

Editorial

Publication Bias: A remediable form of bias?

A recent issue of the *New England Journal of Medicine* included a surprising finding: the primary outcomes of the first three studies were not statistically significant.¹⁻³ Could the long lamented problem of publication bias finally have been resolved?

The broadest definition of publication bias is that research with particular characteristics is more likely to be published than research without those characteristics, such that the published literature is not an accurate representation of all research. Most often, publication bias is used to refer to the fact that research in which a significant outcome is found—i.e. the investigators are able to reject the null hypothesis—is more likely to be published than research in which a non-significant outcome is found, i.e. the researchers are unable to reject the null hypothesis. Some ascribe particular motivations to publication bias; Ben Goldacre has defined publication bias as ‘the practice of selectively publishing trial results that serve an agenda’.⁴ However, it is easier to examine whether a study is published or not than it is to determine the motivation of those involved, so this editorial uses the broader definition.

Evidence of publication bias and possible solutions have been discussed for decades.⁵ Observational studies with negative results have been found to be more subject to publication bias than clinical trials,⁶ but even clinical trials have a high rate of non-publication. Not only were fewer than half of the National Institutes of Health (NIH)-funded studies registered in *clinicaltrials.gov* published within 30 months of trial completion,⁷ but even among trials with results posted in *clinicaltrials.gov*, half had no corresponding published article.⁸ A systematic review of the evidence for publication bias found that trials with positive results are more likely to be published and published faster than those with negative results.⁹ A study of trials in neonates found that negative trials are less likely to be published in high impact factor journals.¹⁰ Finally, another systematic review found that within studies, positive outcomes are more likely to be reported than negative outcomes.¹¹

The evidence for publication bias is too extensive to review exhaustively here, but systematic reviews consistently find that a large amount of research is not being published in a full and transparent way. This publication gap wastes time, effort and funding, as well as breaching patients’ reasons for participating in research. To Ben Goldacre’s point,⁴ missing negative results reduce physicians’ ability to make fully informed prescribing decisions for their patients. Researchers pursue lines of enquiry that have already washed out in others’ laboratories, and therefore when reporting their results they do not present the totality of evidence. Meta-analyses either test and adjust for publication bias statistically or produce skewed results. Evidence-based medicine may be based on evidence from which negative results are missing, thereby defeating its purpose. Most importantly, publication bias impedes the ability of healthcare practitioners to deliver the best care for patients. Despite these major issues for the integrity of the medical research and implications for human health, its solution remains enigmatic. Who is responsible for the publishing gap? Evidence suggests that no individual is to blame, instead everyone may contribute.

Sociology research in the 1970s suggested that the editorial process is to blame, with peer reviewers being more likely to support positive findings that support their personal biases.¹² Editors may be culpable as well, given that in one study higher impact factor journals were more likely to publish positive results.¹⁰ However, the bulk of the evidence suggests that the bias occurs further upstream. For example, one study found no evidence of differential acceptance rates for negative versus positive studies at a major medical journal in the late 1990s.¹³ A systematic review found that the majority of unpublished studies were never submitted, rather having been submitted and rejected.¹¹

Why does publication bias occur? The many possible reasons include problems at every stage of the research and publication process:

- Poorly formulated hypotheses (aka data dredging), in which multiple analyses are run without careful hypothesis generation, and those comparisons that are not significant are not pursued.
- Poorly conducted research or research flawed through no fault of the investigator (which also could lead to a false-positive result, but methodologically flawed research that has a negative result may be more likely to be viewed as fatally flawed than research with a positive result) and therefore uninformative as judged by the researcher or peer reviewers or editors.
- The specific methodological flaws of insufficient power or inadequate methods make the study unable to truly test the hypothesis, such that a negative result is uninformative.
- A hypothesis that is not in a state of equipoise (i.e. a straw man argument) and a result that is uninteresting (a straw man argument could also have a positive result but a negative result may be considered less interesting).
- The researcher is busy and generally uninterested in the time and effort¹⁴ required to publish a study documenting a dead end.
- The researcher considers the negative result a failure (Greenwald⁵ notes that 'in the behavioural sciences, researchers' null hypotheses frequently satisfy the non-statistical definition of null, being "of no value", "insignificant", and presumably "invalid"').
- The negative result could refute a line of research, potentially jeopardizing funding and continued research and impeding a researcher's career path, or in the case of pharmaceutical or device manufacturers, potentially jeopardizing approval, indications, and/or future sales—and therefore is not submitted for publication.
- The negative results are considered not important enough for the journal.
- The negative results conflict with reviewers' or editor's views.

