Assessing treatment effects and publication bias across different specialties in medicine: a large empirical study of the Cochrane Database of Systematic Reviews

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16 Abstract

17 **Objectives** To compare reporting of statistically significant treatment effects and adverse events
18 across medical specialties, to determine associations of statistical significance with journal metrics,
19 to test small-study effects in meta-analyses (when small studies report more extreme treatments
20 effects than large studies), to assess publication bias in funnel plots and to quantify bias-adjusted
21 treatment effects.

22 **Design** Large empirical study of treatment effects.

23 **Methods** We investigated outcomes from 57,186 studies from 1922 to 2019, and overall 99,129
24 meta-analyses and 5,534 large meta-analyses (≥ 10 studies) from the Cochrane Database of
25 Systematic Reviews (CDSR). Descriptive statistics, generalized linear mixed models,
26 regression-based tests, and selection models were used to analyze one of the largest collections of
27 evidence in medicine.

28 **Results** Medical specialties showed differences in the prevalence of statistically significant results
29 of efficacy and safety outcomes. Altogether 19% (95%-CI from 18% to 20%) of the large
30 meta-analyses showed evidence for small-study effects, but only 3.9% (95%-CI from 3.4% to
31 4.4%) showed evidence for publication bias after further assessment of funnel plots. Adjusting
32 treatment effects resulted in overall less evidence for efficacy, and treatment effects in some
33 medical specialties or published in prestigious journals were more likely to be statistically
34 significant while randomized controlled trials (RCTs) were less likely to report a statistically
35 significant effect.

36 **Conclusions** These results suggest that exaggerated effects from small studies cause greater
37 concern than publication bias. It is problematic when studies that report more extreme results
38 become more visible in prestigious journals instead of studies of the highest quality.

39 **Keywords:** Cochrane, systematic reviews, meta-analysis, small-study effects, publication bias

40 **Strengths and limitations of this study**

- 41 • This is one of the few studies providing a large-scale assessment of treatment effects,
42 small-study effects and publication bias across different medical specialties.
- 43 • Many methods are available to assess small-study effects and publication bias, we only
44 considered two methods; however, these were among the most widely used and
45 recommended ones.
- 46 • Bias may be underestimated as the methods have low statistical power and only a subset of
47 large meta-analyses were therefore considered; however, these may reflect among the most
48 relevant medical interventions to date as many studies have been performed.

49 **Introduction**

50 Publication bias is a major concern in clinical research as it affects the combined effects from
51 meta-analyses of intervention studies and distorts the overall evidence for the efficacy of a
52 treatment [1,2]. The problem was already characterized more than half a century ago [3] and a
53 number of studies provided compelling evidence for publication bias by following studies from
54 protocol approval until the publication of outcomes [4,5]. The problem originates when studies
55 with a null result are not considered worthy to be written up and submitted by researchers, or may
56 not be treated favorably in peer review; hence, are less likely to be published [6,7]. Moreover,
57 statistically significant studies are more likely to be published in journals with a high citation
58 impact factor [8] and get more citations [9]. Thus, positive results receive more attention than
59 negative results.

60 Many countries and medical journal publishers require trial registration with the aim to prevent
61 publication bias, for example, the International Committee of Medical Journal Editors (ICMJE).
62 Since 2007 the U.S. Food and Drug Administration Amendments Act (FDAAA) demands that
63 interventional clinical trials report their results directly to the US trial registry “ClinicalTrials.gov”
64 within 1 year of the completion of the study; however, recent research showed that compliance with
65 FDAAA 2007 is poor with 59% of the studies not reporting results in time [10]. The retrieval
66 process of unpublished results can be difficult, time consuming and not always successful. Thus,
67 statistical methods can be useful to not only assess but also adjust meta-analyses for inflated
68 treatment effects and publication bias.

69 In clinical research multiple studies on the same treatment are conducted, and meta-analyses are the
70 established statistical tool to estimate the combined treatment effect. Combined effects are
71 weighted averages of the study effects with effects from large studies having more weight than
72 effects from smaller studies. However, when the chance of publication increases for small studies
73 with large effects, and decreases when there is no effect, then there is a positive association
74 between effect sizes and standard errors of the studies, known as small-study effect [11]. This
75 association is assessed by regression and can be shown as asymmetry in a funnel plot [12], but
76 these methods also have some limitations [13].

77 A small number of studies in meta-analyses and heterogeneity across studies can mislead funnel
78 plot based methods. Even though it is often assumed that publication bias may be a plausible
79 explanation for funnel plot asymmetry, there are also other possible causes, for example, low
80 quality studies that report inflated effect sizes, or clinical heterogeneity of patients when small
81 studies focus on high-risk patients for whom the treatment may be more effective. Therefore, it is
82 important to follow guidelines when applying such methods [14,15]. Sterne et al. [14]
83 recommended Harbord's test [16] for dichotomous outcomes using odds ratios, and Egger's test
84 [12] for continuous outcomes. Also the Cochrane handbook recommends the same tests, provided
85 that there are at least 10 studies [17].

