Covariate adjustment in randomised trials

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Article

Randomised trials often record baseline information about patients. The *txt4two* trial evaluated the use of a mobile health intervention promoting healthy gestational weight gain in women entering pregnancy with a high body mass index (BMI) [Willcox et al. BJOG. 2017;124;1718-28]. *Txt4two* recorded baseline data such as age, pre-pregnancy BMI, and parity. Baseline data is typically used to describe the types of patients enrolled in a trial, and to assess balance between the treatment groups. It can also be useful to include important baseline covariates (those associated with the outcome) in the trial analysis ('covariate adjustment').

Covariate adjustment can increase statistical power (the chance of finding an intervention effect when one exists). The more influential the covariate, the larger the gain; in some cases, power can be increased by over 20% [Kahan et al. Trials. 2014;15:139]. In *txt4two*, patients with a high pre-pregnancy BMI may gain more weight during gestation. For the outcome of gestational weight gain, adjusting for pre-pregnancy BMI could increase power by reducing the unexplained variation of the outcome.

Adjustment can also help protect against chance imbalances in covariates. Randomisation ensures that treatment groups will be balanced on average for both known and unknown factors. However, in any one trial, small imbalances may occur due to chance. If more patients with a high pre-pregnancy BMI were allocated to the intervention arm in *txt4two*, this imbalance could affect the estimate of treatment effect. However, if we have pre-specified that our analysis will adjust for pre-pregnancy BMI, this would account for any imbalance between groups.

Covariate adjustment can also ensure valid results after balanced randomisation is used [Kahan et al. Statistics in Medicine. 2012;31;328-40]. Balanced randomisation is used to ensure important covariates are balanced between treatment arms. However, the covariates used in the randomisation process must then be adjusted for during analysis, as failure to do so can affect the type I error rate (the chance of false-positives).

Txt4two included both adjusted and unadjusted analyses. The adjusted analysis pre-specified the inclusion of important baseline covariates, including age, pre-pregnancy BMI, and parity. For the outcome of gestational weight gain (in kilograms), the adjusted analysis found a statistically significant effect (difference −2.26, 95% CI −4.49 to −0.04, p=0.041), whereas the unadjusted analysis did not (−1.86, 95% CI −3.75 to 0.03, p=0.053). The disparity in these results was primarily due to some small imbalances in important covariates between the groups. The mean pre-pregnancy BMI was 29.6 in the control arm, but 32.5 in the intervention arm, and 57% of women had parity ≥1 in the control arm, but only 51% in the intervention arm. Covariate adjustment accounted for these imbalances, leading to a more accurate estimate of treatment effect.

Covariate adjustment is a simple way to improve the analysis of randomised trials, as it protects against chance baseline imbalances and increases statistical power. Covariates should be measured before randomisation, and should be pre-specified in the protocol.

Useful resources

This paper provides a general overview of covariate adjustment, including selection of covariates, issues with low event rates, and missing data.

- Kahan *et al*. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. Trials. 2014;15:139.

Learning points

- Covariate adjustment can increase statistical power, protect against chance imbalances between treatment arms, and provide valid results after stratified randomisation.

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Reference list

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