Practical 6: Intervention studies

Objectives

At the end of the practical students should be able to:

- Be able to identify the key features of a randomised controlled trial
- Understand the importance of randomisation
- Understand the importance of allocation concealment
- Consider ethical issues in randomised controlled trials

Worldwide, nearly 2 million women are diagnosed with breast cancer each year. Survival is improved if breast cancer is diagnosed at an earlier stage. As a consequence, many countries have put in place mammography screening programmes as mammography allows early detection of breast cancer. Intervention studies have been undertaken to assess the effectiveness of mammography screening.

Section 1: The New York Trial

The New York Trial was one of the first intervention studies to be undertaken on mammography screening and was launched in 1963 (Shapiro, 1988).

All women who were members of the Health Insurance Plan and aged 40-64 were invited to join the study. Women were randomly assigned to receive annual mammography screening for four years or to receive usual care (i.e. no screening). The two groups were the same size. The method of allocation was not described. Women were followed-up for 7 years. The breast cancer mortality rate was compared between the intervention and control arm.

Question 1: What type of study was this?

Question 2: Was the aim of the study to assess the effect of screening on breast cancer incidence or on breast cancer mortality? Would you expect the women in the intervention or the control arm to have a higher incidence of breast cancer?

Question 3: Why do you think the investigators chose to randomise?

Women who had a history of breast cancer were excluded from the study after the randomisation had taken place. However, women in the control arm were not investigated in detail and so the investigators reported that some cancer cases in the control arm were unknown and should have been excluded. Overall, 853 women with a history of breast cancer were excluded from the mammography group and only 336 women from the control arm.

There were no differences between the control and intervention arm in terms of age, religion, marital status or pregnancy, but there was evidence that women in the intervention arm were less likely to report having had a previous breast lump or to be post-menopausal (which increase risk of breast cancer).

Question 4: What are the potential biases that may have arisen due to the exclusion of women with a history of breast cancer?

Question 5:

(i) What are the considerations for us to assess whether the two groups were adequately randomised? *Hint: consider whether it is appropriate to assess this by (a) comparing baseline characteristics and/or (b) reviewing the method used to randomly allocate participants.*

(ii) If the two groups are not adequately randomised, what are the possible implications?

The researchers determining the cause of death among the women were not masked to the screening status of the participants. Fewer "dubious" breast cancer deaths were classified as having definite breast cancer deaths in the intervention group compared to in the control group.

Question 6:

(i) Do you think there was a potential for bias through lack of masking? If so, how?

(ii) Do you think this bias due to lack of masking occurred? If so, what would the impact be on the results?

Only 65% of the women offered screening went to at least one screening session. Some of the women in the control arm may have undergone mammography screening independently.

Question 7: Should the women have been analysed according to the groups to which they were randomised or by actual screening status?

The final results showed that the risk of breast cancer death was 81/31000 in the screening group and 124/31000 in the control group. This gave a risk ratio of 0.65 (95% CI = 0.49-0.86) for the impact of mammography screening on reducing breast cancer mortality.

Question 8: Interpret the risk ratio obtained for the study.

Question 9: Calculate the risk difference for breast cancer mortality between the intervention and control arm. How many women would need to be screened to prevent one breast cancer death (and what is this measure known as)? *Hint: you can refer back to the notes for lecture 2 (Epidemiologic Measures Part II) for a reminder of how these measures are calculated.*

