Selection Bias in Epidemiological Studies

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COVID-19 Antibody Seroprevalence in Santa Clara County, California

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(revised in response to comments received. This remains a preliminary report of the work.)

Sampling: recruited residents of Santa Clara county through ads on Facebook.

Potential for selection bias:

-Recruiting through Facebook likely attracted people with COVID-19–like symptoms who wanted to be tested (the 'worried well'), boosting the apparent positive rate.
-The study also had relatively few participants from low-income and minority populations

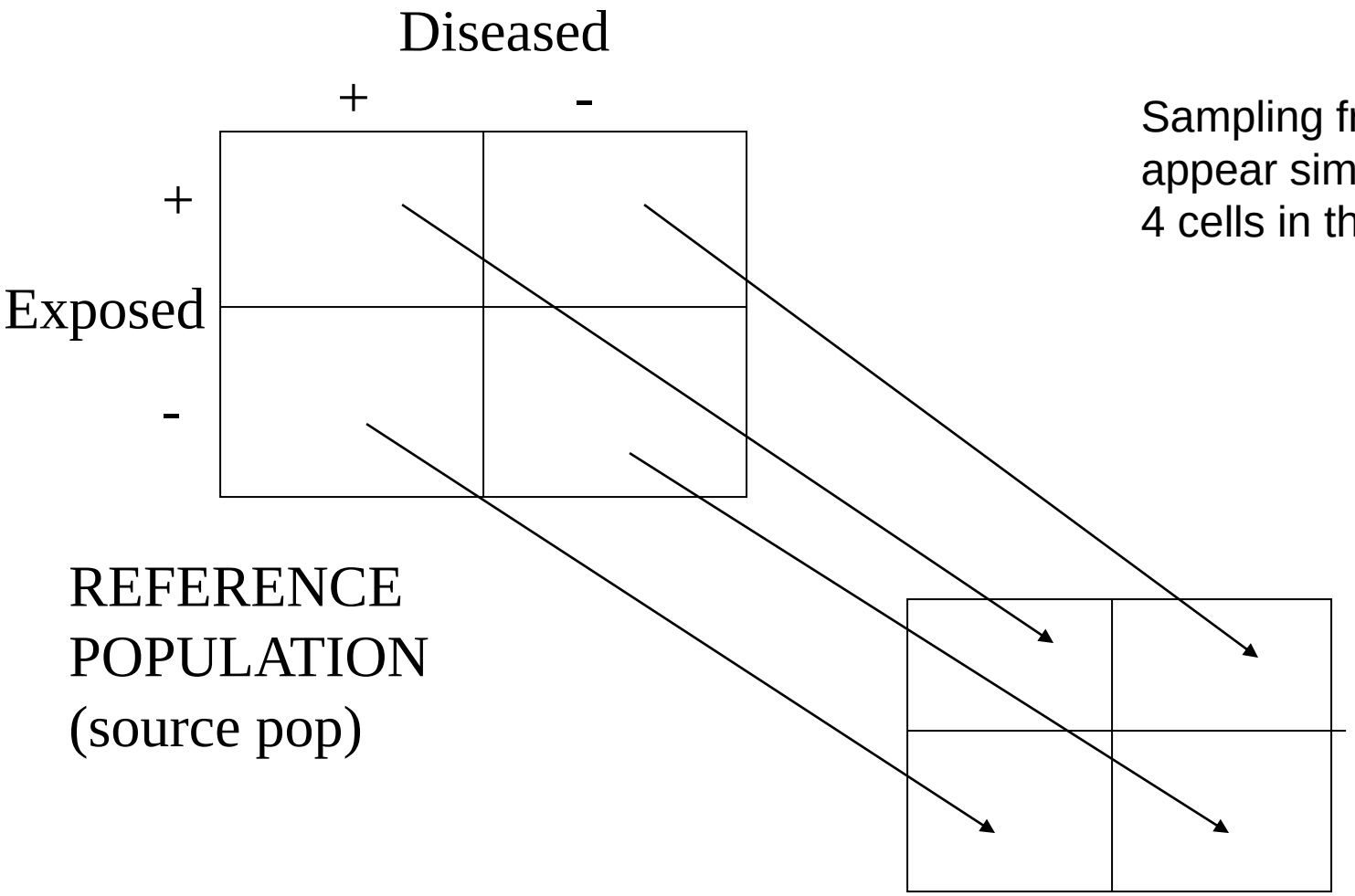
https://www.the-scientist.com/news-opinion/how-not-to-do-an-antibody-survey-for-sars-cov-2-67488

