Publication bias in clinical research

PHILIPPA J. EASTERBROOK  JESSE A. BERLIN  RAMANA GOPALAN  DAVID R. MATTHEWS

In a retrospective survey, 487 research projects approved by the Central Oxford Research Ethics Committee between 1984 and 1987, were studied for evidence of publication bias. As of May, 1990, 285 of the studies had been analysed by the investigators, and 52% of these had been published. Studies with statistically significant results were more likely to be published than those finding no difference between the study groups (adjusted odds ratio [OR] 2.32; 95% confidence interval [CI] 1.25-4.28). Studies with significant results were also more likely to lead to a greater number of publications and presentations and to be published in journals with a high citation impact factor. An increased likelihood of publication was also associated with a high rating by the investigator of the importance of the study results, and with increasing sample size. The tendency towards publication bias was greater with observational and laboratory-based experimental studies (OR = 3.79; 95% CI = 1.47-9.76) than with randomised clinical trials (OR = 0.84; 95% CI = 0.34-2.09). We have confirmed the presence of publication bias in a cohort of clinical research studies. These findings suggest that conclusions based only on a review of published data should be interpreted cautiously, especially for observational studies. Improved strategies are needed to identify the results of unpublished as well as published studies.

Introduction

The existence of publication bias, whereby research with statistically significant results is more likely to be submitted and published than work with null or non-significant results, has been widely suspected. Much attention has been paid to this problem in educational and psychological research but there is now evidence for it in several areas of medical research. The most serious potential consequence of this bias would be an overestimate of treatment effects or risk-factor associations in published work, leading to inappropriate decisions about patient management or health policy. Publication bias may compromise the validity of conventional reviews as well as the quantitative overview techniques of meta-analysis and decision analysis, which often rely solely on published data. For example, Simes performed a meta-analysis of trials comparing alkylating agent monotherapy with combination chemotherapy in advanced ovarian cancer. Summary of published trials only yielded a large and significant survival advantage for combination chemotherapy, but this was not substantiated when all studies in the International Cancer Research Databank, an unbiased list of unpublished and published trials, were used.

How large is this publication bias, and how important is it? Some contend that the problem is exaggerated and that studies with negative results tend to be poorer in quality, weakened by small sample size and type II error, or based on tenuous hypotheses. There is also debate as to who is more responsible for the bias, investigators or editors.

To find out if studies with statistically significant results are more likely to be published and to assess the magnitude of this bias, if any, across different study designs, we examined all studies approved by one UK research ethics committee over a four-year period.

Methods

Study population and design

From the files maintained on all research protocols submitted to and approved by the Central Oxford Research Ethics Committee (COREC) between Jan 1, 1984, and Dec 31, 1987, we abstracted protocol titles, their COREC index numbers, and names of the principal investigators. We then wrote to every principal investigator explaining the purpose of our study, and this was followed by a telephone interview for information on the current status of the study. For projects that had started, we obtained further information on the design, organisation, results, and publication status. Co-investigators were contacted in the absence of, or at the request of, the principal investigator. Questionnaires were posted to 60 investigators (75 studies) who could not be contacted by telephone or who requested a mailed questionnaire. The interviews, coding, and verification of the completed questionnaires were done by P. J. E.

ADDRESS: Division of Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA (P. J. Easterbrook, MRCP, R. Gopalan, MD); Clinical Epidemiology Unit, Section of General Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia (J. A. Berlin, ScD); and Central Oxford Research Ethics Committee, John Radcliffe Hospital, Oxford, UK (D. R. Matthews, MD). Correspondence to Dr Philippa J. Easterbrook.
We recorded the current status of the study (ie, completed, in progress, abandoned, in abeyance, or never started), the department in which it was conducted, the number of data collection sites, and the use of a formal protocol. We also asked about the main purpose of the study, the design (clinical trial, experimental but not a trial, or observational), and the source of funding. Prior sample size estimation (and method used) was noted, as was final sample size, number and nature of comparison groups, data analysis (complete, interim, or none), and the main study findings including attainment of statistical significance. Investigators were also asked about publications and presentations, papers rejected, planned, or still under review, and reasons for non-publication. For clinical trials, specific questions were asked about the treatment under evaluation, any comparison groups (concurrent or historical), randomisation, blinding, and monitoring of adverse effects. The design quality of clinical trials was ranked 0-4, one point being assigned for the use of blinding, and a placebo control. The score of trial quality (0-4) was evaluated in a further model. From these analyses, adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. Likelihood ratio X² statistics were used to assess the fit of each logistic model and to test the significance of predictor variables. Also of interest was whether the magnitude of publication bias varied across different subgroups of studies, so we looked for interactions between the variable for attainment of statistical significance and other predictor variables in a further multivariate model.

