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Different ways to estimate treatment effects in randomised controlled trials

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ABSTRACT

Background: Regarding the analysis of RCT data there is a debate going on whether an adjustment for the baseline value of the outcome variable should be made. When an adjustment is made, there is a lot of misunderstanding regarding the way this should be done. Therefore, the aims of this educational paper are: 1) to explain different methods used to estimate treatment effects in RCTs, 2) to illustrate the different methods with a real life example and 3) to give an advise on how to analyse RCT data.

Methods: Longitudinal analysis of covariance, repeated measures analysis in which also the baseline value is used as outcome and the analysis of changes were theoretically explained and applied to an example dataset investigating a systolic blood pressure lowering treatment.

Results: It was shown that differences at baseline should be taken into account and that regular repeated measures analysis and regular analysis of changes did not adjust for the baseline differences between the groups and therefore lead to biased estimates of the treatment effect. In the real life example, due to the differences at baseline between the treatment and control group, the different methods lead to different estimates of the treatment effect.

Conclusion: Regarding the analysis of RCT data, it is advised to use longitudinal analysis of covariance or a repeated measures analysis without the treatment variable, but with the interaction between treatment and time in the model.

1. Introduction

Within epidemiology a randomised controlled trial (RCT) is considered to be the best way to investigate the effect of a new treatment. Regarding the analysis of RCT data there is a debate in the epidemiological and biostatistical literature, whether an adjustment for the baseline value of the outcome variable should be made [1–6]. Researchers against this adjustment argue that all differences at baseline between the two groups are due to chance and an adjustment for chance is not correct. Researchers in favour of the adjustment argue that an adjustment is necessary to take into account regression to the mean [7–10]. When differences at baseline between the treatment and control group are due to random fluctuations and measurement error, there is a tendency of the average value to go down in the group with the initial highest average value and to go up in the group with the initial lowest average value. This tendency is known as regression to the mean. Suppose that we are performing an intervention study aiming to improve physical activity among children, and that the intervention has no effect at all. Suppose further that at baseline the intervention group has a lower average physical activity level compared to the control group. When no adjustment is made for the baseline differences in the outcome variable, in this particular situation, an artificial intervention effect will be estimated. Due to regression to the mean, the average value of the intervention group tend to increase, while the average value of the control group tend to decrease, leading to this artificial intervention effect. When the control group has the higher average value at baseline, the exact opposite occurs: if there is an actual treatment effect in this situation, it will be underestimated due to regression to the mean. In an RCT, regression to the mean can play a major (confounding) role, because the two groups are randomised from one source population. The consequence of this is that they are expected to have the same average baseline value, i.e. the differences between the two groups at baseline are completely due to random fluctuations and measurement error.

Although it seems that the debate is ended in favour of an adjustment for baseline value of the outcome variable, in the literature there are still many RCT's that do not adjust for the baseline values of the outcome variable [11]. Moreover, in the CONSORT statement, which provides guidelines for reporting results of RCTs, there is no statement about the preferred way of analysing RCT data and whether or not an

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Table 1
Data structure needed to perform a longitudinal analysis of covariance.

id	Outcome	time	Treatment (*X*)	Baseline
1	Y_{t1}	0	1	Y_{t0}
1	Y_{t2}	1	1	Y_{t0}

adjustment for the baseline value should be made.

When an adjustment is made for the baseline value of the outcome variable, there is a lot of misunderstanding regarding the best way of performing this adjustment. Therefore, the aims of the present educational paper are: 1) to explain different methods used to estimate treatment effects in RCTs, 2) to illustrate the different methods with a real life example and 3) to give an advise on how to analyse RCT data.

2. Methods

2.1. Different methods

The following three statistical methods are mostly used to estimate treatment effects in RCTs: longitudinal analysis of covariance (method 1), repeated measures analysis (method 2) and the analysis of changes (method 3). In the explanation of the different methods, two follow-up measurements are considered. However, the methods can be easily extended with more follow-up measurements.

2.1.1. Method 1: Longitudinal analysis of covariance

Table 1 shows the structure of the data used to estimate the parameters for a longitudinal analysis of covariance.

In this method the outcome variable measured at the different follow-up measurements is adjusted for the baseline value of the outcome (equation (1a)).

$$Y_t = \beta_0 + \beta_1 X + \beta_2 Y_{t0} \quad (1a)$$

where, Y_t = the outcome measured at the two follow-up measurements, X = treatment variable, β_1 = overall treatment effect and Y_{t0} = outcome variable measured at baseline.