Now lets define selection bias

- "Distortions that result from procedures used to select subjects and from factors that influence participation in the study."
  - Porta M. A dictionary of epidemiology. Oxford, 2008.
- "Error introduced when the study population does not represent the target population"
  - Delgado-Rodriguez et al. J Epidemiol Comm Health 2004
- Defining feature:
  - Selection bias occurs at:
    - the stage of recruitment of participants
    - and/or during the process of retaining them in the study
  - Difficult to correct in the analysis, although one can do sensitivity analyses

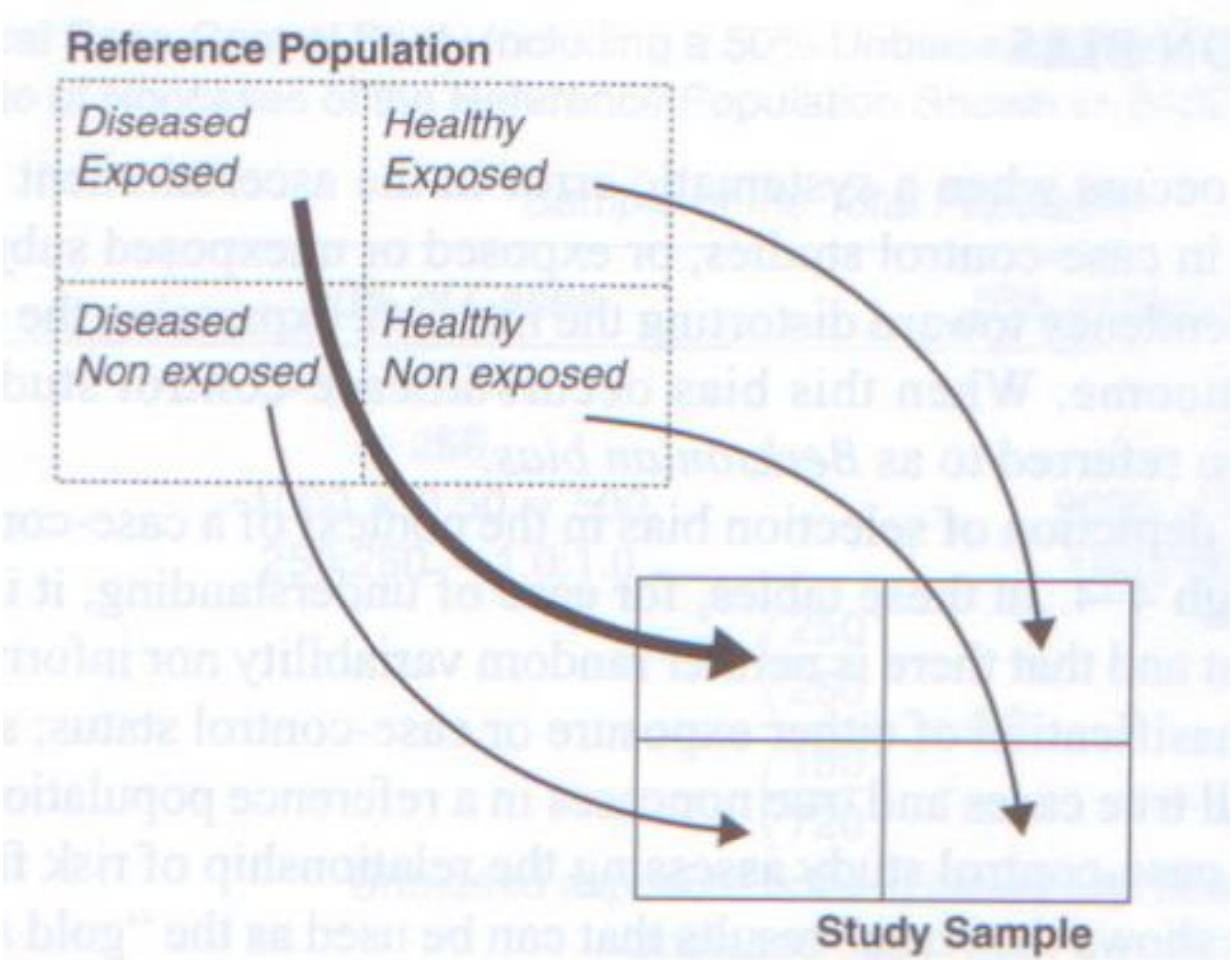
Who gets picked for a study, who refuses, who agrees, who stays in a study, and whether these issues end up producing a "skewed" sample that differs from the target [i.e. biased study base].

