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Regression discontinuity was a valid design for dichotomous outcomes in three randomized trials

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Abstract

Objective: Regression discontinuity (RD) is a quasi-experimental design that may provide valid estimates of treatment effects in case of continuous outcomes. We aimed to evaluate validity and precision in the RD design for dichotomous outcomes.

Study Design and Setting: We performed validation studies in three large randomized controlled trials (RCTs) (Corticosteroid Randomization After Significant Head injury [CRASH], the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO], and PROspective Study of Pravastatin in elderly individuals at risk of vascular disease [PROSPER]). To mimic the RD design, we selected patients above and below a cutoff (e.g., age 75 years) randomized to treatment and control, respectively. Adjusted logistic regression models using restricted cubic splines (RCS) and polynomials and local logistic regression models estimated the odds ratio (OR) for treatment, with 95% confidence intervals (CIs) to indicate precision.

Results: In CRASH, treatment increased mortality with OR 1.22 [95% CI 1.06−1.40] in the RCT. The RD estimates were 1.42 (0.94−2.16) and 1.13 (0.90−1.40) with RCS adjustment and local regression, respectively. In GUSTO, treatment reduced mortality (OR 0.83 [0.72−0.95]), with more extreme estimates in the RD analysis (OR 0.57 [0.35; 0.92] and 0.67 [0.51; 0.86]). In PROSPER, similar RCT and RD estimates were found, again with less precision in RD designs.

Conclusion: We conclude that the RD design provides similar but substantially less precise treatment effect estimates compared with an RCT, with local regression being the preferred method of analysis.

Keywords: Regression discontinuity design; Quasi-experimental trials; Trial design; Causal inference; Logistic regression; Restricted cubic splines; Polynomials; Local logistic regression

1. Introduction

Randomized clinical trials (RCTs) provide the most reliable evidence of effectiveness of medical interventions [1]. Nevertheless, recruitment of sufficient numbers of patients is a challenge in RCTs; it is estimated that less than 50% of the RCTs meet their recruitment targets [2,3]. Patients' treatment preferences and clinicians equipoise are often cited as barriers to recruitment in RCTs [2,4−7]. Patients participating in trials may poorly represent the population of interest [8,9]. Especially, under-representation of older participants and women is well known in RCTs [8,10].

The quasi-experimental "regression discontinuity" (RD) design is an alternative epidemiological design to assess effectiveness of treatment. It has been suggested that RD is the observational design that most resembles an RCT [11,12]. In the RD design, treatment is not assigned randomly but is allocated to a subset of patients, based on a baseline assignment variable, often related to the outcome. The control group consists of a complementary subset of patients not receiving treatment. For example, all patients with an age more than 75 years receive treatment, and patients with an age less than 75 years do not receive treatment and are considered as the control group. Such treatment assignment method may closely resemble clinical practice and may thus facilitate patient inclusion. In the analysis of the treatment effect, a regression model

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What is new?

- Regression discontinuity (RD) design provides similar but substantially less precise treatment effect estimates compared with a randomized clinical trial (RCT) in dichotomous outcomes.
- Local regression is the preferred method of analysis when using an RD design with dichotomous outcomes.
- Global treatment effect estimates from RD designs should only be presented secondary to local average treatment effect estimates and never as the primary parameter of interest.
- A strength of this study is the use of data from three large RCTs to be able to compare the RD results with the RCT estimates and therefore we were able to carefully assess interaction between the assignment variable and treatment.
- Our results suggest when there is no interaction between the assignment variable and treatment—and thus a global treatment effect can be estimated—the results from the restricted cubic splines-adjusted analyses and local logistic regression are more similar to each other than when there is interaction.

is used to compare treatment with the control group, while adjusting for the treatment assignment variable, in this example age.

The RD design is attractive because some of the challenges of the randomization process are avoided. However, the estimates from this quasi-experimental design may be substantially less efficient compared with an RCT [13]. The validity of RD estimates on continuous outcomes is well studied [13–15], but the validity of the RD design with binary outcomes is less known. Only a few examples have been described before [16,17] although many health outcomes are dichotomous. Moreover, the efficiency of modeling approaches is unclear, that is, the precision of estimated treatment effects. The aim of this study was to assess validity and precision of the RD design in studies with dichotomous outcome compared with an RCT. We hereto analyzed data from three large RCTs.

2. Methods

2.1. Patients

Three trials were used to validate the RD design in empirical data. To assess the internal validity of the RD design, we compared RD estimates with the estimates resulting from the RCT data. For the RD design, we used a continuous baseline variable as assignment variable and the dichotomous endpoints of the RCTs.

The "Corticosteroid Randomization After Significant Head injury" (CRASH) trial studied the effect of corticosteroids on death and disability after head injury [18]. CRASH enrolled 10,008 patients between 1999 and 2005. The primary outcome in CRASH was 14-day mortality. We included 9,554 patients with complete outcome data of whom 2,323 died before 14 days (24%). The median age was 33 years (inter quartile range: 23–47 years).

Second, we analyzed 30,510 patients from "the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" trial (GUSTO). Patients were entered between 1990 and 1993. A total of 10,348 patients were assigned to treatment (accelerated tissue plasminogen activator, t-PA), and 20,162 patients were used as control patients receiving streptokinase [19]. The primary outcome was 30-day mortality. The median age was 61 (inter quartile range: 52–69), and mortality occurred in 2,128 (7%). For both CRASH and GUSTO, age was used as the treatment allocation variable.

Third, we analyzed data from "PROspective Study of Pravastatin in elderly individuals at risk of vascular disease" (PROSPER) [20]. This study enrolled 5,804 patients between December 1997 and May 1999, who were assigned to pravastatin (n = 2,891) or placebo (n = 2,913) to reduce the risk of coronary disease in elderly individuals. The outcome was a composite endpoint of coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke at 3.2 years on average after randomization. A total of 881 (15%) of the patients experienced the composite endpoint. The median total cholesterol level was 5.6 mmol/L (inter quartile range: 5.0–6.3 mmol/L) at baseline (Table 1). For PROSPER, we considered baseline total cholesterol as the treatment allocation variable.

2.2. Statistical analysis

To analyze the data as an RD design, we selected those patients with a baseline value above the median of the assignment variable, who were assigned to treatment in the original RCT as the intervention group, and those with a baseline value below the median and not assigned to treatment in the RCT as control group. Histograms of the baseline assignment variables for each study were plotted, as well as binned scatter plots for outcome means for treated and controls at each baseline assignment value. The analysis was based on the intention-to-treat principle. This led to inclusion of approximately half of the RCT patients. The treatment effect was expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs), with adjustment for the baseline variable in a logistic regression model. To compare the RD estimates to the RCT estimates in comparable sample sizes, random samples of 50% from the complete RCT data were drawn (5,000 times). To compare the