Case-control studies

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Introduction to case control designs

Introduction

- The case control (case-referent) design is really an efficient sampling technique for measuring exposure-disease associations in a cohort that is being followed up or “study base”
- All case-control studies are done within some cohort (defined or not)
  - In reality, the distinction between cohort and case-control designs is artificial
- Ideally, cases and controls must represent a fair sample of the underlying cohort or study base
- Toughest part of case-control design: defining the study base and selecting controls who represent the base

New cases occur in a study base

Study base is the aggregate of population-time in a defined study Population's movement over a defined span of time [OS Miettinen, 2007]

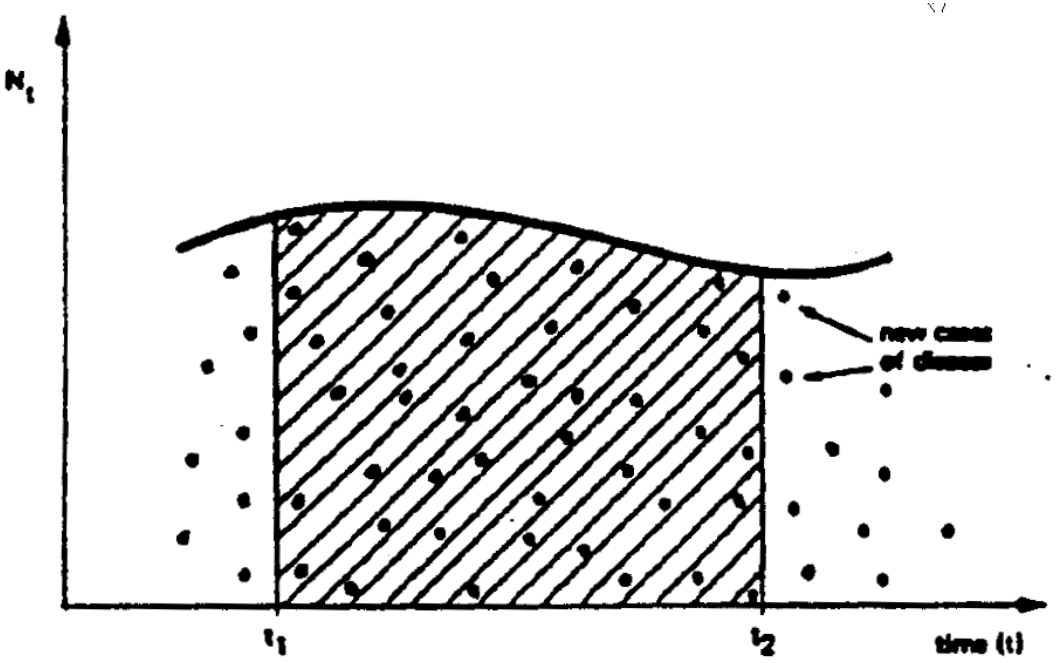


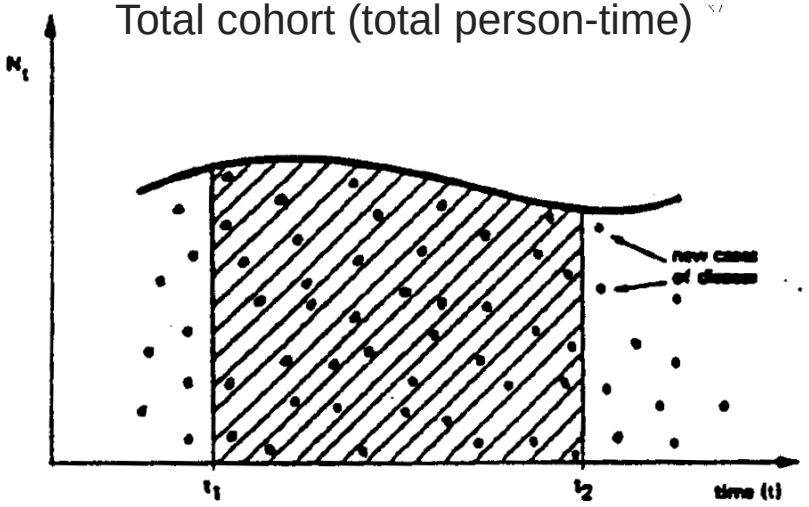
FIGURE 2 *Graphical illustration of the occurrence of new (incident) cases over time in a candidate population (of size N_t at time t)*

Cohort and case-control designs differ in the way cases and the study base are sampled to estimate the incidence density ratio

Morgenstern IJE 1980

Cohort design

Total cohort (total person-time)



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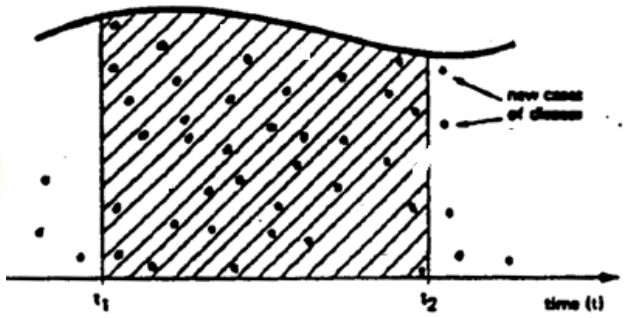
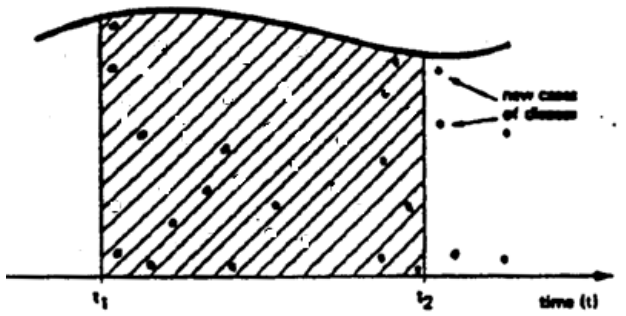


New cases / exposed person-time



New cases / unexposed person-time

$IDR = I_{exp} / I_{unexp}$

The IDR is directly estimated by dividing the incidence density in the exposed person-time by the incidence density in the unexposed person-time

Case-control design: a more efficient way of estimating the IDR

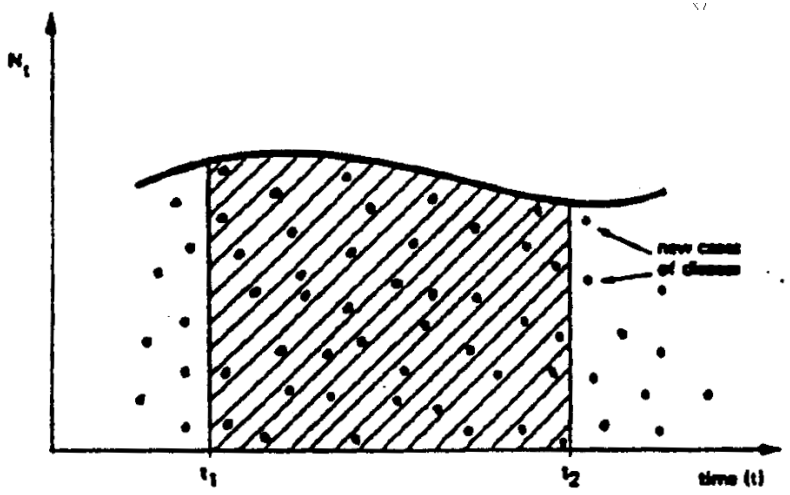


FIGURE 2 *Graphical illustration of the occurrence of new (incident) cases over time in a candidate population (of size N_t at time t)*

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Obtain a fair sample of the cases ("case series") that occur in the study base; estimate odds of exposure in case series

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Obtain a fair sample of the study base itself ("base series"); estimate the odds of exposure in the study base [which is a reflection of baseline exposure in the population]

OR = IDR

The exposure odds in the case series is divided by the exposure odds in the base series to estimate the OR, which will approximate the IDR

Three principles for a case-control study
(Wacholder et al. AJE 1992)

3 principles in case control designs:

- The study base principle
- The deconfounding principle
- The comparable accuracy principle

American Journal of Epidemiology
Vol. 135, No. 9

Selection of Controls in Case-Control Studies

I. Principles

Sholom Wacholder,[1] Joseph K. McLaughlin,[1] Debra T. Silverman,[1] and Jack S. Mandel[2]

A synthesis of classical and recent thinking on the issues involved in selecting controls for case-control studies is presented in this and two companion papers (S. Wacholder et al. *Am J Epidemiol* 1992;135:1029–50). In this paper, a theoretical framework for selecting controls in case-control studies is developed. Three principles of comparability are described: 1) *study base*, that all comparisons be made within the study base; 2) *deconfounding*, that comparisons of the effects of the levels of exposure on disease risk not be distorted by the effects of other factors; and 3) *comparable accuracy*, that any errors in measurement of exposure be nondifferential between cases and controls. These principles, if adhered to in a study, can reduce selection, confounding, and information bias, respectively. The principles, however, are constrained by an additional efficiency principle regarding resources and time. Most problems and controversies in control selection reflect trade-offs among these four principles. *Am J Epidemiol* 1992;135:1019–28.