Unbiased Sampling



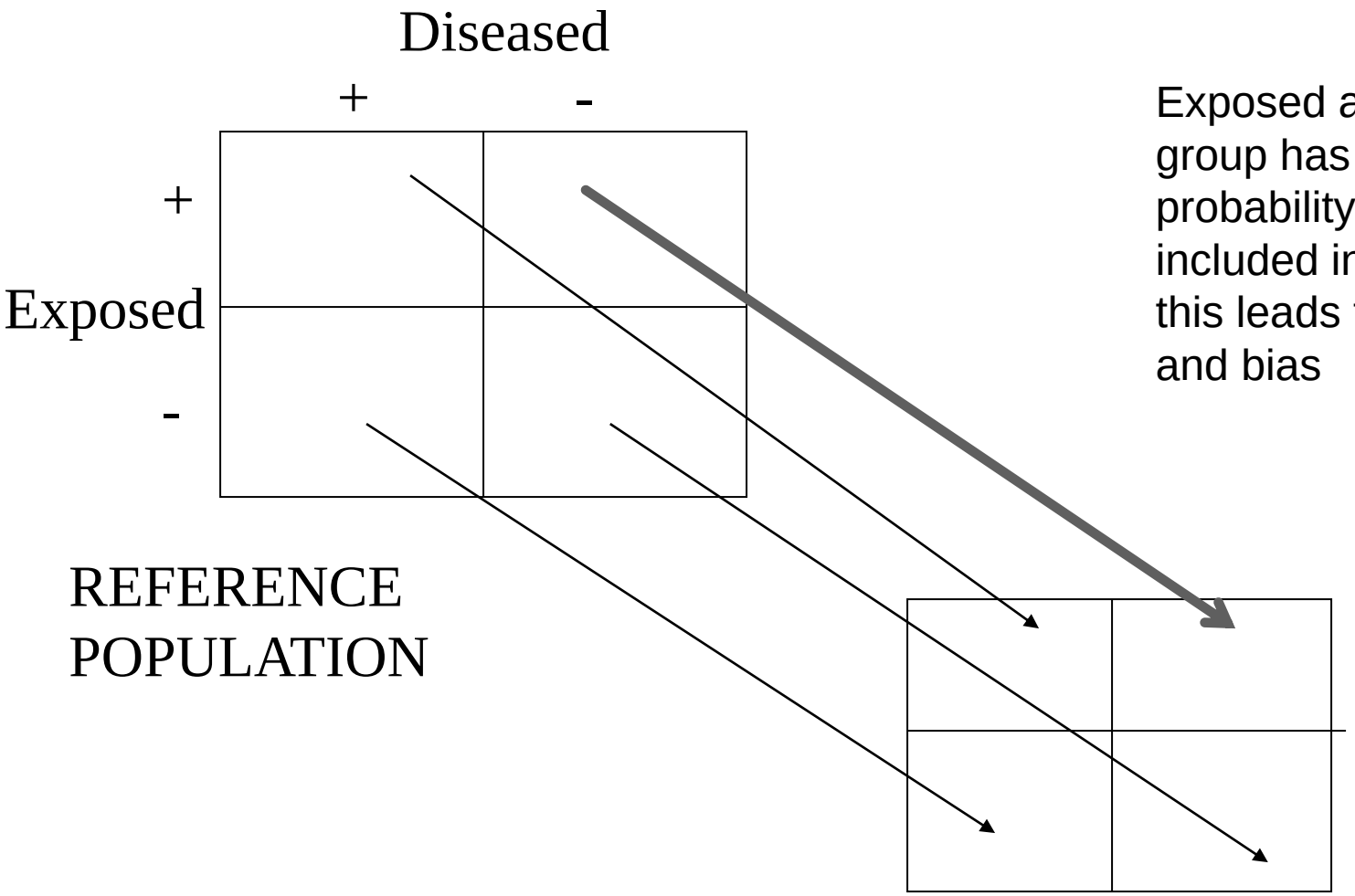
Sampling fractions appear similar for all 4 cells in the 2 x 2 table