86 In contrast to methods based on a funnel plot, selection models explicitly model publication bias.
87 Selection models adjust meta-analytic data by specifying a model that describes the mechanism by
88 which effect sizes may be suppressed. The Copas selection model is among the more sophisticated
89 selection models [18] and investigates whether studies with a certain sample size showing larger
90 effects have a greater probability to enter a meta-analysis. A common feature in both
91 regression-based methods and the Copas selection model [19,20] is that effect estimates can be
92 adjusted for bias. In practice, regression-based adjustments of treatment effects were successful in
93 the prediction of the effect of antidepressant trials from the FDA trial registry using a biased subset
94 of the data [21].

95 Previous research estimated publication bias from the Cochrane Database of Systematic Reviews
96 (CDSR). Sutton et al. [22] estimated with the trim-and-fill method that around 50% of the reviews
97 had missing studies in a total of 48 Cochrane reviews. A large study [15] investigated
98 meta-analyses with binary outcomes from 1,669 Cochrane reviews and found funnel plot
99 asymmetry in 71 (19%) of the 366 meta-analyses that met inclusion criteria for regression-based
100 tests ($p < .10$, two-sided); on the other hand, another study found no convincing evidence for
101 publication bias [23] but they investigated a small subset of only 83 meta-analyses from the CDSR
102 to compare to a matched sample of meta-analyses from psychology. A study using a selection
103 model in 1,106 meta-analysis in the CDSR found positive findings to be 27% more likely to be
104 included in a meta-analysis [24]. An extensive and recent study by Lin et al. [25] investigated
105 30,000 meta-analyses from the CDSR and tested various methods among those regression-based
106 tests (but no selection models) and reported considerable funnel plot asymmetry in 20%–40% of
107 the meta-analyses; however, they included meta-analysis with only five studies which is at odds

108 with the common guideline of at least ten studies. Some methodological studies have been
109 performed with data from the CDSR to evaluate various asymmetry tests and found that Egger's
110 linear regression was most sensitive to detect asymmetry [26,27]. Statistical power can be increased
111 by choosing a more liberal p -value threshold with no substantial increase in false positive rate [28],
112 and indeed in many studies a significance level of $p < 0.10$ is used.

113 These studies were sometimes constrained to only a subset of the CDSR data or to methodology
114 that is generally not recommended such as trim-and-fill which has been shown to be inferior to
115 regression-based methods (Moreno, Sutton, Ades, et al., 2009). Often it was not reported how
116 outcomes related to efficacy were distinguished from outcomes related to adverse events. This is
117 important because for outcomes related to adverse events, if anything, we would expect publication
118 bias to operate in favor of null results. Furthermore, adjustment of the effect sizes is rarely
119 performed, and to the best of our knowledge, none of the studies compared funnel-plot asymmetry
120 and publication bias across different medical specialties.

121 The four aims of our study were a large-scale empirical assessment of the reported effects and their
122 statistical significance in (1) primary studies and in (2) meta-analyses, (3) the prevalence of funnel
123 plot asymmetry and publication bias, and (4) the magnitude of the adjustment of biased estimates
124 across different specialties in medicine. The hypotheses are specified in more detail in
125 Supplementary Table 1. Our primary data source was the CDSR, the probably largest and most
126 reliable collection of evidence in medicine.

127 **Methods**

128 A study protocol was written and the methods were specified in advance including a statistical
129 analysis plan. The protocol was registered on July 9, 2019 (osf.io/3a28k). Deviations from the
130 protocol are specified at the end of the methods sections. The complete pipeline with analysis code
131 written in R is available at osf.io/uv397. Even though this is not a systematic-review itself but a
132 meta-research study on meta-analyses from systematic reviews we report this study following the
133 STROBE guidelines [29], the checklist for this study can be found at osf.io/b6gxf.

134 **Search strategy and study selection**

135 Systematic reviews of the type “intervention” were selected from the CDSR which were 7,931
136 reviews as of November 11, 2019. These reviews assessed the benefits and harms of interventions
137 used in healthcare and health policy and involved primary studies from randomised controlled trials
138 (RCT) as well as observational studies. All studies involved an intervention, for example, a drug, a
139 surgical procedure, a psychotherapy, a device, preventive care, etc.

140 **Data collection**

141 The Cochrane Library conducts systematic reviews and is one of the largest and most reliable
142 sources for evidence in health care. Data from 6,075 (77%) of all the systematic reviews could be
143 retrieved which comprised 253,430 meta-analyses with outcomes from 71,986 primary studies
144 from over 50 million patients (Figure 1A). The primary studies included the sample sizes and the
145 number of events for both arms when the outcome was dichotomous, or the means and standard
146 deviations when the outcome was continuous. We further extended the dataset by scraping
147 additional information for the 6,075 Cochrane reviews: the full reference of the included primary
148 studies (including the journal name) and the the table “characteristics of included studies” which
149 included additional details on the methods, participants, interventions, and outcomes of the
150 intervention studies.

