Cohort and Case-Control Studies

Evidence-Based Practice in Speech-Language Therapy
(SHSC 2033)

Session 5

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Outline

1. Cohort studies
2. Case-control studies
3. Useful tools
4. Group discussion

Introduction

- RCTs are **experimental studies**. They're designed with a high degree of experimental control built in.
- Other kinds of evidence comes from **non-experimental studies**, where there's been no experimental manipulation of participants—and more possibilities for bias and confounds. These are a kind of **observational study**.
- Cohort studies and case-control studies are two kinds of observational studies where naturally occurring events (hypothesized risks, exposures) are observed.
- These are employed in studies of **epidemiology** and sometimes in intervention.

Cohort Studies

What is a cohort study?

- "...the investigator identifies exposed and nonexposed groups of patients, each in a cohort, and then traces their outcome forward in time."[1]
- Usually prospective but can be retrospective
- Observational rather than experimental
- Longitudinal rather than cross-sectional
- (Relative) risk ratios calculated to estimate risk of the exposure

[1] Guyatt, Rennie, Meade, and Cook (2008, p. 147)

Cohort studies

- Most are **prospective**: the study begins and individuals are followed until the outcomes (events of interest) occur.
- Some are **retrospective**: "the outcomes (events of interest) have already happened at some point in the past; the investigator simply goes back even farther in the past and selects exposed and unexposed people; then the question is whether these differ in the development of the outcomes of interest." [2]

[2] Guyatt et al. (2008, p. 147)

Cohort study

BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 10 1956

LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING

A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS

BY

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On October 31, 1951, we sent a simple questionary to all members of the medical profession in the United Kingdom. In addition to giving their name, address, and age, they were asked to classify themselves into one of three groups—namely, (*a*) whether they were, at that time, smokers of tobacco; (*b*) whether they had smoked but had given up; or (*c*) whether they had never smoked regularly (which we defined as having never smoked as much as one cigarette a day, or its equivalent in pipe tobacco or cigars, for as long as one year). All smokers and ex-smokers were asked additional questions. The smokers were asked the ages at which they had started smoking and the amount of tobacco that they were smoking, and the method of smoking it, at the time of replying to the questionary. The ex-smokers were asked similar questions but relating to the time at which they had last given up smoking.

On the basis of their replies to the questionary, we classified the doctors in a few broad groups according to their sex and age, the amount of tobacco they smoked, their method of smoking, and whether smoking had been continued or abandoned. Subsequently we have recorded the deaths occurring in each of these groups. To ensure a high proportion of replies we intentionally made the questionary extremely short and simple. In particular, we did not ask for a life-history of smoking habits, though in studying the incidence of lung cancer, with a long induction period, we realized that the habits of previously have been a light smoker or may since then have given up smoking altogether; we shall have continued to count him, or her, as a heavy smoker. If there is a differential death rate with smoking, we must by such errors tend to inflate the mortality among the light smokers and to reduce the mortality among the heavy smokers. In other words, the gradients we present in this paper may be understatements but (apart from sampling errors due to the play of chance) cannot be overstatements.

In 1954 we published a preliminary report on the results of this inquiry (Doll and Hill, 1954a). The number of deaths from lung cancer was then small (36) and standing alone they would not have justified a firm conclusion. In showing a steadily rising mortality from lung cancer as the amount of smoking increased, they were, however, in close conformity with the figures we had previously found in our extensive retrospective inquiries into the smoking histories of patients with cancer of the lung and other diseases. With the passage of another two years we are now able to present from this prospective inquiry a considerably increased body of data, and, in consequence, a more exhaustive analysis. The four main questions to which we have sought answers are: (1) What are the relative risks of lung cancer associated with the smoking of different amounts of tobacco by different methods? (2) Is there a reduction in the risk if smoking is given up? (3) What is the

Cohort study (Doll & Hill, 1956)

- Research question: What are the relative risks of lung cancer associated with smoking?
- Questionnaires were sent to all doctors in the UK in October 1951 (so the **cohort** was doctors).
- Doctors were asked whether they smoked and were classified into non-smokers, present smokers, and ex-smokers.
- Subsequent deaths were recorded in each group for the next 4 years, 5 months.
- Prospective, longitudinal study

Cohort study methods (Doll & Hill, 1956)

- Questionnaires were sent to 59,600 doctors; 41,024 were completed.
- 40,701 were sufficiently complete to be used.
- 1,854 subsequent deaths were recorded during the period (1,714 over age 35) and the cause of death was noted.

