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ORIGINAL ARTICLE

In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias

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Abstract

Objective: To assess the utility of funnel plots in assessing publication bias (PB) in meta-analyses of proportion studies.

Study Design and Setting: Meta-analysis simulation study and meta-analysis of published literature reporting peri-operative mortality after abdominal aortic aneurysm (AAA) repair. Data for the simulation study were stochastically generated. A literature search of Medline and Embase was performed to identify studies for inclusion in the published literature meta-analyses.

Results: The simulation study demonstrated that conventionally constructed funnel plots (log odds vs. 1/standard error [1/SE]) for extreme proportional outcomes were asymmetric despite no PB. Alternative funnel plots constructed using study size rather than 1/SE showed no asymmetry for extreme proportional outcomes. When used in meta-analyses of the mortality of AAA repair, these alternative funnel plots highlighted the possibility for conventional funnel plots to demonstrate asymmetry when there was no evidence of PB.

Conclusion: Conventional funnel plots used to assess for potential PB in meta-analyses are inaccurate for meta-analyses of proportion studies with low proportion outcomes. Funnel plots of study size against log odds may be a more accurate way of assessing for PB in these studies.

Keywords: Publication bias; Funnel plot; Proportional outcomes; Meta-analysis; Abdominal aortic aneurysm; Peri-operative mortality

1. Introduction

Evidence-based medicine is dependent on an adequate understanding of the literature. Meta-analyses are frequently put forward as the highest level of evidence on any given topic. However, as with all statistical techniques, the interpretation of data presented in meta-analyses is subject to error. Proportion data from observational studies and other sources are frequently used by clinicians to counsel patients and to compare practices and are frequently combined in meta-analyses. Meta-analyses should contain an assessment of the potential for publication bias (PB) to have influenced the results of the analysis. PB can occur when studies with statistically significant results or clinically favorable results are preferentially published. Indeed, studies that have statistically significant results are twice as likely to be published as null studies [1]. Furthermore, studies that have positive findings are both more likely to be published and published more quickly than those with negative findings [2]. The exact prevalence of PB is impossible to ascertain but it is estimated that about 50% of the literature on any given topic is unpublished [3,4].

As a group of academic vascular surgeons, we have developed an interest in the use of meta-analysis to estimate outcomes after vascular surgery [5–7]. In this work, we have used funnel plots [8] to assess our datasets for the presence of potential PB (which we suspect we have seen on a number of occasions). In our field, we frequently assess procedures with low proportional outcomes such as elective abdominal aortic aneurysm (AAA) repair (peri-operative mortality rate ≈ 4%) and have developed concerns that conventional methods for

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The study was an analysis of previously published data and as such no ethical approval was required.

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What is new?

Key findings

- Conventional funnel plots appear to be an inaccurate way of assessing publication bias (PB) in meta-analyses of proportion studies with extreme proportional outcomes.
- Funnel plots of study size against log odds may be a more accurate method of assessing PB and are robust across all proportional outcomes.

What this adds to what is known?

- Funnel plots are the commonest statistical method of assessing PB but the utility and accuracy of such plots in meta-analyses of proportion studies have not been addressed.

What is the implication, what should change now?

- Our study brings into question the accuracy of using traditional funnel plots as a method of assessing publication in meta-analyses of proportion studies and introduces an alternative funnel plot that can be used for analysis.

constructing funnel plots for these low proportional outcomes may be over-estimating the degree of funnel plot asymmetry, concerns shared by other authors [9–11]. Previous work has addressed this issue in meta-analyses of randomised control trials (RCTs) and in the assessment of diagnostic tests but not in meta-analyses of proportion data. These studies focused on the accuracy of funnel plots in detecting PB and investigated alternative methods of plotting the vertical axis including using standard error (SE), precision (1/SE), variance, and sample size [9,12–14]. Furthermore, Tang [15] has previously demonstrated, using meta-analyses of RCTs, that the inclusion of a single study with a much lower proportional outcome than the rest of the included studies disproportionately distorts the results. The author suggested methods to avoid introducing bias into such a scenario including the assessment of the effect of study size on the weighting of the results. However these findings have yet to be assessed in meta-analyses of proportion studies [15]. Low proportional outcomes are not isolated to proportion and non-comparative data and also occur in interventional research. For the purpose of this study, 'events' in the simulation dataset detailed in the following relate to mortality but could also be an expression of an alternative outcome such as those observed in interventional research. In this study, we have focused on proportion data.