151 Furthermore, we collected citation information from Google Scholar (May 2020;
152 scholar.google.com) for 40,306 (70%) and the journal rankings from SCImago (February, 2020;
153 www.scimagojr.com) for 39,270 (69%) of the primary studies selected for analyses in Figure 1B.
154 Software in R to fetch and process data from the CDSR and the other sources is available at
155 osf.io/uv397.

156 **Data processing**

157 Beside the outcomes related to the efficacy of an intervention, there were also outcomes related to
158 adverse events (13.5%), withdrawal/dropout from the study (2.4%), and bias/sensitivity analyses
159 (1.3%). We identified and categorized the outcomes using regular expressions on the comparison
160 name, outcome name, and subgroup name as provided by the CDSR.

161 The 53 Cochrane review groups were merged into 19 medical specialties, see Supplementary Table
162 2. Assignment was based on thematic overlap, e.g. various cancer groups into “oncology”, various
163 neurological conditions into “neurology”.

164 **Inclusion criteria**

165 The data selection process for the analyses conducted is shown in Figure 1B–C. The analysis of the
166 effect sizes (Figure 1B) included all effects from published primary studies. We checked that all the
167 reported effects from the primary study were unique because the CDSR data can include the same
168 effect more than once, for example, when different systematic reviews included the same primary
169 study.

170 For the analysis of the combined effects from meta-analyses the number of primary studies was at
171 least 2 (Figure 1C). Furthermore, we excluded meta-analyses that appeared more than once or that
172 contained the same study effect more than once, for example, when the same meta-analysis was
173 conducted but with different subgroup analyses, or when a meta-analysis contains multiple
174 subgroup analyses that were sensitivity analyses. Meta-analyses based on subgroups were generally
175 included because within the hierarchical structure of the CDSR (comparisons, outcomes and
176 subgroups) systematic reviewers sometimes analyzed what actually were different comparisons as
177 different subgroups (e.g. different comparison of drugs).

178 For the asymmetry tests, selection model analysis, and adjustment of effect sizes (Figure 1D) in the
179 meta-analyses we strictly followed the guidelines by Ioannidis and Trikalinos [15] and used the
180 following four inclusion criteria: (1) the meta-analysis contains ≥ 10 studies, (2) heterogeneity $I^2 <$
181 50%, (3) the ratio of the minimum and maximum study variance > 2 , and (4) at minimum one
182 primary study must show a statistically significant effect.

183 **Statistical analyses**

184 We used Wilson confidence intervals for proportions and Wald confidence intervals for odds ratios
185 and coefficients from regression. Differences in proportions across medical specialties were
186 assessed with a Pearson’s χ^2 -test without continuity correction.

187 **Effect sizes from primary studies**

188 Effect sizes from primary studies included various outcome measures, the most common were risk
189 ratios (46%), mean differences (26%), odds ratios (11%), standardized mean differences (SMD)
190 (8%), Peto odds ratios (5%), risk differences (1.5%) and hazard ratios (1.1%), others were not
191 considered but the above mentioned represented 98% of all the primary study effect sizes reported
192 in the CDSR. Comparing reported effect sizes from primary studies across medical specialties
193 required harmonization. We recalculated all effect sizes for the primary studies using `escalc()`
194 from the R package `metafor` [30]. For continuous outcomes the SMD (Hedges' g), for
195 dichotomous outcomes the odds ratios was used. Odds ratios were transformed into Hedges' g
196 which were then transformed into Pearson's r [31]. Statistical significance was calculated with a
197 Wald's test which was performed on the original effect measure as reported in the CDSR (e.g., risk
198 ratio, hazard ratio, etc.); for mean differences we applied a two-sample Student's t -test.

199 **Combined effect estimates from meta-analyses**

200 We used the R package `meta` [32] for conducting meta-analyses for continuous outcomes (Hedges'
201 g) and binary outcomes (odds ratio). The combined effect from the random effects meta-analysis
202 was converted into a Pearson's r [31]. Statistical significance was determined by random effects
203 meta-analyses of the original effect measures as specified in the CDSR.

204 **Asymmetry tests and adjustment of combined effects**

205 Given the vast number of methods that now exist to study publication bias and sometimes lack
206 proper validation [33], we constrained our analyses to three widely used methods, the
207 regression-based Egger's test [12], Harbord's tests [16] and the Copas selection model analysis
208 [19,20]. We used the package `meta` [32] to detect funnel plot asymmetry in a meta-analysis using
209 the original effect measure as reported in the CDSR with Egger's linear regression; for
210 meta-analyses with odds ratios as effect measure we applied Harbord's test. Meta-analyses of Peto
211 odds ratios were performed with odds ratios, and meta-analysis of hazard ratios or risk differences
212 were performed with risk ratios instead; funnel plots of risk differences are not recommended [17].
213 All tests were performed one-sided ($p < 0.05$); the rationale for this will be explained further below.

