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METHODOLOGY

Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials

J Pildal,[1,*] A Hróbjartsson,[1] KJ Jørgensen,[1] J Hilden,[2] DG Altman[3] and PC Gøtzsche[1]

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Background Randomized trials without reported adequate allocation concealment have been shown to overestimate the benefit of experimental interventions. We investigated the robustness of conclusions drawn from meta-analyses to exclusion of such trials.

Material Random sample of 38 reviews from The Cochrane Library 2003, issue 2 and 32 other reviews from PubMed accessed in 2002. Eligible reviews presented a binary effect estimate from a meta-analysis of randomized controlled trials as the first statistically significant result that supported a conclusion in favour of one of the interventions.

Methods We assessed the methods sections of the trials in each included meta-analysis for adequacy of allocation concealment. We replicated each meta-analysis using the authors' methods but included only trials that had adequate allocation concealment. Conclusions were defined as not supported if our result was not statistically significant.

Results Thirty-four of the 70 meta-analyses contained a mixture of trials with unclear or inadequate concealment as well as trials with adequate allocation concealment. Four meta-analyses only contained trials with adequate concealment, and 32, only trials with unclear or inadequate concealment. When only trials with adequate concealment were included, 48 of 70 conclusions (69%; 95% confidence interval: 56–79%) lost support. The loss of support mainly reflected loss of power (the total number of patients was reduced by 49%) but also a shift in the point estimate towards a less beneficial effect.

Conclusion Two-thirds of conclusions in favour of one of the interventions were no longer supported if only trials with adequate allocation concealment were included.

Keywords Bias (epidemiology), double-blind method, methods, randomized controlled trials, meta-analysis

Introduction

Concealment of treatment allocation and blinding are important safeguards against bias in randomized controlled trials.[1] Allocation concealment serves to avoid selection bias by concealing what treatment the next patient will receive, if enrolled. Without concealment the person in charge of enrolment might channel patients with a better prognosis into his or her preferred treatment, for instance by influencing whether a patient enters the trial at all. The blinding of key trial persons (e.g. patients, treatment providers and data collectors) is sometimes referred to as double-blinding. However, 'double-blinding' is inconsistently interpreted. For instance, some believe it means that patients and treatment providers are blinded, others that patients and data collectors are blinded.[2,3]

Empirical studies show that the effects of experimental interventions measured as odds ratios are exaggerated

[1] The Nordic Cochrane Centre, Rigshospitalet, DK.
[2] Department of Biostatistics, University of Copenhagen, DK.
[3] Centre for Statistics in Medicine, Oxford, UK.
* Corresponding author. The Nordic Cochrane Centre, Rigshopitalet, 3343 Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: jp@cochrance.dk

on average by 21% [ratio of odds ratios (ROR): 0.79, 95% confidence interval (CI): 0.66–0.95], if allocation concealment is unclear or inadequate, and by 18% (ROR: 0.82, 95% CI 0.71–1.05), if trials are not reported as 'double-blind'.[4–10]

To reduce the risk of introducing interventions based on trial results that are inflated, a simple approach would be to rely only on trials with clear indication of adequate allocation concealment. A similar exclusion of trials not reported as 'double-blind' would be more difficult to interpret; since, as opposed to allocation concealment that can and should always be performed, blinding may be impossible or the feasibility of it doubtful. In addition, the term 'double-blind' is inconsistently used. Thus, our primary aim was to estimate the fraction of conclusions based on statistically significant results in meta-analyses that would no longer be supported if only trials with reported adequate allocation concealment were included. Our secondary aim was to assess the impact of absence vs presence of reported adequate allocation concealment in trials on the effect estimates. We also studied how double-blinding—as a possible confounder—was related to allocation concealment and how absence of double-blinding affected the treatment effect estimate.

Methods

Identification and selection of reviews

We aimed to retrieve 70 published reviews containing one or more meta-analyses, with about half of them being Cochrane Reviews. This number was arbitrarily chosen based on our anticipation of how informative the meta-analyses would be and the workload. Reviews were eligible if the authors concluded that one of the assessed interventions was superior to the other and if this preference was supported by the first statistically significant result of a meta-analysis reported in the abstract. When a review presented several meta-analyses, only the meta-analysis identified as described was included. Reviews were excluded if:

- The first statistically significant result of a meta-analysis reported in the abstract was not for a binary outcome.
- Substantial uncertainty existed concerning what the authors of the review perceived as experimental and conventional treatment.
- There were more than 40 trials in the first statistically significant meta-analysis reported in the abstract.
- A genuine meta-analysis was not performed.
- The abstract of the review explicitly stated that it was partly based on non-randomized trials.