Selection bias occurs when selection probabilities are influenced by exposure or disease status



Szklo & Nieto. Epidemiology: Beyond the Basics. 2007

Biased sampling: Worried well might have a higher probability of being included



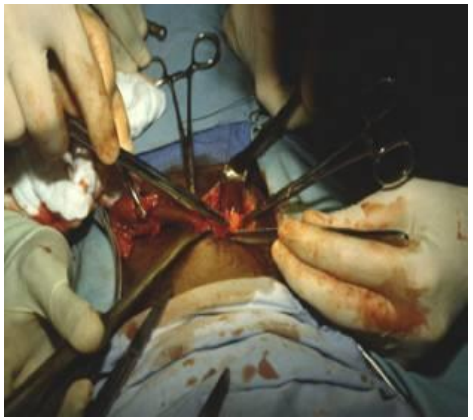
Exposed and healthy group has a higher probability of being included in the study: this leads to imbalance and bias

Selection bias in randomized controlled trials

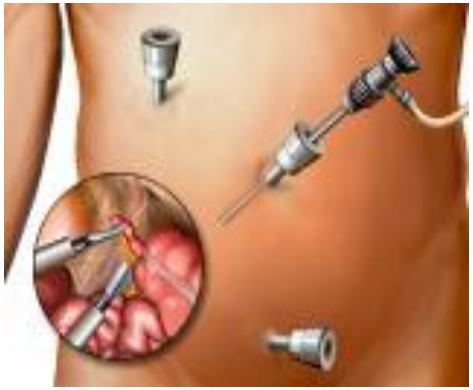
- Examples:
  - Bias due to lack of allocation concealment
    - RCT on thrombolysis with alternating day allocation
    - RCT comparing open versus laparoscopic appendectomy
  - Bias due to attrition
    - If attrition in treatment arm is different from attrition in the control arm

Hansen JB, Smithers BM, Schache D, Wall DR, Miller BJ, Menzies BL. Laparoscopic versus open appendectomy: prospective randomized trial. *World J Surg* 1996;20:17-20; discussion 21.

A prospective randomized trial comparing laparoscopic appendectomy with open appendectomy in patients with a diagnosis of acute appendicitis was conducted between October 1992 and April 1994. Of the 158 patients randomized, 7 patients were excluded because of protocol violations (conversion to laparotomy in 4, appendix not removed in 3). The 151 patients randomized to either a laparoscopic (n = 79) or an open appendectomy (n = 72) showed no difference in sex, age, American Society of Anesthesiology (ASA) rating, or previous abdominal surgery. The histologic classification of normal, catarrhal, inflamed, suppurative, and gangrenous appendicitis was not different between the two groups. Conversion from laparoscopic to open appendectomy was necessary in seven patients (9%) who had advanced forms of appendiceal inflammation. When compared to open appendectomy the laparoscopic group had a longer median operating time (63 minutes versus 40 minutes), fewer wound infections (2% versus 11%), less requirement for narcotic analgesia, and an earlier return to normal activity (median 7 days versus 14 days). There was no difference in morbidity, and both groups had a median time to discharge of 3 days. Laparoscopic appendectomy is as safe as open appendectomy; and despite the longer operating time, the advantages such as fewer wound infections and earlier return to normal activity make it a worthwhile alternative for patients with a clinical diagnosis of acute appendicitis.



- The trial ran smoothly during the day. At night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one; and the limited operating room availability made the longer laparoscopic procedure an annoyance.
- Reluctant to call in a consultant, and particularly reluctant with specific senior colleagues, the residents sometimes adopted a practical solution. When an eligible patient appeared, the residents checked the attending staff and the lineup for the operating room and, depending on the personality of the attending surgeon and the length of the lineup, held the translucent envelopes containing orders up to the light. As soon as they found one that dictated an open procedure, they opened that envelope. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy group according to the passed-over envelope.
- If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.
- This story demonstrates that if those making the decision about patient eligibility are aware of the arm of the study to which the patient will be allocated --if randomization is unconcealed (unblinded or unmasked)-- they may systematically enroll sicker-- or less sick-- patients to either treatment or control groups.
- This behavior will defeat the purpose of randomization and the study will yield a biased result.