214 The `metasens` package [34] was used to adjust combined effects via a regression-based method
215 known as limit meta-analysis [35,36] and the via Copas selection model [19,20]. The adjustments
216 were performed with the log odds ratios for dichotomous outcomes and with the SDMs for

217 continuous outcomes in order to harmonize and compare results across medical specialties on the
218 Pearson's r scale [31].

219 For the assessment of whether the adjustment increased or decreased the evidence for an
220 intervention we determined the side that favours the treatment as the side where there were more
221 studies with a statistically significant effect. While it is possible in a meta-analysis that a majority
222 of studies do not show evidence for a treatment benefit, it is unlikely that a majority of studies
223 demonstrate a statistical significant effect in the unexpected, opposite direction. Once the
224 anticipated side of the treatment effect was determined, a one-sided regression-based test ($p < 0.05$)
225 could be performed which had the advantage to exclude situations where asymmetry was caused by
226 smaller studies showing a larger effect in the unexpected direction. Thus, the operationalization of
227 small-study effects by means of asymmetry tests was more accurate.

228 **Small-study effect with probable publication bias**

229 Asymmetry tests can discover that smaller studies report stronger evidence for a treatment but do
230 not directly assess publication bias, and it is important to further evaluate funnel plot asymmetry
231 [13]. Thus, we further assessed the funnel plots with asymmetry ($p < 0.05$) and determined the
232 proportion of smaller studies with a significant result vs. a null result in any of the top 50%, 33%
233 and 25% of the studies with the largest standard errors (the smallest studies). If an equal or larger
234 number of studies were found we assume “small study-effects with probable publication bias” as
235 publication bias seems more likely in such situations. On the other hand, when more null results
236 were present in all of the quantiles then publication bias seems less likely, for example, in situations
237 where there is strong evidence for asymmetry but only a minority studies were statistically
238 significant. While publication bias may theoretically still be possible and there are “hidden” studies
239 in the funnel plot, their impact may not be so severe when a majority of the smaller studies that
240 were published show a null result.

241 **Change in evidence for treatment effects**

242 We converted the p -values from the combined treatment effects from the fixed effects
243 meta-analysis, from the bias-adjusted regression-based analysis and from the Copas selection
244 model analysis into Bayes factors bounds [37] and categorized those into six levels of evidence
245 from “weak” to “decisive” against the null hypothesis [38]. The change in evidence after

adjustment was determined by comparing the proportion of treatment effects falling in those categories.

Modeling of outcomes: statistical significance, small study-effects and bias adjustment

Six generalized linear mixed-effects (labeled 1–6 in the following text) were performed with the R package `lme4` [39] for the binary outcome statistical significance ($p < 0.05$, two-sided) of the treatment effects in primary studies (1) and combined effects from meta-analyses (2). We modeled the evidence for asymmetry using the test statistic (t -score) from the regression-based test (3) as well as the binary outcome (4) of whether the asymmetry tests gave a positive result or not ($p < 0.05$, one-sided). We also modeled the change in Pearson's r after adjustment with regression-based adjustment (5) and Copas adjustment (6). The explanatory variables for model 1 were the medical specialties (19 levels), the journal rank quartile (4 level), the study size, the number of citations per year, the publication year and whether the study was a RCT (binary). The explanatory variables for the models 2–6 were the medical specialties (19 levels), the median journal rank (across studies), the total sample size (across studies), the median number of citations per year (across studies), the review year and the number of studies in the meta-analysis.

Explanatory variables that were right-skewed were $\log_2$ transformed. Random effects accounted for dependencies and nesting in the data; these were the study id to model results from primary studies, and the Cochrane review id for the meta-analyses. The models were in more detail specified in the study protocol section 4.3.

Missing data

There was no missing data for the outcomes variables treatment effect from primary studies, combined treatment effect from meta-analyses, assessment of small-study effect, or adjustment by regression. For adjustments of treatment effects by Copas 143 (2.6%) meta-analyses were not estimable.

We performed complete case analysis with missing data in the explanatory variables used in the six regression models. Missing data were in publication year (14%), journal rank (31%), and number of citations (32%) with a total of 44% of the cases excluded for the outcome variable statistical significance of the primary studies. The missing data mainly affected published studies in journals with no journal rank or no citation information available. Google Scholar only provides data if the study has at least a single citation. For the outcome statistical significance of meta-analyses missing

276 data were in the explanatory variables median journal rank (6%) and median number of citations
277 (11%) with a total of 14% of the cases excluded. For the four remaining regression models with the
278 outcomes publication bias (continuous and binary) and bias adjustments (regression-based and
279 Copas) missing data were in the median journal rank (2%), and median number of citations (3%)
280 with a total of 4% of the cases excluded.

