4

Figure 1. Number of PubMed-Indexed Articles Published Each Year Between 1986 and 2014 That Carry the Tag "Systematic Review" or "Meta-analysis" for Type of Publication



major medical journals, nonsystematic information synthesis was very suboptimal.[10] Meta-analysis methods have been available for almost a century, but their use in biomedicine was infrequent until the 1990s,[11] perhaps due to limited knowledge of them by physicians and lack of popular software to perform them in massive scale. Currently, systematic reviews have essentially caught up with the need to synthesize the old literature. Nevertheless, the accelerated publication of systematic reviews and meta-analyses continues to be impressive, corresponding to 67% and 132% increases, respectively, between 2010 and 2014, as compared to only a 27% increase for all PubMed-indexed items.

Of note, items tagged as "reviews" also continue to be produced on a large scale, even more so than "systematic reviews" (106,110 "reviews" published in 2014 versus 82,530 in 2010, a 29% increase). The major, frequent problems with nonsystematic reviews have been highlighted repeatedly.[10,12,13] Any criticism of systematic reviews and meta-analyses in this article should not be seen as a suggestion to revert to nonsystematic reviews.

Current Coverage of the Literature by Systematic Reviews and Meta-analyses

Despite the geometric growth of systematic reviews and meta-analyses, only a small fraction of data from empirical biomedical studies are included in such efforts. In a random sample of 259 articles with empirical data from PubMed (2000-2014),[14] only 19 (7%) have had their data considered for inclusion in a systematic review and 16 of these 19 have had their data eventually incorporated in data syntheses. However, these estimates pertain to a mixture of very different types of data, from cell biology to randomized trials. Usually for each study, there is no other study to review it together with for comparison. Most investigators in most fields loathe performing a replica of a previous study. This is probably a consequence of the requirement to promise novelty and innovation imposed on researchers by funding agencies and promotion committees. Only a tiny fraction of biomedical articles are truly disruptively innovative.[15] The vast majority of articles are neither innovative nor identical to previous work. Studies may be similar, but they are made deliberately different in one or more aspects. For example, in an empirical evaluation of 60 published studies on risk factors for pterygium

(a very common eye condition), no pair of studies considered the exact same factors or used identical adjustments for "known" risk factors.[16]

In that same random sample of 259 articles with empirical data from PubMed (2000-2014),[14] only 8 (3%) claimed to be replications relating to previous studies and only 8 (3%) were cited by subsequent studies claiming to be replications addressing the same question. Investigators generally do not admit that they examine the same questions as previous work, most likely because they do not want to be thought of as producing what is commonly derided as "me too" articles. The reality is that almost all of these articles address questions that have been largely previously investigated. Yet the masquerade is so well done that a systematic reviewer may be at a loss as to whether these studies can be put together in a systematic review that will not depend on multiple subjective, and thus questionable, selection choices. The shallow quest for "innovation" creates articles that exhibit an idiosyncrasy more typical of artistic endeavors ("my creation is unique, or *sui generis*") rather than the sciences, which cherish universalism, communalism,[17] and, above all, reproducibility.

Meta-analyses of Experimental Animal Studies

While much "basic" research is in this state of pseudo-innovative masquerade in the quest for making a questionable case for novelty, experimental studies, in particular randomized trials, are more difficult to make so different from one another so as to be non-amenable to systematic review and meta-analysis. Even for preclinical research, randomized trials of animal experiments can be grouped together and meta-analyzed. In fact, several initiatives in the last decade, in particular the compilation of animal experimental studies by the CAMARADES coalition,[18,19] have allowed the efficient practice of systematic reviews and meta-analyses of all trials in this field. The conclusions of these initiatives are that animal-based experimental research is largely unreliable not because animals cannot inform us about human diseases but because this research is affected by major quality deficits, selective reporting, and other biases.[18-21] One evaluation of such research found that main quality features such as proper randomization and blinding of investigators assessing outcomes are rarely adhered to.[22] Other efforts have addressed

biases in animal studies of experimental treatments or toxicology assessments of chemicals.[23-26] Instead of performing more such animal studies and retrospective meta-analyses thereof that highlight more of these same biases, research in these fields should be recast with better study methods, and a prospective design of meta-analyses that includes all the studies launched. Probably for similar quality reasons, reproducibility is also low for other types of preclinical research (eg, drug target research on in vivo and cell culture models).[27,28] The discovery pipeline for interventions with large impact on health outcomes and health policies will continue to suffer from this bottleneck.[29]