These selection criteria were applied on reviews identified as follows: in the Cochrane Library 2003, issue 2 all reviews containing at least one meta-analysis with a binary outcome were numbered randomly by an IT specialist not otherwise involved in the project. Reviews were assessed for eligibility in the random order. The PubMed database, years 2001 and 2002 was searched with the strategy:

> (randomi* OR controlled OR blind* OR placebo OR 'controlled ? trial') AND
> (meta-analysis OR metaanalysis Field: All Fields, Limits: Meta-Analysis)

Reviews identified in PubMed were assessed for eligibility in the order of publication date.

One author (J.P.) assessed all abstracts of reviews from both sources for eligibility. Those abstracts that did not meet any exclusion criteria were assessed in duplicate by two authors as to whether the conclusion favoured one of the interventions. If they independently agreed that this was the case, then the full text of the review was retrieved and reassessed for eligibility including independent assessments of whether classification of interventions as experimental or conventional was unequivocal. Disagreements led to exclusion.

Retrieval of trials and assessment of methodology

Original articles were retrieved for all the trials in the included meta-analyses. If the methods section in a trial report referred to another report for details, this was also obtained. A student not otherwise involved in the project photocopied the methods sections of the reports of the included trials. Pairs of authors assessed the adequacy of allocation concealment and of double-blinding independently and blinded to the results sections. We used the criteria reported by Schulz *et al*.[4] for classification of allocation concealment:

Trials with 'adequate concealment' employed central randomization including pharmacy-controlled randomization (where a pharmacy remote from the clinical ward allocated the treatment); numbered or coded bottles or containers; serially numbered, opaque, sealed envelopes; or the trialists presented other descriptions that implied convincing concealment. Methods were deemed to provide 'inadequate concealment' if it was obvious to which treatment the next patient would be allocated (alternation, use of case record numbers, dates of birth, etc.). Trials with 'unclear concealment' did not report on allocation concealment or reported an approach that did not clearly fall into one of the other categories.

Trials were categorized as 'double-blind' if described as double-blind; or if patients and treatment providers were explicitly reported as blinded. Trials reported to be placebo-controlled without any indication that the treatments might be distinguishable or that investigators might have become unblinded before the onset of the treatment were also categorized as double-blind. 'Patients and assessor'-blinding was not categorized as double-blinding because lack of blinding of treatment providers might increase the risk that trials with unclear reporting on allocation concealment in reality had inadequate concealment.

Extraction of 2×2 data for each meta-analysis

Most of the trial 2×2 data necessary for our replication of the individual meta-analyses were extracted from the reviews. When absent in the review, data were sought in the trial reports. If the methods sections of the reviews and trial reports did not allow unequivocal identification of the exact numbers, we contacted the authors of the reviews.

Data analysis and statistics

For the primary analysis we first replicated the meta-analyses using the review authors' method of analysis while retaining all trials in the analysis. When 2×2 data were unobtainable, we

used the point estimates and standard errors from the meta-analyses and did an inverse variance analysis[11] using a fixed or random effects model depending on the authors' original method. Next, we redid each meta-analysis, but included only those trials that had reported adequate allocation concealment (primary analysis). Here, and for all later analyses, we had to give up the distinction between unclear and manifestly inadequate concealment because the latter was too rare. We did not correct any of the review authors' errors of analysis (counting the same control group twice, etc.), as we wished to isolate the impact of requiring reported adequate allocation concealment. We defined the review authors' conclusions not to be supported by the reduced data if our estimates were not statistically significant at a two-sided 5% significance level.

Loss of statistical support might here be due to loss of data or to differentially biased treatment effects in the discarded vs retained trials. This was investigated among the meta-analyses with a mixture of trials with and without reported adequate concealment in the following way: we assumed that the point estimates obtained in the reduced meta-analyses still had the statistical precision of the unreduced analyses, and calculated whether or not that would restore the original statistical support. Thus, an adjusted *z*-value was defined as the *z*-value in the reduced data set x $\sqrt{}$[(total number of participants in the original data set)/(total number of participants in the reduced data set)]. If the adjusted *z*-value was below 1.96 then the loss of statistical significance was interpreted as being caused by a shift in the point estimate rather than loss of statistical power.

For the secondary analysis we used an approach described by Sterne *et al*.[12] Briefly, we estimated the ROR by comparing trials with absence vs presence of reported adequate allocation concealment in a univariate random effects meta-regression in each meta-analysis. To ensure consistency we recalculated the effect estimates where necessary, so that all results were expressed as undesirable events (e.g. presence of symptoms rather than absence of symptoms). Since the odds in the numerator of the odds ratio of each trial were for the experimental treatment, OR<1 represents superiority of the experimental intervention. The ROR estimates were then combined in a random effects generic inverse variance meta-analysis. We used the I^2 quantity to report the percentage of variability between meta-analyses that could not be ascribed to chance.[13] Reviews for which 2×2 data could not be obtained, or where all trials either were with or without reported adequate allocation concealment, did not contribute to this analysis. Corresponding analyses were employed to estimate the impact of absence vs presence of double-blinding on the treatment effect estimate. Analyses were performed using Stata software, version 8 (StataCorp) and RevMan software, version 4.2.3 (Nordic Cochrane Centre, The Cochrane Collaboration: available from http://www.cochrane.org).