Many authors construct funnel plots with outcome (x-axis) against the SE (or its reciprocal) as a measure of individual study size and variability (y-axis) [12]. However, this approach may not be suitable for all analyses. Meta-analyses of observational or non-comparative studies are commonly performed where the outcome estimates are simply the proportions of concerned outcomes observed in individual studies, and the outputs from these studies are frequently used for decision models and economic evaluations and also for their descriptive value. These types of analyses often assess extreme proportional outcomes. For example, meta-analyses of mortality in endovascular AAA repair will have outcome values as low as 3%. Some time ago [9], the observation was made that for relative effect measures, such as odds ratios and relative risks, the SE of the outcome is actually correlated with the size of the effect. Similarly, for a proportion, which is commonly transformed to the log odds scale due to better statistical properties for meta-analysis, its SE is dependent on the value of the log odds (and the underlying proportion). Consider a study in which r out of n patients were observed to have an event, leading to a proportion of r/n. The associated log odds is $\ln(r/(n-r))$ with SE $\mathrm{sqrt}(1/r + 1/(n-r))$. It can be seen by substituting different r's into the formulae for a fixed n that the SE naturally increases as r approaches 0 or n (and thus P approaches 0 or 1). In Fig. 1, for a fixed study size of 100, we plot the curve generated by plotting the SE of the log odds against the log odds. Observe the "U" shaped relationship, compared with plotting the log odds against sample size, which—of course—results in a straight horizontal line. This relationship will distort the appearance of a funnel plot using SE (or a function of it) as the vertical axis, particularly when the underlying proportion is quite extreme and there may be a risk of attributing funnel plot asymmetry to PB for such outcomes when, in fact, the funnel plot asymmetry is nothing more than an artifact of the method of funnel plot construction. Previous work has focused on effect measures including relative risk and weighting bias to assess whether funnel plot asymmetry is incorrectly attributed to PB [15]. We hypothesized that study size, which is not influenced by extreme outcomes measured on a log odds scale (Fig. 1) is a better value for the vertical axis of funnel plots when assessing meta-analyses of non-comparative studies.

The aim of this study therefore, was to test this hypothesis using both simulation and real data. Additionally, we evaluate the utility of conventional and alternative funnel plots in this context.

2. Funnel plots using simulated data

2.1. Methods

We simulated meta-analysis datasets in which no PB existed. Specifically, we generated a meta-analytic dataset comprising 100 simulated (single arm) studies. The sample size of each of the studies was determined stochastically by sampling from an exponential distribution ($\lambda = 1$) Studies

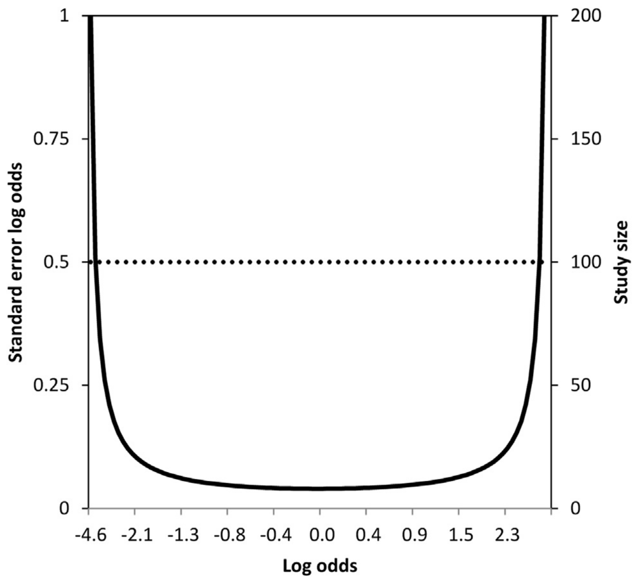

Fig. 1. The association between the standard error of log odds and outcome plotted as log odds for hypothetical outcomes ranging between 0% and 100% for a proportion study of size $n = 100$ (solid, U-shaped line), with study size superimposed (dashed, horizontal line) for demonstration purposes.