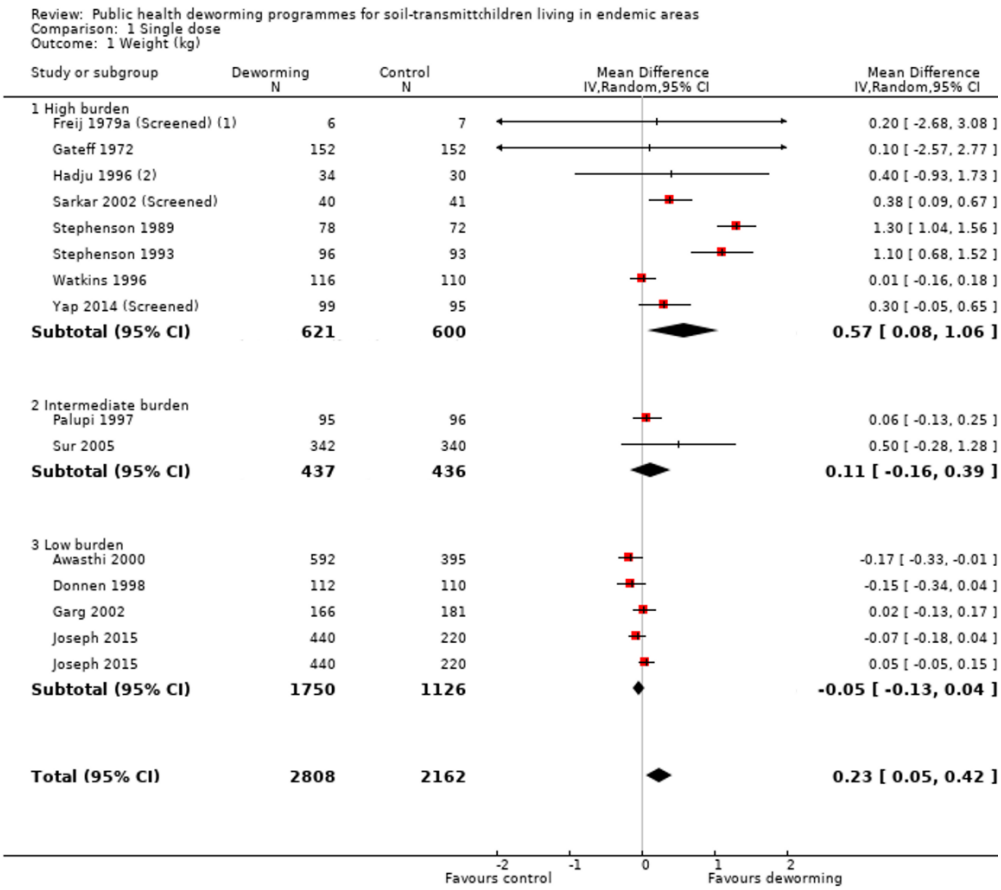
Question 10: Do you think it would be ethical to undertake further intervention studies on mammography after the publication of results from the New York Trial?

Section 2: Meta-analysis

A Cochrane meta-analysis – where the results of multiple RCTs are combined statistically - was undertaken to review the evidence from randomised controlled trials that assessed the effect of deworming all children aged 16 years or less, in areas where soil-transmitted helminths (intestinal worms) are endemic.

The results of this meta-analysis for one of the primary outcomes (mean weight gain in kg, over a follow-up of between 4 weeks and 1 year) are displayed below in a forest-plot. The authors analysed the studies in categories based on the level of 'worm burden' (a combination of prevalence and intensity of infection) of the area the study was conducted in, as well as reporting the overall effect across all studies.

Each row of the forest-plot corresponds to an individual study, with the square and horizontal line representing the point estimate and 95% confidence interval respectively. The rows in bold text with a diamond represent the point estimate and confidence intervals when the studies are combined and averaged.



Question 11: Interpret the difference in results between trials conducted in a high 'worm burden' areas compared to trials conducted in intermediate or low 'worm burden' areas.

Question 12: Based only on the figure, what recommendations would you make about offering deworming as a public health measure?

Section 3 (To do in your own time): The Malmo Study

Another intervention study was undertaken in Malmo, Sweden, to assess the impact of mammography screening on reducing breast cancer mortality (Andersson, 1988).

Women aged 45-69 who lived in Malmo were randomly allocated to receive mammographic screening every 18-24 months for five years or to the control arm of usual care. Women previously treated for breast cancer were not excluded. The women were followed for 7 years and death from breast cancer was the primary outcome.

The age distribution was very similar in the intervention and control arms. The investigators assigning cause of death were masked to the screening status of the participants, but the women were not masked as to their screening status. The researchers reported a risk ratio of 0.96 (95% CI = 0.68-1.35) for the impact of mammography screening on reducing breast cancer mortality.

Question 13: Do you think randomisation worked in this study?

Question 14: Do you think bias may have occurred in this study in the determination of outcome (i.e. breast cancer death) due to lack of double-masking in this study?

Question 15: Interpret the result of the study.

References

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