Results

Characteristics of included meta-analyses and component trials

The selection process for Cochrane Reviews and other reviews is outlined in Figure 1. After two rounds, 181 Cochrane Reviews and 128 other reviews had been assessed, and 38 Cochrane Reviews and 32 other reviews were included. A larger fraction of Cochrane Reviews was excluded because no preference was stated in the conclusion, rate difference 28% (95% CI 14–42%), $P = 0.0002$. The 38 Cochrane Reviews comprised a total of 202 trials and a median of four trials per meta-analysis (10th to 90th percentile range: 2–12).[14–51] The 32 other reviews comprised 297 trials with a median of seven trials included per meta-analysis (10th to 90th percentile range: 4–17).[52–84] Two reviews, based on 6 and 17 trials, respectively, had three trials in common. As the overlap was very small and the reviews addressed different outcomes, no data were excluded.

Overall, only 82/499 (16%) of trials had adequate allocation concealment, including 51% of participants; 379 trials (76%) had unclear and 38 trials (8%) had inadequate concealment. More trials in Cochrane Reviews reported adequate allocation concealment (25% vs 10%). A larger fraction of trials with adequate allocation concealment also had double-blinding. Trials with adequate allocation concealment and trials with double-blinding tended to be larger, more recent, and include fewer non-English reports than their counterparts (Tables 1 and 2).

We compared our assessment of adequacy of allocation concealment to that of the Cochrane review authors. When we used the same instructions that Cochrane Review authors are expected to follow, the only extra detail required was for the 'numbered coded vehicles'-method to be reported with the vehicles as being sequentially administered. Yet, we found that among 202 trials we categorized 92 trials (46%) differently than the review authors; mainly because the review authors did not use the criteria or applied them more laxly. The latter caused an overestimation of adequacy of allocation concealment in 75 trials (36%).

Although all reviews purportedly included randomized trials only, our reassessments revealed that seven trials were not randomized. However, as this is a pragmatic study the reviews containing these trials were not excluded, and the few non-randomized trials were treated in the analyses as having inadequate allocation concealment.

In the meta-analyses that contained a mixture of trials with and without reported adequate concealment, we were able to reproduce the meta-analyses to within two rounding units (e.g. 0.02 when an odds ratio scale was used) with two exceptions, but even here the discrepancy was less than a tenth of the associated standard error.

Conclusions no longer supported

In total, 34 meta-analyses included a mixture of trials with and without reported adequate allocation concealment, whereas 32 meta-analyses exclusively contained trials with unclear or inadequate concealment, and four meta-analyses exclusively contained trials with adequate concealment. Forty-eight of 70 conclusions (69%; 95% CI 56–79%) lost support when only trials with adequate concealment were included.

Among the 34 meta-analyses with a mixture of trials with and without reported adequate concealment, 16 (47%) lost support. *P*-values and average precision before and after exclusion of trials without reported adequate concealment