with sample sizes less than 10 were removed from this dataset. For each simulated study, the number of patients experiencing events was generated using a binomial distribution. Five separate outcomes for each study were generated with underlying proportions 0.1, 0.3, 0.5, 0.7, and 0.9. Two different funnel plots were constructed for each outcome, the first, a "traditional" one, plotting log odds vs. 1/SE (log odds) and the second plotting log odds vs. study sample size. All simulation was carried out in R (v2.15.0).

2.2. Results

The results of the simulation study are shown in Fig. 2. Of the 100 simulated studies, 10 had sample sizes less than 10 and were removed from the analysis. We observed that for mid-range proportional outcomes (represented by an outcome of 0.5) there was little asymmetry irrespective of the method used to construct the funnel plots. However, for low and high proportional outcomes, the conventional method of constructing funnel plots using log odds (x-axis) and 1/SE log odds (y-axis) resulted in funnel plot asymmetry. Methods of funnel plot construction based on the sample size demonstrated little asymmetry irrespective of the outcome measure used (ie, log odds) across the range of proportional outcomes modeled.

3. Assessment of study size−based funnel plots using real study outcome data

3.1. Methods

Studies reporting the peri-operative mortality of AAA were identified to assess the utility of the alternative (study size−based) funnel plots used in the simulation study. This subject was chosen because it is an area well known to the authors, and the recent evolution of surgical techniques from open to endovascular techniques has yielded a large volume of data. Furthermore, AAA repair can be considered as four distinct categories (elective open AAA repair [EAAA], elective endovascular AAA repair [EVAR], endovascular repair of ruptured AAA [REVAR], and open repair of ruptured AAA), each with proportional outcomes that vary from low proportional outcomes (EVAR) to proportional outcomes of approximately 0.5 (ruptured open AAA repair [RAAA]). This permits the assessment of funnel plots across a range of proportional outcomes using real data. Datasets for inclusion in the study were identified by literature searches for previous meta-analyses and the individual study data from the articles identified were used to construct funnel plots for each of the aforementioned outcomes. The study flow diagram is shown in Appendix at www.jclinepi.com.

3.1.1. Search strategy

We aimed to identify all meta-analyses concerning the outcomes of AAA repair, extract the individual study data from each meta-analysis and then use this data to construct funnel plots. JPH and AS independently performed literature searches of Medline (1950−2011), Embase (1980−2011), and The Cochrane Library (July 2011) databases using PubMed search engine (U.S. National Library of Medicine, Bethesda, MD, USA) and Ovid search engine (Ovid Technologies Inc., New York, NY, USA). Searches were restricted to articles in English and those with human subjects. The following keywords were used: [abdominal] and [aortic] and [aneurysm/aneurism] and [meta-analysis] and [analysis]. The search was carried out on April 17, 2011 and 2,754 articles were identified.

3.1.2. Inclusion/exclusion criteria

Articles included in the study had to report a meta-analysis with the operative mortality of AAA repair as an outcome measure and provide peri-operative mortality data for each individual study within the meta-analysis. The article had to be related to one or more of the following categories: EAAA, RAAA, elective endovascular aneurysm repair, and REVAR. Articles without meta-analyses were excluded. Mortality was defined as either 30-day or in-patient mortality. Meta-analyses without mortality as an endpoint and studies without crude mortality data were excluded. Study eligibility was assessed by JPH and MJB, and any disagreement was resolved by consensus.

3.1.3. Data abstraction and extraction

Individual studies (each primary study contributing to the meta-analyses identified in the literature search) were categorized into the four outcome groups (EAAA, EVAR, RAAA, and REVAR). The utility of funnel plots for determination of PB in each of the four categories was assessed. This was achieved by pooling the outcome (mortality) from each primary study extracted from the selected meta-analyses.

