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Covariate adjustments in randomized controlled trials increased study power and reduced biasedness of effect size estimation

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Abstract

Objectives: This study aims to show that under several assumptions, in randomized controlled trials (RCTs), unadjusted, crude analysis will underestimate the Cohen's *d* effect size of the treatment, and an unbiased estimate of effect size can be obtained only by adjusting for all predictors of the outcome.

Study Design and Setting: Four simulations were performed to examine the effects of adjustment on the estimated effect size of the treatment and power of the analysis. In addition, we analyzed data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study (older adults aged 65−94), an RCT with three treatment arms and one control arm.

Results: We showed that (1) the number of unadjusted covariates was associated with the effect size of the treatment; (2) the biasedness of effect size estimation was minimized if all covariates were adjusted for; (3) the power of the statistical analysis slightly decreased with the number of adjusted noise variables; and (4) exhaustively searching the covariates and noise variables adjusted for can lead to exaggeration of the true effect size. Analysis of the ACTIVE study data showed that the effect sizes adjusting for covariates of all three treatments were 7.39−24.70% larger than their unadjusted counterparts, whereas the effect size would be elevated by at most 57.92% by exhaustively searching the variables adjusted for.

Conclusion: All covariates of the outcome in RCTs should be adjusted for, and if the effect of a particular variable on the outcome is unknown, adjustment will do more good than harm.

Keywords: Adjustment; Cohen's *d* effect size; Covariates; Data analysis; Epidemiology; Trials

1. Introduction

In scientific and medical research, most studies have been devoted to investigate causal relationships between a treatment and an outcome. According to the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/), systematic reviews of randomized controlled trials (RCTs) and individual RCTs provide the highest level of evidence for causal relationships, and therefore, the RCT design is preferred over other study designs. However, there is a lack of global consensus on how to report the results of RCTs, including ambiguities regarding adjusted analysis [1−5], handling of missing variables [6,7], and conflict of interest with the funding bodies [8,9], all of which affect the reliability of the reported effect sizes. This study focuses specifically on the impact of the choice between reporting crude, unadjusted treatment effects, or effects after adjusting for baseline characteristics or covariates [1−5].

The CONSORT Statement 2010 [10], the gold standard of guidelines for reporting results of RCTs, does not specify about whether unadjusted or adjusted analyses should be used. It states only that all adjusted analyses should be planned and that if adjusted analyses were conducted the reasons should be explained. This practice has been advocated for more than 20 years [11], but not all published articles on RCTs have abided by the CONSORT Statement.

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What is new?

Key findings

- Analysis of RCT studies with continuous outcome variables with unadjusted covariates will lead to bias in effect size estimation. Such a bias can be reduced by adjusting all covariates of the outcome.

What this adds to what was known?

- By exhaustively searching the combination of covariates that maximize the effect size estimation will elevate the effect size estimation.

What is the implication and what should change now?

- All covariates of the outcome in RCTs should be adjusted for, and if the effect of a particular variable on the outcome is unknown, adjustment will do more good than harm.

Several systematic reviews found that more than half of the adjusted analyses were reported without reasons [1,4,5]. Furthermore, adjusted analyses are uncommon in the literature, in which only 20–30% of articles published from 2001 to 2010 did so [1–5], despite the ample evidence from both simulation studies and sensitivity analyses with real data showing that adjusting covariates would increase the power of the statistical analysis. Various simulation studies have shown that adjustment of covariates could reduce the required sample size to achieve a prespecified power [12–16]. Furthermore, the strength of this reduction increased with the association between the covariates and the outcome and was independent of sample size and the balance across treatment and control groups [12,14]. In sensitivity analyses with real data, adjusting for covariates could reduce the required sample size by 10–30% [17–23]. In the above sensitivity analyses with real data that reported both the unadjusted and adjusted effects of treatment, all adjusted effects were stronger than their unadjusted counterparts [18,22,23].

In sum, the above studies support the adjustment for covariates in estimating the treatment effect of RCTs, as this method could increase the power of the statistical analysis. However, adjusted analyses were seldom performed, probably because the evidence was from simulation studies and sensitivity analyses that could not be generalized to unexamined scenarios. The application of adjusted analysis had been advocated and explained for more than 60 years [24], but according to the authors' best knowledge, there is no mathematical proof (although simple and straightforward) of the bias of unadjusted analysis, and the underlying reason for the increase in power by adjusting for covariates remains unknown by most trial analysts. Here, we argue that the increase in power is due to the improved estimation of the unadjusted effect size, in which the effect size of the treatment is underestimated when the analysis is unadjusted. Using a continuous, normally distributed outcome variable as an example, we proved that, under the assumption of uniform effect of covariates, an unadjusted analysis will underestimate the effect size of the treatment. This underestimation is due to the additional uncertainty in the distribution of the covariates and the bias increase with the association between the covariates and the outcome. To the other extend, it is possible for data analysts to selectively report favorable results (i.e., to maximize the effect size of a treatment) by an exhaustive search of all possible adjustment options. With the aim of providing guidelines for covariate adjustment in RCTs, we performed simulation studies and sensitivity analysis with real data to illustrate the effect of adjusting and not adjusting for covariates (defined as variables having causal effect on the outcome) and noise variables (defined as variables not having causal effect on the outcome) and the effect of exhaustive search of all possible adjustment options on effect size estimation.

2. Methods

2.1. Modeling the effect of treatment and covariates

In the following section, we denote the outcome by Y and the k covariates by X_j, $j = \{1,\ldots,k\}$. We assume that the treatment has a consistent effect T on all subjects, that is, we assume homogeneity of treatment effects or no heterogeneity of effects and that the effect of covariate X_j equals B_j. For subject i in the treatment group, the outcome $Y_i|(i\in \text{treatment})$ equals

$$T + \sum_j B_j X_{j,i} + \varepsilon_i, \qquad \text{(eqn.1)}$$

where ε_i is the error term that follows a normal distribution with variance σ^2. For subject i in the control group, the outcome $Y_i|(i\in \text{control})$ equals

$$\sum_j B_j X_{j,i} + \varepsilon_i. \qquad \text{(eqn.2)}$$

Therefore, the observed variance of the outcome in both treatment and control groups, Var (Y), equals $\sum_j \mathrm{Var}(B_j * X_j) + \mathrm{Var}(\varepsilon) = \sum_j B_j^2\ \mathrm{Var}(X_j) + \sigma^2$ which is larger than σ^2, the true variance. The Cohen's d effect size of the treatment effect, defined as T/σ_{pooled}, depends on the definition of σ_{pooled}. We can set σ_{pooled} as the standard deviation of Y or as the standard deviation of the error term. As Cohen's d effect size is a measure to standardize the mean difference between two groups, using the standard deviation of Y as the σ_{pooled} will fail to do so because the effect size varies with the strength of effects of the