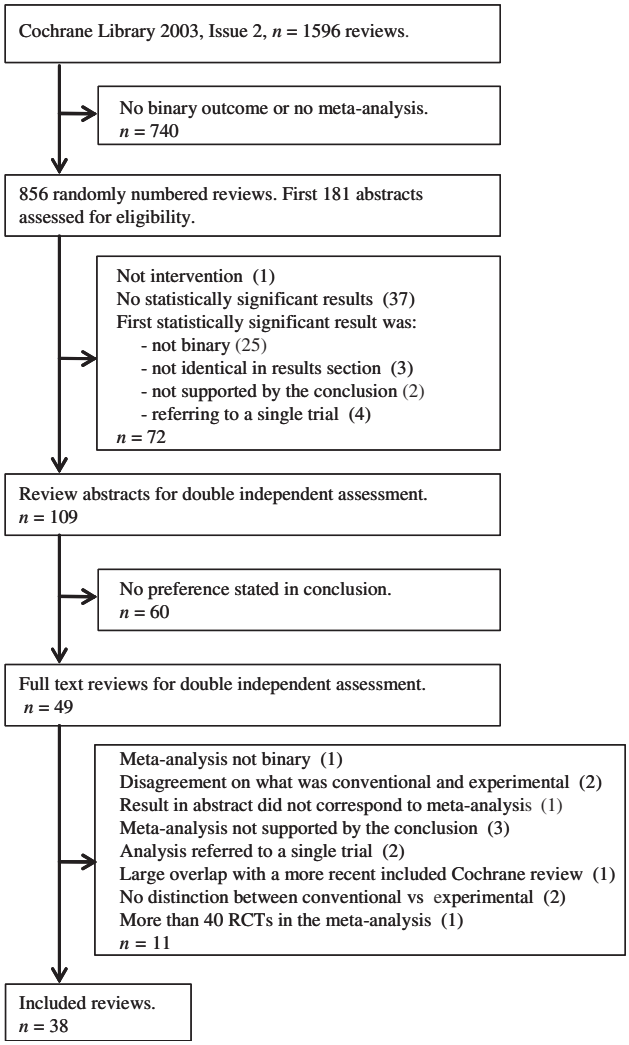

Figure 1 Flow chart of the selection of reviews

Table 1 Characteristics of trials related to adequacy of allocation concealment

	Adequate concealment $n = 82$	Unclear concealment $n = 379$	Inadequate concealment $n = 38$
Double-blinding	56 (68%)	119 (31%)	2 (5%)[a]
Trial size[b] Median (10th to 90th percentile range)	160 (44–1827)	117 (35–476)	93 (30–259)
Publication year[c] Median (10th to 90th percentile range)	1996 (1986–2001)	1994 (1984–99)	1984 (1965–95)
Non-English language[d]	2 (2.5%)	18 (4.8%)	0 (0%)

[a] These two trials were reported to be parallel double-blind trials, but with no indications that randomization had taken place.
[b] Does not include data from four trials in one meta-analysis based on unpublished data that are no longer available from the company.
[c] Includes trials published as abstracts only. Eleven trials were unpublished.
[d] Five unpublished trials from countries where the first language is not English did not contribute.

Table 2 Characteristics of trials related to presence or absence of double-blinding

	Double-blinded $n = 177$	Not double-blinded $n = 322$
Reported adequate concealment	56 (32%)	26 (8%)
Trial size[a] Median (10th to 90th percentile range)	161 (40–1250)	100 (33–383)
Publication year[b] Median (10th to 90th percentile range)	1995 (1986–2000)	1994 (1981–99)
Non-English language[c]	4 (2%)	14 (4%)

[a] Does not include data from four trials in one meta-analysis based on unpublished data that are no longer available from the company.
[b] Includes trials published as abstracts only. Eleven trials were unpublished.
[c] Five unpublished trials from countries where the first language is not English did not contribute.

in these meta-analyses are shown in Table 3. Five of these 16 meta-analyses (31%) were estimated to loose support if the statistical power had been the same, i.e. they lost support because of a shift in the point estimate.

Overestimation of treatment benefit

Of the 34 meta-analyses containing trials with as well as without reported adequate concealment, four did not contribute to the analysis because 2 × 2 data were unobtainable and one because it contained only two trials. In the remaining 29 meta-analyses the pooled estimate of the ratio of the treatment effect estimates from trials with unclear or inadequate allocation concealment compared to those from trials with adequate concealment was an ROR of 0.90 (95% CI: 0.81–1.01; $P = 0.08$, $I^2 = 0\%$) (Figure 2). Hence, there was a non-significant trend towards a seemingly more beneficial effect of the experimental treatment in the trials without reported adequate allocation concealment.

Table 3 *P*-values and average precision before and after exclusion of trials without reported adequate concealment

	Before exclusion $n = 34$ (%)	After exclusion $n = 34$ (%)
$P > 0.10$	0	12 (35)
$0.05 < P < 0.10$	0	4 (12)
$0.01 < P < 0.05$	10 (29)	6 (18)
$0.001 < P < 0.01$	7 (21)	5 (15)
$P < 0.001$	17 (50)	7 (21)
Average precision (1/SE)*	9.10	5.56

*Standard error of the intervention effect expressed on the natural logarithm scale.

Among the 20 meta-analyses comprising a mixture of trials without and with double-blinding, the corresponding ROR was similar: ROR 0.94 (95% CI: 0.80–1.10; $P = 0.41$, $I^2 = 2.5\%$) (Figure 3).

We explored how our result adds to the current evidence of the impact of lack of reported adequate concealment using a random effects generic inverse variance meta-analysis.[4–9] The overall estimate was an ROR of 0.82 (95% CI: 0.71–0.94); $P = 0.006$, $I^2 = 84.1\%$), implying an 18% better outcome (when expressed on the OR scale) in the experimental treatment groups in trials without reported adequate allocation concealment; i.e. an 18% lower failure rate when treatment failures are few (Figure 4). However, the individual estimates were heterogeneous ($P < 0.00001$). The corresponding estimate for absence vs presence of double-blinding was an ROR of 0.91(95% CI 0.83–1.00; $P = 0.05$, $I^2 = 21.2\%$) (Figure 5).