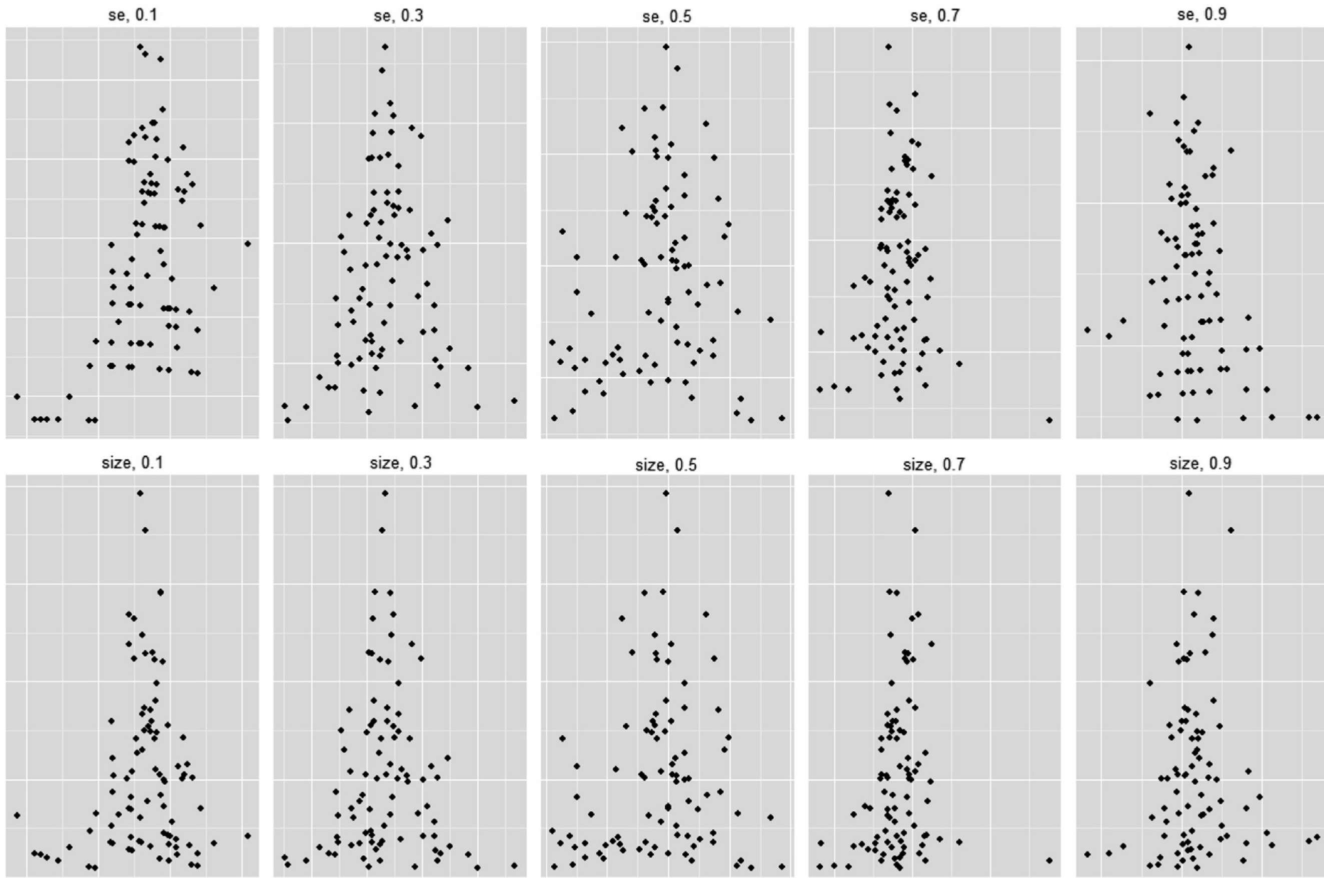

Fig. 2. Panel plot of results of the simulation study showing funnel plots for hypothetical meta-analyses containing 90 studies of various sizes with random proportional outcomes. The top row shows studies simulated from conventional funnel plots of log odds (outcome) against 1/SE and shows, from left to right proportional outcomes of 0.1, 0.3, 0.5, 0.7, and 0.9. The bottom row shows studies simulated from the same dataset but plotted as log (odds outcome) against study size. SE, standard error.