Guyatt et al. Users guides to the medical literature. AMA Press, 2002: page 269.

Selection bias in cohort studies

- Sources:
  - Bias due to a non-representative “unexposed” group
    - Key question: aside from the exposure status, are the exposed and unexposed groups comparable?
  - Bias due to non-response
    - More likely if non-response is linked to exposure status (e.g. smokers less likely to respond in a study on smoking and cancer)
  - Bias due to attrition (withdrawals and loss to follow up)
    - Bias will occur if loss to follow-up results in risk for disease in the exposed and/or unexposed groups that are different in the final sample than in the original cohort that was enrolled
    - Bias will occur if those who adhere have a different disease risk than those who drop out or do not adhere (‘compliance bias’)

Healthy User and Healthy Continuer Bias: HRT and CHD

- HRT was shown to reduce coronary heart disease (CHD) in women in several observational studies
- Subsequently, RCTs showed that HRT might actually increase the risk of heart disease in women
- What can possibly explain the discrepancy between observational and interventional studies?
  - Women on HRT in observational studies were more health conscious, thinner, and more physically active, and they had a higher socioeconomic status and better access to health care than women who are not on HRT
  - Self-selection of women into the HRT user group could have generated uncontrollable confounding and lead to "healthy-user bias" in observational studies.
  - Also, individuals who adhere to medication have been found to be healthier than those who do not, which could produce a "compliance bias" [healthy user bias]

Michels et al. Circulation. 2003;107:1830

Selection bias in case-control studies

- Sources:
  - Bias in selection of cases
    - Cases are not derived from a well defined study base (or source population)
  - Bias in selection of controls
    - Controls should provide an unbiased sample of the exposure distribution in the study base
    - Control selection is a more important issue than case selection!