Discussion

Two-thirds of the conclusions that favoured one of the interventions based on a meta-analysis lost support if only

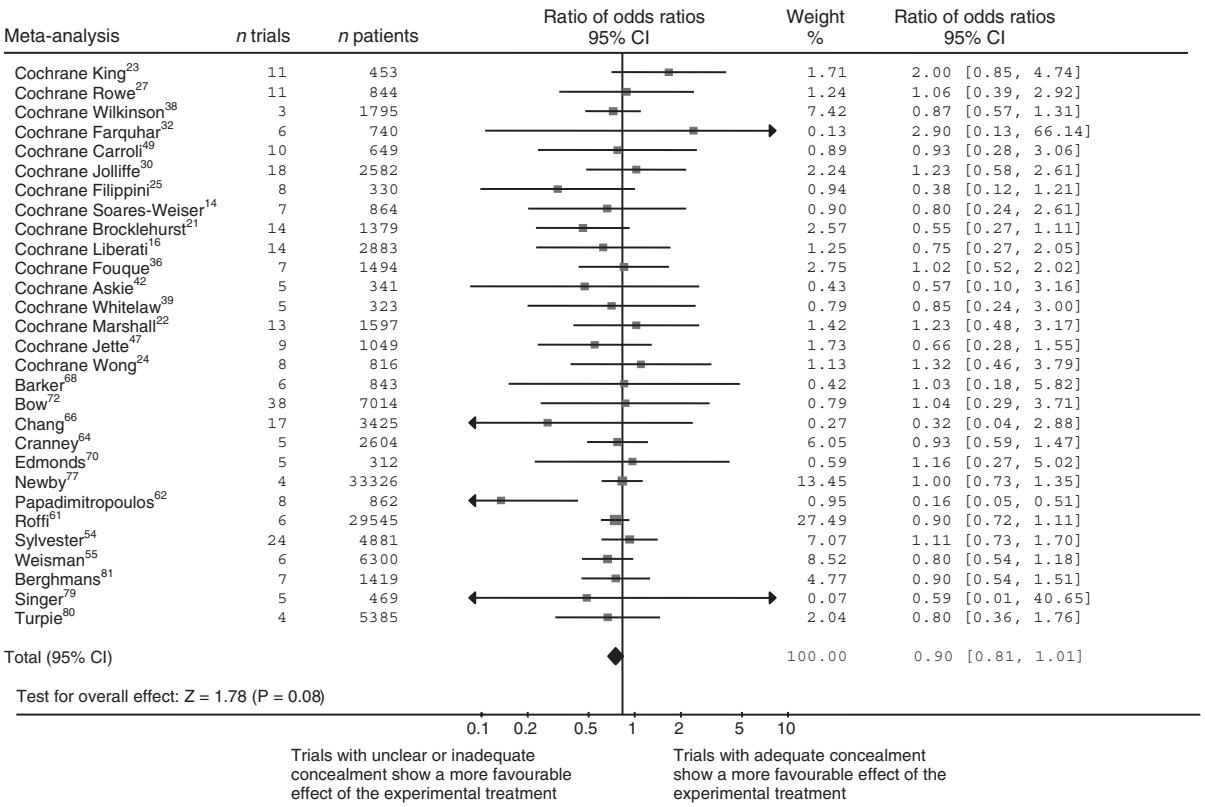

Figure 2 Comparisons of results from trials without vs with reported adequate allocation concealment presented as ratios of odds ratios (RORs) from trials within each meta-analysis. RORs below 1 indicate that trials without adequate concealment show a more beneficial treatment effect. An over-all ROR estimate was calculated in a random effects generic inverse variance meta-analysis