281 **Changes from the initial protocol**

282 We used the binary outcome of whether the effects were statistically significant but did not specify
283 this clearly in the research hypothesis and just used the term “effect size” instead of “statistical
284 significance of effect size” (protocol section 3: 1c and 2c; 4.3: 1c and 2c). We named the regression
285 model for hypothesis 2c but we did not specify the dependent variable in the statistical analysis
286 plan (protocol section 4.3; 2c). We were able to add a binary variable RCT (yes/no), i.e. whether a
287 study was reported as a randomized controlled trial, and used this additional variable in the
288 modeling (protocol section 4.3; 1c). We used categorical quartiles of the journal rank instead of the
289 continuous variable (protocol section 4.3; 1c); these were provided by SCImago themselves. We
290 applied Harbord’s test only for odds ratios and not generally for all binary outcomes as specified in
291 the protocol (protocol section 4.4).

292 **Patient and public involvement**

293 There was no patient and public involvement in this study.

294 **Results**

295 **1 Effect sizes from primary studies**

296 **Descriptives of primary studies**

297 We analyzed a total of 276,904 treatment effects from 57,162 studies. Studies were published
298 between 1922 to 2019; Psychiatry & mental health had the largest number of studies (8,091) and
299 Neonatology the smallest (1,600). The median study sample size was $N = 91$ (IQR 46–212). The
300 largest median effects (median Pearson’s r) were observed in Anesthesia & pain ($r = 0.23$; IQR
301 0.10–0.39) and Skin & wounds ($r = 0.23$; IQR 0.10–0.42), the lowest in public health & work ($r =$
302 0.13; IQR 0.05–0.25). For safety outcomes we analyzed 47,466 effects from 13,812 studies. For a
303 detailed description of all the variables from primary studies, see Supplementary Table 3–5.

304 **Statistically significant effects in primary studies**

305 Generally, we observed more significant effects for efficacy outcomes than for adverse events with
306 the exception of Oncology and in Pregnancy & childbirth (Figure 2A, Supplementary Table 6). The
307 proportions of significant effects in efficacy and safety outcomes differed among specialties (both p
308 < 0.0001). The largest were 36% in two specialties, Skin & wounds (95%-CI 0.35–0.38) and
309 Anesthesia & pain (95%-CI 0.36–0.37); the smallest was 18% in Neonatology (95%-CI 0.18–0.19).
310 For safety outcomes, the largest proportion of 29% was in Oncology (95%-CI 0.27–0.31) and the
311 smallest of 8% was in Emergency & trauma (95%-CI 0.07–0.10). We found no association between
312 the proportion of statistically significant effects versus the median sample size across the medical
313 specialties (Figure 2B). We performed a p -curve analysis and found that all the specialties had a
314 right-skewed shape and no inflation of p -values close to $p = 0.05$ (Supplementary Fig. 1).

315 **Odds for a statistical significant effect in a primary study**

316 We modeled the binary outcome of whether a treatment effect was statistically significant. We
317 found that the odds for a significant result was highest with a 1.9-times increase in Anesthesia &
318 pain (OR = 1.93; 95%-CI 1.79–2.08), and lowest with a 38% reduction in Pregnancy & childbirth
319 (OR = 0.62; 95%-CI 0.58–0.67), see Figure 2C and Supplementary Table 7. Primary studies
320 published in the 2nd, 3rd or 4th journal rank quartiles were all associated with higher odds for a
321 statistically significant result (compared to the the 1st quartile); the strongest effect had the top
322 quartile (Q4) that showed a 1.5-fold increase of the odds (OR = 1.52; 95%-CI 1.32–1.75). Positive
323 associations with significance were found for $\log_2$ study size (OR = 1.15; 95%-CI 1.14–1.17) and
324 $\log_2$ number of citations per year (OR = 1.07; 95%-CI 1.06–1.08); and negative associations for
325 publication year (per 10 years; OR = 0.94; 95%-CI 0.92–0.96) and when a primary study was an
326 RCT (OR = 0.90; 95%-CI 0.86–0.94).

327 **2 Combined effect estimates from meta-analyses**

328 **Descriptives of the meta-analyses**

329 A total of 98,966 random effects meta-analyses were calculated from 4,737 intervention reviews.
330 The largest number of meta-analyses were from Psychiatry & mental-health (13,906); and the
331 median total sample size in the meta-analyses across studies was $N = 523$ (IQR 220–1,395). The
332 combined effects (median Pearson's r) were largest in Skin & wounds ($r = 0.20$; IQR 0.08–0.37)

333 and lowest in Pregnancy & childbirth ($r = 0.09$; IQR 0.04–0.20) and neonatology ($r = 0.09$; IQR
334 0.04–0.20), see descriptives in Supplementary Table 8.