**Definitions**

An **experimental study** was defined as one in which one or more variables were controlled by the investigator, in order to monitor the effect on a process or outcome. If it was not a clinical trial it was called a non-trial experimental study, and was defined as any study designed to learn about the population under study rather than about the procedure or treatment used. Most of these were laboratory-based. In an **observational study** the investigator observed a process or disease without intending to alter it during the study. Studies were classified as **statistically significant** if the main outcome attained a p value of <0.05, as showing a **non-significant trend** if the difference carried a p value of ≥0.05. or as **null** if no difference was observed between the two study groups. When formal testing of significance was not done or was not possible, as when there was no comparison group, studies were categorised into one of three groups, depending on whether they revealed striking observations, definite but not striking observations, or null findings. Investigators were also asked to rate the clinical or scientific importance of their results from 1 ("not at all important") to 10 ("extremely important").

**Publication** meant acceptance by a journal (published or in press), but not book chapters or published meeting abstracts or proceedings. Every study resulting in a journal publication was assigned a journal citation **impact factor** that measures citation frequency by computing the ratio between citations in subsequent years and citable items published in the journal. This was used as an indicator of the scientific standing and dissemination of the published work. Impact factors for published studies were categorised into quintiles for further analysis.

**Statistical methods**

We used independent sample t-tests for comparison of the means of continuous variables, χ² tests with Yates' correction for comparison of proportions, and the Mantel-Haenszel test for the significance of linear trends. Univariate analyses for variables significantly associated with publication status were followed by backward, stepwise logistic regression analyses (BMDP Statistical Software, Los Angeles). The variables included were: study design, existence of a protocol, funding source, number of study centres, sample size (<20 vs >20), conducted as part of a research thesis or as a pilot study, main study outcome, rating of importance of study result (1-3 = low, 4-6 = intermediate, 7-10 = high). Design variables specific to clinical trials were included in a separate multivariate model for clinical trials, and included the use of a concurrent comparison group, random treatment allocation, treatment blinding, and a placebo control. The score of trial quality (0-4) was evaluated in a further model. From these analyses, adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. Likelihood ratio χ² statistics were used to assess the fit of each logistic model and to test the significance of predictor variables. Also of interest was whether the magnitude of publication bias varied across different subgroups of studies, so we looked for interactions between the variable for attainment of statistical significance and other predictor variables in a further multivariate model.

**Results**

We identified 720 studies approved by COREC over the four year period. 13 of these studies were subsequently withdrawn by the investigators, and 5 were excluded because they were not formal research studies. 172 studies were considered lost to follow-up, either because no current address was available or because the principal investigator had retired, died or was currently resident overseas. Of the 530 remaining studies, 455 were the subject of telephone interviews: the response rate to the additional 75 mailed questionnaires was 63% (47). Inadequate information was provided by the investigators on 15 studies, and this left 487 studies (contributed by 216 investigators). No significant differences were found between those studies for which the investigator was located and interviewed and those for which the investigator was lost to follow-up or failed to respond to the mailed questionnaire, in either the numbers of studies approved per investigator, year approved, main department of study, or type of study design.
As of May, 1990, 287 (59%) studies had been partly (recruitment alone) or fully (recruitment and follow-up) completed; 100 had never started, 58 had been abandoned or were in abeyance, and 42 were still in progress. We assumed that only studies that had been analysed had the potential for being written up and published, so tests for publication bias were restricted to these. 285 studies had been analysed, including 30 of the 100 abandoned or in abeyance. The reasons given for failure to analyse 32 completed studies were that analysis was planned or underway (5), the sponsoring pharmaceutical company had not released the raw data (14), the investigator was too busy or had lost interest (8), and insufficient data (5). No significant differences were found between analysed and non-analysed studies in the numbers of studies approved per investigator, year approved, study department, or the type of study design.

Characteristics of 285 analysed studies (table I and II)

90% were completed studies. 52% were clinical trials, 18% were laboratory-based experimental studies, and 30% were observational (three-quarters of these being epidemiological or laboratory-based cross-sectional studies). The pharmaceutical industry funded 38% of the projects, government and charitable sources 25%, and 17% received no financial support. The median sample size was 37 (range 3 to 37 000). 48 studies were pilot investigations and 67 were conducted as part of a research thesis.