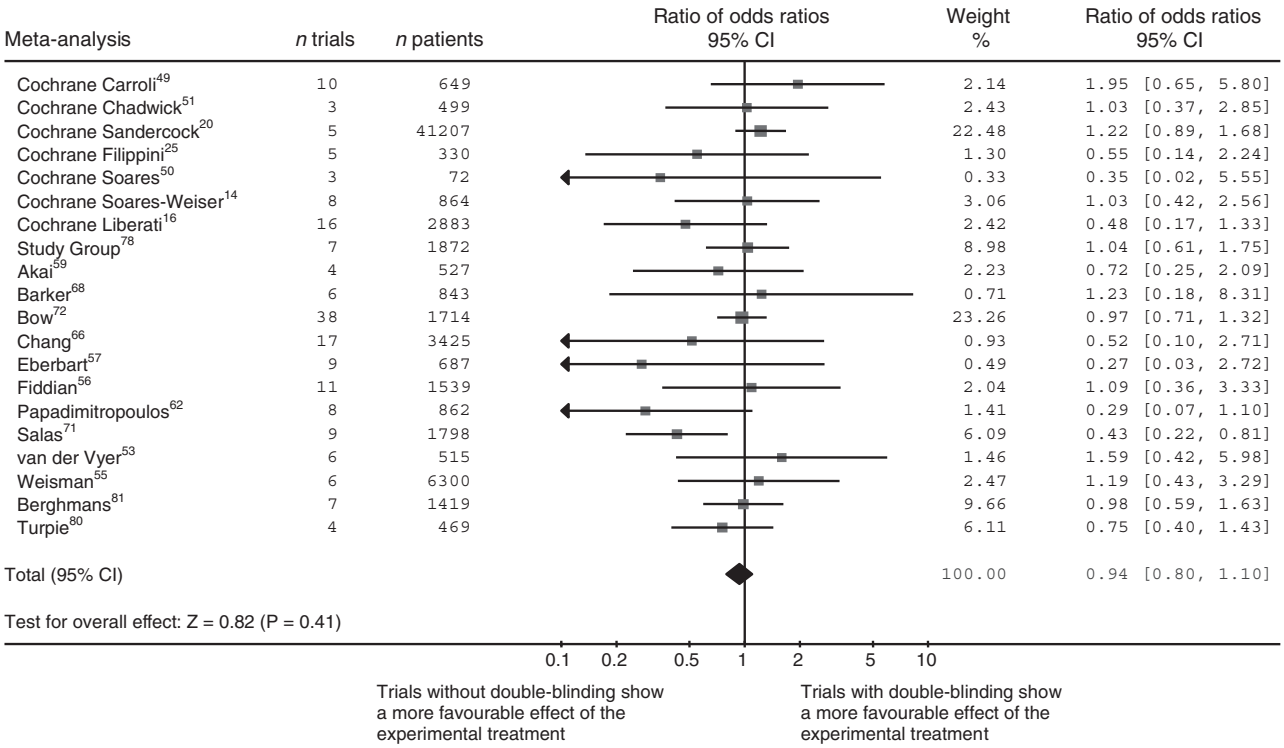

Figure 3 Comparisons of results from trials without vs with double-blinding presented as ratios of odds ratios (RORs) from trials within each meta-analysis. RORs below 1 indicate that trials without double-blinding show a more beneficial treatment effect. An overall ROR estimate was calculated in a random effects generic inverse variance meta-analysis

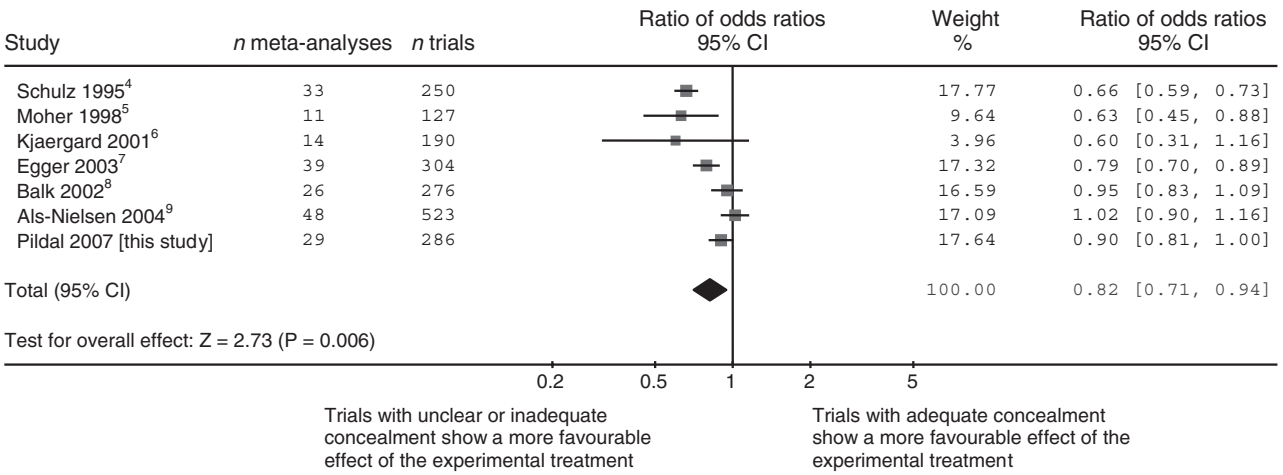

Figure 4 Meta-analysis of how the present study adds to the other published studies of the impact of allocation concealment on treatment effect estimates. RORs below 1 indicate that trials without adequate concealment show a more beneficial treatment effect. RORs were combined in a random effects generic inverse variance meta-analysis

trials with adequate allocation concealment were included. This was mainly because of loss of statistical power but also because estimates of treatment effects tended to be less beneficial.

Strengths and limitations of this study

We aimed to achieve consistent and valid assessments of allocation concealment and double-blinding by retrieving all the original trial publications and reassessing the adequacy of these components in duplicate and blinded to the results sections. We required a convincing mechanism for allocation concealment to be described in order for a trial report to be classified as having adequate concealment, whereas for double-blinding, a statement that the trial was double-blind was sufficient for it to be classified as such. It could also have been interesting to assess whether a convincing mechanism for double blinding