While some of these possible causes are understandable and not publishing may even be justifiable in some circumstances, if such studies are not available somewhere for researchers to access, the resources to conduct the study are wasted and no one can learn from the negative results.

Given the many possible sources of bias, how can publication bias be addressed? The fundamental issues of poorly formulated hypotheses and poorly designed or conducted research need to be addressed at their source, with researchers being well trained in research methods and protocols being carefully considered and reviewed before the study commences. All studies, observational as well as interventional, should be registered; this step would not only help surface the negative trials that did not turn out as hoped but also would help reveal the observational study questions that have already been addressed. Study results should be posted on registries where possible (e.g. *clinicaltrials.gov*) and when permitted by journal policy. Regardless, study results should be published in full whether or not the results are significant, and whether they add new results or merely confirm previous findings—given that reproducing study results can be as important as the initial finding. Honest assessments of possible reasons for negative results should be discussed. Editors who may have a personal bias should recuse themselves or, in the case of personal preference for a particular outcome (e.g. the success of a particular public health measure), focus on the study methodology when reaching a decision on a paper; if the topic is important for the journal and the methodology is sufficiently strong, the study should be considered regardless of whether the results confirm that bias.

While some of these solutions may be difficult to realize, some progress towards transparency is already under way. According to US law, the results of any studies by sponsors of clinical trials of US medications or biologics that were not completed before 26 December 2007, must be posted with their trial registration on *clinicaltrials.gov*.¹⁵ As of July 2014, clinical trial sponsors are required to post clinical trial results in the European Clinical Trials Database (EudraCT), managed by the European Medicines Agency (EMA).¹⁶ The US Department of Health and Human Services recently proposed a rule whereby the requirements for posting clinical trials results also apply to 'unapproved, unlicensed, and uncleared' products.¹⁷ Unfortunately, simply requiring posting of summary results has not been enough to ensure that they are in fact posted,¹⁸ but expanding the requirement is a step in the right direction. Finally, the All Trials initiative¹⁹ has urged 'all trials registered, all results reported' and as of 4 December 2014, it was supported by 81 751 individuals and 531 organizations.

Some journals also have taken steps in the right direction. One journal created a section

devoted to publishing negative results.²⁰ Another journal requires that authors of not only clinical trials and systematic reviews but also observational studies submit study protocols along with the study whenever possible, and clarify any discrepancies between the protocol and reported results; they also strongly encourage the registration of observational studies.²¹ The availability of supplemental online files for nearly all journals means that page limitations should not be a reason for incomplete and selective reporting. Many journal publishers have signed on to support the All Trials initiative, and some journals have pledged to consider negative and otherwise unpublished trials, regardless of age of the study and date of trial registration, via the RIAT (Restoring Invisible and Abandoned Trials) initiative.²² Journals such as *PLOS ONE* consider the validity of the methodology of primary importance to the decision to publish rather than the results and implications, and the *Journal of Negative Results in Biomedicine* exists for the primary intent of publishing negative results.

These are steps in the right direction but much more effort is needed, beginning with the training of researchers and evolution of the ethos of academia and funding agencies. Researchers need to be encouraged to conduct well-designed significant research and be rewarded for publishing accurate accounts rather than penalized when that research does not pan out in the desired direction. Grant reviewers need to expect not a flawless series of confirmed hypotheses to find a researcher worthy of funding but acknowledge the practical realities of research. Journals need to ensure that primary results are presented in the study abstract whether they are positive or negative and that all results are published. Authors need to seek out and cite important negative as well as positive research, and meta-analysis authors need to seek results from their many possible sources, including trial registration sites. Healthcare practitioners need to be aware of publication bias and seek all evidence when making treatment decisions.

The publication of negative trials in a major medical journal is important and noteworthy. However, many more unpublished and unreported studies remain buried. As with all kinds of bias, publication bias has many sources and will require many approaches before the underlying issues are solved. However, everyone—investigators, funding agencies, promotion and tenure committees, peer reviewers, editors, and readers and authors—need to recognize their part and work to ensure better and full reporting of research. Resources are too precious and the work too important to do anything less.

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