The concept of the “study base”

- Definitions of the “study base” concept (first introduced by Olli Miettinen)
  - The aggregate of total population-time in which cases occur
  - The members of the underlying cohort or source population** (from which the cases are drawn) during the time period when cases are identified

**The source population may be defined directly, as a matter of defining its membership criteria; or the definition may be indirect, as the *catchment population* of a defined way of identifying cases of the illness. The catchment population is, at any given time, the totality of those in the ‘were-would’ state of: were the illness now to occur, it would be ‘caught’ by that case identification scheme [Source: Miettinen OS, 2007]

The study base principle

- The study base principle
  - Goal is to sample controls from the study base in which the cases arose
  - Controls serve as the proxy for the complete study base
  - Controls should be representative of the person-time distribution of exposure (exposure prevalence) in the study base (i.e. be representative of the study base)
  - Controls should be selected independent of the exposure

Overall, the key issue is are the controls an unbiased sample of the study base that generated the cases?

  - “simplest” (in theory not in practice) way to do this is to randomly sample controls from the study base

Types of study base: primary

- Primary study base
  - The base is defined by the population experience that the investigator wishes to target
    - Usually a well defined cohort study already ongoing (e.g. Nurses Health Study; Framingham Heart Study)
  - The cases are subjects within the base who develop disease
  - Generally implies that all cases are identifiable (although not all are necessarily used)
  - Example: a nested case-control study within the Nurses Health Study cohort

Primary study base: example

Published by Oxford University Press on behalf of the International Epidemiological Association *International Journal of Epidemiology* 2006;**35**:1514–1521

doi:10.1093/ije/dyl197

Risk factors for skin cancers: a nested case–control study within the Nurses' Health Study

Jiali Han,[1,3]* Graham A Colditz[1,2] and David J Hunter[1,2,3]

Accepted 2 August 2006

Background Constitutional factors and sun exposure are associated with skin cancer risk. However, these relations are complex and differ according to skin cancer type.

Methods We examined the associations of constitutional risk factors and sun exposure with the risks of three types of skin cancer simultaneously and evaluated the interaction between constitutional susceptibility and sun exposure in a nested case–control study within the Nurses' Health Study [200 melanoma, 275 squamous cell carcinoma (SCC), and 283 basal cell carcinoma (BCC) cases, and 804 controls]. Information regarding skin cancer risk factors was obtained from the retrospective supplementary questionnaire.

Results Constitutional susceptibility was an independent risk factor for all three types of skin cancer. Sunlamp usage or tanning salon attendance was a risk factor for melanoma after adjusting for potential confounding variables (OR for ever vs never usage, 2.06, 95% CI 1.30–3.26). Higher sun exposure while wearing a bathing suit was an independent risk factor for all three types of skin cancer. We observed a significant interaction between constitutional susceptibility and sun exposure while wearing a bathing suit on melanoma risk (*P*, interaction, 0.03); women with the highest susceptibility and highest exposure had an OR of 8.37 (95% CI 3.07–22.84). This interaction was weaker and non-significant for SCC and BCC.

Conclusions These data largely confirm past studies on risk factors for skin cancer but provide evidence of difference on the strength of these risk factors for melanoma compared with SCC and BCC.

Types of study base: secondary

- Secondary study base
  - Cases are defined before the study base is identified
  - The study base then is defined as the source of the cases; controls are people who would have been recognized as cases if they had developed disease

- Examples: primary or secondary base?
  - Imagine a study of brain tumors at the Montreal Neurological Institute (the cases are all cases of brain tumor during 2008). What would be the study base? Primary or secondary?

Secondary study base: example

Risk factors for acute myocardial infarction in a rural population of central India: A hospital-based case–control study

SAMIR S. PATIL, RAJNISH JOSHI, GAUTAM GUPTA, M. V. R. REDDY, MADHUKAR PAI, S. P. KALANTRI

Background. There is a paucity of data on the relative importance of various traditional risk factors for coronary artery disease among rural Indians. We conducted a prospective case–control study to determine the risk factors for acute myocardial infarction in a rural population of central India.

Methods. We recruited 111 consecutive patients admitted to our hospital with a first episode of acute myocardial infarction and 222 age– and sex–matched controls. Demographics, anthropometric measures, lipids, blood glucose, smoking and other lifestyle factors were compared among cases and controls. Multivariate analyses were used to identify the risk factors independently associated with acute myocardial infarction.

Results. Elevated fasting blood glucose (odds ratio [OR] 8.9; 95% confidence interval [CI] 4.5, 17.9), abnormal waist–hip ratio (OR 3.0; 95% CI 1.7, 5.4) and income (OR 4.0 and 5.9 for the high– and middle–income categories, compared to the lowest category) were independently associated with the first episode of acute myocardial infarction. Abnormal triglycerides (OR 1.7; 95% CI 0.9, 3.1) and current smoking (OR 1.9; 95% CI 0.9, 4.0) were risk factors but were not statistically significant.

Conclusion. Reduction in blood glucose levels and truncal obesity may be important in controlling the burden of coronary artery disease in rural Indians.

Natl Med J India 2004;17:189–94

Cases

All consecutive patients with AMI admitted to our critical care unit between December 2001 and April 2003 were included in the study. AMI was diagnosed if patients fulfilled 2 of 3 criteria: typical ischaemic chest pain, raised concentrations of creatinine kinase-MB in the serum, and typical ECG findings including development of pathological Q waves.[13] Patients were excluded if they had a past history of myocardial infarction or presented more than 24 hours after the onset of symptoms. Written informed consent was obtained from all patients eligible for inclusion in the study.

Controls

We chose two age- and sex-matched controls for each case. Controls were recruited from patients admitted at the same time to the surgical wards for minor surgery such as hernia repair, hydrocele or cataract extraction, or from those visiting the out-patient department for minor complaints related to the eye, ear, nose and throat, and for general health examination. Patients were excluded from the control group if they had clinical evidence of liver disease (jaundice, ascites, oedema or splenomegaly) or if they had had angina or an AMI in the past. We obtained a 12-lead ECG in all controls and excluded those with an abnormal ECG.

Tradeoffs in the use of primary vs. secondary study bases

- Primary
  - Easier to sample for controls because the base is well defined (e.g. NHS or Framingham cohort)
- Secondary
  - Control sampling may be difficult because it is not always clear if a subject is really a member of the base
  - Case ascertainment is complete by definition
- For both types
  - The base and the case need to be defined so that the cases consist exclusively of all (or a random sample of all) cases having the study outcome in the base
  - The controls need to be derived from the base in such a way that they accurately reflect the exposure distribution in the study base

The deconfounding principle

- The study base principle guides the selection of who can be entered into the study
- The deconfounding principle deals with the problems created when the exposure of interest is associated with other possible risk factors. These other risk factors are unmeasured since measured confounders could be handled in the analysis.
- Confounders in one study base may not necessarily be confounders in another study base
- Confounding by a factor is (theoretically) eliminated by eliminating variability in that factor.
- For example, if gender is a possible confounder, selecting only men or only women completely eliminates the variability of gender.
  - This restriction in variability is the rationale for the choice of controls from the same neighborhood or family etc.

The comparable accuracy principle

- Comparable accuracy principle
  - The accuracy of the measurement of the exposure of interest in the cases should be the same as that in the controls
    - Example: in a study of the effect of smoking on lung cancer it would not be appropriate to measure smoking with urine cotinine levels in the cases and with questionnaires in the controls
    - Example: in a study of a fatal disease, it is suspect to measure an exposure by questioning the relatives of diseased cases but questioning the actual controls
  - Bias caused by differential errors in the measurement of cases and controls should be eliminated (e.g. use the same measurement tools in the same way for cases and controls).

Summary of three principles of case control study design

Summary

- If the principles of study base comparability, deconfounding, and comparable accuracy are followed, then any effect detected in a study should (hopefully!) not be due to:
  - Differences in the ways cases and controls are selected from the base (selection bias)
  - Distortion of the true effect by unmeasured confounders (confounding bias)
  - Differences in the accuracy of the information from cases and controls (information bias)

Two important rules for control selection are:

- Controls should be selected from the same population - the source population (i.e. study base) - that gives rise to the study cases. If this rule cannot be followed, there needs to be solid evidence that the population supplying controls has an exposure distribution identical to that of the population that is the source of cases, which is a very stringent demand that is rarely demonstrable.
- Within strata of factors that will be used for stratification in the analysis, controls should be selected independently of their exposure status, in that the sampling rate for controls should not vary with exposure.