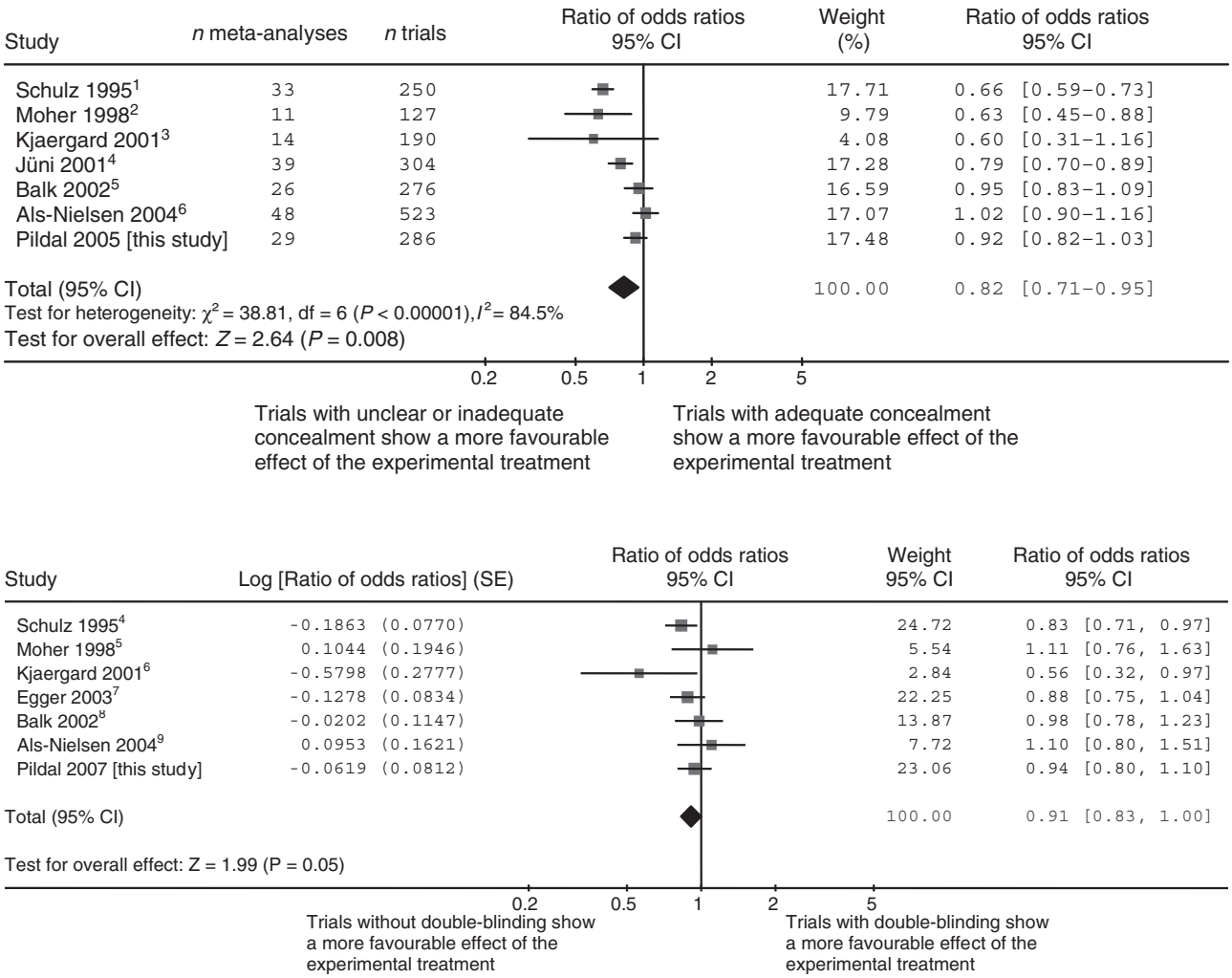

Figure 5 Meta-analysis of how the present study adds to the other published studies of the impact of double-blinding on treatment effect estimates. RORs below 1 indicate that trials without double blinding show a more beneficial treatment effect. RORs were combined in a random effects generic inverse variance meta-analysis. Only one study[7] besides our own made the number of meta-analyses and trials that contributed to the estimates available

had been employed in the trials described as double-blind; however, trial authors frequently do not provide information on who was blinded by which means.[85,3]

Most randomized controlled trials have low statistical power and a level of reported bias protection comparable with those included in the random sample of meta-analyses in our study.[87–89] Accordingly, our primary finding can probably be generalized to the evidence that supports current health care interventions.

We used $P < 0.05$ as the cut-off point for deciding whether a preference in a conclusion was supported by the data; more conclusions would have lost support if we had been able to adjust for the trials authors' multiple testing. However, the level of reporting (i.e. unspecified primary outcomes and uncertain number of tested outcomes) in the reviews did not allow such adjustments.

The estimated impact of adequacy of allocation concealment and double-blinding on the intervention effect was protected against confounding by disease area and type of intervention because it was based on meta-analyses. However, it may have been confounded by other trial characteristics potentially associated with the level of bias susceptibility as shown in Tables 1 and 2. Furthermore, a statistical interaction between allocation concealment and double-blinding may exist. However, the meta-analyses were too few and too small to permit exploration of these possibilities.

