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No evidence for intervention-dependent influence of methodological features on treatment effect

Wilco C.H. Jacobs[a,*], Moyo C. Kruyt[b], Wouter A. Moojen[a], Ab J. Verbout[b], F. Cumhur Oner[b]

[a]*Department of Neurosurgery, Leiden University Medical Centre (LUMC), PO Box 9600, 2300 RC Leiden, The Netherlands*
[b]*Department of Orthopaedic Surgery, University Medical Center Utrecht (UMCU), PO Box 85500, 3508 GA Utrecht, The Netherlands*

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Abstract

Objectives: The goal of this systematic review was to evaluate if the influence of methodological features on treatment effect differs between types of intervention.

Study Design and Setting: MEDLINE, Embase, Web of Science, Cochrane methodology register, and reference lists were searched for meta-epidemiologic studies on the influence of methodological features on treatment effect. Studies analyzing influence of methodological features related to internal validity were included. We made a distinction among surgical, pharmaceutical, and therapeutical as separate types of intervention. Heterogeneity was calculated to identify differences among these types.

Results: Fourteen meta-epidemiologic studies were found with 51 estimates of influence of methodological features on treatment effect. Heterogeneity was observed among the intervention types for randomization. Surgical intervention studies showed a larger treatment effect when randomized; this was in contrast to pharmaceutical studies that found the opposite. For allocation concealment and double blinding, the influence of methodological features on the treatment effect was comparable across different types of intervention. For the remaining methodological features, there were insufficient observations.

Conclusion: The influence of allocation concealment and double blinding on the treatment effect is consistent across studies of different interventional types. The influence of randomization although, may be different between surgical and nonsurgical studies. © 2013 Elsevier Inc. All rights reserved.

Keywords: Risk of bias; Research design; Randomization; Allocation concealment; Effect modifier; Epidemiologic

1. Introduction

To reduce the risk of bias in clinical studies, several well-recognized methodological actions can be taken such as randomization and blinding. Whether these methods are effective in preventing bias can be studied with meta-epidemiologic studies [1]. It is generally assumed that differences in treatment effects (i.e., effect-size difference or risk difference) between comparable studies with different methodological features indicate an influence of these methodological features. Such meta-epidemiologic studies show, for example, a distinct dampening influence of randomization in a broad range of medical disciplines [2]. Also, allocation concealment and blinding were related to a decreased treatment effect in trials with subjective outcome parameters [3]. Furthermore, sponsoring by industry [4] has shown to influence the effect size, especially conclusions drawn from study results, and study size appeared to be negatively correlated with treatment effect size in osteoarthritis trials [1]. Methodological features are often studied within different medical disciplines, and the results do show variation. For example, allocation concealment showed a smaller treatment effect in pregnancy and childbirth studies [5] but a (nonsignificant) larger effect in cardiovascular disease studies [6].

However, it seems more logical to study the influence of methodological features within types of intervention, rather than medical disciplines, because the type of intervention has more implications on the study methods than in which medical discipline the study is performed. For example, blinding has different consequences for the logistics of pharmaceutical studies (placebo pills) compared with how it influences the design of surgical studies (sham surgery). Comparing types of interventions, randomization showed consistently smaller treatment effects than nonrandomized studies in pharmaceutical (internal medicine) studies [7], whereas for surgical procedures, randomization appeared to yield similar treatment effects as nonrandomized studies [8].

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* Corresponding author. Tel.: +31-6-14368681; fax: +31-71-5266987.
E-mail address: W.c.h.jacobs@lumc.nl (W.C.H. Jacobs).

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What is new?

Key findings

- Although randomization has been shown to dampen the treatment effect in pharmacological trials, this influence was not observed in surgical studies. Also, the influence of allocation concealment and double blinding appeared to be consistent across studies of various intervention types.

What this adds to what was known?

- It was known that randomized studies yield smaller effect sizes. However, the influence of methodological features on the treatment effect appears to be different for separate types of interventions; as for surgical interventions, randomized studies were similar and may even yield larger treatment effects than observational studies.

What is the implication and what should change now?

- For research on surgical interventions, observational study designs should not be discarded too easily because this design was not shown to be related to potential treatment effect overestimation. Further meta-epidemiologic studies should be performed to examine which study design yields the most valid results.

Knowledge about the variation of influence of methodological features across intervention types can be of value for the choice of optimal research designs for specific types of interventions. The goal of our study was to evaluate with a systematical search and appraisal of the evidence if influence of methodological features in clinical studies differs between types of interventions.

2. Methods

As far as appropriate for a systematic review on meta-epidemiologic studies, general methodology for conducting and reporting a systematic review as defined by The Cochrane Collaboration and the PRISMA statement was followed.

2.1. Search and selection

To identify meta-epidemiologic studies we searched the following databases:

1. Pubmed—MEDLINE (1949 to May 2011)
2. Embase (1974 to May 2011)
3. Web of Science (1945 to May 2011)
4. Cochrane (CDSR, CENTRAL, DARE, Method studies, and HTA; issue 5, 2011)

The search strings are given in Table 1. One reviewer performed the search and downloaded all references found into a reference manager database, excluding duplicates. The studies were selected by two reviewers (W.C.H.J. and Mahrouz Foumani/W.A.M.), with a referee if necessary (M.C.K.), on the following criteria:

1. The study had to be a systematic review of meta-analyses, secondary analysis of one meta-analysis, or a systematic search of primary studies.
2. The methodology had to be systematic in the sense of including a systematic and reproducible search strategy, providing a description of selection criteria, and describing methods for analysis of the methodological feature.
3. The study had to analyze the influence of methodological feature(s) quantitatively as a relative odds ratio (ROR), relative risk ratio (RRR), or regression coefficient (RC) for the treatment effect of medical interventions, including uncertainty measurement [standard deviation (SD), standard error (SE)].
4. The methodological feature were items related to internal validity, including (1) sample size, (2) randomization, (3) allocation concealment, (4) blinding (care provider, patient, or observer, or double), (5) study sponsoring (commercial, not commercial, or none), (6) patient exclusions, or (7) intention-to-treat analysis.
5. The methodological feature was an item related to specific methodology of primary studies, excluding studies evaluating:
   - ‘‘Quality’’ as a composite score
   - Items related to methodology of reviews (e.g., publication bias)
   - Items related to the specific disease or patient entities.

The study had to be published as a complete article (excluding abstracts) in a peer-reviewed journal.

The reference lists, citation tracking results, and ‘‘related studies’’ in Pubmed were screened by one reviewer (W.C.H.J.), and inclusions were checked and confirmed by a second reviewer (W.A.M.).

2.2. Data extraction

Data were extracted from the included studies by one reviewer (W.C.H.J.) with a predeveloped form and checked by a second reviewer (W.A.M.). From each study, we extracted first author, year of publication, indication, intervention, type of intervention, type of studies (meta-epidemiologic, secondary, or primary), amount of included studies, outcome used for effect-size calculation, and

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