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Should we adjust for background variables in a randomised controlled trial?

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In a randomised controlled trial there should be no systematic differences in background variables between the groups before treatment. But sometimes it can be sensible to adjust for some pre-defined variables in the statistical analyses.

In some studies there are background variables which are strong predictors for the outcome variable. In an observational study, the distribution of background variables often differs between the groups. Such variables may act as confounders, and cause bias in the estimated effect unless they are adjusted for in the analysis. In a randomised controlled trial, there will be no systematic differences. But it is possible to increase the statistical power, and hence the precision of the effect estimate, by adjusting for such variables (1) page 419. The effect on statistical power is studied in (2, 3), where the authors adjusted for up to four prognostic variables, and for three variables that were unrelated and were 'noise'. Statistical power could increase substantially by including strong prognostic variables, and the power was only slightly reduced when including noise variables.

Increased precision

In a randomised controlled trial we compared two treatment pathways for patients with hip fractures (4, 5). The primary outcome variable was mobility, measured by the screening test Short Physical Performance Battery (SPPB). This is a scale variable ranging from 0 to 12, and a difference of more than 0.5 is regarded as clinically relevant (4). The patient's age, sex and fracture type were pre-defined as possible predictors of mobility, and the authors adjusted for these in the analyses. We found a clinically relevant and statistically significant effect four months after surgery (Figure 1). The adjusted analysis gives practically the same estimate, but a narrower confidence interval and a lower p-value than the unadjusted analysis, which is usually the case. It may be relevant to adjust for such predictors also in logistic regression, but then the estimate will be more difficult to interpret. (1, p. 417).

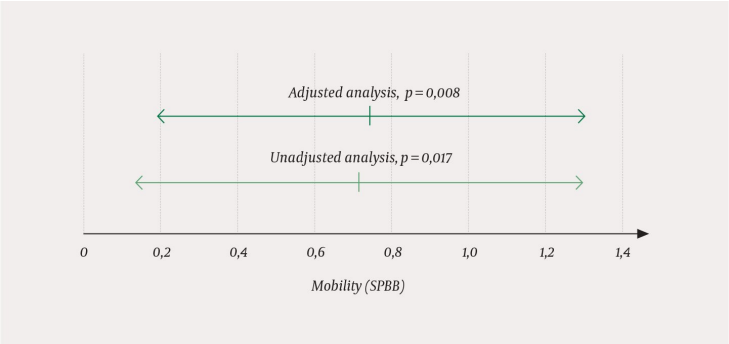

Figure 1 *Comparison of two treatment pathways for patients with hip fractures (4). Effect on mobility measured by the Short Physical Performance Battery (SPPB), four months after surgery, from a linear mixed-effects model. Estimate, 95 % confidence interval, and p-value from the adjusted analysis reported in (4), and from an unadjusted analysis of the same data.*

It is essential to pre-define which variables to adjust for, to avoid post hoc 'shopping' for the background variables that give the lowest p-value. All the three pre-defined background variables were retained in the analysis in (4), even though sex turned out to have no effect (data not shown).

Another example is analysis of covariance in a randomised controlled trial where the outcome variable is measured before treatment and at follow-up (6). The baseline value of the outcome variable is usually a very strong predictor and can increase the precision of the effect estimate.

Stratification and multicentre studies

If randomisation is carried out separately within categories of background variables, for example age or sex, this is called stratified randomisation. It is recommended to adjust for these stratification variables in the analysis (7).

Some studies recruit patients from several centres, such as several clinics. Patients from the same clinic are often more similar to each other than patients from different clinics. This ought to be reflected in the analysis.

Conclusion

It can sometimes be sensible to adjust for background variables in a randomised controlled trial. However, these variables must be pre-specified before performing analyses.

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