To assess the effect of the treatment at the different follow-up measurements, time and the interaction between the treatment variable and time are added to the model (equation (1b)).

$$Y_t = \beta_0 + \beta_1 X + \beta_2 Y_{t0} + \beta_3 time + \beta_4 X \times time \quad (1b)$$

In this model, the regression coefficient for the treatment variable reflects the treatment effect at the first follow-up measurement. The treatment effect at the second follow-up measurement is calculated as the sum of the regression coefficient for the treatment variable and the regression coefficient for the interaction between the treatment variable and time ($\beta_1 + \beta_4$).

2.1.2. Method 2: Repeated measures

Table 2 shows the structure of the data used to estimate the parameters of a repeated measures analysis.

In the repeated measures analysis, the values of all three measurements of the outcome variable (i.e. the baseline value as well as the two follow-up measurements) are used as outcome in the analysis. The model includes time, which is either continuous when a linear development over time is assumed or represented by dummy variables when a non-linear development over time is assumed (because all three measurements are used as outcome, two dummy variables are needed to represent time) and the interaction between treatment and time (equations (2a) and (2b)).

Table 2
Data structure needed to perform the analyses described in method 2.

Id	outcome	time	treatment	baseline
1	Y_{t0}	0	1	Na
1	Y_{t1}	1	1	Na
1	Y_{t2}	2	1	Na

Na = not applicable.

$$Y_t = \beta_0 + \beta_1 X + \beta_2 time + \beta_3 time \times X \quad (2a)$$

$$Y_t = \beta_0 + \beta_1 X + \beta_2 dummytime_1 + \beta_3 dummytime_2 + \beta_4 dummytime_1 \times X + \beta_5 dummytime_2 \times X \quad (2b)$$

In model 2a, the regression coefficient for the treatment variable reflects the differences between the groups at baseline. To obtain the overall treatment effect over time, time must be coded 1 for both follow-up measurements. The sum of the regression coefficient for the treatment variable and the regression coefficient for the interaction between the treatment variable and time then reflects the overall treatment effect. In the model with the two dummy variables (equation (2b)), the treatment effect at the first follow-up measurement is calculated as the sum of the regression coefficient for the treatment variable and the regression coefficient for the interaction between the treatment variable and the first dummy variable for time ($\beta_1 + \beta_4$), while the treatment effect at the second follow-up measurement is calculated as the sum of the regression coefficient for the treatment variable and the regression coefficient for the interaction between the treatment variable and the second dummy variable for time ($\beta_1 + \beta_5$).

An assumed advantage of repeated measures analysis is that subjects with only a baseline value, but with missing data at all the follow-up measurements are still part of the analysis. When applying longitudinal analysis of covariance (method 1), individuals with only a baseline measurement are not part of the analysis. Although some researchers claim that the repeated measures analysis takes into account the differences between the groups at baseline, there is actually no adjustment for the baseline differences. Therefore, an alternative to model 2 is developed in which the treatment variable is not part of the model, but its interaction with time still is (equations (2c) and (2d)).

$$Y_t = \beta_0 + \beta_1 time + \beta_2 time \times X \quad (2c)$$

$$Y_t = \beta_0 + \beta_1 dummytime_1 + \beta_2 dummytime_2 + \beta_3 dummytime_1 \times X + \beta_4 dummytime_2 \times X \quad (2d)$$

Because the treatment variable is not in the model, the baseline values for both groups are assumed to be equal and are reflected in the intercept of the model (i.e. β_0). The treatment effects can be directly obtained from the regression coefficients for the interactions between the treatment variable and time (the overall treatment effect over time; β_2 in equation (2c)) or between the treatment variable and the two dummy variables for time (treatment effect at the two time-points; β_3 and β_4 in equation (2d)).

2.1.3. Method 3: Analysis of changes

In the third method, not the actual values at the different time-points are modelled, but the changes between the baseline measurement and the first follow-up measurement and between the baseline measurement and the second follow-up measurement (equation (3a)).

$$Y_t - Y_{t0} = \beta_0 + \beta_1 X \quad (3a)$$

Although, it is sometimes suggested that the analysis of changes takes into account the difference at baseline, this is not the case and therefore this method can also be performed with an adjustment for the baseline value of the outcome variable (equation (3b)).

$$Y_t - Y_{t0} = \beta_0 + \beta_1 X + \beta_2 Y_{t0} \quad (3b)$$

As in method 1, the model can be extended with time and the interaction between the treatment variable and time to estimate the effect of the intervention at the different follow-up measurements (equations