Duplicate studies included in one or more meta-analyses were only included in the overall dataset once. Data abstracted from the contributing studies in each meta-analysis consisted of number of participants (study size) and mortality (n). Studies with mortality included as a percentage were converted into crude mortality and rounded to an integer as appropriate. Studies where mortality was included as odds were converted into crude mortality and rounded to an integer.

3.1.4. Evaluation of funnel plot utility for the assessment of PB

To construct funnel plots from the individual study, data obtained from the meta-analyses and the proportional study data were converted to a log odds scale, and the SE of the log odds calculated for each study. As for the simulated data, 'traditional' funnel plots were constructed for each of the four outcome categories. In addition, funnel plots using study size on the vertical axis, rather than the reciprocal of the SE, and log odds outcome scales on the horizontal axis were constructed. For each of the four outcome categories, individual meta-analyses were performed to obtain a point of reference for the overall outcome in each group.

Meta-analyses were carried out using standard techniques (random-effects generic inverse variance meta-analysis conducted using R package meta). Studies with zero events, for which the log odds and its SE are undefined, had 0.5 added to the number of events and 1 added to the study size to enable inclusion in the analysis.

In addition to the funnel plots, two standard tests for asymmetry were performed. These were the Egger and Peter tests that use a weighted regression to test for small study effects. Egger test regresses on the SE weighted by the precision, whereas Peter's fits a linear regression for the inverse of the total sample size, weighted according to the number of events and non-events [16].

Both analyses were conducted using Stata 12.1. Egger test was implemented using the metabias command, whereas a weighted regression model was fitted for the Peter test.

4. Results

A total of 15 meta-analyses reporting the outcomes of AAA repair were identified [5−7,17−28], and data from the individual studies within each of these analyses were used to construct funnel plots for the peri-operative mortality of RAAA, EAAA, EVAR, and REVAR. We first constructed conventional funnel plots of log odds against the inverse of the SE log odds for each contributing study and then compared these with funnel plots constructed using study size on the vertical axis. Neither the conventional funnel plot nor the alternative plot for RAAA (pooled mortality estimate, 46.7%) demonstrated asymmetry (Fig. 3). The conventional funnel plot for EAAA demonstrated an asymmetric pattern (pooled mortality estimate, 5.2%) but this asymmetry became greatly reduced when using a funnel plot with study size as a vertical axis measure (Fig. 3). For elective EVAR (pooled mortality estimate, 3.1%), there was no evidence of funnel plot asymmetry in any funnel plots constructed (Fig. 3) but for REVAR (pooled mortality estimate 21.2%; Fig. 3), the conventional funnel plot demonstrated reduced asymmetry, whereas no discernible funnel pattern could be seen in the alternative plot.

Formal statistical testing for asymmetry reflected the observed asymmetry in the funnel plots. Conventional funnel plots of EAAA, EVAR, and REVAR in which there was observed funnel plot asymmetry was confirmed by Egger test (which is based on SE; Table 1.). Similarly, Peter test, which is based on study size, confirmed the observed asymmetry for EVAR and REVAR only (Table 1).

5. Discussion

This is the first study to formally assess the utility of funnel plots for the detection of PB in meta-analyses of noncomparative, proportion studies. In this study, we have demonstrated that funnel plots, as traditionally constructed, may be a potentially misleading method for the assessment of PB in such analyses. This is particularly true for low or high proportional outcomes, and there is the potential that funnel plot asymmetry in these circumstances could be mistakenly interpreted as demonstrating PB, whereas it may be partially or completely explained by scale artifact because of correlations between outcome measures and measure of precision. We have shown that an alternative method of funnel plot construction, using sample size as the measure of accuracy instead of the inverse of SE on the y-axis, may be preferential in such circumstances.