Selection bias in case-control studies

630 THE NEW ENGLAND JOURNAL OF MEDICINE March 12, 1981

COFFEE AND CANCER OF THE PANCREAS

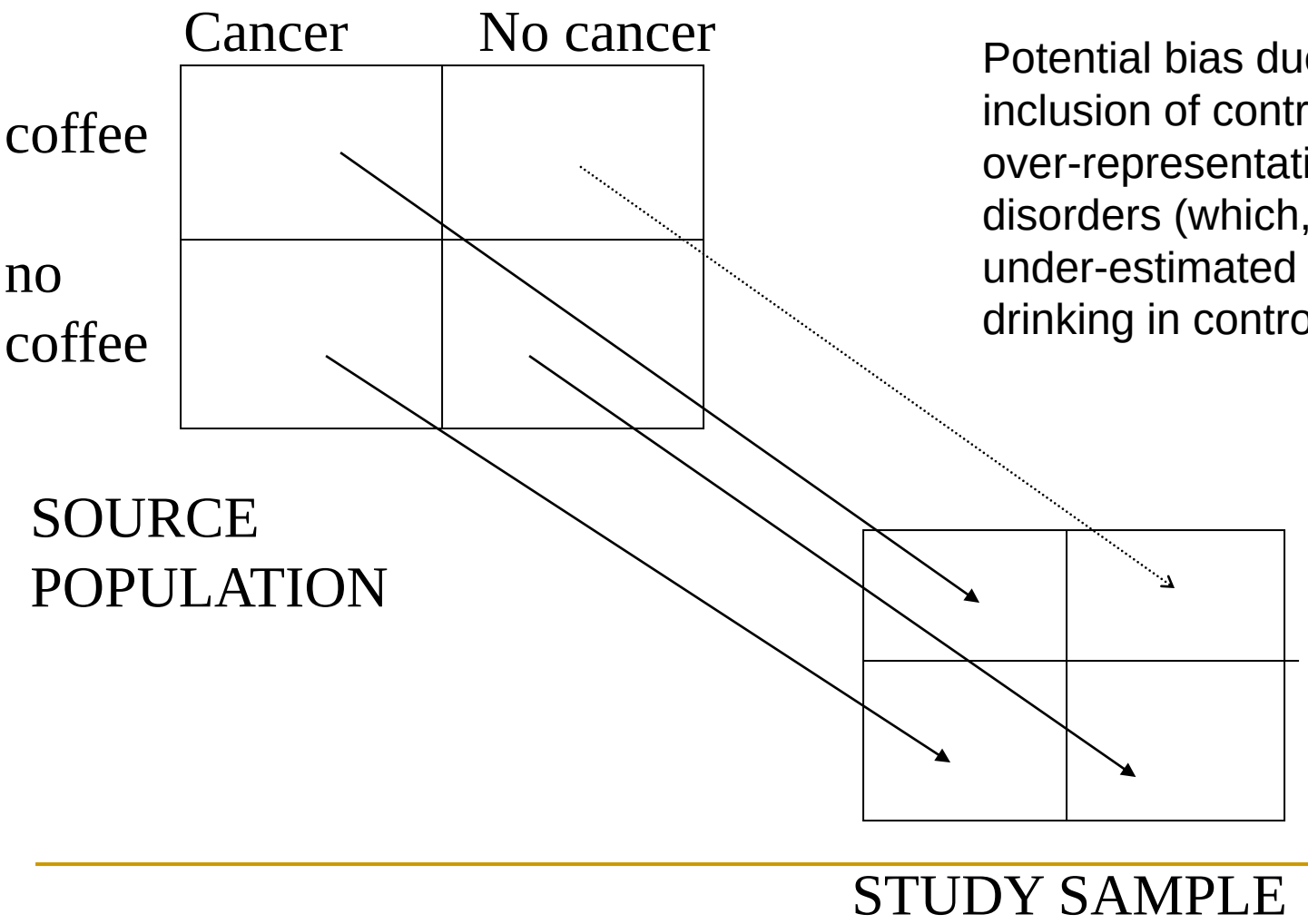
BRIAN MACMAHON, M.D., STELLA YEN, M.D., DIMITRIOS TRICHOPOULOS, M.D., KENNETH WARREN, M.D., AND GEORGE NARDI, M.D.

Abstract We questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee. There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea. A strong association between coffee consumption and pancreatic cancer was evident in both sexes. The association was not affected by controlling for cigarette use. For the sexes combined, there was a significant dose-response relation ($P \sim 0.001$); after adjustment for cigarette smoking, the relative risk associated with drinking up to two cups of coffee per day was 1.8 (95 per cent confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7). This association should be evaluated with other data; if it reflects a causal relation between coffee drinking and pancreatic cancer, coffee use might account for a substantial proportion of the cases of this disease in the United States. (N Engl J Med. 1981; 304:630-3.)

Controls in this study were selected from a group of patients hospitalized by the same physicians who had diagnosed and hospitalized the cases' disease. The idea was to make the selection process of cases and controls similar. It was also logistically easier to get controls using this method. However, as the exposure factor was coffee drinking, it turned out that patients seen by the physicians who diagnosed pancreatic cancer often had gastrointestinal disorders and were thus advised not to drink coffee (or had chosen to reduce coffee drinking by themselves). So, this led to the selection of controls with higher prevalence of gastrointestinal disorders, and these controls had an unusually low odds of exposure (coffee intake). These in turn may have led to a spurious positive association between coffee intake and pancreatic cancer that could not be subsequently confirmed.

