

ENDGAMES

STATISTICAL QUESTION

Confounding in clinical trialsPhilip Sedgwick *reader in medical statistics and medical education*

Centre for Medical and Healthcare Education, St George's, University of London, Tooting, London, UK

Researchers investigated whether a low glycaemic index diet in pregnancy reduced the incidence of macrosomia—babies large for their gestational age—in an at-risk group. A randomised controlled trial study design was used. The intervention was a low glycaemic index diet from early pregnancy. The control group received no dietary intervention. Participants were women without diabetes, aged 18 or over, all in their second pregnancy between January 2007 and January 2011, and who had previously delivered an infant weighing more than 4 kg. In total, 800 women were recruited, of whom 396 were randomised to intervention and 404 to control.¹

The primary outcome was birth weight. Of the 396 women allocated to intervention, 372 (93.9%) provided data at follow-up, compared with 387 (95.8%) of the 404 women allocated to control. A per protocol analysis was performed. No significant difference existed between treatments in absolute birth weight, birthweight centile, or ponderal index.

Which of the following statements, if any, are true?

- The random allocation of women to treatment minimised confounding at baseline.
- For a variable to confound the association between treatment (intervention or control) and outcome, it must be associated with birth weight.
- For a variable to confound the association between treatment (intervention or control) and birth weight, it must be unequally distributed between treatment groups.
- The association between treatment and birth weight may have been confounded by women being lost to follow-up.

Answers

Statements *a*, *b*, *c*, and *d* are all true.

The purpose of the trial was to investigate whether a low glycaemic index diet from early pregnancy, when compared with no dietary intervention, reduced the incidence of macrosomia in an at-risk group. Women were allocated to treatment group by simple random allocation. The aim of randomisation was to achieve treatment groups similar in baseline characteristics, thereby minimising confounding (*a* is true). Confounding is a difference between treatment groups in

the characteristics that influence the association between the treatment and outcome measures. These include demographic characteristics, prognostic factors, and other characteristics that may influence someone to participate in or withdraw from a trial. Therefore, if confounding was minimised at baseline, then any differences between the treatment groups in outcomes at the end of the trial would be due to differences in treatment and not to differences in baseline characteristics. Obviously this depends on all participants, once randomised to treatment, being followed until the end of the trial.

To illustrate the phenomenon of confounding in the above trial, consider the variable maternal age. To be a potential confounding factor, maternal age must have three properties. Firstly, it must be associated with the outcome measure, birth weight (*b* is true). Maternal age is one of several factors known to influence birth weight, and therefore this criterion is met. Secondly, maternal age must not be an effect of treatment (intervention or control), nor be a factor in the causal pathway between the treatment and outcome—that is, the treatment must not “cause” the factor, maternal age, that results in the outcome birth weight. Obviously, maternal age is not caused by treatment exposure and therefore would not be on the causal pathway between treatment and outcome. Thirdly, for maternal age to confound the relation between treatment and outcome, it must be unequally distributed between the treatment groups (*c* is true). The aim of randomisation was to achieve treatment groups similar in baseline characteristics, including maternal age. Provided that this balance was achieved at baseline and maintained throughout the study follow-up, then maternal age would not have confounded the association between treatment (intervention or control) and the outcome birth weight.

Random allocation will achieve treatment groups that are similar in baseline characteristics only if the sample size is large enough. However, no exact figure can be given as to how large the sample must be to achieve this. It is generally accepted that although randomisation will control confounding, it will only ever minimise it and never eliminate it. This is because it is unlikely that treatment groups will be exactly similar in all patient characteristics, regardless of sample size. Obviously, as sample size increases, the potential for confounding is reduced.

In clinical trials it is not uncommon for participants to drop out or be lost to follow-up. Of the 396 women allocated to intervention, 372 (93.9%) provided data at follow-up, compared with 387 (95.8%) of the 404 women allocated to the control group. Therefore, the similarity in baseline characteristics of the treatment groups achieved by randomisation may not have existed at follow-up. When the study was analysed, there was therefore the potential for confounding (*d* is true). It may be difficult to estimate the extent of any potential confounding. Although it would be possible to statistically test for differences between treatment groups in the characteristics of those women who were followed up, not all characteristics that lead to confounding are easily quantifiable. Confounding is more likely if the reason that women were lost to follow-up was related to treatment.

The researchers undertook a per protocol analysis—that is, they included in the analysis only those women who completed the trial. Sometimes in clinical trials an intention to treat analysis is performed—that is, the treatment groups are analysed as they were intended to be treated, and all participants are included regardless of whether they completed the treatment protocol. This therefore maintains the composition of the treatment groups achieved at baseline and reduces the potential for confounding resulting from an imbalance in baseline characteristics. Intention to treat and per protocol analyses have been described in previous questions.^{2,3}

In the above trial, no significant difference existed between treatments in absolute birth weight, birthweight centile, or ponderal index. It is possible that if confounding existed then any association between treatment and birth weight could have been missed. It is also possible that confounding results in spurious associations. For example, the secondary outcome measure in the above trial was gestational weight gain. The researchers reported that significantly less gestational weight gain occurred in women in the intervention arm. It is possible that this significant result was due to confounding, if it existed.

Confounding may occur in experimental and in observational studies. It is possible sometimes to minimise confounding at the design stage, such as by randomisation, as in the above trial, or by matching in case-control studies, as described in a previous question.⁴ Confounding may also be dealt with at the analysis stage. Confounding at the analysis stage can be dealt with in several ways, some of which have been described before,^{5,6} and further ways will be described in future questions.

- 1 Walsh JM, McGowan CA, Mahony R, Foley ME, McAuliffe FM. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. *BMJ* 2012;345:e5605.
- 2 Sedgwick P. Analysis by intention to treat. *BMJ* 2011;342:d2212.
- 3 Sedgwick P. Analysis by per protocol. *BMJ* 2011;342:d2330.
- 4 Sedgwick P. Why match in case-control studies? *BMJ* 2012;344:e691.
- 5 Sedgwick P. Odds ratios and adjusting for confounding. *BMJ* 2010;341:d6833.
- 6 Sedgwick P. Derivation of hazard ratios. *BMJ* 2011;343:d6994.

Cite this as: *BMJ* 2012;345:e7951

© BMJ Publishing Group Ltd 2012