The difference between effect modification and covariate confounding

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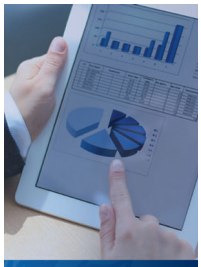

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The difference between effect modification and covariate confounding

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Learning points

- When effect modification is present the effect of a risk factor (such as having gestational diabetes) on an outcome (such as cardiovascular disease) will be different in different subgroups (for example by those who are overweight).
- Effect modification can also be investigated in randomised trials to identify if the effect of a treatment differs between subgroups.

Fadl et al.[1] describe a case–control study evaluating whether gestational diabetes mellitus (GDM) is associated with increased risk of future cardiovascular disease (CVD) and whether this risk differs for different subgroups of women. One subgroup they looked at was weight status (normal or overweight). It was concluded that GDM is indeed a useful marker of CVD risk, and the increase in risk of CVD indicated by GDM is higher in women who are overweight. It was, therefore, concluded that weight status is an effect modifier.

Effect modification differs from confounding. Confounding occurs when a variable to some extent accounts for the observed effect of a risk factor. In our example, this would mean that the association between GDM and CVD could be explained by the fact that women with GDM are more likely to be overweight whereas women without GDM are more likely to be of normal weight. Under this scenario, the observed increase in risk of women with GDM would actually be representing the association between weight status and CVD. This can be modelled by including weight status (overweight or normal weight) as an independent variable in a regression model. Such a model would assume that having GDM increases the CVD risk to the same degree for normal and overweight women.

If, however, having GDM increases the risk of CVD more in overweight women than in normal weight women then weight status is an effect modifier. For example, the value of GDM as a predictor of risk might be stronger in overweight compared with normal weight women. Effect modification can be investigated informally by performing linear regression on separate subgroups. In our example, we would perform two separate linear regressions of the characteristic GDM on CVD, one for 'overweight' women and a second for 'normal weight' women (our two subgroups). In a more formal approach, effect modification can be tested for in multivariable linear regression by including the 'interaction between weight status (overweight or normal weight) and GDM' as an independant variable (an interaction test). Then the *P* value for an interaction test indicates whether the two effect sizes are significantly different, i.e. whether weight status is an effect modifier.

Effect estimates are usually presented within subgroups (or stratified by subgroups), for example the odds ratio for GDM as a risk factor of CVD within normal weight women and separately within overweight women.

Analysis models accounting for effect modifiers allow the researcher to identify population groups with higher risk or, in a clinical trial setting, participants for whom an intervention might be more effective. For example, we might wish to evaluate whether labetalol is less effective for treating gestational hypertension in different ethnic subgroups. Subgroups of interest should be specified a priori, clinically plausible and limited, thereby avoiding spurious results due to chance.

Useful resources

- https://www.youtube.com/watch?v=stCCd7CUTVY
- TJ Vander Weele. Confounding and effect modification: distribution and measure. *Epidemiol Method* 2012;1(1):55–82

Disclosure of interest

Completed disclosure of interests form available to view online as supporting information.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article. ■

Reference

1 Fadl H, Magnuson A, Östlund I, Montgomery S, Hanson U, Schwarcz E. Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case–control study. *BJOG* 2014;121:1530–6.