Rothman et al. Modern Epidemiology, 2008

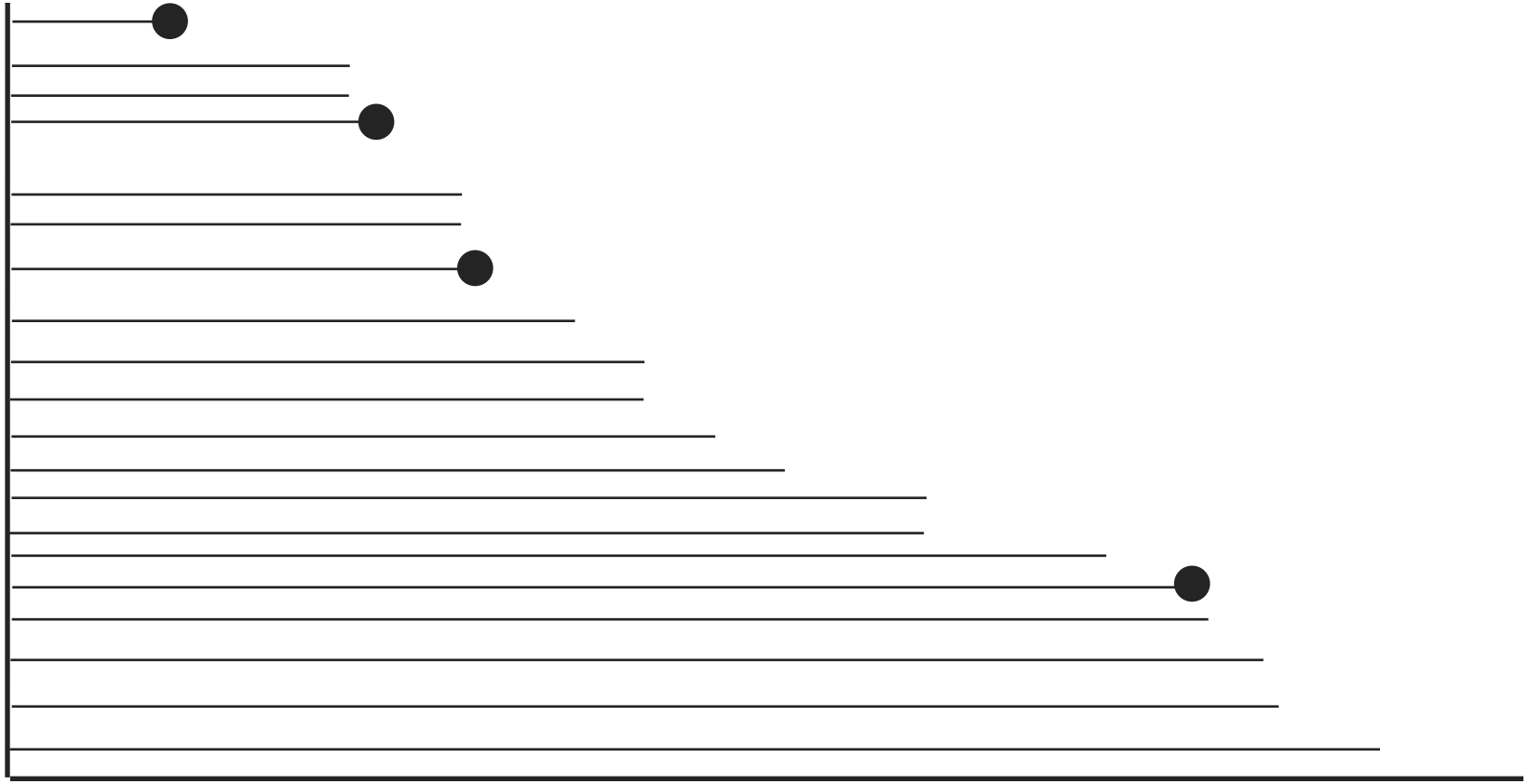
Control sampling strategies

1) Cumulative sampling (i.e. traditional case-control design): from those who do not develop the outcome until the end of the study period (i.e. from the "survivors" or prevalent cases)

2) Case-cohort design (case-base; case-referent) sampling: from the entire cohort at baseline (start of the follow-up period; when cohort is established)

3) Incidence density case control design (risk-set sampling): throughout the course of the study, from individuals at risk ("risk-set") at the time each case is diagnosed

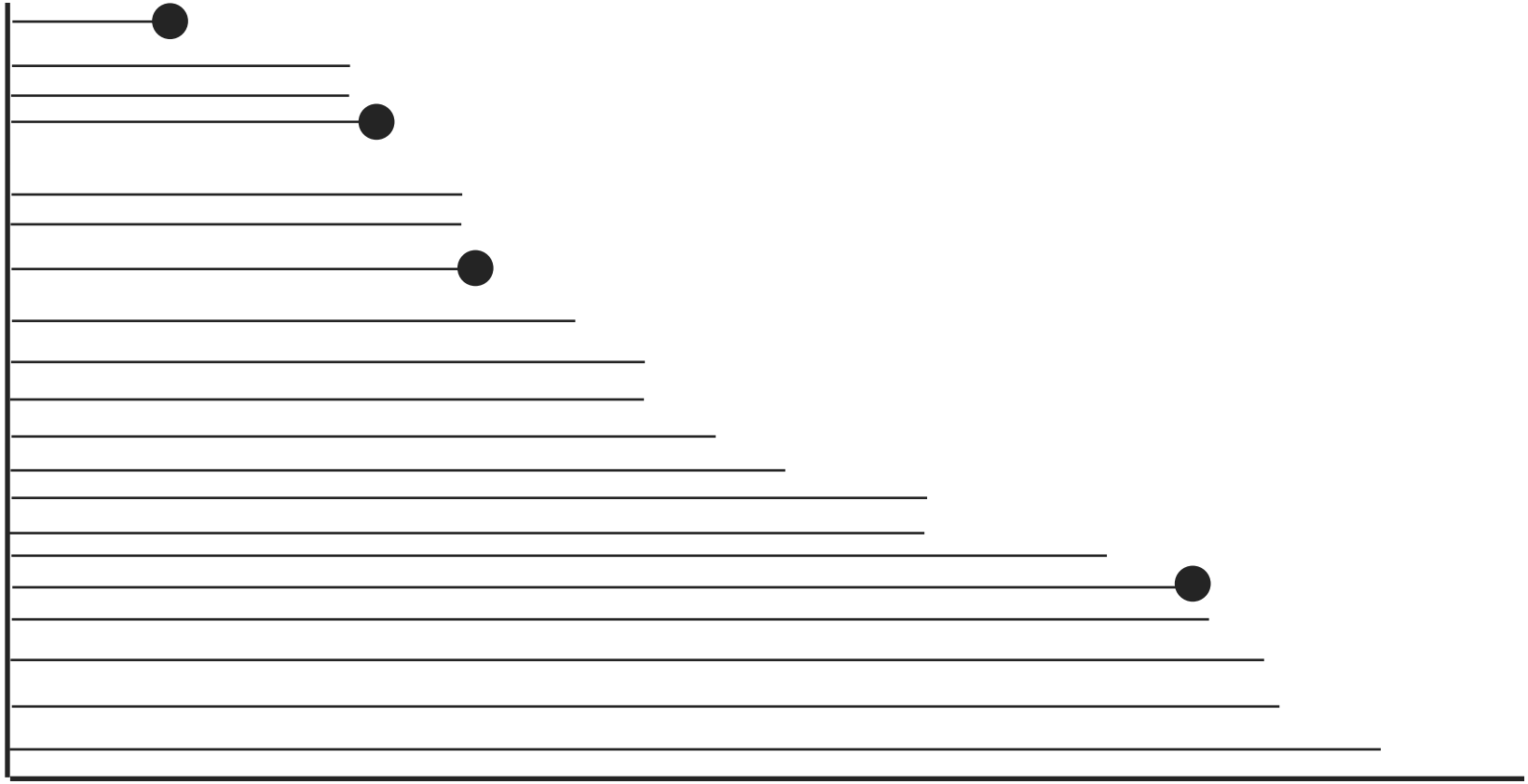
Underlying Hypothetical Cohort



Time

Courtesy: Kris Filion

Cumulative Sampling



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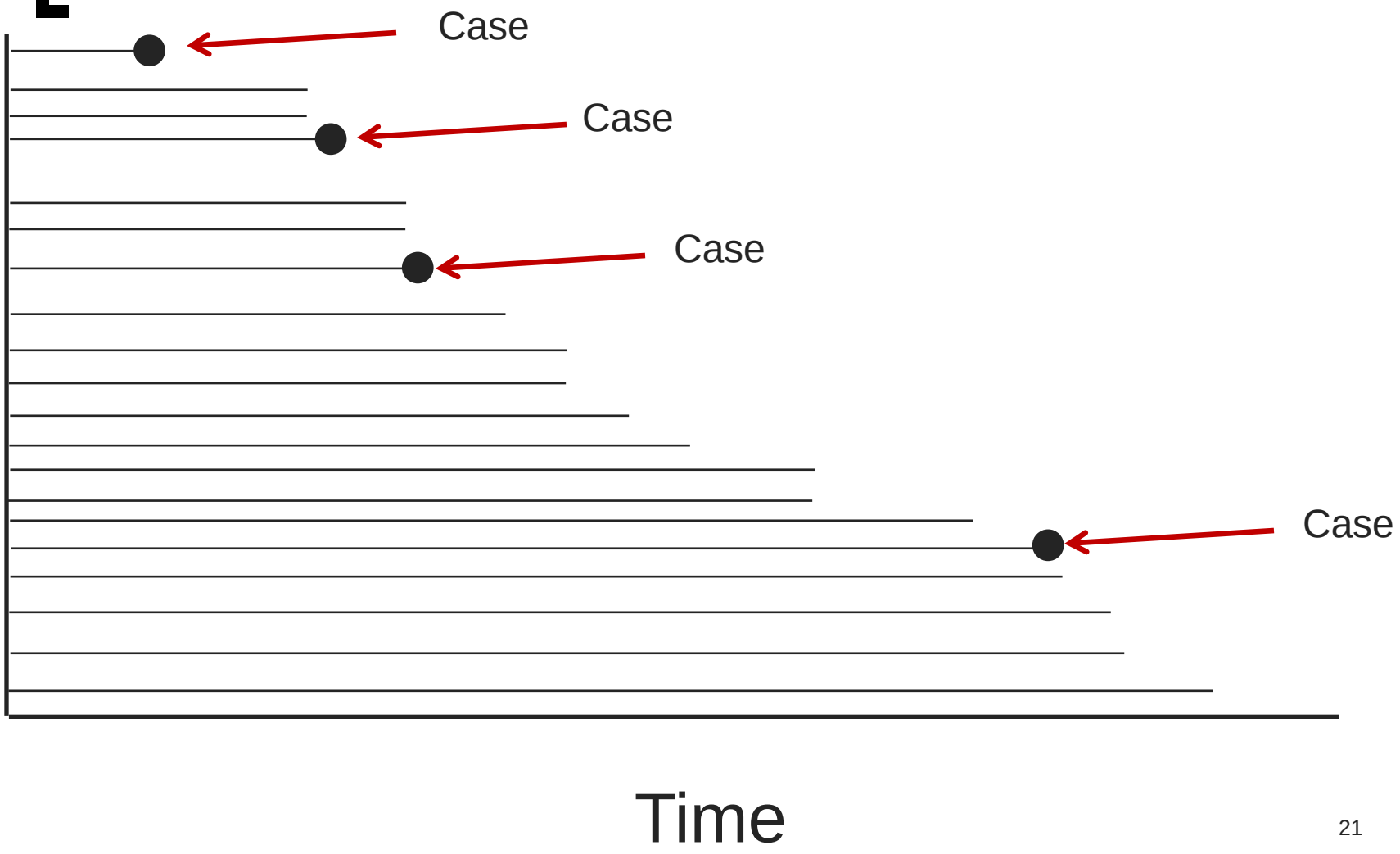