Of the 148 clinical trials most were phase II (27%) or phase III (58%) trials, there being 7 pharmacokinetic studies (phase I), 2 phase IV trials, and 8 studies that could not be classified. 77% were designed to evaluate a drug, 12% a device or procedure, and 11% a policy or programme. 65% were sponsored by the pharmaceutical industry. Randomisation was the dominant method of treatment allocation (70%).

A statistically significant result was found less frequently and a null result more frequently with clinical trials than with observational studies. Compared with unfunded studies, government-sponsored studies were more likely to yield statistically significant results. Sample size did not differ significantly between the two groups. For clinical trials alone, absence of treatment blinding and the use of non-random or non-concurrent controls, were more likely to generate statistically significant rather than null results. There was a trend towards a greater number of statistically significant results with poorer quality studies, as judged by the combined quality score (data not shown). Also not shown in detail are ratings of the importance of study results by the investigator; these were significantly associated with attainment of statistical significance (p = 0.0001). Of 97 studies with null results, only 24 (25%) were given a high rating on importance, compared with 69 (45%) of those with statistically significant study results (p = 0.002).

Statistical significance and publication status

By May, 1990, 207 (73%) of the studies had generated at least one publication and/or presentation, including those currently in press. 138 had been published (78 of these were also presented at meetings) and 69 had just been presented. 92% of publications were reports of the main study results, the remainder being subgroup analyses or descriptions of new methodology.

The univariate relation between significance for the main outcome and publication status shows clear evidence of publication bias (table III). 68% of published and presented studies had statistically significant results compared with only 65% of those only published, 55% of those only presented, and 29% of those neither published nor presented. Conversely, only 15% (23/154) of the studies with statistically significant results remained unpublished or unpresented compared with 44% (43/97) of those with null results. The unadjusted OR for publication with a statistically significant versus a null study result was 2.96 (CI 2.40-8.63). When the same analyses were repeated without the 77 non-comparative studies, the results were virtually unchanged. For clinical trials alone, the association was less striking, with an unadjusted OR for publication of 2.10 (CI 0.98-4.52) and for publication and/or presentation of 2.78 (CI 1.26-6.17).

Most published studies generated a single publication, although one study resulted in 60 publications and 20 presentations. The number of publications or presentations generated by a study was significantly greater for those with a statistically significant result compared to those with a null
result (p = 0.002; Mann-Whitney test). Of the 50 studies that generated 2 or more publications, only 6 were from studies with null results.

Studies with statistically significant results were also published more frequently than studies with null results in prestigious journals, as defined by a higher journal impact factor. The mean citation impact for those journals publishing studies with statistically significant results was 0.9 (0.16). Only 16% of studies with null results were published in journals in the highest quintile of citation impact factor. The mean citation impact for those journals publishing studies with statistically significant results was 1.62 (SE 0.15) and for those publishing studies with null results was 0.9 (0.16). Only 16% of studies with null results were published in journals in the highest quintile of citation impact factor, compared with 27% of those with statistically significant results.

Investigator reasons for not publishing

Table IV lists the reasons the investigators gave for failure to publish. Of the 78 unpublished studies, 23 (29%) had statistically significant results, 12 (15%) non-significant results, and 43 (55%) null results. The most frequent reason was that a paper had been written but not yet submitted, or submitted but not yet accepted. For the 43 unpublished studies with null results, the presence of a null result was the most frequent reason for failing to write up the study. Another frequent reason was methodological limitations, and this was cited more often for studies with null results. Editorial rejection was cited infrequently (9%) as the reason for studies remaining unpublished, with positive and negative studies equally represented. The sponsoring pharmaceutical companies were blamed for non-publication in 11%, since they managed the data and were therefore considered responsible for initiating publication. However, 10 of these studies were reportedly conducted solely for the purpose of a product licence application and were not intended for publication.

Multivariate analysis

Logistic regression analysis (table V) confirmed that a statistically significant result for the main study outcome was independently predictive of publication when adjusted for study design, the presence of a comparison group, source of funding, sample size, rating on importance of study results, and whether or not it was pilot study. The magnitude of the association was slightly greater when publication and/or presentation was the dependent variable (OR = 3.56; CI 1.82-6.99). Studies with a high importance rating by the investigator were significantly more likely to be published than those with a low rating. Pilot investigations were significantly less likely to be published.