Relation of our findings to those of other studies

The range of proportions of health care interventions that are supported by randomized controlled trials is wide. It depends on specialty and varies between 11% and 65%.[90] That most conclusions lost support in our study is consistent with the high prevalence of trial reports with unclear or inadequate allocation concealment.[91] Furthermore, authors of systematic reviews frequently do not take the assessed level of bias protection into account in the analysis and interpretation of their results.[92] Fewer trials in our sample had adequate allocation

concealment (25% of trials in Cochrane Reviews and 10% of trials in other reviews) than in other similar studies (36–40%).[4–8] This may partly be due to differences in the applied criteria, e.g. Kjaergard *et al*.[6] did not require that envelopes had to be serially numbered or opaque, whereas Schulz *et al*.[4] and Moher *et al*.[5] did. Egger *et al*.[7] relied on the quality assessment by the authors of Cochrane reviews who tended to apply the criteria more laxly than Schulz *et al*.[4], Moher *et al*.[5] and us. Another difference is that Schulz *et al*.[4], Egger *et al*.[7] and Als-Nielsen *et al*.[9] selected meta-analyses with at least one trial with adequate allocation concealment, and Kjaergard *et al*.[6] selected meta-analyses with at least one trial comprising more than 1000 patients. Thus, trials with adequate allocation concealment might be overrepresented in these studies.

We found that 69% of meta-analyses lost statistical significance when trials with unclear or inadequate allocation concealment were excluded, and 47% when only the meta-analyses with a mixture of trials were considered. An estimate corresponding to the latter was reported in another study to be 38%, which might to a larger extent have been due to a shift in the point estimate rather than loss of power, since this study showed a larger impact of allocation concealment on the treatment effect estimate, and had a larger fraction of trials with adequate concealment.[7]

Our estimate of the impact of unclear or inadequate allocation concealment was less than those reported in the first four similar studies (Figure 4).[1] A fifth study by Balk *et al*.[8] found an ROR of 0.95 (0.83–1.09), but it has been questioned because one of the inclusion criteria was statistically significant heterogeneity between the included trials in each meta-analysis,[93] which could introduce too much noise to allow detection of the full effect of lack of reported adequate concealment. However, this does not apply to our study or to a sixth study, that found an ROR of 1.02 (0.90–1.16).[9] Several explanations for these varying findings are possible. First, confounders may have differentially influenced the results of the studies, e.g. the individual bias protection components might have been correlated with each other to a different extent in the different studies. Whether (and how) this was taken into account varied. Secondly, the apparent impact of absence of a bias protection component might differ according to subgroups, which might be differentially represented in the different studies. For example, the impact of unclear allocation concealment might be less in a cohort where drug trials with double-blinding comprise a large subgroup, because an adequate method for allocation concealment (numbered coded vehicles) is frequently employed in these trials, but often not explicitly described in the trial report.[94] Thirdly, the studies used slightly different criteria for adequate allocation concealment and different strategies for statistical analysis.

Implications for research, clinicians and policy makers

Most conclusions favouring an intervention would lose support if trials with unclear or inadequate allocation concealment were excluded from the meta-analysis. This may seem too radical, especially since the bias associated with these trials appears to be smaller and less consistent than previously thought. Furthermore, the remaining trials might still be affected by other sources of bias, for instance selective reporting of significant outcomes.[89] Yet, results of meta-analyses should always be accompanied by sensitivity analyses presenting the results with and without trials with unclear or inadequate bias protection. While sensitivity analyses will allow the reader to gauge the possible impact of bias, decisions still have to be made whether or not the investigated interventions should be implemented. To guide such decisions, further research on the size and direction of different types of bias under different circumstances is warranted.

In addition, steps to prevent bias and avoid uncertainty regarding the level of bias protection should be taken. First, the gatekeepers of trial protocols (primarily drug-regulatory authorities and research ethics committees) should insist on description of methods to ensure allocation concealment and sanction only protocols with adequate methods. Secondly, trial protocols should be publicly available to facilitate critical appraisal of trials and thirdly, the CONSORT statement,[91] which requires explicit and appropriate reporting on measures taken to protect a trial against bias, should be broadly enforced.

KEY MESSAGES

Already known on this topic:

- On average, randomized controlled trials without reported adequate allocation concealment exaggerate the experimental treatment effect.
- So far there has been no estimate of how many conclusions drawn from meta-analyses that would loose support if only trials with reported adequate allocation concealment were relied upon.

What this study adds:

- Two thirds of conclusions drawn from meta-analyses loose support if only trials with reported adequate allocation concealment are relied upon.
- The impact of reported allocation concealment and double-blinding on the treatment effect estimate is smaller and less consistent than previously thought.
- It would be too radical to routinely only rely on trials with reported adequate allocation concealment.

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