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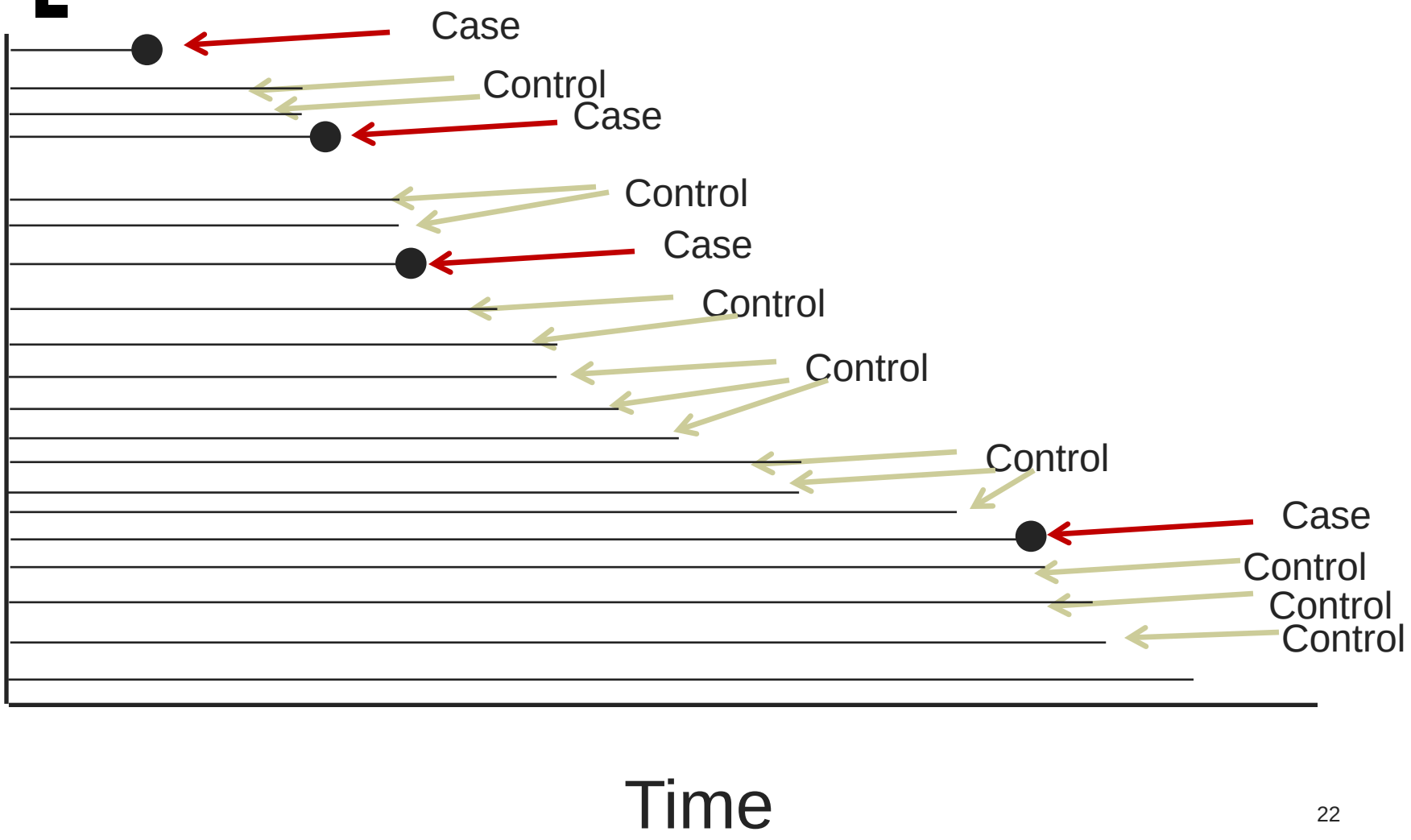

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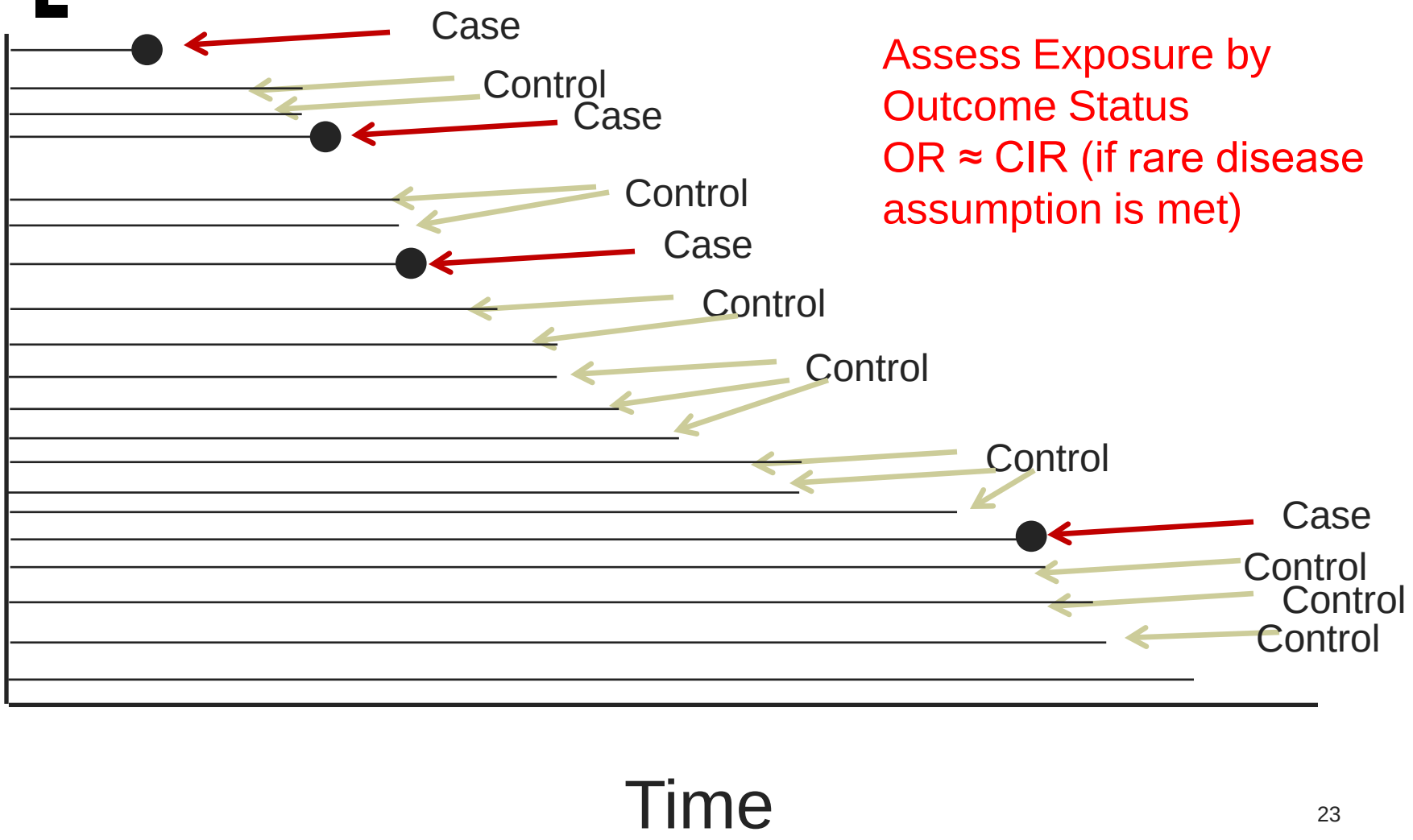
Cumulative Sampling Case-Control Study