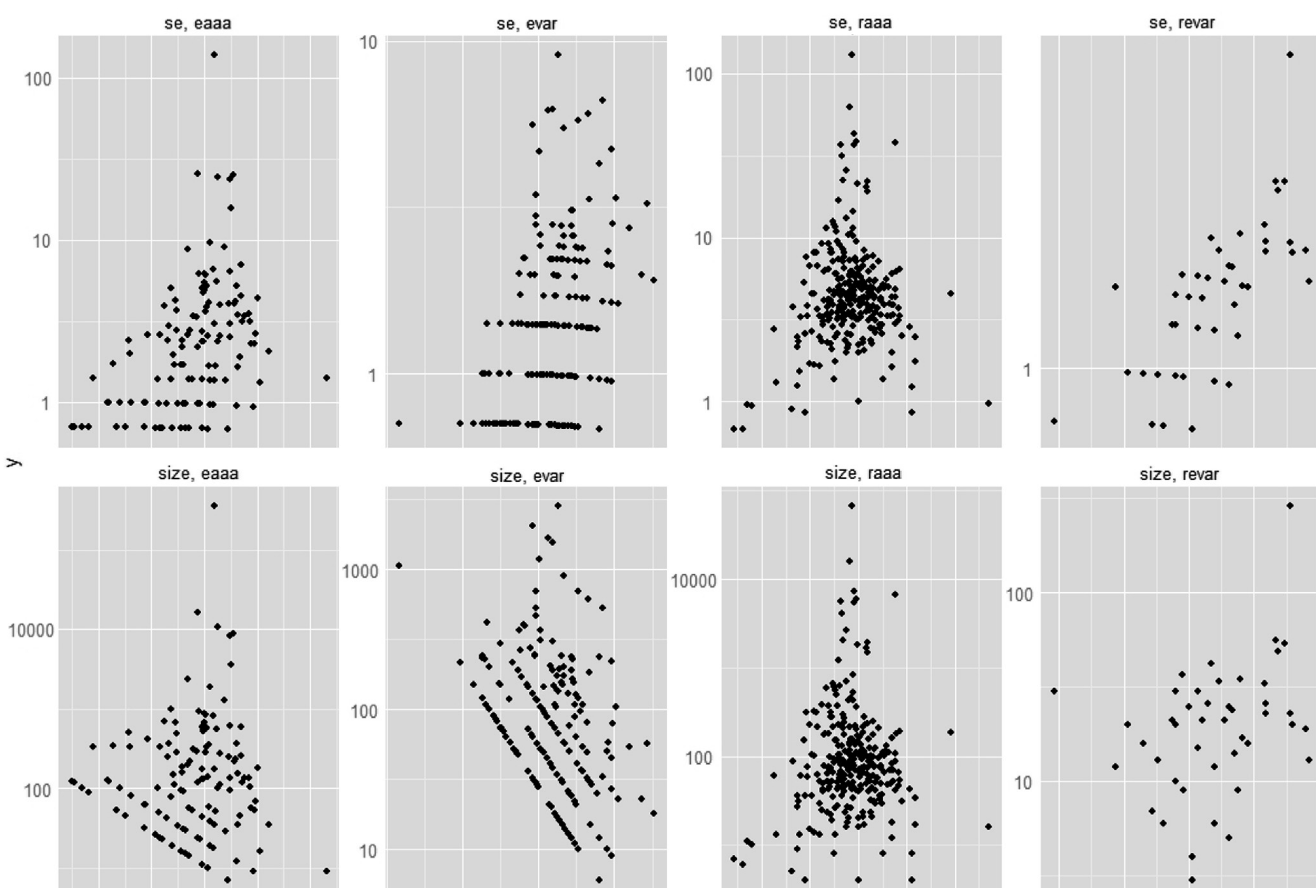

Fig. 3. Panel of funnel plots for real study data. Meta-analysis of studies reporting outcomes of peri-operative mortality for ruptured open AAA repair (first column), elective open AAA repair (second column), elective endovascular AAA repair (third column), and ruptured endovascular AAA repair (fourth column). Funnel plots constructed using the traditional method (1/SE vs. log odds outcome) are shown in the top row and funnel plots constructed using study size on the vertical axis are shown in the bottom row. SE, standard error.