MacMahon et al. N Engl J Med. 1981 Mar 12;304(11):630-3

Case-control Study of Coffee and Pancreatic Cancer: Selection Bias

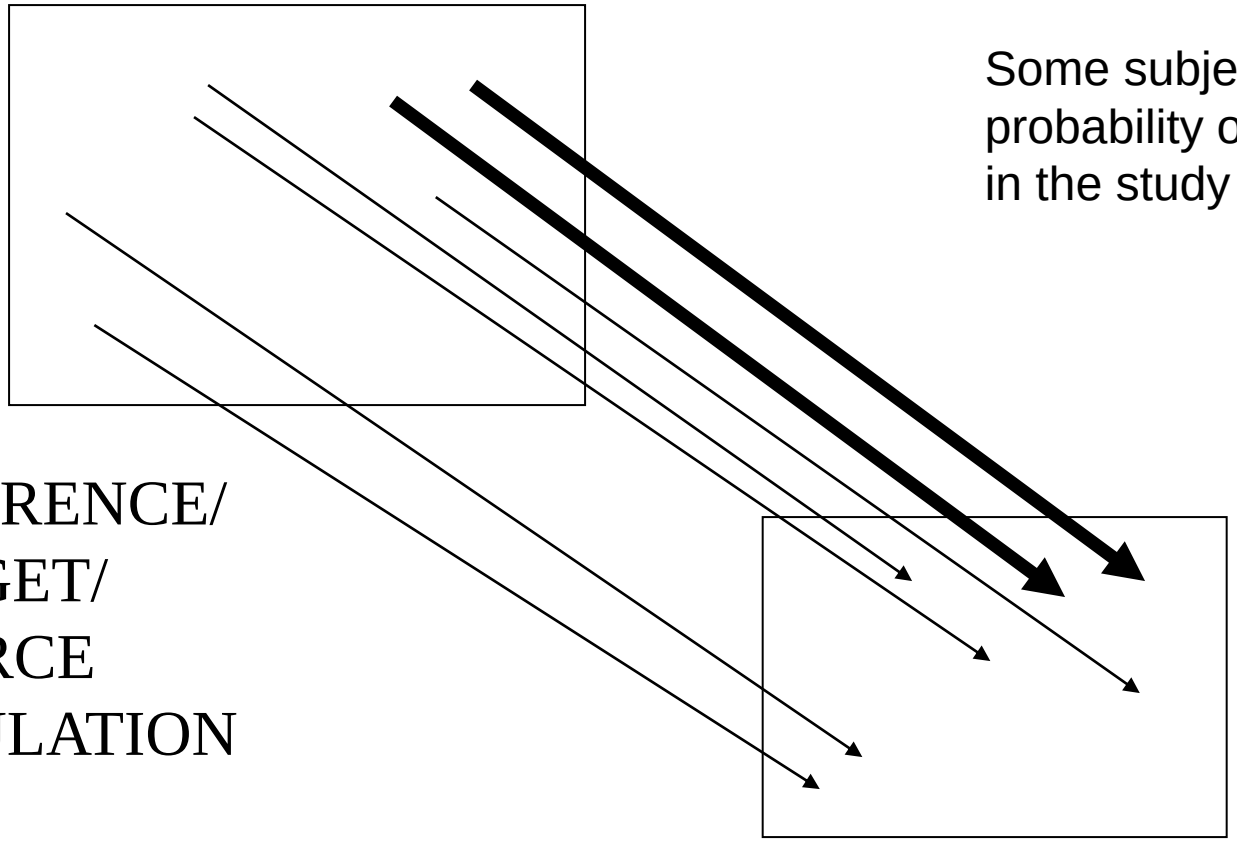


Potential bias due to inclusion of controls with over-representation of GI disorders (which, in turn, under-estimated coffee drinking in controls)

Selection bias in cross-sectional studies

- Sources:
  - Bias due to sampling
    - Selection of “survivors” or “prevalent” cases
    - Non-random sampling schemes
    - Volunteer bias
    - Membership bias
  - Bias due to non-participation
    - Non-response bias

Descriptive Study: Biased sampling



Some subjects have a higher probability of being included in the study sample

REFERENCE/
TARGET/
SOURCE
POPULATION

STUDY SAMPLE

Selection bias in telephone surveys

Table 1 Continuing and emerging challenges for telephone survey research

Ongoing challenges	New and emerging challenges
Selecting participants	
Sampling	Cell phone sampling
Telephone coverage	Number portability
Response rates	Answering machines
Participation rates	Caller ID
Call scheduling	Privacy managers and call blocking
Collecting information	
Reliable and valid responses	Privacy and confidentiality
Mode effects	Respondent burden