Meta-analyses of Randomized Trials of Humans

For meta-analyses of clinical research, especially randomized controlled trials of interventions, the situation is also discouraging. The main deficiency 25 years ago was that there were very few meta-analyses of randomized trials of humans. The Cochrane Collaboration was launched[30] in 1992 at a time when a meta-analysis of randomized trials (or any meta-analysis) was still a rare event. The Cochrane Collaboration attracted many volunteers and innovative methodologists in an effort to systematically integrate evidence on all medical and health care–related interventions.[31] It set high standards, and Cochrane reviews systematically scored higher in quality assessments than other reviews.[32-34] As of December 4, 2015, the Cochrane Database of Systematic Reviews included 9,170 entries of systematic reviews, which was close to the original anticipation that 10,000 reviews would be needed to cover the entire evidence base of medicine and health care.[35] However, Cochrane is currently the source of only a small minority of the systematic reviews and meta-analyses produced about the effects of medical interventions.[36]

At present, for the majority of topics there is more than simply 1 meta-analysis of randomized trials. An empirical evaluation[37] examined 73 meta-analyses that had been published in 2010. Of those, 49 (67%) had at least 1 more meta-analysis published on the same topic by the end of 2012. The median was 2 meta-analyses, but the maximum was up to 13 meta-analyses on the same topic.

One may argue that some redundancy is useful.[38] There may be some benefit in having several independent authors look at the same data to

see whether they reach the same results and conclusions. Others may argue that if an original meta-analysis did not look at all the outcomes of interest, then other meta-analyses are needed to examine the different outcomes that were not included in the original study. The above-mentioned empirical survey[37] suggests that these excuses can go only so far: 23% of the subsequent meta-analyses included 1 or more authors of the original meta-analyses, and 65% of the subsequent meta-analyses did not include any additional outcomes. Even when published meta-analyses on the same topic examine different outcomes, the practice of presenting these outcomes in different articles is suboptimal and confusing. Decision making requires a thorough examination of all the main outcomes of interest, including both benefits and harms,[39] and it makes sense to have those presented in the same place.

Since 2010 (the index year for the above-mentioned survey[37] of overlapping meta-analyses), the number of systematic reviews and meta-analyses of randomized trials of humans produced and published has continued to escalate at the same pace as presented in Figure 1 for all systematic reviews and meta-analyses in general. Apparently, about half of the published systematic reviews pertain to reviews of trials: a search with "trial* OR randomi* OR treatment*" gives 9,628 systematic reviews in 2010 and 15,284 in 2014, representing 56% and 53% of all systematic reviews in these years, respectively. The proportion of trial-related articles is similarly high among meta-analyses. For comparison, the number of full-text articles classified in PubMed as "randomized controlled trials" has remained stable over these years, and it was 23,133 in 2014. Given that many randomized controlled trials have multiple publications to present their data (eg, of 191 primary trials published in high-impact journals in 2009, 88 [46%] had a total of 475 secondary publications published by February 2014)[40] and that several of the articles tagged as "randomized controlled trials" in PubMed are not actually publications of randomized trials, it is possible that nowadays there are more systematic reviews of randomized trials being published than new randomized trials.

Yet it is important to note that overlapping meta-analyses can often be confusing because they may reach different conclusions. Several authors have previously tried to offer some guidance on what to do when different meta-analyses exist on the same topic, especially when their conclusions are different.[1,41-44] However, navigating through these discrepancies can be demanding even for investigators who are well trained

in evidence-based medicine and highly conversant on these methods. One is often left with a taste of powerful subjectivity pervading what should seemingly have been objective, quantitative methods. The framing of the question, the choice of eligible studies, the selection of comparisons, populations, and outcomes of interest, the types of data extracted, and the statistical methods used, along with many other factors, allow for substantial diversity in the final results. More importantly, the interpretation of even the same results can differ across systematic reviews and meta-analyses on the same topic, especially when the authors have strong motivations to reach specific conclusions. The next section discusses potential financial conflicts of interest, but conflicts and opinions may not be based on financial factors. Academic opinions and conflicts can also be very strong.[45] When data are selected and synthesized retrospectively, the selection and synthesis may be made to fit to the strong opinions and expectations of the editors and reviewers.[46]