335 **Statistical significance of the combined effects**

336 The proportion of statistically significant results varied across specialties ($p < 0.0001$), the largest
337 was 49% in Anesthesia & pain (95%-CI 0.47–0.50), and the lowest was 21% in neonatology
338 (95%-CI 0.20–0.22), see Supplementary Table 9. We performed a p -curve analysis and observed
339 that all the specialties had a right-skewed shape with no inflation of p -values close to $p = 0.05$
340 (Supplementary Fig. 2).

341 **Odds for a statistical significant effect in a meta-analysis**

342 We modeled the binary outcome of statistical significance of the combined effects from the
343 meta-analyses (Figure 2D and Supplementary Table 10). We found the highest odds with a 2.5-fold
344 increase in Anesthesia & pain (OR = 2.46; 95%-CI 1.97–3.06) and the lowest with a 43% reduction
345 in Pregnancy & childbirth (OR = 0.57; 95%-CI 0.47–0.68). The number of studies ($\log_2$) included
346 in a meta-analyses had 1.6-fold higher odds for a statistically significant result (OR = 1.60; 95%-CI
347 1.56–1.65). Positive associations with significance had the $\log_2$ sample size (OR = 1.08; 95%-CI
348 1.07–1.10) and the $\log_2$ number of citations (OR = 1.04; 95%-CI 1.02–1.06). The journal rank and
349 the review year showed no evidence for an effect.

350 **3 Small-study effects and publication bias**

351 **Prevalence of small study-effects**

352 A total of 5,534 meta-analyses from 949 Cochrane systematic reviews were assessed that satisfied
353 our inclusion criteria. We found small-study effects in 1,054 (19%) of the meta-analyses (95%-CI
354 from 18% to 20%), the distribution of p -values is in Figure 3A. Infectious diseases had the highest
355 prevalence which was 35% (95%-CI from 0.25 to 0.45) and Genetics & endocrinology the lowest
356 with 10% (95%-CI from 0.06 to 0.17), see Figure 3B.

357 **Modeling small study-effects**

358 We modelled the test statistic (t -score) from the regression-based test for funnel plot asymmetry
359 (Figure 3C and Supplementary Table 11). Infectious diseases (0.34; 95%-CI 0.02–0.66) and
360 Anesthesia & pain (0.30; 95%-CI from 0.12 to 0.48) showed larger small-study effects compared to
361 the mean across the specialties; Lungs showed less small-study effects (-0.19; 95%-CI from -0.37

362 to -0.01). The number of studies ($\log_2$) (0.27; 95%-CI from 0.22 to 0.33) was associated with
363 stronger small-study effects, the sample size ($\log_2$) with less (-0.04; 95%-CI from -0.07 to -0.01).

364 Looking at the binary outcome small-study effects (yes/no) we observed similar results. Infectious
365 diseases had a 3-fold increased odds for small-study effects, (OR = 3.00; 95%-CI 1.26–7.16), see
366 Figure 3D and Supplementary Table 12. The number of studies ($\log_2$) included in the meta-analyses
367 had 2-fold higher odds for small-study effects (OR = 2.23; 95%-CI 1.89–2.63).

368 **Small-study effects with probable publication bias**

369 Funnel plots of the meta-analyses with evidence for small-study effects were further assessed. From
370 the 1,054 meta-analyses with small study-effects we identified 214 meta-analyses (20%) having
371 small study-effects with probable publication bias which was 3.9% (95%-CI from 3.4% to 4.4%) of
372 the total of 5,534 meta-analyses included. Examples of evidence for small-study effects versus
373 small-study effects with probable publication bias are shown in Figure 5A and Figure 5B,
374 respectively. The intercepts from the regression-based tests which reflect the magnitude of the bias
375 showed more extreme values for small-study effects with probable publication bias than without
376 (Figure 3E); 99.5% of these were considered as substantial small-study effects based on the
377 categorization by Lin et al. [25].

378 Overall 378 (40%) from 949 Cochrane systematic reviews had at least one meta-analysis with
379 small-study effects and 115 (12%) reviews had at least one meta-analysis that showed small-study
380 effects with probable publication bias, see Figure 3F for results per medical specialty.

381 **4 Adjustment of effect estimates from meta-analyses**

382 Regression-based adjustment of the 1,054 meta-analyses with small-study effects resulted in a
383 reduction of the effects in 99% of the cases and the median change in the combined effect
384 (Pearsons's r) was -0.09 (Figure 4A); for Copas selection model the reduction was in 77% of the
385 cases and the median change was -0.02 (Figure 4B).

