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Opinion article

Publication bias in dermatology systematic reviews and meta-analyses

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ABSTRACT

Systematic reviews and meta-analyses in dermatology provide high-level evidence for clinicians and policy makers that influence clinical decision making and treatment guidelines. One methodological problem with systematic reviews is the under representation of unpublished studies. This problem is due in part to publication bias. Omission of statistically non-significant data from meta-analyses may result in overestimation of treatment effect sizes which may lead to clinical consequences. Our goal was to assess whether systematic reviewers in dermatology evaluate and report publication bias. Further, we wanted to conduct our own evaluation of publication bias on meta-analyses that failed to do so.

Our study considered systematic reviews and meta-analyses from ten dermatology journals from 2006 to 2016. A PubMed search was conducted, and all full-text articles that met our inclusion criteria were retrieved and coded by the primary author. 293 articles were included in our analysis. Additionally, we formally evaluated publication bias in meta-analyses that failed to do so using trim and fill and cumulative meta-analysis by precision methods.

Publication bias was mentioned in 107 articles (36.5%) and was formally evaluated in 64 articles (21.8%). Visual inspection of a funnel plot was the most common method of evaluating publication bias. Publication bias was present in 45 articles (15.3%), not present in 57 articles (19.5%) and not determined in 191 articles (65.2%). Using the trim and fill method, 7 meta-analyses (33.33%) showed evidence of publication bias. Although the trim and fill method only found evidence of publication bias in 7 meta-analyses, the cumulative meta-analysis by precision method found evidence of publication bias in 15 meta-analyses (71.4%).

Many of the reviews in our study did not mention or evaluate publication bias. Further, of the 42 articles that stated following PRISMA reporting guidelines, 19 (45.2%) evaluated for publication bias. In comparison to other studies, we found that systematic reviews in dermatology were less likely to evaluate for publication bias. Evaluating and reporting the likelihood of publication bias should be standard practice in systematic reviews when appropriate.

1. Introduction

Systematic reviews of medical literature incorporate data from similar studies to help clinicians and policy makers make informed, evidence-based decisions regarding patient care and health policy [1]. Systematic reviews often contain a meta-analysis, a statistical method of collating data from individual studies. These reviews promote timely, knowledgeable decisions in public health and clinical practice [1,2]. In particular, the Cochrane Skin Group Systematic reviews have had a notable influence on dermatology clinical practice and guidelines [3]. For example, the American Academy of Dermatology created guidelines on treatments for pregnant women with psoriasis using results from a Cochrane Skin Review on safety of topical corticosteroids in pregnancy [4].

One criticism regarding the validity of systematic reviews and meta-analyses is publication bias [5]. Publication bias exists when statistically non-significant data from unpublished literature is omitted from systematic reviews and meta-analyses [6]. Easterbrook et al. [7] found that studies with statistically significant results were more likely to be published than those finding no statistically significant difference between groups. Further, studies

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with statistically significant outcomes were more likely to lead to a greater number of publications, presentations, and were more likely to be published in journals with high impact factors [8]. Publication bias has implications for clinical decision making when its presence leads to overestimated effect sizes in interventional studies. Consequently, ineffective or even dangerous treatments can be falsely viewed as effective and safe [6]. Given the practical consequences associated with publication bias, it should be formally evaluated and planned for in systematic reviews.

Methods to minimize publication bias in systematic reviews include: searching without limiting by outcome, searching prospective trials registers, searching informal sources, including meeting abstracts and PhD theses, and contacting authors and pharmaceutical companies [9]. When suitable, a formal evaluation of publication bias should also be done to measure the likelihood and severity of publication bias. However, not all methods of assessing publication bias apply to each systematic review and meta-analysis. For example, many statistical tests have been developed to objectively demonstrate publication bias, but these tests perform poorly when the number of studies is small and heterogeneity is large in a meta-analysis [10]. It should also be mentioned that most methods for evaluating publication bias are applicable to interventional studies when odds ratios do not stray greatly from one. Systematic reviews of diagnostic accuracy studies are likely to contain large odds ratios, therefore, standard publication bias test would not be recommended [10].

We focused our study specifically on dermatology literature to investigate what practices are used by systematic reviewers in this specialty. Here, we systematically evaluate publication bias in high impact factor dermatology journals to illustrate the depth to which publication bias is discussed and formally evaluated, paying attention to methods used to minimize and evaluate publication bias. We also evaluate a subset of systematic reviews that neglected to mention and formally evaluate publication bias.