For some topics, the extent of redundancy in meta-analyses of randomized trials has reached epidemic proportions. For example, the empirical evaluation of overlapping meta-analyses[37] identified 11 such meta-analyses of statins for prevention of atrial fibrillation after cardiac surgery published over 4 years. The first one, published in February 2008, had a non–statistically significant summary effect, but the second one, published in June 2008 and including more trials, already showed a highly statistically significant and clinically sizeable benefit from statins in this setting. This did not change materially in the subsequent 9 meta-analyses published through late 2012. Some of those even had practically identical results. Of note, subsequent meta-analyses did not cite systematically among their references the prior meta-analyses on the same topic.[37] An extension of the search for any additional meta-analyses published on this same topic from January 1, 2013, through December 4, 2015, identified another 10 potentially eligible meta-analyses. In total, 21 meta-analyses have addressed statins for prevention of atrial fibrillation after cardiac surgery. Two, perhaps three, such meta-analyses would be reasonable to have. The rationale for the others is unclear. Given that the data for a meta-analysis of the published literature are readily available in public, it is not even clear to what extent a meta-analysis may even "copy" data from previous meta-analyses done on the same topic (see some examples of such "copycat" behavior hovering on plagiarism at http://www.scientificamerican.com/article/for-sale-your-name-here-in-a-prestigious-science-journal/). Another possibility

is that massive production of redundant meta-analyses of industry products serves as a marketing tool, some sort of petty advertisement, much like seeding randomized trials[47] or like reprints of pivotal trials distributed by pharmaceutical company representatives to physicians.[48]

Massive Production of Conflicted Meta-analyses: Antidepressants as a Case Study

Antidepressants offer a case study of the confusing effects of having redundant meta-analyses with different conclusions and of the transformation of meta-analyses into marketing advertisements. Clinical research on antidepressants exemplifies some of the major problems facing clinical trials. Multiple small trials are conducted, most of them with industry support, with meaninglessly short follow-up, with outcomes that can be measured in a variety of scales of only modest clinical relevance, with "creative" analyses of the data, and with extensive publication bias and other selective outcome reporting.[49] Meta-analysis is a natural choice to try to understand which are the best drugs and how much different they are in terms of effectiveness and tolerability from their competitors.

Some of these efforts have evaluated multiple antidepressants as part of the same analysis. However, a comparison[50] of the results of several meta-analytic evaluations that addressed the effectiveness of and/or tolerability for diverse antidepressants[51-53] showed that their ranking of antidepressants was markedly different. These studies had been conducted by some of the best meta-analysts in the world, all of them researchers with major contributions in the methods of meta-analysis and extremely experienced in its conduct. However, among 12 considered drugs, paroxetine ranked anywhere from first to tenth best and sertraline ranked anywhere from second to tenth best. This does not even account for the fact that some of these trials' data were not trustworthy to start with, as has been exemplified by a number of reanalyses of the raw data from the clinical trials. For example, the recent reanalysis[54] by independent investigators of Study 329, a pivotal trial of paroxetine and imipramine versus placebo, reached entirely opposite conclusions to those published originally. Paroxetine had been originally claimed to be effective and safe. Upon reanalysis, it was found to be ineffective and to carry unacceptably high rates of adverse events with major harms.[54]

Many other reanalyses of the same raw data from the same trials have reached different results and conclusions than those of the original publications in diverse fields beyond antidepressants.[55-58] However, even if available trial results are perfectly accurate, how can it be that the best meta-analysts in the world can reach such different conclusions in the case of antidepressants? The answer seemed to be that diverse trials and outcomes were considered because of different eligibility criteria. A critical question to ask then is, who decides on whether the eligibility criteria are good, better, excellent, or optimal?