386 We applied a mixed-model to all 5,534 included meta-analyses to find associations with effect
387 change after regression-bases adjustment and Copas adjustment (Figure 4C–D). For regression,
388 larger adjustments were required for Infectious diseases (-0.05; 95%-CI from -0.08 to -0.02) and
389 Anesthesia & pain (-0.02; 95%-CI from -0.040 to -0.001). Similarly, Copas required larger

adjustments for Infectious diseases (-0.02; 95%-CI from -0.027 to -0.006) and Anesthesia & pain (-0.01; 95%-CI from -0.016 to -0.003). Kidney & transplant had smaller adjustments; however, this was weak evidence. Furthermore, the sample size ($\log_2$) was associated with smaller adjustments with both methods, the median SJR with smaller adjustment with Copas, and the number of studies was associated with less adjustment for regression, see Supplementary Table 13–14.

Adjustment by regression generally performed a stronger shrinkage of the treatment effects compared the Copas selection model analysis; however, the adjustments were consistent between the two methods across the the medical specialties and across meta-analyses (Figure 5E–F). Compared to the regression-based method Copas applied zero or near-zero adjustment in a number of cases.

Change of evidence for treatment effects

The change of evidence via Bayes factor bounds in 5,534 meta-analyses was assessed by comparing the strength of the evidence after adjustment. The adjustment of the effects changed the overall evidence in many meta-analyses when effects were adjusted with regression but not so with Copas. The proportion of meta-analyses with very strong or decisive evidence for a treatment effect decreased from 32% down to 7% (regression) but only from 32% to 31% for Copas adjustments, see Figure 5G.

Discussion

Here, we found that 19% from 5,534 large meta-analyses (≥ 10 studies) have evidence for small-study effects demonstrating that smaller studies reported larger effects which affected 40% of the Cochrane systematic reviews. Most evidence for small-study effects was found in infectious diseases which also required larger adjustment compared to other specialties. The number of studies in a meta-analysis was strongly associated with small-study effects indicating that more studies improve the statistical power to detect bias. It is striking that our result were highly consistent with the previously reported prevalence of asymmetry in 19% from a total of 366 meta-analyses [15]; we applied exactly the same inclusion criteria for the meta-analyses but the main differences were our 15-times larger dataset and that we also considered continuous outcomes which suggests a broader generalizability of our results.

418 Systematic assessment of funnel plots suggested that publication bias may not be the main driver
419 behind small-study effects. Only about 4% of the 5,534 meta-analyses demonstrated small-study
420 effects with probable publication bias. It is worth noting that regression-based methods do not take
421 into account the statistical significance of the study effects. Therefore, other reasons for smaller
422 studies reporting larger effects must be considered: confirmation bias, lower quality studies,
423 selection bias in the treatment groups, outcome switching, post-hoc searches for statistical
424 significance, or incomplete reporting of statistically non-significant results [40]. However, all these
425 biases have the same effect on meta-analyses: they all lead to an exaggeration of the combined
426 treatment effect.

427 Regression-based adjustment of meta-analyses changed the evidence of the treatment effects in
428 many cases from decisive to weak while Copas performed a more conservative adjustment with a
429 majority of meta-analyses that received no or near zero adjustment. The two methods are
430 fundamentally different: while regression is based on funnel-plot asymmetry, Copas analysis
431 directly models publication bias and the selection process. Our further assessments of funnel-plots
432 suggested that small-study effects with probable publication bias is much less common and is more
433 in line with the adjustments from Copas analysis. On the other hand regression-based methods tend
434 to overcorrect in some situations, for example, when the adjusted effect turned smaller than the
435 smallest effect reported in a study. This is not in line with an often cited report [21]; but this report
436 is based on a single meta-analysis which cannot be generalized. Future studies may apply shrinkage
437 methods [41] to regression-based adjustments.

438 We found that some medical specialties were more likely to report a statistically significant effect,
439 for example in Anesthesia & pain and Skin & wounds while others were less likely to do so, for
440 example Pregnancy & childbirth and Neonatology. These findings were even confirmed when
441 looking at combined effects from meta-analyses. Reasons for this could be a higher number of true
442 effects in a field, varying statistical power between fields, or differences in reporting of statistically
443 significant versus non-significant results. We replicated previous findings that studies with a
444 statistically significant effect were more likely to be published in prestigious journals [8] and also
445 received a higher number of citations [9,42] which can indeed contribute to publication bias [43].
446 We also showed that when studies were of higher quality, such as an RCT, they were less likely to
447 report a statistically significant effect. It is highly problematic when studies that report more
448 extreme results become more visible in prestigious journals instead of studies of the highest quality.