Cohort study results[4]

Cause of death	No. deaths	Non-smokers[3]	All smokers[3]
Lung cancer	84	0.07	0.90
Other cancer	220	2.04	2.02
Other respiratory	126	0.81	1.13
Coronary thrombosis	508	4.22	4.87
Other causes	779	6.11	6.89
All causes	1,714	13.25	15.78

[3] Standardized death rates per year per 1,000 men aged 35 or more.

[4] Adapted from Doll and Hill (1956, Table V, p. 1073).

Cohort study results (Doll & Hill, 1956)

- The risk of lung cancer in smokers was found to be about 13 times that of non-smokers. (Risk ratio[5] $= 0.90/0.07 = 12.9$)
- Threats to **external validity**:
  - Be careful not to over-generalize these results.
  - They're based on male doctors (not the general population) and only those who responded to the questionnaire.
  - Participants weren't randomized to smoking and non-smoking groups, so confounds may have been present.
  - They're based on a previous generation of people. (Think of advances in health care, etc.)

[5] Also known as **relative risk**.

Levels of evidence for intervention studies[6]

1a Systematic reviews (SR) & meta-analyses (with homogeneity) of RCTs

1b Individual RCT (with narrow confidence interval)

2a SR (with homogeneity) of cohort studies

2b Individual cohort study (including low quality RCT)

3a SR (with homogeneity) of case-control studies

3b Individual case-control studies

4 Case-series (and poor quality cohort and case-control studies)

5 Expert opinion without explicit critical appraisal; bench research

[6] http://www.cebm.net/index.aspx?o=1025

Another example

- The "Growing up in New Zealand" study[7]
- Designed to "to improve the lives of their generation and answer the fundamental question: What makes us who we are?"
- A pre-birth cohort study
- 7,000 children being followed from before birth to early adulthood (21 years planned)

[7] http://www.growingup.co.nz/en/about-the-study.html

Case-Control Studies

What is a case-control study?

"Case-control studies also assess associations between exposures and outcomes. . . . [they provide] an alternative design that relies on the initial identification of cases—that is, patients who have already developed the target outcome—and the selection of controls—persons who do not have the outcome of interest." [8]

[8] Guyatt et al. (2008, p. 146)

Case-control studies

- People with a condition (cases) are compared to those without the condition (controls) with regard to putative risk factors or exposures.
- Usually retrospective; observational
- Usually less expensive and quicker to do than a cohort study
- Odds ratios (ORs) are calculated to estimate risk (see handout on Moodle).

Case-control study

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

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In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of population—both in total and, particularly, in its older age groups. Stocks (1947), using standardized death rates to allow for these population changes, shows the following trend: rate per 100,000 in 1901–20, males 1.1, females 0.7; rate per 100,000 in 1936–9, males 10.6, females 2.5. The rise seems to have been particularly rapid since the end of the first world war; between 1921–30 and 1940–4 the death rate of men at ages 45 and over increased sixfold and of women of the same ages approximately threefold. This increase is still continuing. It has occurred, too, in Switzerland, Denmark, the U.S.A., Canada, and Australia, and has been reported from Turkey and Japan.

Many writers have studied these changes, considering whether they denote a real increase in the incidence of the disease or are due merely to improved standards of diagnosis. Some believe that the latter factor can be regarded as wholly, or at least mainly, responsible—for example, Willis (1948), Clemmesen and Busk (1947), and Steiner (1944). On the other hand, Kennaway and Kennaway (1947) and Stocks (1947) have given good reasons for believing that the rise is at least partly real. The latter, whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance, in Germany, Müller (1939) found that only 3 out of 86 male patients with cancer of the lung were non-smokers, while 56 were heavy smokers, and, in contrast, among 86 "healthy men of the same age groups" there were 14 non-smokers and only 31 heavy smokers. Similarly, in America, Schrek and his co-workers (1950) reported that 14.6% of 82 male patients with cancer of the lung were non-smokers, against 23.9% of 522 male patients admitted with cancer of sites other than the upper respiratory and digestive tracts. In this country, Thelwall Jones (1949—personal communication) found 8 non-smokers in 82 patients with proved carcinoma of the lung, compared with 11 in a corre-

Case-control study (Doll & Hill, 1950)

- "...to determine whether patients with carcinoma of the lung differed materially from other persons in respect of their smoking habits or in some way which might be related to the atmospheric pollution theory." (p. 740)
- 20 London hospitals were asked to notify all patients admitted with carcinoma of the lung (cases).
- For each case, researchers also interviewed a control patient from a group of non-cancer patients of the same sex, within the same age group, and in the same hospital at about the same time.
- Case and control patients were interviewed using a questionnaire and asked about their smoking history.[9]
- Retrospective study

[9] A smoker was defined "as a person who had smoked as much as one cigarette a day for as long as one year."