Ideally, people who have no stake in the results should perform systematic reviews and meta-analyses,[46] excluding not only those with financial conflicts of interest but even those who are content experts in the field. According to this line of argument,[46] content experts can and should be consulted, but they should not be authors. The debate remains open about who else should participate as consultants or authors in systematic reviews. For example, patients may be more relevant than experts in prioritizing outcome measures.

Independence of systematic reviews is rare in meta-analyses of antidepressants. The market of antidepressants is worth many tens of billions of dollars per year. In the United States, about 10% of people currently take antidepressants, and the use of these drugs has increased fourfold over the last 15 years. Given that evidence-based medicine has become so successful, an increasing number of physicians and even patients want to see a systematic review and meta-analysis to be convinced that a treatment is worth adopting. For antidepressants, the supply of meta-analyses is astonishing. An empirical evaluation[59] searched PubMed for meta-analyses assessing antidepressants for depression published from January 2007 through March 2014. The search period started after the big debate about whether antidepressants might increase the risk of suicides and suicide-related death.[60] The search[59] identified 185 eligible meta-analyses published over these 7 years, representing a high-output factory of such studies. Of the 185 meta-analyses, 54 (29%) had authors who were employees of the assessed drug's manufacturer, and 147 (79%) had some industry link (sponsorship or authors who were industry employees and/or had conflicts of interest). The survey did not examine how many of the remaining 38 meta-analyses had content experts as authors.

This is a clear example of an area where meta-analyses are emerging as a powerful marketing tool. Only 58 (31%) of the 185 meta-analyses of antidepressants for depression had any negative statements about

antidepressants (eg, any caveat about their efficacy or safety) in the concluding statement of their abstract. Meta-analyses including an author who was an employee of the manufacturer of the assessed drug were 22 times less likely to have negative statements about the drug than other meta-analyses (1/54 [2%] vs 57/131 [44%], $p < 0.001$).[59]

There are 2 types of meta-analyses that contribute particularly to the multitude of favorable meta-analyses. The first type is pooled analyses conducted by industry employees. These analyses usually mobilize the raw, individual-level data and typically combine information from several trials on a single agent or multiple agents produced by a single manufacturer. This methodology provides a very narrow view of evidence because for most diseases and indications, the available contesting treatment options are multiple.[61] Despite the advantage of using individual-level information, these pooled analyses may be among the most inbred and conflicted type of research. Not surprisingly, almost all the published articles of this type reached favorable conclusions about the assessed drug.[59] The second type is meta-analyses where the industry has supported the authors directly (for the particular meta-analysis) or indirectly by promoting their careers in various ways (eg, research grants, speaker bureau membership, paid advisory board positions). This approach does not provide the best setting to perform an objective meta-analysis. These authors may consciously or subconsciously pay their due tribute to their current or former sponsors.

The differential conclusions and adoption of industry-partisan views in systematic reviews and meta-analyses sponsored by the industry have also been seen in several other empirical evaluations by investigators in other fields on various topics.[62-67] These empirical evaluations have highlighted that industry-sponsored systematic reviews often reach more favorable conclusions than other systematic reviews, even though they use the same primary data.[62,64] Differential use of selection criteria for eligible studies or choice of data or of synthesis methods may also serve to create favorable final inferences.[62-67] Some prominent examples include neuraminidase inhibitors,[65] menopausal hormone treatment,[66] and hydroxyethyl starch.[67] Systematic reviews and meta-analyses can become partisan tools for expressing biased opinion sprinkled with evidence, almost like biased editorials[68] or biased expert guidelines.[69,70] In fact, conflicted expert guidelines often use conflicted systematic reviews and meta-analyses, and the messages are further propagated by conflicted expert editorials. Meta-analyses, guidelines, and editorials may all become

