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Adjustment for baseline value in longitudinal randomised trials

MEDICINE AND NUMBERS

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The baseline value of an outcome variable is normally a strong predictor for the value of the outcome variable at a later time. In a longitudinal randomised, controlled trial, this should be taken into account.

Let us look at an example: In 2012, all inhabitants of Trondheim aged 70 to 77 years were invited to participate in the 'Generation 100' exercise training study (1). Of 1 567 participants, 400 were randomised to high-intensity exercise training, 387 to moderate intensity and 780 to a control group that was recommended to follow the health authorities' advice on physical activity. The participants were examined at baseline and after one, three and five years. The trend in maximum oxygen uptake, VO_2-max, is shown in Figure 1. It turned out that the average level increased in all groups during the first year.

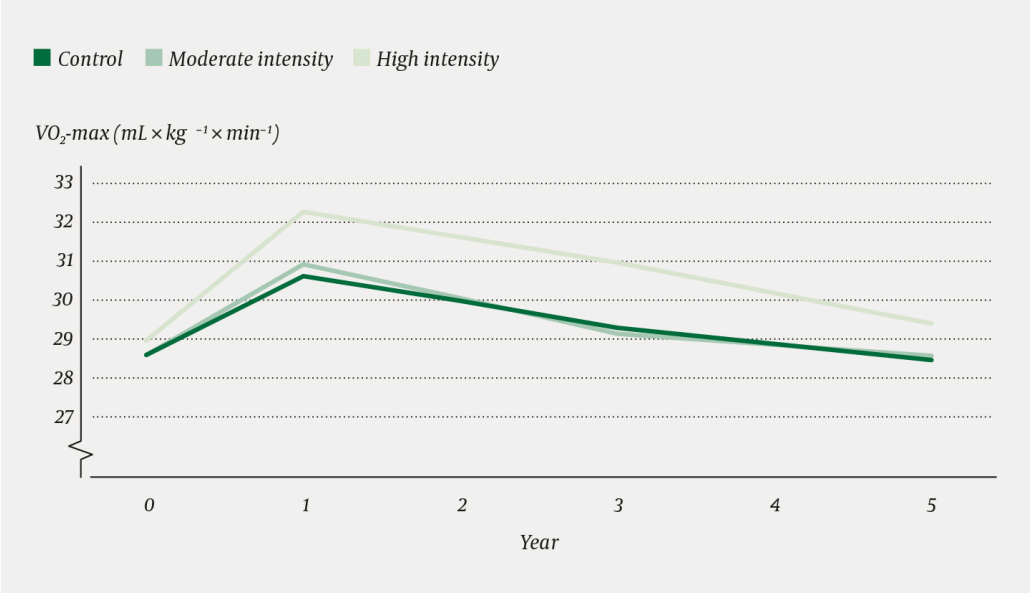

Figure 1 Average value of VO2-max at four time points (0, 1, 3 and 5 years) in three groups from the randomised controlled 'Generation 100' trial. Reprinted from (1) with permission from the BMJ.

Different methods

The relevant research question is whether there are any differences between the groups after one, three or five years. A linear mixed effects model is well suited for analyses of longitudinal data (2). There are many possible ways to approach the analysis, and we will look at the consequences of different approaches: one with no adjustment for baseline value and two with an adjustment.

As fixed effects we include exercise training group with three categories and time with four time points as categories. In addition, we include the interactions between group and time, to account for the fact that the changes over time may vary between the groups.

In a randomised trial, a more precise estimate is obtained if the baseline value is taken into account, provided it can be assumed that this value does not vary systematically between the groups (3). This can be done by omitting the main effect of the exposure at baseline (4, 5). This may sound odd, but it is actually a way to adjust for the baseline value of the outcome variable. Coffman et al. (4) use the term *constrained analysis* for this adjustment method, because a constraint is added to the effect that that there can be no systematic differences in the baseline value. It is important to note that the recommendation to adjust for the baseline value rests on the assumption that the measurement of the value is blinded with regard to what group the participant is to be randomised to. The recommendation is not based on any observed similarities or differences in the baseline value. Moreover, the baseline value of the outcome variable shall not be included as an independent variable, as long as it is included as a dependent variable.

Another way to adjust for baseline value is by longitudinal covariance analysis. This is also a linear mixed effects model, but here the baseline value is adjusted for by including it as an independent variable instead of as part of the outcome

variables. In this case, exercise group with three categories and time with only the three follow-up time points as categories, but not their interactions, are included as fixed effects (5). This is a generalisation of analysis of covariance with one follow-up time point as described in (3).

As seen from Table 1, the unadjusted analysis yields the widest confidence interval. The two other methods adjust for the baseline value and give a narrower confidence interval, and both can be recommended. In our study (1), we adjusted for the baseline value with constraint, as specified in the analysis plan.

Table 1

Effect of high-intensity exercise training on maximum oxygen uptake (VO2-max) compared to the control group after one year, estimated with three different analysis models. Based on data from (1).

Method	Estimate (95 % confidence interval), *p*-value
Unadjusted	1.22 (0.43 to 2.01), $p = 0.002$
Adjusted with constraint	1.00 (0.51 to 1.50), $p < 0.001$
Longitudinal analysis of covariance	1.01 (0.50 to 1.52), $p < 0.001$

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