Week 7 seminar (Part 1): SUDDEN INFANT DEATH SYNDROME

Introduction

This tutorial looks at how epidemiologists investigate the causes of rare diseases and the way that the information obtained may be used in disease prevention and control. By way of illustration we will be looking at the causes of sudden infant death syndrome (SIDS) or 'cot death'.

Sudden infant death syndrome (SIDS)

SIDS can be defined as the sudden death of an infant that is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause. SIDS is the third commonest cause of infant death after perinatal causes and congenital anomalies. Around 60% of SIDS deaths occur between 4 weeks and 4 months, generally at home, more often in urban areas, at night and in late winter or early spring. About 60% of SIDS cases are male. They are more frequent in socio-economically deprived communities. Often the infant has been lain down to sleep and is later found lifeless.

As identifiable causes of death in infancy have gradually decreased in frequency, interest in SIDS has increased. Historically, various possible causes for SIDS were suggested, including mild infections, abnormalities of respiratory control mechanisms and 'overlaying'. More recently a potential role for thermal stress (overheating) was suggested as a possible cause. Some studies showed that many babies were put down to sleep under excessive amounts of bedding. A study from Hong Kong found that despite the hot humid climate, there was a low incidence of SIDS and it was suggested that this was because babies were lain down to sleep on their backs (supine). This led to the suggestion that the prone sleeping position (lying on the front) might be a risk factor for SIDS.

In a study in SW England Fleming and colleagues found evidence to suggest that overheating and prone sleeping position were risk factors for SIDS (BMJ 1990; 301: 85-9). Following this paper, in 1991 the Chief Medical Officer and the Chief Nursing Officer jointly wrote to all doctors and Regional and District Nursing Officers to draw their attention to the advice of a group of experts on SIDS. A national campaign – 'Back to Sleep' - reinforced this advice to all those who might have responsibilities for the care of infants. The CMO advised that the risk of cot death can be reduced "if babies are not placed on their tummies to sleep".

Following this campaign, SIDS rates fell, suggesting that it had probably had an impact (rates in England and Wales 1.7/1000 live births in 1990 and 0.61/1000 in 1995), however appreciable numbers of SIDS cases still occurred, suggesting that other risk factors were also important. Therefore Fleming et al subsequently went on to carry out a larger and more detailed study of risk factors (set reading, BMJ 1996 paper):

1. Why did they decide to use a case-control design? Why was a cohort study or randomised trial not feasible?

2. Explain who the cases were and how they were identified.

3. Explain who the controls were and how they were identified. Why were they matched with cases on age and place of residence, and why were there four controls for every case?

4. What information was collected about the cases and how was this obtained?

5. What information was collected about the controls and how was this obtained?

6. What is the health outcome of interest in this study?

7. What are the risk factor exposures of interest in this study?

8. What do the results in Table 1 of the paper show regarding the relation between sleeping position and death from SIDS?

9. Summarise what was found in relation to how warmly the babies were wrapped (the tog value of the bedding) (Table 2 of the paper). What was the effect of controlling for socioeconomic status and possible reasons for this effect?

10. What conclusions can be drawn from the multivariate analyses presented in Table 4? Is tog value still a risk factor?

11. What do the 95% confidence intervals around the adjusted risk estimate for prone position mean, and why are they so wide?

12. Discuss whether there might have been significant biases influencing the results.

Week 7 seminar (Part 2): SMOKING AND MORTALITY

Introduction

This tutorial looks at how cohort studies can provide more convincing evidence than case-control studies for a causal link between an exposure and a disease outcome. This will be illustrated by the seminal study by Doll and Peto on the relation between smoking and mortality.

British Doctors study of smoking and mortality

Observations of time trends in lung cancer mortality in the UK showed a steep rise beginning in the 1930's, twenty years or so after consumption of tobacco had started to increase. This led Doll and Hill to carry out a case-control study of lung cancer and smoking which found a positive association and was published in 1950.

In 1951 they began a long-term follow-up study of British doctors. A questionnaire was sent which asked about their smoking habits (as smoking was common in the general population there was no need to select the cohort on the basis of exposure). They received replies from 34,440 men (69%). As the majority of doctors in 1951 were men they only received 6,207 replies from women and subsequent follow-up has focused on the men. Further questionnaires were sent at intervals to those still alive and living in the UK and participants were asked about changes in smoking habit.

In 1954, 1956 and 1964 they published the results of the short-term follow-up of this cohort which confirmed a significantly increased risk of death from lung cancer in smokers. Subsequently more detailed analyses have been reported after 20 years (set reading, BMJ 1976 paper) and 40 years of follow-up. In 1971 10,074 men had died and 2,459 men were living abroad. The response rate to a further questionnaire about smoking habits in 1971 from those still alive and living in the UK was 98%.

1. **a) What was the sampling frame for the cohort?**
   b) What are the advantages and disadvantages of studying a cohort of doctors?
   c) Why do you think the response rate was so high from those still alive in 1971? Why are high response rates important?
   d) How was cause of death ascertained? How reliable will this information be?

2. **Table II in the 1976 BMJ paper shows the average number of cigarettes smoked by the male doctors in the cohort between 1951 and 1971 as a % of the number smoked by UK men of the same age. Describe the data.**

3. **Table III in the paper shows the age-standardised annual mortality rates per 100,000 men after 20 years of follow-up for selected diseases according to smoking habit.**
   a) What do you conclude from this Table?

b) Why do you think that heavy smoking is associated with higher mortality from cirrhosis?
c) Calculate the relative mortality rates for lung cancer and ischaemic heart disease for heavy smokers (25+ cigarettes per day) compared with non-smokers.
d) Compare this table with the results table for eating red meat (week 1). Both papers investigate a dose response relationship between exposure to a risk factor and deaths but were published over 30 years apart.

Notes on the presentation of the table:

1. There is a typo in the paper in Table 3: for amount smoked it should say ≥25, not ≤ 25.

2. The chi-square test statistic has been presented and not the p-values. Larger values will lead to smaller p-values. Larger values of the test statistic indicate a bigger difference between the numbers of deaths observed in smokers and non-smokers and numbers of deaths expected if the death rates were the same.

4. **The changing smoking habits of the cohort over time provided a "natural experiment". Table X (10) in the paper shows the mortality from selected diseases in ex-smokers compared with mortality expected in lifelong non-smokers, according to the number of years since stopping smoking. What do these data show?**

5. **What possible explanations should you consider before deciding whether smoking may cause of lung cancer and IHD?**

6. **What changes to the study design and analysis could be made in a future study to exclude confounding of the association between smoking and IHD by other risk factors?**

From the public health point of view we are interested in the number of deaths that could be avoided in the population if the exposure were to be eliminated. This can be expressed as the **attributable risk** (or risk difference), that is the excess absolute mortality rate in exposed individuals eg smokers which is attributable to their exposure.

7. **Calculate the relative risks and attributable risks of death from lung cancer and IHD among smokers using data in Table IV of the paper (comparing non-smokers and current cigarette smokers).**

8. **What is your conclusion from these results?**

9. **Whilst smoking rates have fallen substantially over the past 50 years, about a quarter of young adults in the UK currently smoke. What are the different strategies being used to try to reduce the prevalence of smoking further?**