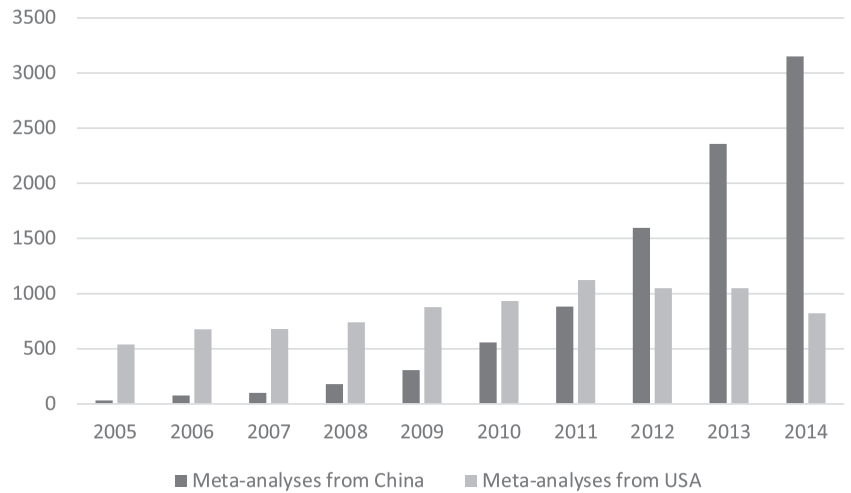
instruments spreading the same bias to different readers who are more influenced by one or another type of article.

Chinese Meta-analyses, Especially of Genetic Associations

Another way to look at the increase of systematic reviews and meta-analyses is to examine their geographic provenance to understand which countries are mostly responsible for the rapid growth of this factory. In 2014, of the 9,135 articles classified as "meta-analyses" in PubMed, over a third (n = 3,150, 34%) have author affiliations from China, making China the most prolific producer of English-language, PubMed-indexed meta-analyses. The United States is a remote second with only 822 meta-analyses (9%). A dramatic change in the geography of meta-analysis happened in a very short period of time. In 2005, meta-analyses from China were rare, and meta-analyses from the United States were more than 15 times more common (n = 539 from the United States vs n = 33 from China). By 2012 China had surpassed the United States in production. Currently, China is publishing 4 times more meta-analyses than the United States, and the gap continues to widen. This is a change of epidemic proportions (Figure 2).

An empirical evaluation published in 2013 tried to understand what was driving this rapid growth.[71] The rise of meta-analyses from China pertains to all types of meta-analyses, including those of randomized trials, epidemiological studies, diagnostic test studies, and any other kind of design. This trend has continued in the time since that empirical evaluation; for example, in 2014, among meta-analyses of trials and treatments (those identified with the search string "trial* OR randomi* OR treatment*"), 27% of the total come from China. The strong impetus of China to become a major power in biomedical research (and beyond), the incentives to publish in English-language and PubMed-indexed journals, and the large numbers of emerging Chinese authors have buttressed this epidemic growth. The share of China in meta-analyses has been growing much faster than in other types of publications, for example, trials, epidemiological studies, or bench research.[71] Perhaps the reasons for this are that meta-analyses can be done with little or no money; they have acquired large impact and importance for biomedicine and health care as the top of the pyramid in most hierarchies of evidence[72];

Figure 2. Number of PubMed-Indexed Articles Published Each Year Between 2005 and 2014 That Carry the Tag "Meta-analysis" for Type of Publication and Have Author Affiliations From China or From the United States (USA)



they can be published in prestigious journals; and they are often heavily cited.[73]

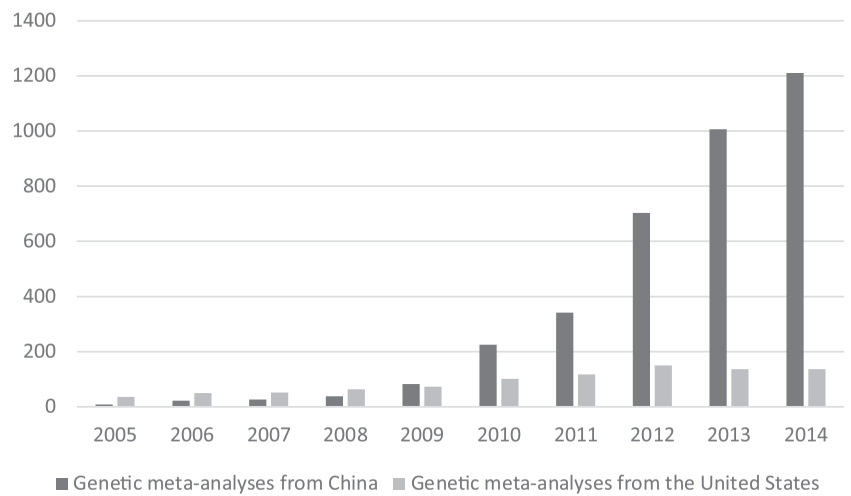
Interestingly, the most spectacular rise of Chinese meta-analyses has occurred in the field of genetics.[71] The search string "gene OR genetic OR polymorphism OR genome OR mutation OR haplotype" was used to identify such articles. By mid-2012, China was already producing about half of all such meta-analyses.[71] In 2014, China published 1,210 such genetic meta-analysis articles out of a global total of 1,910, that is, 63% of the global production, while the United States published only 136 (7%) (Figure 3).