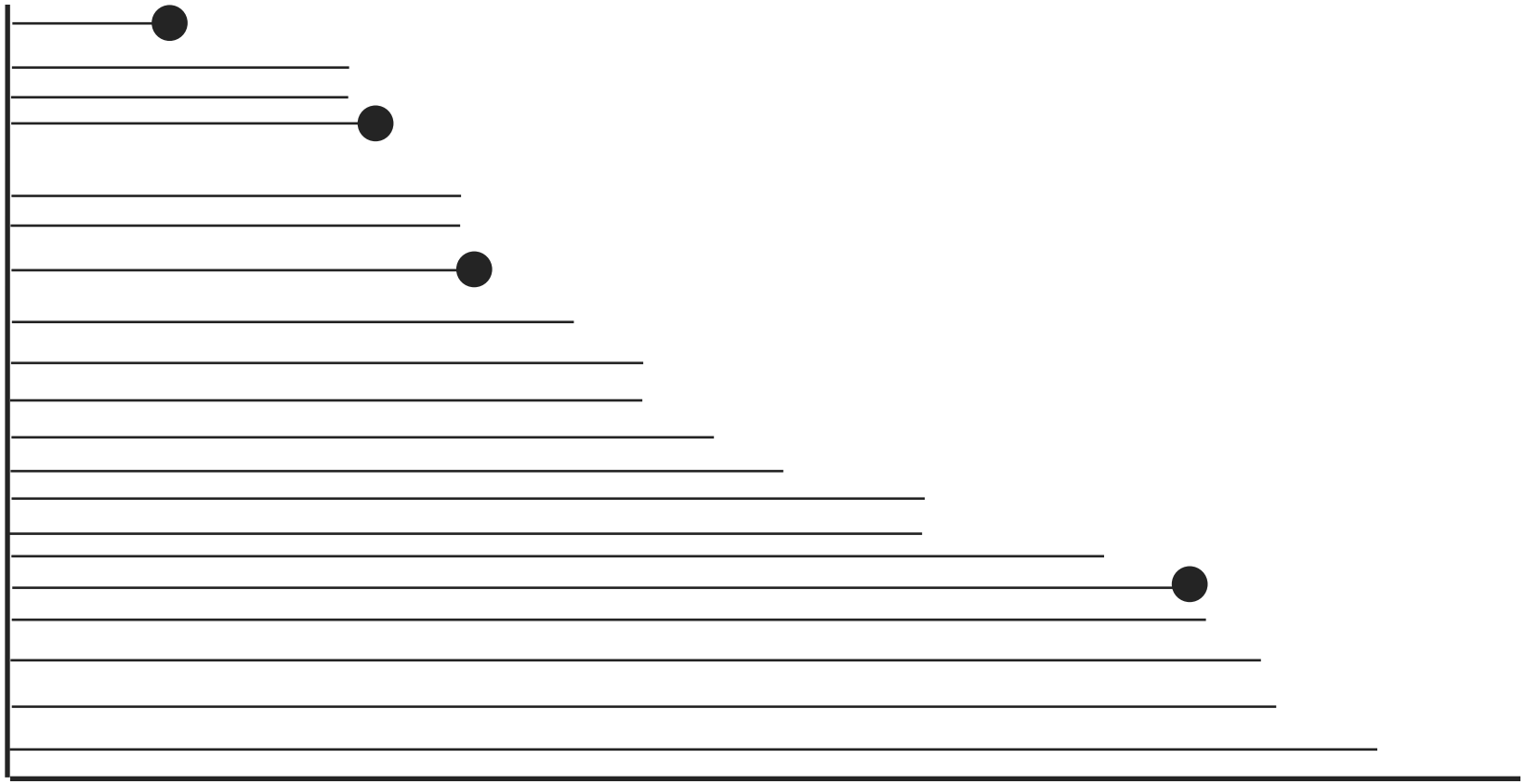


Assess Exposure by Outcome Status

OR ≈ CIR (if rare disease assumption is met)

Courtesy: Kris Filion

Case-Cohort sampling



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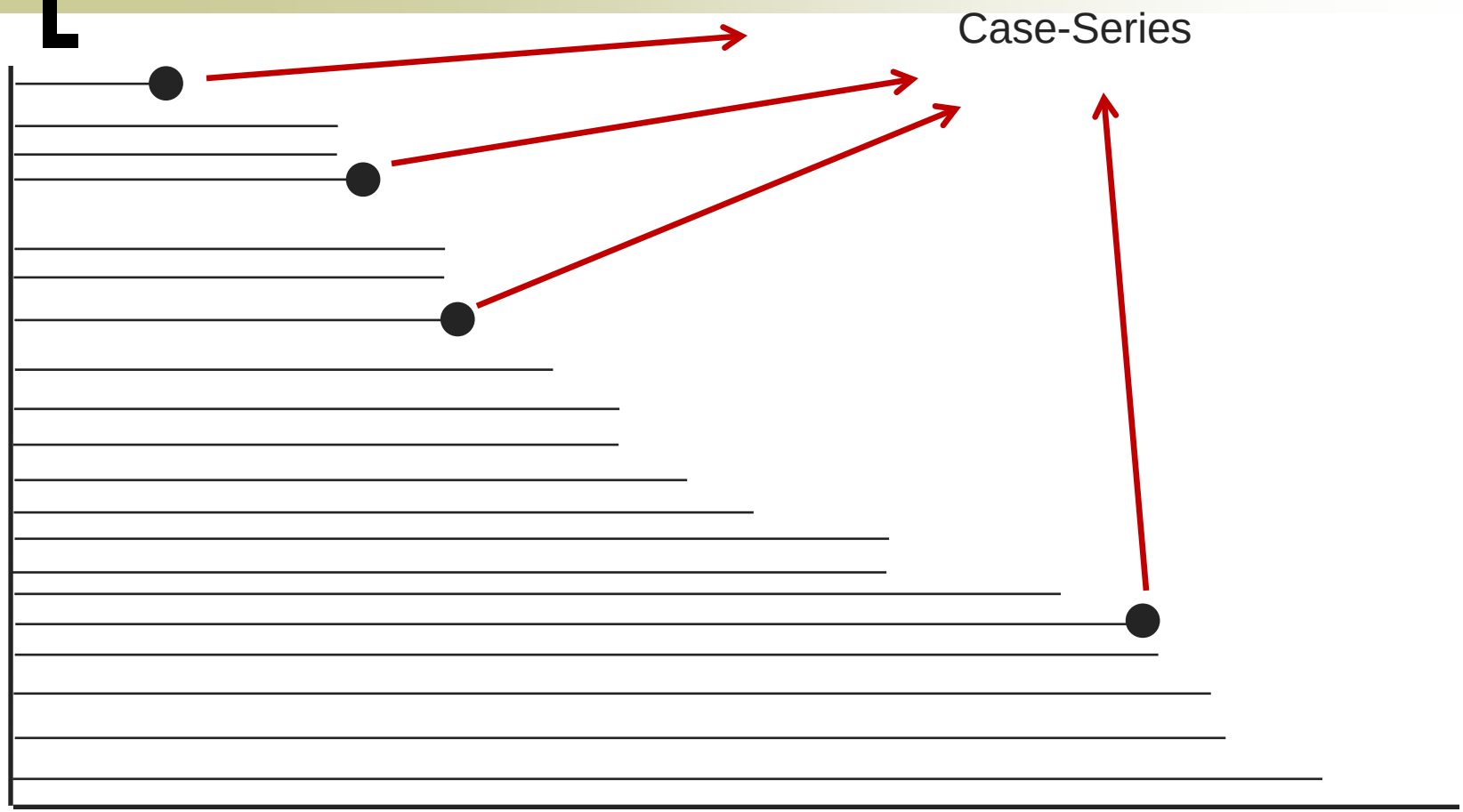
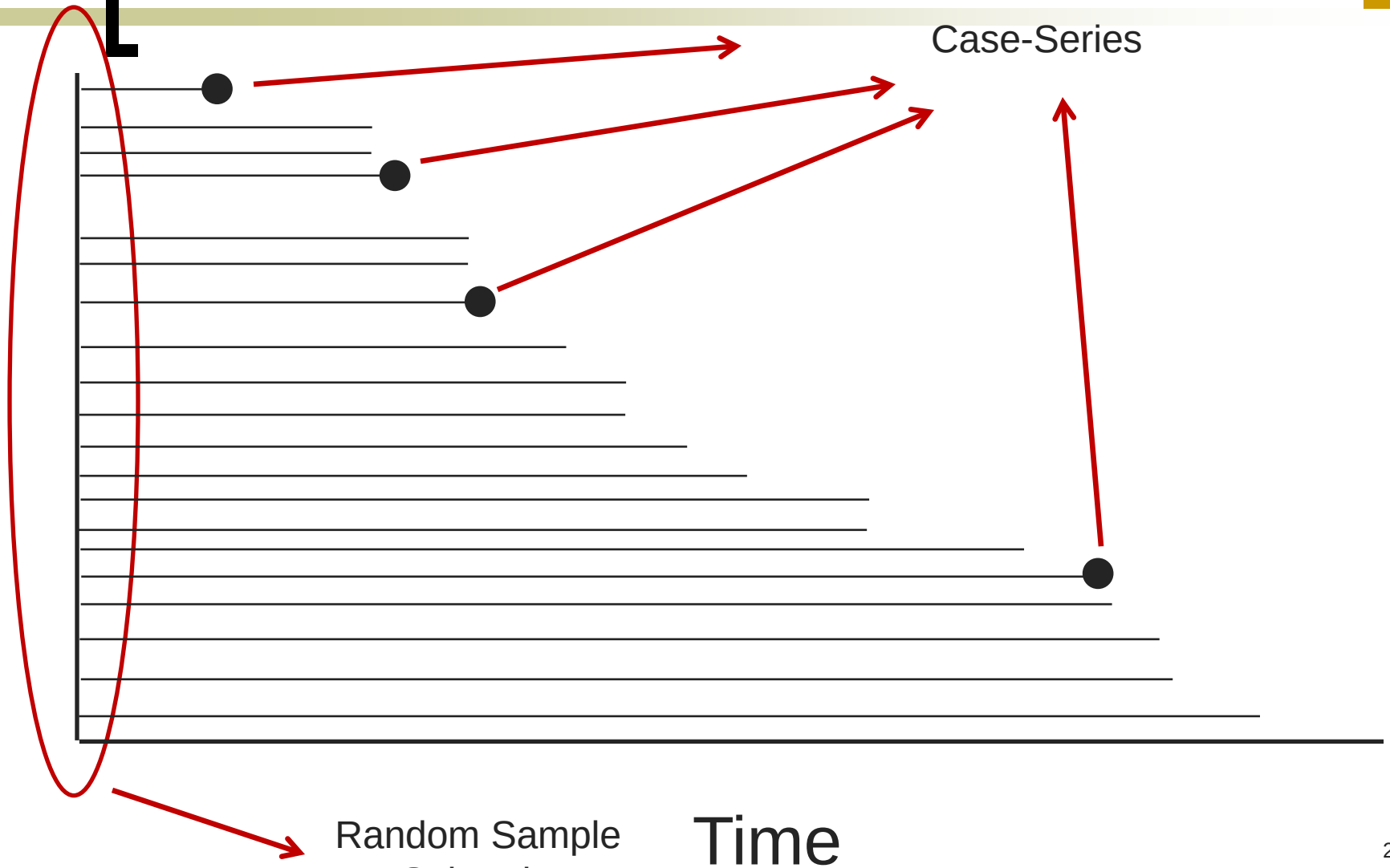
Courtesy: Kris Filion