449 Our study had some limitations. First, regression-based methods have been criticised to have a lack
450 of statistical power [44] and there are also other situations where regression methods (and also
451 selection models) may fail: large heterogeneity, no significant studies, or all studies are of similar
452 sizes. Therefore, we followed available guidelines for inclusion criteria of suitable meta-analyses
453 [14,15]. We only included 5,534 (5.6%) compared to the 98,966 meta-analyses; most were
454 excluded because the number of studies was smaller than ten. However, this selection of
455 meta-analyses may represent the more relevant medical interventions where many studies have
456 been conducted. In some cases our meta-analyses do not exactly correspond to the ones performed
457 in Cochrane Systematic Reviews as these also include unpublished findings; we excluded these as
458 our aim was to assess publication bias when unpublished data is not considered. Altogether,
459 systematic reviewers considered unpublished studies in 115 (11%) of the 1,054 meta-analyses with
460 small-study effects, and in 26 (12%) of the 214 meta-analyses that have small-study effects with
461 probable publication bias. It seems that finding unpublished evidence is limited.

462 Around half of systematic reviews, in some specialties even less, do not evaluate publication bias
463 and should do so more often [45,46]. However, our findings suggest that large, potentially
464 exaggerated effects due to small studies give rise to greater concern than publication bias.
465 Advanced funnel plots with contours [47] and regression based tests are helpful to identify these
466 problems but are not specific to publication bias alone, and novel and innovative methods may
467 prove to be more suitable [48]. Investigators should also provide individual patient data (IPD) to
468 combat publication bias and other biases in the future [49].

469 **Data Availability**

470 All data used in this study are openly available from the Cochrane Library
471 (<https://www.cochranelibrary.com/>), Google Scholar (<https://scholar.google.com/>) and SCImago
472 (<https://www.scimagojr.com/>). Data are also available from the corresponding authors upon
473 reasonable request.

474 Code Availability

475 Software in R to fetch the data from the Cochrane Library and Google Scholar, as well as the
476 analysis pipeline to process and analyze the data and produce all the figures, tables and the
477 supplementary information is available at osf.io/uv397.

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577 **Author contributions**

578 S.S. and L.H. designed the study. S.S. developed software and collected the data. S.S. and G.K.
579 analysed the data. S.S. wrote the first draft of the manuscript and all authors commented on
580 subsequent versions.

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584 **Competing interests**

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586 **Patient consent for publication**

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592 **Additional information**

593 Supplementary Information accompanies this paper at osf.io/dtqs5. The study protocol is available
594 at osf.io/3a28k.

Figure Captions

a Selection of systematic reviews

b Selection of treatment effect from primary studies

c Selection of combined treatment effect estimates from meta-analyses

d Inclusion of meta-analyses for asymmetry and publication bias tests

¹Effect sizes unique in a medical specialty; the effect sizes unique across specialties were $n = 453,397$

²Not estimable as specified in the CDSR

Figure 1 Selection process from the Cochrane Database of Systematic Reviews (CDSR). (A) Data from 77% of the systematic reviews were retrieved. Selection of treatment effects from primary studies (B) and selection of meta-analyses (C-D).

Figure 2 Statistically significant results across medical specialties. (A) Proportion (with 95%-CI) of reported statistically significant effects in published studies for efficacy and safety outcomes. (B) Relationship between the proportion of statistically significant effects and the median sample size. Odds ratios (with 95%-CI) for a statistically significant effect in a primary study (C) and in a combined effect from a meta-analysis (D).

Figure 3 Small-study effects in meta-analyses across medical specialties. (A) Distribution of p -values from regression-based tests, p -values < 0.05 (one-sided) were considered as evidence for small-study effects in meta-analyses (red). (B) Prevalence (with 95%-CI) of small-study effects across the medical specialties. (C) Regression estimates (with 95%-CI) for small-study effects with the outcome t -scores from regression-based tests. (D) Same but for a binary outcome (small-study effects yes/no). (E) Distribution of intercepts (magnitude of small-study effects) from regression-based test. (F) Number of systematic reviews affected by bias.

Figure 4 Adjustment of treatment effects. (A) Distribution of effect changes (Pearson's r) from meta-analyses after adjustment by regression; (B) same for Copas adjustment. (C) Variables associated with effect changes, negative estimates reflect shrinkage of effects; (D) same for Copas adjustment. (E) Adjustment by regression versus Copas across specialties; (F) same across all meta-analysis. (G) Strengths of evidence against the null of no treatment effect before (random effects meta-analysis) and after adjustment (regression and Copas).

616 **Figure 5** Enhanced funnel plots. Randomly picked examples of funnel plots with small-study effects (A); and
617 small-study effects with probable publication bias (B). Small black circles are studies; statistically significant
618 ones in red. The shades of gray are different levels of statistical significance (gray is $p < 0.05$, light gray is p
619 < 0.01). The gray vertical line is the null, the dashed line the fixed effects, the dotted line the random effects
620 estimate. The red diamond (regression) and green rectangle (Copas) are the adjusted effects, also as
621 numbers (with 95%-CI) at the bottom (unadjusted random effects estimate in black). The p -value is from the
622 asymmetry test by regression, k the number of studies. Above the funnel plots are the medical specialty, the
623 outcome and comparison name; on the right the review id, meta-analysis id and the subgroup name.