The empirical evaluation[71] examined more closely these articles from China. At face value they looked excellent; that is, their reporting was done appropriately, with careful tabulations, and publication venues were respectable English-language journals. However, almost all of them are likely to have reached misleading conclusions. The reason is that they used the same recipe (now mostly abandoned) that led to many thousands of articles with misleading results by American and European teams in the 1990s and early 2000s: candidate gene studies with single or a few genes and variants addressed one at a time, by single teams, with small sample sizes, and with fragmented reporting of the literature subject to publication bias. Meta-analyses collating such studies almost always give nominally statistically significant results at $p < 0.05$, but this means very little based on what is known in the current era of genomics. In fact, almost 99% of these claimed associations were not validated when tested in very large consortia with very large sample sizes and no selective reporting, where the entire genome was assessed.[74]

Production of Meta-analyses by Contractors

Another group that is apparently involved in massive production of meta-analyses is contractors. Many contracting companies have emerged in the last 15 years operating in the domain of evidence synthesis. Some examples of such contractors include the Mapi Group, Abacus International, Evidera, and Precision for Value. These companies are contracted mostly by pharmaceutical and medical device industries to run meta-analyses for them. These industries are highly interested in such evidence synthesis tools for the reasons described above but also

Figure 3. Number of PubMed-Indexed Articles Published Each Year Between 2005 and 2014 That Carry the Tag "Meta-analysis" for Type of Publication, Have Author Affiliations From China or From the United States, and Are Identified by the Search String "gene OR genetic OR polymorphism OR genome OR mutation OR haplotype"[a]



[a]Same search strategy as in Ioannidis and colleagues.[71]

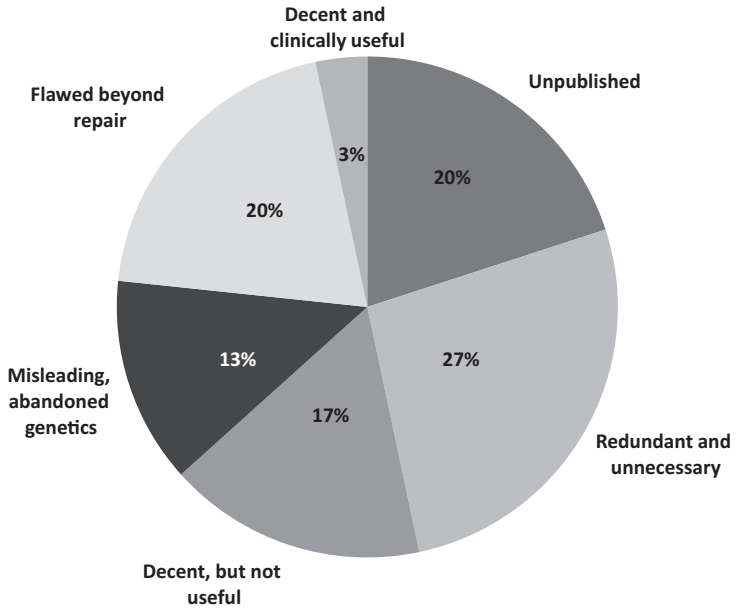
as a means to obtain extra insights about the relative merits of their products and of those manufactured by competitors. The contracts pay very well, and the meta-analyses are done professionally and at high efficiency, often using advanced techniques, for example, network meta-analysis.[75]