Case-Cohort



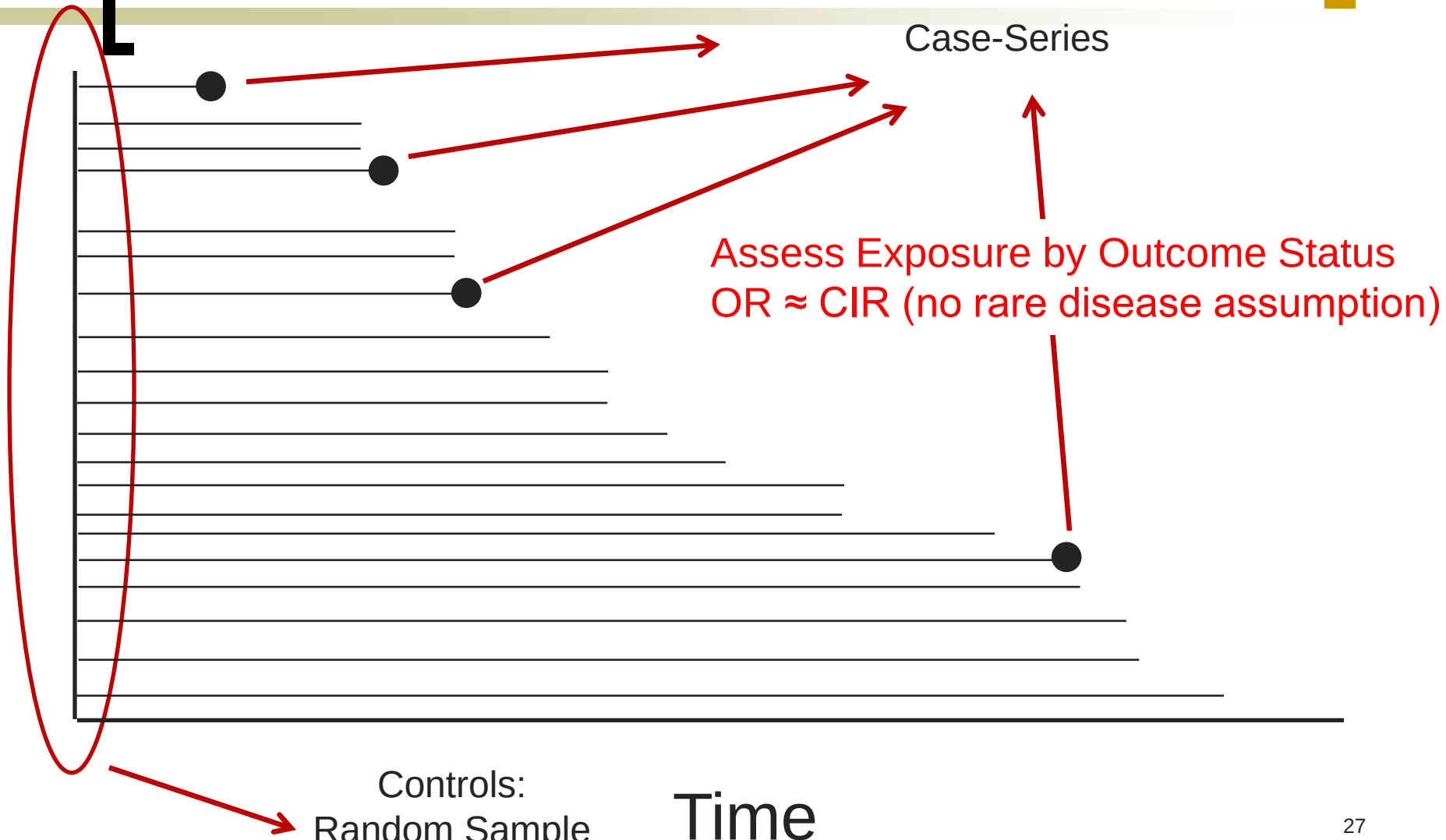
Courtesy: Kris Filion

Case-Cohort



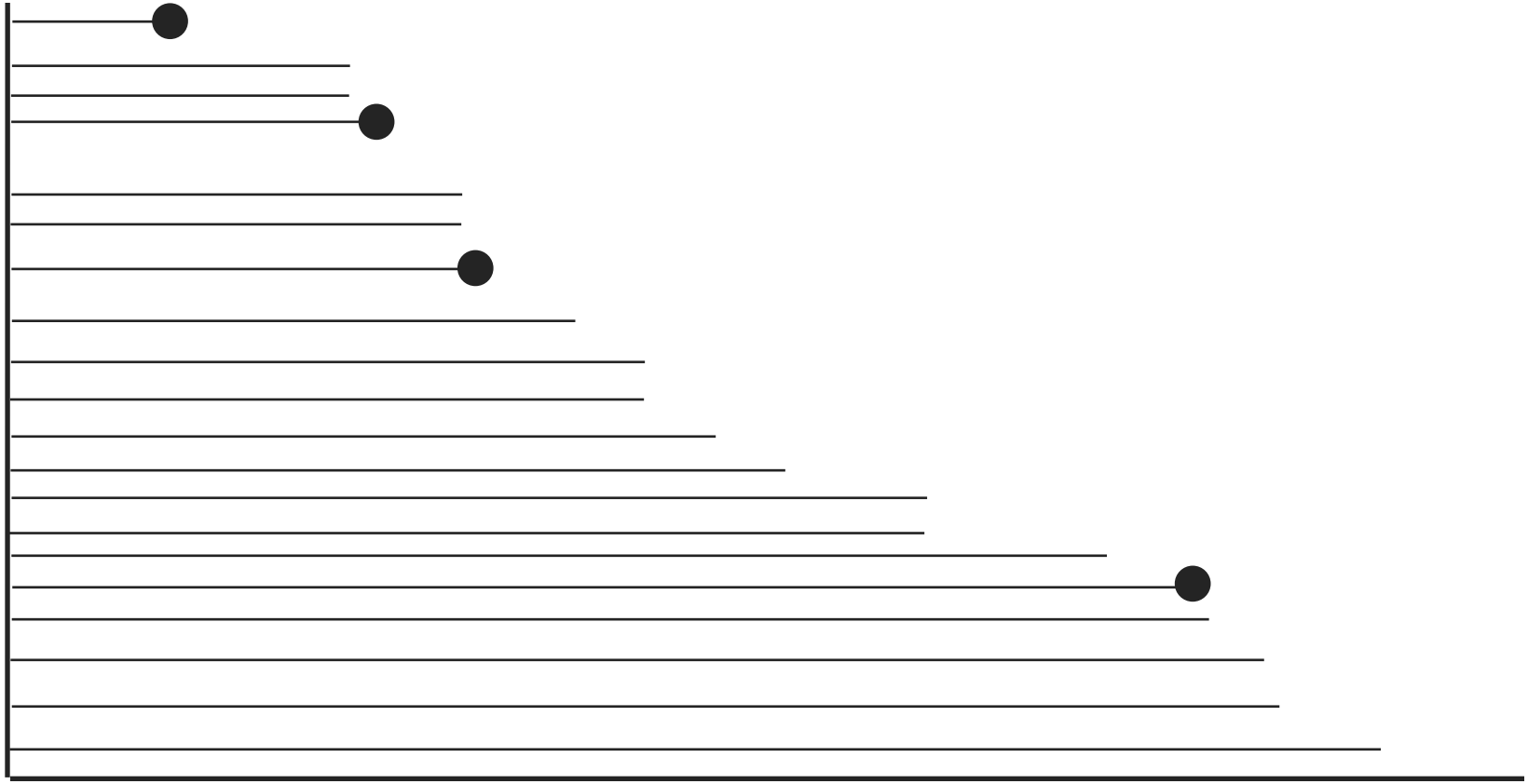
Courtesy: Kris Filion

Case-Cohort



Courtesy: Kris Filion

Incidence density sampling (nested case-control)