Table 1. The *P*-values obtained from Egger and Peter tests for each outcome

AAA category	Egger's test (*P*-value)	Peter's test (*P*-value)
Elective open AAA repair	0.014	0.542
Elective endovascular AAA repair	$<$0.001	$<$0.001
Ruptured open AAA repair	0.471	0.704
Endovascular repair of ruptured AAA	$<$0.001	0.006

In meta-analyses of RCTs, smaller studies with higher mortality are most commonly the ones missing from the literature. This has also been shown to occur in meta-analyses of tests of diagnostic accuracy [29]. One might also expect this to be the case in meta-analyses of proportion studies. Indeed, the area missing in the funnel plot illustrating open elective AAA repair represents those studies. However, that trend is not seen in any of the other funnel plots. Furthermore, the asymmetry seen in the funnel plot for EAAA was lost when the graph was re-plotted using log odds (mortality) against study size. Funnel plot asymmetry does not necessarily indicate PB. For meta-analyses of RCTs, it is more likely that asymmetry indicates PB, particularly when supported by statistical tests for asymmetry. In addition, PB may not cause funnel plot asymmetry. For example, if small studies with outcomes, the same as the overall meta-analysis, are not published, there may be a missing central portion of the funnel that would not influence observed or statistical asymmetry. The implications of this for proportion data are that there are many reasons for funnel plot asymmetry other than PB. As a result, readers need to be aware of these issues and interpret funnel plots with these issues considered.

In the meta-analyses identified as part of the literature search for this study, only one-third (5 of 15 studies) assessed PB using statistical techniques, and funnel plots were used in all cases. Seven of the remaining 10 studies without statistical assessment of PB mentioned it as a cause of bias but only one study attempted any other form of analysis [27]. Only three studies did not acknowledge the effect PB could have on interpretation of the results [19,22,23]. These findings highlight the variation in the assessment of PB in meta-analyses of mortality in AAA repair but show that overall this is better than in other areas. Song et al. performed a survey of published systematic reviews and demonstrated that between 30% and 50% of meta-analyses of treatment, diagnostic and risk factor reviews discussed potential for PB and between 20% and 30% tested for PB with the most commonly adopted strategy being the construction of funnel plots [4]. In the era of expanding numbers of meta-analyses, one should be cautious in interpreting the conclusions of meta-analyses of non-comparative proportion studies. In addition, meta-analyses with funnel plots assessing PB must be scrutinized to ensure the reader is clear that potential asymmetry of the plots is not because of small study numbers or extreme proportional outcomes.

Clearly, further investigation in this area is warranted. Previous studies of PB have largely focused on the problem of PB in RCTs with much less research being done on proportion studies (with comparative or non-comparative outcomes) [4]. But, as the contexts in which meta-analysis approaches are applied continue to diversify, we suspect such analysis will become more common. In addition to intervention outcome data of the form considered for aortic aneurysm repair, proportions are considered in the assessment of diagnostic accuracy, as well in many types of frequency estimates used in (economic) decision modeling. We believe further assessments in these contexts would be beneficial to ascertain the generality of our findings. An advantage of the context in which we chose to explore funnel plot asymmetry over RCT contexts was the availability of large number of studies for our funnel plots. Perhaps the largest limitation to the assessment of PB in a trial context is the difficulty in making accurate inferences due to the relatively small number of studies available. We believe visual inspection of funnel plots (using sample size) is informative. However, the development and evaluation of formal statistical tests to deal with funnel asymmetry for proportion outcomes may still be desirable, and we would encourage their development. These could potentially be based on regression type approaches using sample size as the covariate as has been done previously for comparative outcomes (where correlations also can exist between outcome and its precision) [13,30–32].

Acknowledgments

Author contributions: J.P.H. performed the literature search, analyzed the data, produced the figures, and alongside M.J.B. co-wrote the manuscript. A.S. performed a literature search and assisted in production of the figures. A.J.S. was involved in study design, statistical analysis, and was available for statistical advice and edited the manuscript. R.H.B. assisted with statistical analysis and production of figures. R.D.S., alongside M.J.B., conceived the study and edited the manuscript. M.J.B. was involved in study conception and design, analyzing the data, editing the figures, and writing the manuscript.

Appendix

Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jclinepi.2014.03.003.

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