In contrast to Chinese genetic meta-analyses, much of the time there is little or no incentive to publish the results of contractor-produced meta-analyses. Publication takes time and effort to prepare the manuscript and then go through painful reviews and revisions, while contractors can instead spend their time working on other contracts. Moreover, pharmaceutical and medical device corporations may not wish to disclose the results of some meta-analyses, especially if the results are not favorable for their sponsored products. Some contractors may take pride that they have done and published numerous meta-analyses, a proof of professional skill. However, others may not place emphasis on their publication record. To my knowledge, there are no contractors that claim that they must publish all the meta-analyses they perform. To do otherwise might easily discourage many, if not all, industry clients. The extent to which these practices may introduce publication bias in meta-analyses, specifically in meta-analyses addressing the effectiveness and safety of interventions, is unknown and requires more empirical study.

Flawed Meta-analyses and Correct but Noninformative Meta-analyses

Numerous empirical evaluations have addressed the prevalence of flaws in the design, conduct, analysis, and reporting of published systematic reviews and meta-analyses in diverse disciplines.[76-82] Their discussion goes beyond the goals of this article, but overall, the results of these empirical assessments suggest that low quality and major flaws are very common. Preregistration of full protocols has been proposed as a means to improve transparency and perhaps also to help increase the quality of these studies. However, only a small fraction of systematic reviews (perhaps 10%-20%) are recorded in registers such as PROSPERO before they start.[83-85] Moreover, given that published data are already available, it is questionable whether a retrospective systematic review can really ever be truly preregistered as the studies and data to be reviewed and combined are already in public view. Furthermore, systematic review

Figure 4. A Summary Overview of Currently Produced Meta-analyses



preregistration does not guarantee that the protocol is complete, let alone that the methods used are appropriate and that the conduct, analyses, and reporting are not flawed, even if the protocol is correct.

Finally, even when systematic reviews and meta-analyses are well done and have none of the problems mentioned above, most may still not be informative. A very common conclusion, in particular for meta-analyses of randomized trials, is that the evidence is weak or insufficient; thus, the review is not informative on what the best interventions are in terms of patient care or health policy.[86-88]

Conclusion

Figure 4 summarizes the current production of meta-analyses in biomedicine and compiles data from PubMed searches and the other evidence presented above in this article.

As mentioned above, 9,135 meta-analyses were published and indexed in PubMed in 2014. The numbers for systematic reviews are probably more than threefold (n = 28,959 in 2014 using the "systematic review" search tag in PubMed). One may debate whether all of these articles are really systematic reviews since the extent to which they follow systematic methods for searching and integrating evidence can vary. For example, Moher and colleagues[89] estimated the number of stringently defined systematic reviews published in 2004 as approximately 2,500, while the PubMed search tag for "systematic review" gives 8,989 items for the same year. Meta-analyses can be defined and counted with more consistency; for example, the PubMed search tag for "meta-analysis" gives 1,594 published meta-analyses in 2004, as opposed to approximately 1,300 estimated by Moher and colleagues,[89] who excluded articles without systematic literature searches (eg, pooled analyses of individual-level data on some drug[s] by the pharmaceutical industry). In an updated evaluation by Page et al.,[90] published while the current paper was copyedited, an estimated 8,000 systematic reviews and more than 5,000 meta-analyses published in 2014 using the same criteria as in the 2004 evaluation. The following estimates presented here thus focus on meta-analyses.

The number of unpublished meta-analyses is unknown. In theory, as discussed, meta-analyses are attractive to publish, but even large randomized trials (which are also very attractive to publish) have nonpublication rates exceeding 30%.[91,92] Moreover, as mentioned above, there is a large number of contractors performing meta-analyses without any incentive to publish. Therefore, a minimum 20% nonpublication rate for produced meta-analyses may be speculated. The rate may be higher for systematic reviews that lack the quantitative attraction of meta-analyses. Analyses of registry data may offer insights into nonpublication rates for systematic reviews and meta-analyses but may still be biased (registered protocols are more likely to be pursued for publication). At least 1 survey of authors suggested that non-publication of systematic reviews was common,[93] and another empirical evaluation showed that even for Cochrane systematic reviews, 19% remained unpublished 8 years after their protocol had been drafted.[94]

Of the published meta-analyses, as discussed above, about 1 in 6 are largely misleading meta-analyses of genetics literature (mostly published by China); probably another 1 in 3 are redundant, unnecessary meta-analyses of other research types. Of the remaining, about half have

serious methodological flaws, and many others are decent but have noninformative evidence. Good and truly informative meta-analyses are a small minority (see Figure 4).

