Practical 5: Confounding and causality

Objectives

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

- Recognize when a variable may be a confounder of an association between an exposure and outcome.
- Describe how confounding can be dealt with at the design stage and the analysis stage of a study.
- Be able to recognise when confounding has occurred.
- Realise the importance of considering potential confounders from the outset of a study so that they may be measured and controlled for in analysis.
- Describe the basic criteria for determining causality.

Question 1: Diabetes and CHD

Data from two studies - the Framingham Heart Study and the Framingham Offspring Study - were used to explore the relationship between diabetes (risk factor/exposure) and coronary heart disease (CHD) mortality (outcome) (Natarajan S et al. 2003).

5243 men and women were recruited into the study between 1971 and 1975 and were followed up over a period of 20 years. Baseline data, including whether or not they had diabetes, were collected from participants. Over the course of the follow-up period, deaths from CHD (defined as deaths from myocardial infarction, coronary insufficiency, or angina pectoris) were extracted from the government's vital registry.

The incidence rate ratio for the association between diabetes and CHD death was 2.1 (95% CI 1.3-3.3) among men and 3.8 (95% CI 2.2-6.6) among women.

Question 1a: Describe the association between diabetes and CHD death in this study.

Question 1b: The researchers found that people with diabetes were more likely than people without diabetes to be smokers, and were generally older and had higher body mass index (BMI) and higher blood pressure. Could these factors confound the association between diabetes and CHD mortality? What additional information would help you to answer this question?

Question 1c: How can researchers deal with potential confounders of the relationship between diabetes and CHD mortality in the analysis?

Question 1d: Another study investigating the same association between diabetes and CHD did not collect data on any of these potential confounders. Are there any options available to those researchers to deal with confounding in the analysis stage?

Question 1e: Rate ratios of the association between diabetes and CHD mortality among women in the Framingham study are presented below.

Regression model	Rate ratio (95% CI)
Unadjusted	8.6 (2.1-12.4)
Adjusted for age	5.2 (3.0-9.0)
Adjusted for age, smoking, serum cholesterol, hypertension, and BMI	3.8 (2.2-6.6)

(i) Was there evidence of confounding by age? Explain your answer.

(ii) Explain how age might be a potential confounder.

(iii) Was there evidence of confounding by other variables? Explain your answer.

(iv) Can the association between diabetes and CHD mortality be explained entirely by confounding variables?

Question 2: Cholera and water

Epidemiologists investigated risk factors for cholera in a rural area. They administered a questionnaire to all healthy adult residents about their water usage and asked residents who subsequently developed symptoms of cholera to present to an emergency clinic to confirm infection and receive treatment.

During the investigation scientists confirmed that one of the drinking wells in the village was contaminated with *Vibrio cholerae* bacteria; at least some of the cases arose from drinking water from this well. The epidemiologists wanted to know whether using river water for doing washing was an additional risk factor. Using questionnaire and clinic data, they generated the following table:

	Uses river water for washing: YES	Uses river water for washing: NO
Cholera diagnoses	210	70
Person-years	30,000	15,000

1. What are the comparison groups? What is the outcome of interest? What is the null hypothesis?

2. Calculate and interpret a relative measure of effect for the relationship between using river water for washing and the rate of cholera infection.

3. The epidemiologists wondered whether using the contaminated drinking well or not would confound the relationship between river water use and cholera infection. Draw a diagram to explain how confounding could affect the answer you provided to #2.

The epidemiologists stratified their analysis, as seen in following table.

	Contaminated drinking well		Other drinking wells	
	Uses river water for washing: YES	Uses river water for washing: NO	Uses river water for washing: YES	Uses river water for washing: NO
Cholera diagnoses	150	50	60	20
Person-years	20,000	10,000	10,000	5,000

4. Calculate the two stratum-specific relative measures of effect and the weighted average of these two. Interpret these measures of effect.

5. What do you conclude about risk of cholera associated with using river water? If necessary, revise your answer to #3.

Question 3: Causation

[EACH GROUP TO CHOOSE 1 SITUATION TO DISCUSS; CAN DO MORE IF TIME PERMITS]

Consider the four situations below, which are all real examples from published studies. Do you agree with the conclusions? Suggest reasons for the associations identified.

a) Vitamin A supplementation and maternal mortality. A randomised controlled trial was conducted in Nepal (West et al, 1999). 7,241 women were given a placebo and 14,948 were given either vitamin A or beta-carotene supplementation. There was strong evidence of a reduction in maternal mortality in the 12 weeks after delivery in the supplemented groups compared to the placebo groups (relative risk 0.56, 95% CI 0.37-0.84). However, when looking at cause of death there was a smaller reduction for obstetric causes (RR 0.73, 0.38-1.41) or infections (0.78, 0.39-1.58). Most of the reduction in risk was driven by a fall in deaths related to injury (including burns, drowning, snakebite and hanging, RR 0.10, 0.01-1.14) and due to miscellaneous causes (including anaemia, asthma and leukaemia, RR 0.26, 0.09-0.73).

   Conclusion: Vitamin A and beta-carotene supplementation reduces maternal mortality.

b) Underweight and mortality. A large cohort study in the USA compared mortality rates by level of BMI (Flegal et al., 2005). In crude analysis, people who were underweight had an increased mortality rate compared to people of normal weight. However, people who were underweight were more likely to smoke and more likely to have underlying diseases than people of normal weight.

   Conclusion: It is healthier to be normal weight than underweight.

c) Amyl nitrate and Kaposi's sarcoma. In the very early days of the HIV/AIDS epidemic, a study compared characteristics of men with and without Kaposi's sarcoma (Marmor

et al., 1982). Kaposi sarcoma was seen in individuals with AIDS. Amyl nitrate is a recreational drug. An association was found between inhaling Amyl nitrate and Kaposi's sarcoma.

Conclusion: Use of Amyl nitrate causes Kaposi's sarcoma.

d) MMR and autism. A study of 12 children who had both stomach and behavioural problems (including autism) were recruited into the study (Wakefield et al., 1998; Retracted). The investigators found that onset of behavioural problems were associated by the parent with MMR vaccination in 8 of the 12 children.

Conclusion: MMR vaccination causes autism.

Bibliography

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