Multivariate analysis of the subgroup of 148 clinical trials failed to demonstrate a statistically significant OR for publication bias (OR = 1.59; CI 0.70-3.60). Government sponsorship was not found to have a statistically significant effect on the likelihood of publication, although only 10 clinical trials received government funding, but company-sponsored trials were significantly less likely to be published or presented (OR = 0.17; CI 0.05-0.53). Quality of trial design was not found to be associated with likelihood of publication, whether individual determinants of design quality or the composite score were used.

We also calculated the multivariate adjusted OR for a study with a statistically significant result versus a null result being submitted for publication—ie, published, rejected, still under review by a journal, and awaiting submission. The OR of 2.94 (CI 1.43-6.01) for submission was higher than the OR of 2.32 for actual publication, suggesting that the investigators play an important role in publication bias.

Risk of publication bias: subgroup analyses

We examined for susceptibility to publication bias among various subgroups of studies. Significant heterogeneity in susceptibility to bias was found only across different study designs (likelihood ratio $\chi^2$, p = 0.05). The adjusted OR for publication bias in observational and laboratory-based experimental studies was 3.79 (CI 1.47-9.76), compared to only 0.84 (CI 0.34-2.09) for randomised clinical trials. Interactions according to the presence of a comparison group and investigator rating of the importance of study results, though present, were not significant. For clinical trials alone, randomised trials were significantly less susceptible than non-randomised trials to publication bias (OR = 0.73; CI 0.28-1.91 and OR = 10.26; CI 1.76-59.78, respectively). The OR for bias was also less for studies with a concurrent versus a non-concurrent comparison group, a high versus a low investigator study rating and for a sample size above 20.

Discussion

We have confirmed the presence of a systematic selection bias in the publication process according to study results. Studies with a statistically significant result for the main outcome of interest were more likely to be submitted for publication and more likely to be published than studies with null results, after adjustment for confounding factors. These findings are consistent with those of a similar study conducted at a major medical research institution in the United States, where the investigators found an adjusted
OR for publication of 2·7 (CI 1·67-4·36) for studies with statistically significant results.13 We also found that studies with at least one significant result generated a greater number of publications and presentations and were more likely to be published in high-profile journals. Thus, positive studies tend to receive more attention, through publication in major medical journals, than negative studies. This is important since a highly "visible" publication may have a profound impact on medical practice, even if the results are subsequently demonstrated to be unreliable.14 We also identified a similar bias in the presentation of abstracts at meetings, as has been noted previously.8

Rejection of a manuscript by an editor was an infrequent reason (9%) for a study remaining unpublished, regardless of the results. However, failure of the investigator to submit for publication (on account of either null results, limitations in methodology, loss of interest, or unimportant results) accounted for 39% of the reasons given for non-publication. The OR of 2·94 for a study with statistically significant versus null results being submitted for publication further supports the role of the investigator in the bias towards selective publication of significant results. This is consistent with the findings of other surveys.5 13 A more precise estimate of editorial bias in publication could be achieved through a review of the acceptance rates for publication of a random sample of manuscripts submitted to various journals, according to the direction and statistical significance of their results, adjusted for methodological quality and journal policy (eg, originality).

The hypothesis that publication bias might be explained by confounding factors, especially quality of study design, was tested in the multivariate analysis and not upheld. As in another recent study,15 we identified no independent association between quality of design and likelihood of publication. Furthermore, we found no evidence that studies with significant results were superior to studies with null results in quality of design—indeed clinical trials with null results were more likely to have been randomised and to have used treatment blinding. This suggests that bias against the publication of null results, regardless of quality, is a powerful force in the publication process.

We estimated that the number of studies in our analysis should give us 80% power to detect a difference in full publication rate of at least 20% between studies with statistically significant results and those with null results at the alpha=0·05 level. Although our sample size was not intended to provide significant results for subgroup analyses, we did identify interesting trends in susceptibility to publication bias across different study designs. The adjusted OR for publication was larger with observational and laboratory-based studies than for clinical trials, for which it was close to unity. For clinical trials, publication bias was greatest for those of small sample size, with a non-concurrent control group, or non-randomised treatment allocation. It seems that those studies most susceptible to publication bias are also those known to be more prone to the problems of bias and confounding, that can threaten the validity of conclusions.7 Publication bias may thus enhance the impact of these potentially flawed studies.