Despite the unfavorable evidence presented above, systematic reviews and meta-analyses can still have major value. Actually, their credibility and utility are probably better than almost any other type of biomedical article published (other than large randomized trials).[95] Under ideal circumstances, these systematic tools can inform about what is known and what is not known with appropriate representation of the accompanying uncertainty. Under non-ideal circumstances, the main utility of systematic reviews and meta-analyses, conversely, has been to reveal how unreliable published evidence is. This is still an important mission, and these tools have been repeatedly put to good use to probe various biases in single topics and across many topics of interest in meta-epidemiological studies.[96,97]

The pervasive documentation of bias suggests that more should be done to improve the quality of the primary evidence rather than expect systematic reviews to correct deficiencies after the fact. Systematic reviews have currently become a high-output factory where very different stakeholders with various motives are involved: methodologists, academics, scholars, policymakers, health care professionals, altruistic volunteers, eager authorship-seekers, serious business professionals, and many others who may see systematic reviews as marketing tools. Some methodologists are working on how to make this factory even more prolific, for example, by creating software and automata that streamline the meta-analysis production process.[98] This technological facilitation may be a nice contribution for those interested in performing rigorous reviews, but it may also make things worse in the hands of those who are not concerned about high quality. The process of conducting poor-quality systematic reviews is already easy enough to subvert evidence synthesis in massive scale. Moreover, many clinicians, researchers, and editors who read these reviews are not knowledgeable as to how to differentiate between high- and low-quality systematic reviews, and some biases may evade the attention of even experienced methodologists.

A major overhaul is needed on the generation of biomedical evidence and its credible synthesis. Eventually, prospective meta-analyses designed and conducted by nonconflicted investigators may need to become the key type of primary research. Production of primary data,

teamwork, replication, and meta-analyses can be integrally connected, as in the case of human genome epidemiology consortia.[5] Simply expecting fragments to be pieced together retrospectively with subjective choices may not be the best option. However, it is unlikely that all research agendas can be preemptively prespecified. Thus, the need for well-done, reliable retrospective systematic reviews and meta-analyses as secondary research is unlikely to disappear. More widespread availability and sharing of individual-level data,[58,99,100] better enforcement of study preregistration and accessibility of study results (eg, for randomized trials),[101,102] transparent and complete reporting of analyses and of all major (core) outcomes,[103-105] and increased funding and promotion incentives to improve reproducible research practices[106] may reduce biases in the available information that is synthesized by systematic reviews and meta-analyses. The question of who should be the authors and sponsors of systematic reviews and meta-analyses also remains open. The same applies to whether conflicts of interest can be tolerated (if they are transparently reported) or should be avoided altogether, as has been proposed for guidelines.[70]

A large number of stakeholders may influence some of these discussed policy changes. There have been several efforts that have tried to set standards for systematic reviews and meta-analyses not only for the reporting level of their results[107,108] but also their protocols,[109] and overall design and conduct.[110] While these standards may improve some aspects of systematic reviews and meta-analyses, they do not yet cover all their applications. Moreover, there is a need to move beyond single systematic reviews and meta-analyses and to focus on the big picture of the research agenda and the massive, often redundant and conflicted, production of these influential articles. The culture of research-funding bureaucracy in some countries may sometimes complicate matters further, and elected officials who control funding agencies may have little or no knowledge and understanding of the importance of and the issues involved in systematic reviews and meta-analyses. It is difficult to identify all the dishonest, or just greedy, or simply incompetent people who can somehow corrupt the process of prioritizing and commissioning reviews. Major progress may require more concerted action among key stakeholders such as journals, funders, elected officials controlling funding agencies, institutions, scientists, physicians, and patients, who should appreciate the pivotal role of systematic reviews and

meta-analyses and not compromise for less quality, accountability, and transparency.

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