Case-control study results (Doll & Hill, 1950)[10]

	Smokers	Non-smokers	Total
Lung cancer	647	2	649
Controls	622	27	649

[10] Results for male patients. Adapted from Table IV of study and from Bland (2000, p. 242).

Case-control study results (Doll & Hill, 1950)

- In case-control studies, relative risk is approximated by the **odds ratio**: $(647/2)/(622/27) = 14.04$ [11]
- The risk of lung cancer in smokers is about 14 times that of non-smokers.
- The 95% CI is wide [3.3, 59.3] due to the small number of non-smokers, particularly for lung cancer cases.[12]
- Consider threats to external validity

[11] Bland (2000, p. 242)
[12] Bland (2000, p. 243)

Smoking and lung cancer

Initial study

Doll and Hill's case-control study of 1950 concluded that the risk of lung cancer in male smokers is about 14 times that of non-smokers.[13]

Subsequent study

In their cohort study of 1956, they reported a similar finding (risk about 13x higher in smokers).[14]

[13] Bland (2000, pp. 241–242)

[14] Bland uses the term *risk* in summarising the findings, although the number was an OR.

Levels of evidence for intervention studies[15]

1a Systematic reviews (SR) & meta-analyses (with homogeneity) of RCTs

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[15] http://www.cebm.net/index.aspx?o=1025

Risk factors for late talking[16]

Risk factor	Odds ratio	95% CI
Male sex	2.74	[1.96, 3.84]
Family history of late talking	2.11	[1.40, 3.19]
Two or more children in family	2.08	[1.39, 3.10]
Early neurobiological growth		
- Percent optimal birth weight $< 85\%$	1.89	[1.18, 3.02]
- Prematurity ≤ 36 weeks	1.84	[1.04, 3.25]
- Gross motor skills (ASQ)	3.12	[1.30, 7.52]
- Fine motor skills (ASQ)	2.39	[1.20, 4.78]
- Adaptive skills (ASQ)	2.65	[1.66, 4.22]
- Personal-social skills (ASQ)	5.53	[2.06, 14.87]

[16] $N = 1766$, of which 238 were LTs, defined using Communication scale of the Ages and Stages Questionnaire at 2.1 years of age (Zubrick, Taylor, Rice, & Slegers, 2007, Table 3); adjusted ORs reported.

Useful tools for cohort and case-control studies

Reporting standards for authors (STROBE)

`http://www.equator-network.org`

Critical appraisal checklists for readers (SIGN)

`http://www.sign.ac.uk/checklists-and-notes.html`

Relative risk calculator

`https://www.medcalc.org/calc/relative_risk.php`

Odds ratio calculator

`https://www.medcalc.org/calc/odds_ratio.php`

Press Release[17]

Medical experts refute singers' claims of flu vaccine risks

"Cantopop singers have recently made warnings against flu vaccines. In a leaked WhatsApp audio recording, Ms Kay Tse On-kei said flu vaccines contained mutated bacteria and mercury. [Her] claims were rejected by HKU microbiologist Professor Yuen Kwok-Yung. Dr Ho Pak Leung, Director of the HKU Centre for Infection, . . . emphasized that medical issues should be separated from entertainment. HKU Dean of Medicine Professor Gabriel Leung said these comments made by well-known figures had no support from the scientific and medical fields.

HKU released findings of a study on the effectiveness of the vaccine type for the current flu season. It found that the flu jabs were 66% effective. The study looked into the data of 1,078 children who were admitted to hospitals between December 4 last year and January 31 this year. All the children suffered from fever and acute respiratory illness. Among the 339 confirmed with flu, only 22 had been vaccinated. Of the remaining 739 children who were unaffected by the virus, 103 had received seasonal flu vaccinations. (Major local papers)"

[17] HKU Daily Media Highlights, 2018-02-11

Group discussion

- Break up into your assigned groups.
- Decide whether the flu vaccine has been effective in Hong Kong based on the data in the press release.
- Use SIGN checklist 4 for case-control studies to critically appraise the research article.
- Document where you found information addressing each point.
- Upload checklist for your group by 11.45am.

References

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