Time

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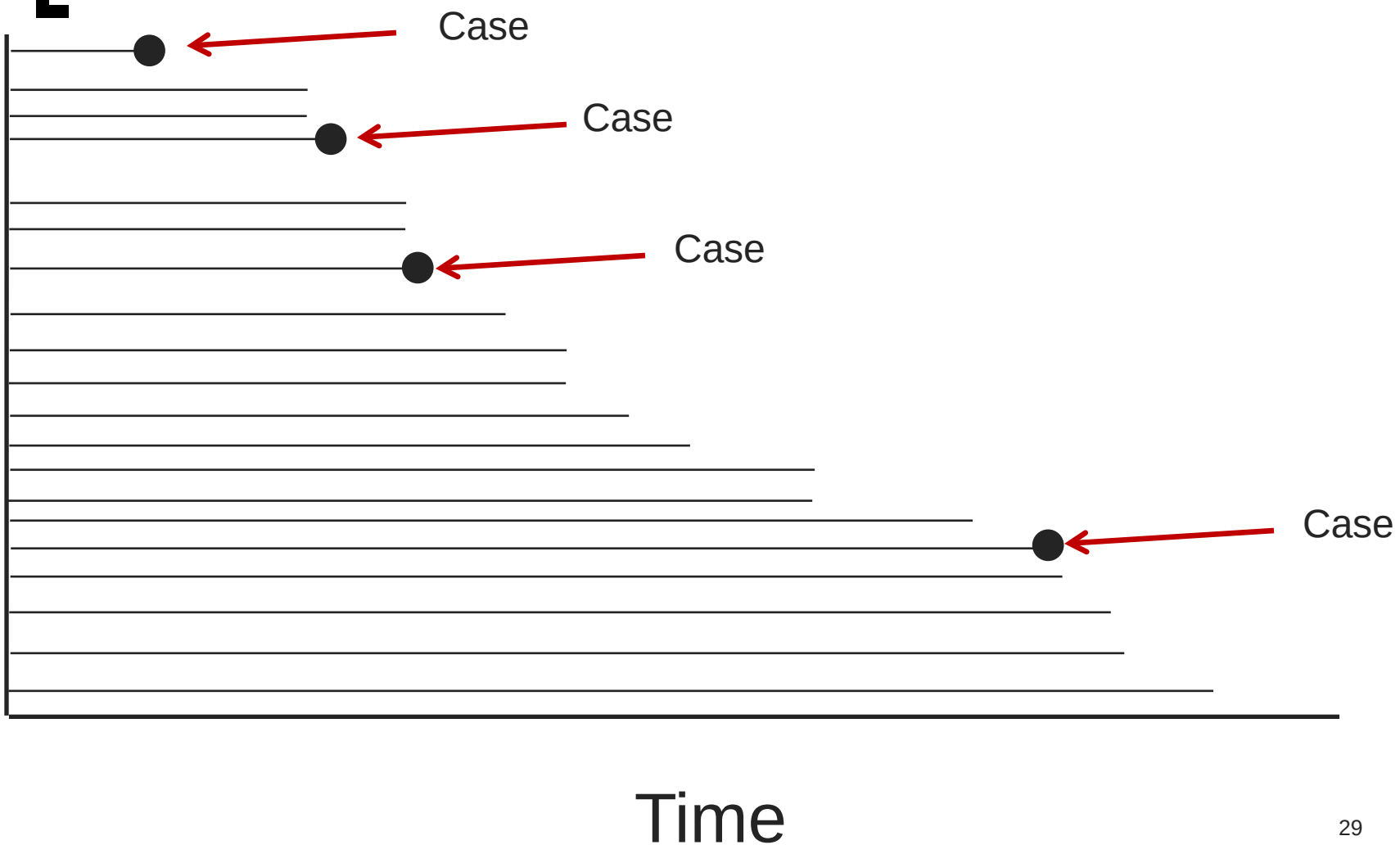

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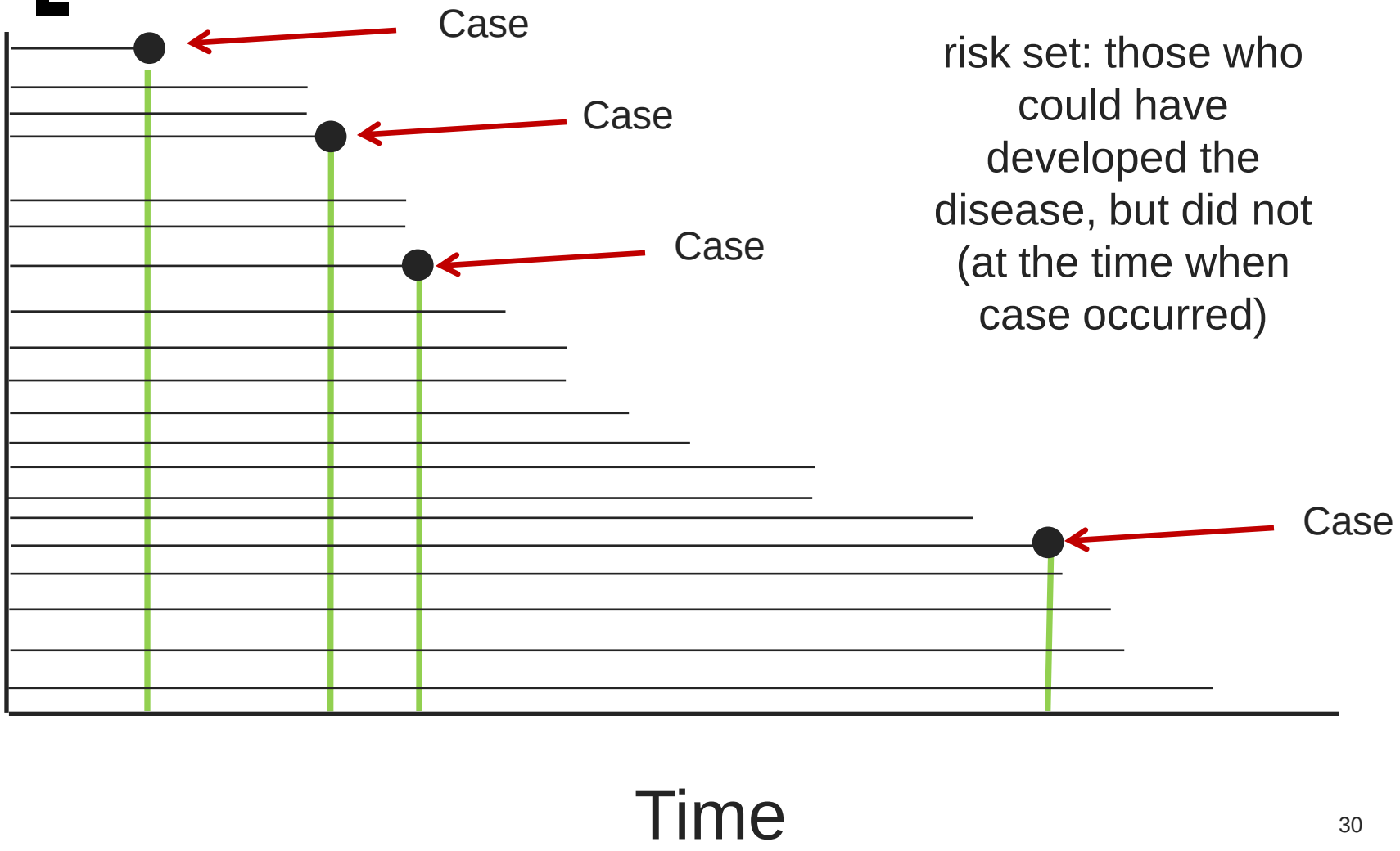

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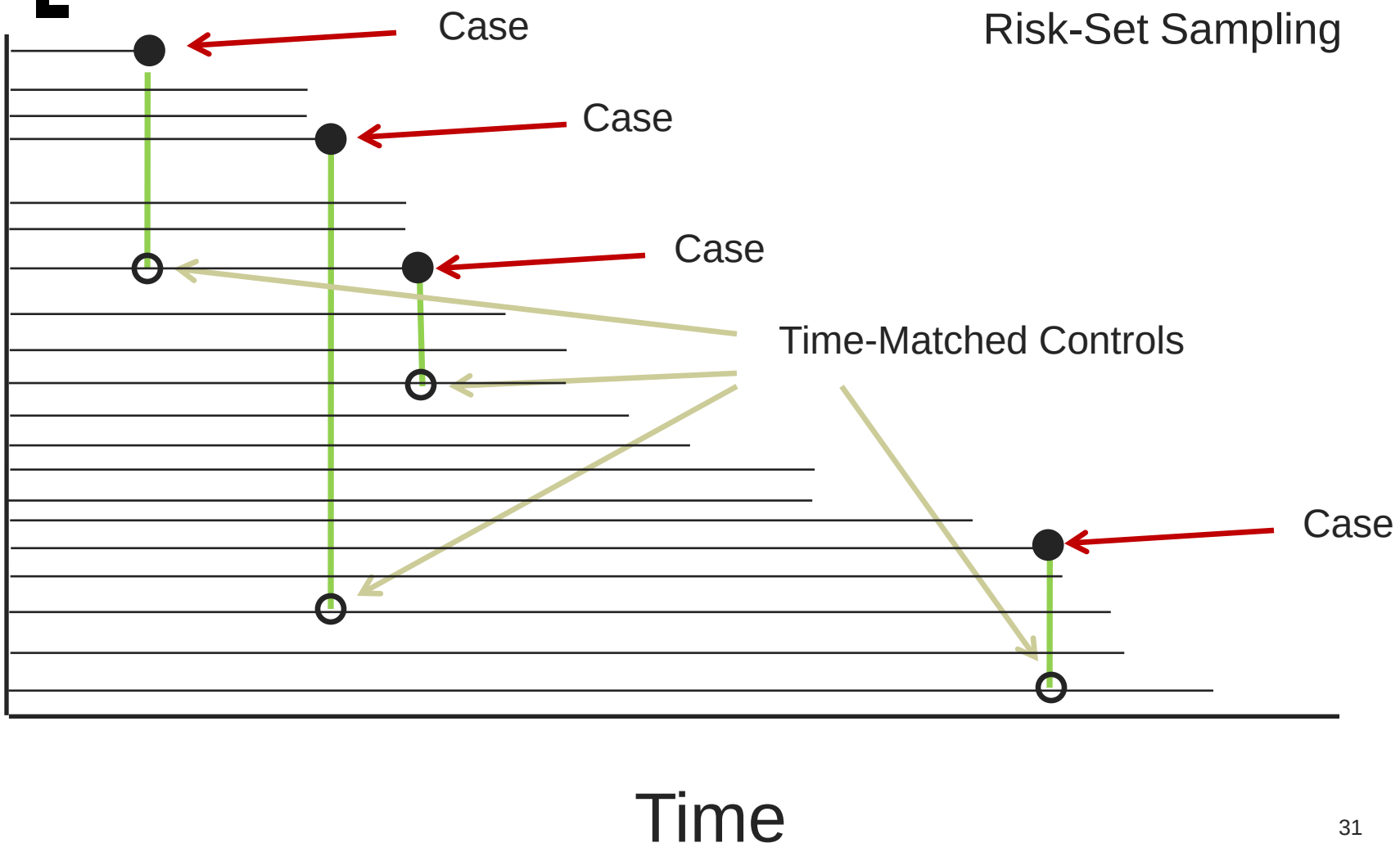