One other factor significantly predictive of publication was a high rating on the importance of the study findings by the investigator, underscoring the contribution of an investigator's enthusiasm for a study in determining its publication fate. The high likelihood that government-sponsored studies will result in publication can be explained by certain attributes common to these mainly Medical Research Council-backed investigations. Many were large multicentre trials involving a considerable investment of resources, that were likely to be written up, whatever the outcome, and for these reasons were probably also perceived by journal editors as being more reliable and worthy of publication. We found that studies sponsored by a pharmaceutical company were less likely to be published, whatever the results. Others have reported considerable selectivity in the submission for publication of drug company sponsored studies, according to the direction of the results.17 18 A possible explanation for the difference in our findings is that many company-sponsored trials were dose-formation comparisons or small trials designated for use in product licencing applications rather than for publication. However, for 14 such trials, the raw data were not made available for independent analysis, and the investigators never learned of the study findings.

The main implication of publication bias is that the conclusions of literature reviews or meta-analyses based on only published work may be misleading. This is important because the results from meta-analysis seem very precise and convincing, and are beginning to have an impact on clinical practice and on the planning of future research. The number of published meta-analyses has quadrupled over the past few years, and although an increasing number involve the use of controlled clinical trials, some two-thirds are based on the more bias-prone observational studies, as revealed by a computerised literature search for 1982-89 by P. J. E. We found observational studies to be at especially high risk for publication bias, apart from their known susceptibility to other biases. Standards for evaluating the quality of such studies need to be refined to ensure their proper use in future meta-analyses. Similarly, clinical trials that are small and non-randomised should only be used with great caution.

There are other potential harmful effects of publication bias. Awareness of its existence is likely to perpetuate the tendency of investigators to use multiple comparisons or subgroup analyses ("data dredging") to generate a positive result. There is also the risk that authors will place undue emphasis on any significant differences and give scant attention to non-significant analyses. Also, as a result of the continued under-reporting of negative studies, well-conducted ones may be duplicated needlessly.

Statistical correction for publication bias in meta-analyses19-21 is limited by assumptions about missing data. Other proposals for reducing this bias focus on editorial practices—for example, encouraging peer review on the basis of methods rather than results22 and providing space for short reports of negative studies. Investigators are also being encouraged to make better use of confidence intervals rather than relying on significance testing.23 The most direct way to circumvent publication bias is to obtain data on all studies, published and unpublished. However, attempts to identify unpublished trials retrospectively through a survey of investigators have proved laborious and frequently unsatisfactory.24 A better solution is to establish registration of clinical studies ab initio.25 26 27 This provides a sampling frame for meta-analyses that is free from publication bias since studies are registered regardless of publication status. Several such registries exist but clinicians are often unaware of them. A directory of registries of clinical trials has recently been developed, and should be helpful in this regard.28
Investigators and editors should be encouraged to recognise the seriousness of publication bias and to submit and accept, respectively, well-conducted studies directed at important questions, no matter what the outcome.

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Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition

NORMAN SHARPE  
HEATHER SMITH  
JUDY MURPHY  
SALLY GReAVES  
HAMISH HART  
GREG GAMBLE

Left ventricular dysfunction can be improved with angiotensin-converting-enzyme inhibition started 1 week after myocardial infarction or later. To see whether earlier intervention may confer greater benefit, a double-blind study was carried out in which 100 patients with Q wave myocardial infarction, but without clinical heart failure, were randomly allocated treatment with captopril 50 mg twice daily or placebo starting 24–48 h after onset of symptoms. Left ventricular volumes were measured regularly during 3 months of treatment and after a 48 h withdrawal period by means of two-dimensional echocardiography. The placebo group showed significant increases in left ventricular end-diastolic (LVEDVI) and end-systolic (LVESVI) volume indices, with the ejection fraction unchanged. By contrast, the captopril group showed a slight but not significant rise in LVEDVI and a significant reduction in LVESVI with ejection fraction increased significantly. At 3 months there was a 4–6% difference in the change in ejection fraction from baseline between the groups (p < 0.0001). Most of the treatment benefit was evident at 1 month and there were no changes in left ventricular volumes after 48 h withdrawal of treatment at 3 months. Heart failure requiring treatment with frusemide developed in 7 patients in each group during the study period; 3 of these (1 captopril-treated, 2 placebo-treated) had to be withdrawn from the trial with severe heart failure requiring open treatment. Thus early treatment with captopril is effective in preventing the ventricular dilatation that can occur after Q wave myocardial infarction.


Introduction

Existing treatment for clinical congestive heart failure is effective in producing sustained haemodynamic and symptomatic improvement and better ventricular function and survival,1,2 but since many patients have severe