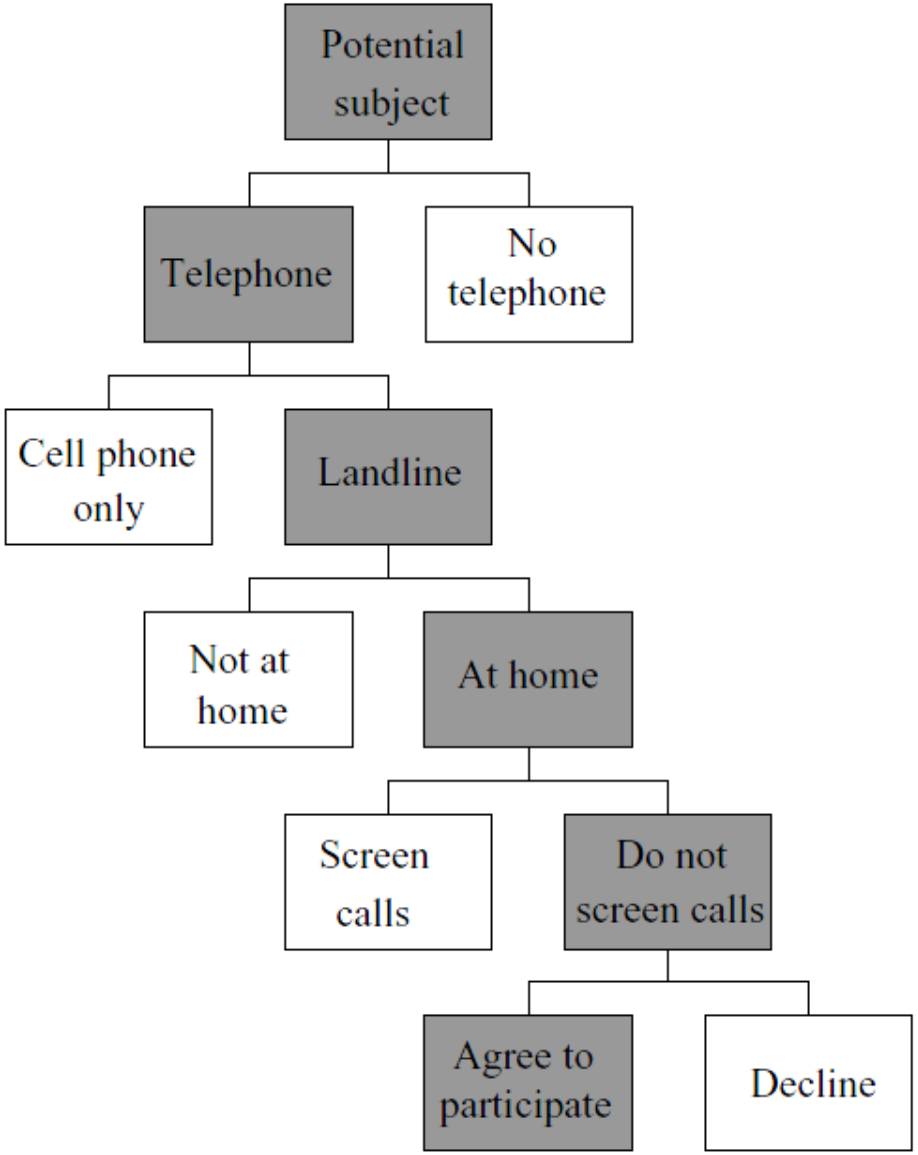


Figure 1

Steps in the selection of participants in telephone surveys.

Annu.Rev.PublicHealth 2007.28:113–26

Example: non-response bias

- Survey to estimate prevalence of self-reported chronic diseases in a city in India (Pai et al, 1999)
- 705 adults were interviewed (of an eligible population of 808)
  - 29.1% had been told (by a doctor or health professional) that they had hypertension
- Proxy data was obtained for 32 of the non-responders [who could never be contacted, despite repeated attempts]
  - 45.8% of non-responders had self reported hypertension
  - If these people had been included, the overall prevalence would have been higher

Prevalence of self-reported hypertension	Responders n=705	Non-responders n=32
	29.1%	45.8%

Can selection bias be “fixed”?

- Not easy
  - Best avoided at the design stage; can try hard to retain participants in the study
- Can collect data to ‘estimate’ magnitude/direction of selection bias and do sensitivity analysis
  - e.g., collect data from a sample of non-respondents, and use this to do sensitivity analysis
- Effect estimates can be ‘adjusted’ if selection probabilities are known