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ENDGAMES

STATISTICAL QUESTION

Observational study design

Philip Sedgwick *reader in medical statistics and medical education*

Centre for Medical and Healthcare Education, St George's, University of London, Tooting, London, UK

Researchers investigated the effect of the dose of levothyroxine on the risk of fractures in older adults.[1] A cohort was identified retrospectively from population health databases for Ontario, Canada. Men and women were included if they were aged over 70 years and had been prescribed replacement levothyroxine treatment for hypothyroidism for the first time between 1 April 2002 and 31 March 2007. The cohort comprised 213 511 prevalent users of levothyroxine. The records of the cohort members were examined until 31 March 2008, and the occurrence of any fracture after the prescription of replacement levothyroxine treatment was recorded. Fracture was defined as the first visit to an emergency department or admission to hospital for any fracture of the wrist or forearm; shoulder or upper arm; thoracic spine, lumbar spine, or pelvis; hip or femur; or lower leg or ankle.

During follow-up, 22 236 cases of hip fracture were recorded in the cohort. For each case of hip fracture five controls were identified, with cases and controls matched for age (within 1 year), sex, and duration in cohort (within 30 days of follow-up). The researchers reported that among people aged 70 years or more, current levothyroxine treatment was associated with a significantly increased risk of fracture, with a strong dose-response relation.

Which one of the following best describes the above study design?

a) Case-control study

b) Cohort study

c) Cross sectional study

d) Nested case-control study

Answers

Answer *d* best describes the above study design.

Case-control, cohort, cross sectional, and nested case-control studies are all observational in design. In an observational study the investigators do not intervene in any way but simply record the lifestyle choices and treatment decisions of the study participants; typically the aim is to investigate possible associations between risk factors and disease outcomes. This is in contrast to experimental studies, such as clinical trials, where the investigator influences which treatment regimen a participant receives and records the effects on outcomes.

The nested case-control study design (answer *d*) is an observational design that incorporates a case-control study within a cohort study. In the above example, a cohort of adults was identified from population health databases for Ontario, Canada. Men and women were included if they were aged over 70 years and had been prescribed replacement levothyroxine treatment for hypothyroidism for the first time between 1 April 2002 and 31 March 2007. The health records in these databases would have been collected prospectively. However, the cohort was retrospective because it was identified after the health databases had been collated. The records of cohort members were examined from their first prescription of levothyroxine until 31 March 2008, and any fractures were noted. Any cohort member who experienced a fracture became a case. For each case up to five controls—that is, cohort members who had not experienced a hip fracture—were identified. Cases and controls were matched for age (within 1 year), sex, and duration in cohort (within 30 days of follow-up).

Answer *a* is false. In a case-control study, two groups of people are chosen on the basis of their disease status: one with the disease (the cases) and one without (the controls). Case-control studies are retrospective in design, with people being asked about past exposure to proposed risk factors. The aim is to provide insight into which factors may increase or reduce the risk of the disease. Because data are collected retrospectively in case-control studies they are prone to recall bias—that is, the systematic difference between cases and controls in the accuracy of recalled information regarding exposure to risk factors. Recall bias has been described in detail in a previous endgame.[2] Although the nested case-control study in the above example was retrospective in design, the data in the population health databases would have been collected prospectively. Therefore, one of the advantages offered by the above nested case-control study design is that the data were not prone to recall bias.

Answer *b* is false. In a traditional cohort study all participants would have been included in the statistical analysis. The above study was based on a retrospective cohort. However, although all cases of fracture were included, only a proportion of the

p.sedgwick@sgul.ac.uk

controls were. Cases and controls were matched for age, sex, and duration in the cohort. Matching of cases with controls meant that the matching variables were adjusted for as potential confounders when the study was designed, which was more efficient than making adjustments during statistical analyses. Although only a proportion of the controls in the cohort were included in the statistical analysis, any loss in statistical accuracy through having a smaller sample size as a result of matching would have been minimal. Because cases and controls were matched on age, sex, and duration in the cohort, it was not possible to examine the effects of these variables on the relation between levothyroxine dose and risk of fractures in older people. Although age, sex, and duration of levothyroxine prescription may be related to fracture risk they were not of interest as potential risk factors in the above study.

Answer *c* is false. Cross sectional studies are typically carried out at a single point in time. They may be used to record peoples' perceptions, behaviours, or attitudes to—for example, the triple measles, mumps, and rubella vaccine. Cross sectional studies may also be used to estimate the prevalence of a medical condition in the population—for example, hearing impairment.

Competing interests: None declared.

1 Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon PA, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. *BMJ* 2011;342:d2238.
2 Sedgwick P. What is recall bias? *BMJ* 2012;344:e3519.

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