2. Methods

2.1. Article selection

Using the Science Citation Index impact factor, we identified the 10 highest ranking dermatology journals. Next, a PubMed search was conducted for systematic reviews and/or meta-analyses published in the *Journal of Investigative Dermatology*,*Archives of Dermatology*, *Pigment Cell & Melanoma Research*, *JAMA Dermatology*, *Journal of American Academy of Dermatology*, *The British Journal of Dermatology*, *Experimental Dermatology*, *Contact Dermatitis*, *Journal of Dermatologic Science*, and *Acta Dermato-Venereologica* from 2006 to the current date of the search. The following search string was used: (((meta-analysis[Title/Abstract] OR "meta-analysis as topic"[MeSH Terms]) OR systematic review[Title/Abstract]) OR meta-analysis[Publication Type]) AND (((((((((“The Journal of investigative dermatology”[Journal] OR “Archives of dermatology”[Journal]) OR “Pigment cell & melanoma research”[Journal]) OR “JAMA dermatology”[Journal]) OR “Journal of the American Academy of Dermatology”[Journal]) OR “The British journal of dermatology”[Journal]) OR “Experimental dermatology”[Journal]) OR “Contact dermatitis”[Journal]) OR “Journal of dermatological science”[Journal]) OR “Acta dermato-venereologica”[Journal]) AND (“2006/01/07”[PDat]: “2016/01/04”[PDat]). This search strategy was a modification of Montori et al., which was shown to be sensitive to identifying systematic reviews and meta-analyses [11]. The search was conducted on January 4, 2016.

Our PubMed search produced 357 results. All full-text articles were retrieved and screened using PubMed and EndNote. After removal of duplicate articles and assessment of all full-text articles, the number of studies included in our review was 293 (Fig. 1).

2.2. Review process and coding

Intra-rater agreement was assessed to determine consistency of coding by randomly selecting a subset of 10 systematic reviews and having the primary author (PA) code them a second time. Accuracy was found to be 90%. The following elements were coded: (a) title, (b) authors' name(s), (c) year of publication, (d) journal name, (e) type of systematic review, (f) type of primary study, (g) was “publication bias” mentioned, (h) was publication bias formally evaluated, (i) what methods were used to evaluate publication bias, (j) was publication bias found, (k) what were the conclusions or implications of publication bias, (l) which databases were searched, (m) how many databases were searched, (n) were foreign languages searched, (o) what resources did reviewers use to search grey literature, (p) were clinical trials registries searched, (q) was a hand search performed, (r) how many studies were included in the systematic review, (s) was a meta-analysis included in the systematic review, (t) were reporting guidelines used.

2.3. Publication bias assessment

When calculating percentage of reviews that used some method to formally evaluate publication bias, we excluded reviews without meta-analyses, reviews of diagnostic test accuracy, and meta-analyses with fewer than 10 primary studies from our denominator. We also took systematic reviews that did not formally evaluate for publication bias and conducted our own formal evaluation. In order to be included in this analysis, a systematic review had to have at least one meta-analysis with at least 10 primary studies to ensure that test power was high enough to delineate chance from real funnel plot asymmetry [12]. 75 articles of the 293 met initial inclusion criteria, but 54 were excluded for lacking at least 10 primary studies in the largest meta-analysis or having insufficient data for analysis. Therefore, 21 articles were evaluated for publication bias.

To formally evaluate publication bias, we first replicated the results from meta-analyses that met our initial inclusion criteria. If a systematic review had more than one meta-analysis, we conducted our analysis on the meta-analysis with the most primary studies. We then performed the trim and fill test on each meta-analysis to estimate the number of missing studies that might exist in a meta-analysis and the effect that these studies might have on the outcome [13]. In one meta-analysis multiple primary studies had to be excluded in order to analyze results. This decreased the number of primary studies below 10, eliminating it from analysis. After performing trim and fill tests, we then conducted cumulative meta-analysis by precision tests on each meta-analysis looking for positive drift. When effect sizes are sorted by precision, positive drift suggests that small magnitude effects from small sample size studies have been omitted [14]. Included in our cumulative meta-analysis by precision test was the calculation of Cohen's d value; a measure of effect size. We used the absolute Cohen's d value of 0.5 as a cutoff for evaluating publication bias, keeping in mind that any absolute value from 0.5 to 0.79 is evidence of moderate publication bias and any value greater than 0.8 is evidence of severe publication bias [15]. Stata13.1 was used to perform statistical analysis (StataCorp, 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

3. Results

Publication bias was mentioned in 107 articles (36.5%) and most frequently in the *British Journal of Dermatology* ($n = 39$). However, the proportion of publication bias mentioned was greatest in the *Journal of Dermatologic Science* ($n = 6/8$, 75%). Publication bias was