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ENDGAMES

STATISTICAL QUESTION

Relative risks versus odds ratios

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Researchers investigated the effectiveness of a probiotic drink containing *Lactobacillus* for the prevention of any diarrhoea associated with antibiotic use in hospital. A randomised double blind placebo controlled trial study design was used. The intervention consisted of the probiotic drink twice a day during a course of antibiotics and for one week afterwards. The control group received a placebo drink consisting of a longlife sterile milkshake. The primary outcome was the occurrence of antibiotic associated diarrhoea during follow-up.[1]

Participants were hospital patients aged over 50 years. In total, 135 patients were recruited to the trial and randomised to the intervention (n=69) or placebo (n=66). Twelve patients receiving the intervention and 10 in the placebo group did not complete their treatment protocol or were lost to follow-up. A smaller proportion of the probiotic group developed diarrhoea associated with antibiotic use compared with the placebo group (7 (12%) *v* 19 (34%); relative risk 0.36, 95% confidence interval 017 to 0.79). When adjusted using logistic regression to control for other factors, the effects of the probiotic drink in reducing antibiotic associated diarrhoea remained (odds ratio 0.25, 95% CI 0.07 to 0.85). The researchers concluded that consumption of the probiotic drink reduced the incidence of antibiotic associated diarrhoea.

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

a) It was possible to estimate the population at risk

b) It was not possible to derive an adjusted relative risk

c) The odds ratio is an estimate of the population relative risk

d) The odds ratio is a measure of the strength of the association between the intervention and antibiotic associated diarrhoea compared with placebo

Answers

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

The aim of the trial was to test the effectiveness of a probiotic drink containing *Lactobacillus* for the prevention of antibiotic associated diarrhoea. A randomised controlled trial was performed that compared the probiotic drink with placebo. Participants were recruited from hospital wards.

Patients were randomised to treatment to eliminate allocation bias and minimise confounding at baseline. In particular, if the sample size for a trial is large enough then random allocation will achieve groups of patients similar in baseline characteristics. Otherwise, if treatment groups differed at baseline it may result in confounding. Confounding is a difference between treatment groups in those factors that affect treatment and outcome measures. Such factors include demographics, prognostic factors, and other characteristics that influence someone to participate in or withdraw from a trial. If confounding exists then any differences between treatment groups in outcome may not be the result of differences in treatment received but of differences in characteristics at baseline. Confounding in clinical trials has been described in a previous question.[2]

After randomisation the treatment groups were followed prospectively. Each treatment group therefore estimated the population at risk (*a* is true). Estimating the population at risk has been described in a previous question.[3] In this case, the risk of any antibiotic associated diarrhoea for the intervention and placebo groups estimated the risk in the population if the entire population had received the probiotic drink or placebo. It was therefore possible to calculate the relative risk as a measure of the strength of the association between the probiotic drink and antibiotic associated diarrhoea compared with placebo. Risks and relative risks have been described in a previous question.[4] The relative risk was equal to 0.36 (95% confidence interval 0.17 to 0.79). Therefore, the risk of antibiotic associated diarrhoea was reduced by 64% in the intervention group compared with the placebo group. The reduction in risk was significant because the 95% confidence interval for the population relative risk did not include unity.

Despite the randomisation of participants to treatment, confounding may still have existed because the sample size was small. Confounding between treatment groups is reduced as sample size increases. The researchers identified and recorded a series of factors thought to influence treatment and outcome, which would therefore confound the observed association between treatment and antibiotic associated diarrhoea. These factors included age; sex; indication for antibiotics; number of antibiotics; smoking; alcohol consumption; body mass index;

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serum albumin, thyroxine, and C reactive protein; white cell count; and plasma concentrations of creatinine, potassium, and sodium.

It was not possible to derive an adjusted relative risk (*b* is true)—that is, a relative risk adjusted for the simultaneous effects of those variables thought to confound the observed association between treatment and outcome. However, it was possible to derive an odds ratio as an estimate of the population relative risk (*c* is true). Odds and odds ratios have been described in a previous question.[5] Odds ratios can be adjusted for confounding using a statistical method known as logistic regression.[6] Relative risks and odds ratios can always be calculated for studies in which it is possible to estimate the population at risk. However, only odds ratios can be obtained for studies in which it is typically not possible to estimate the population at risk, such as case-control studies.[7]

Odds and odd ratios are an alternative way of expressing probability. The odds of antibiotic associated diarrhoea for a treatment group is the ratio of the number of participants who experienced diarrhoea to those who did not. The odds ratio is the ratio of the odds of antibiotic associated diarrhoea for the probiotic group to those for the placebo group. It is a measure of the strength of the association between the probiotic drink and antibiotic associated diarrhoea compared with placebo (*d* is true). The effects of the probiotic drink in reducing antibiotic associated diarrhoea when compared with placebo remained significant when adjusted using logistic regression to control for other factors (odds ratio 0.25, 0.07 to 0.85). Because the association between treatment and antibiotic associated diarrhoea was significant after adjusting for confounding, the intervention is said to be independently associated with the outcome.

For the example above, the odds ratio of 0.25 indicates that the odds of antibiotic associated diarrhoea for the probiotic treatment group were one quarter of those for the placebo group. The probiotic drink reduced the occurrence of antibiotic associated diarrhoea compared with placebo. However, it is difficult to quantify the association, not least because odds and odds ratios are not easy to interpret. It has been proposed that the sample odds ratio is a good estimate of the population relative risk and can be interpreted as a relative risk when the disease or outcome is rare in the population, typically when the prevalence is less than 10%. In the example above, the odds ratio is probably not a good estimate of the population relative risk because the risk for the placebo group of antibiotic associated diarrhoea was 0.34 (34%), suggesting that the outcome is not rare in the population.

When the outcome is not rare in the population, if the odds ratio is used to estimate the relative risk it will overstate the effect of the treatment on the outcome measure. The odds ratio will be greater than the relative risk if the relative risk is greater than one and less than the relative risk otherwise. In the example above, if the adjusted odds ratio were interpreted as a relative risk, it would suggest that the risk of antibiotic associated diarrhoea is reduced by 75% for the intervention relative to the placebo group. However, this would overestimate the reduced risk associated with the probiotic drink because the outcome of antibiotic associated diarrhoea is not rare in the population. Straightforward formulas have been suggested to adjust the treatment effect estimated by the adjusted odds ratio.

Competing interests: None declared.

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