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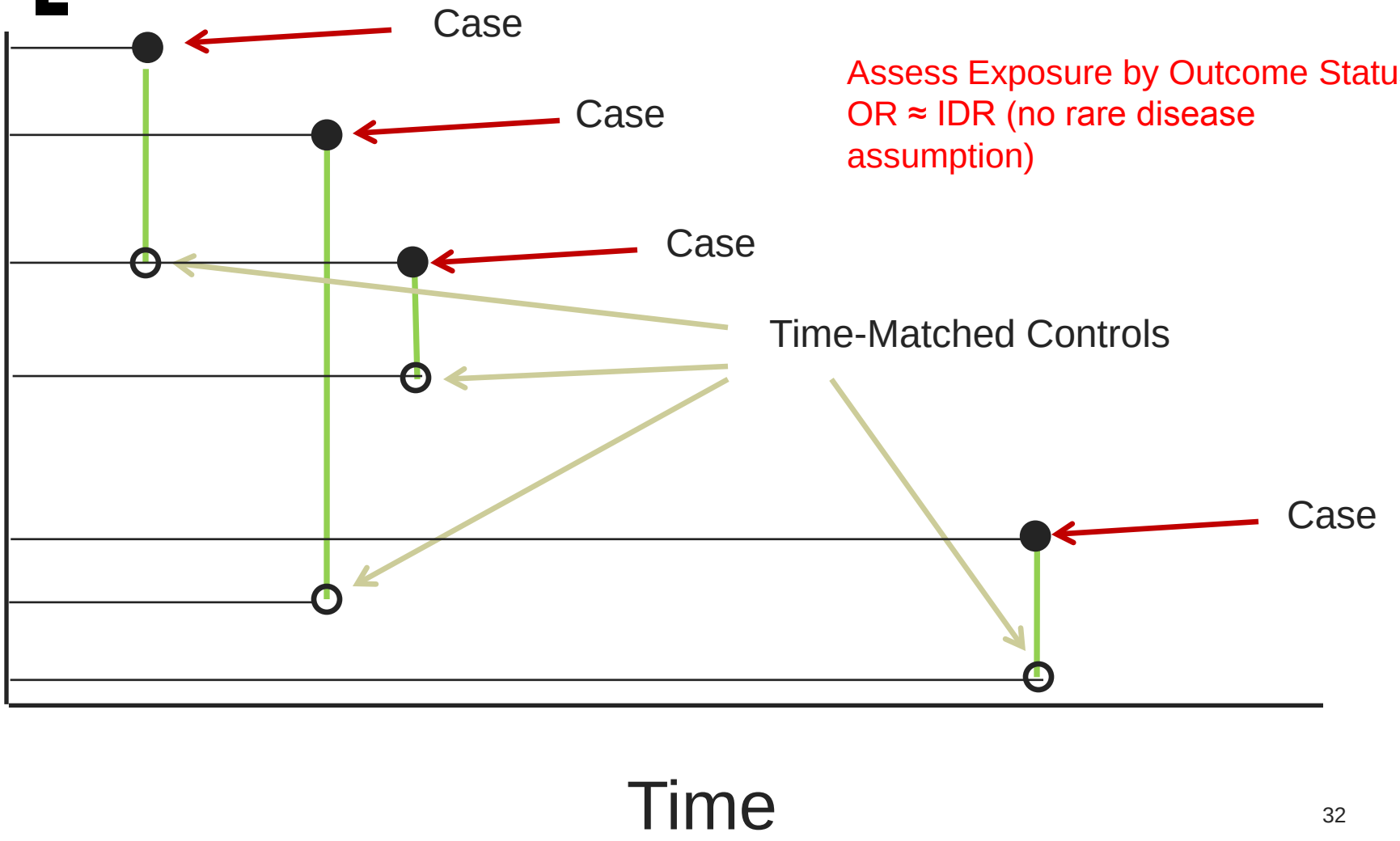
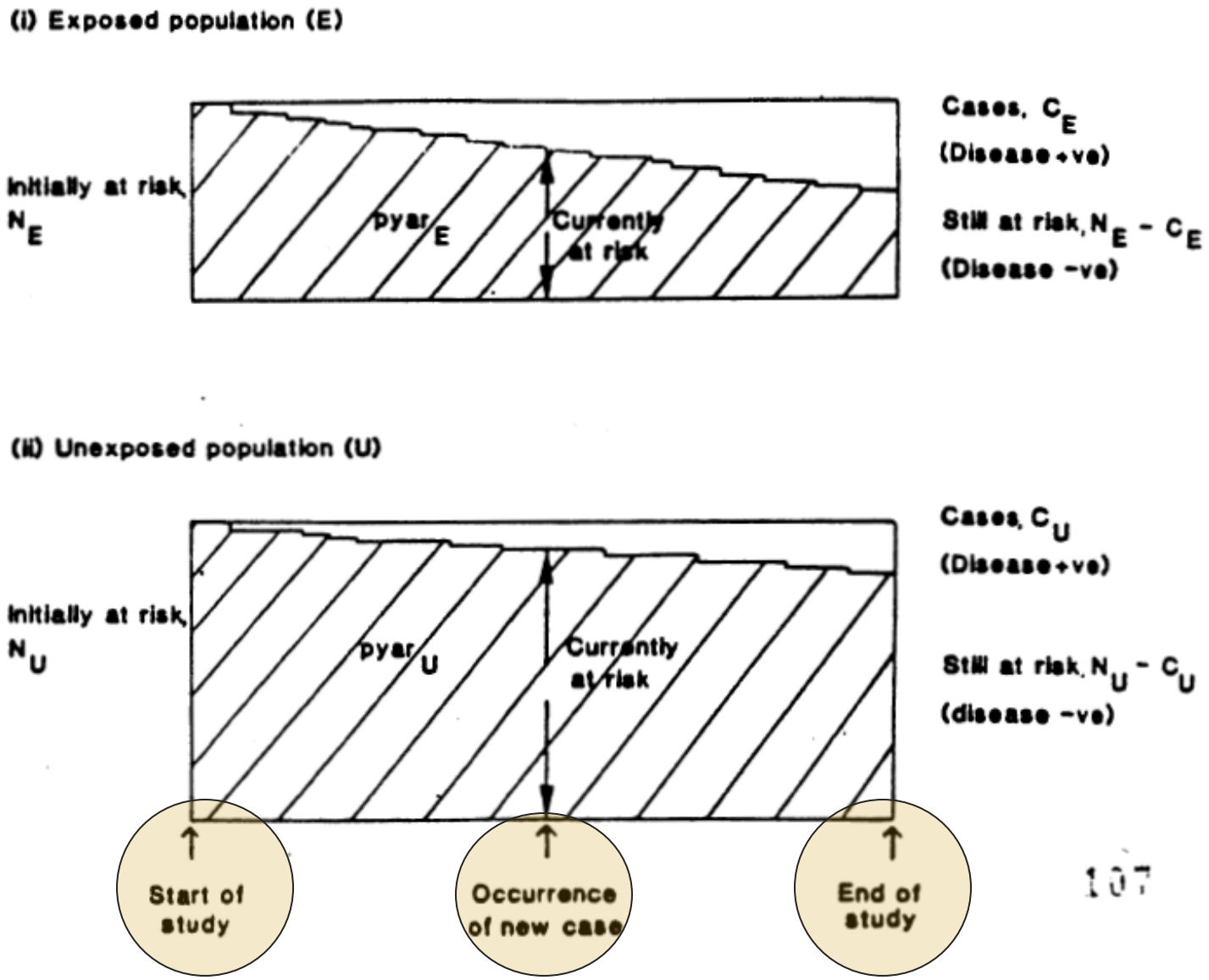
Incidence density sampling (nested case-control)



Assess Exposure by Outcome Status
OR ≈ IDR (no rare disease assumption)

Courtesy: Kris Filion

Understanding the 3 potential groups that can be sampled



Adapted from Rodrigues et al. IJE 1990

Case-control study: cumulative sampling of controls ("still at risk")

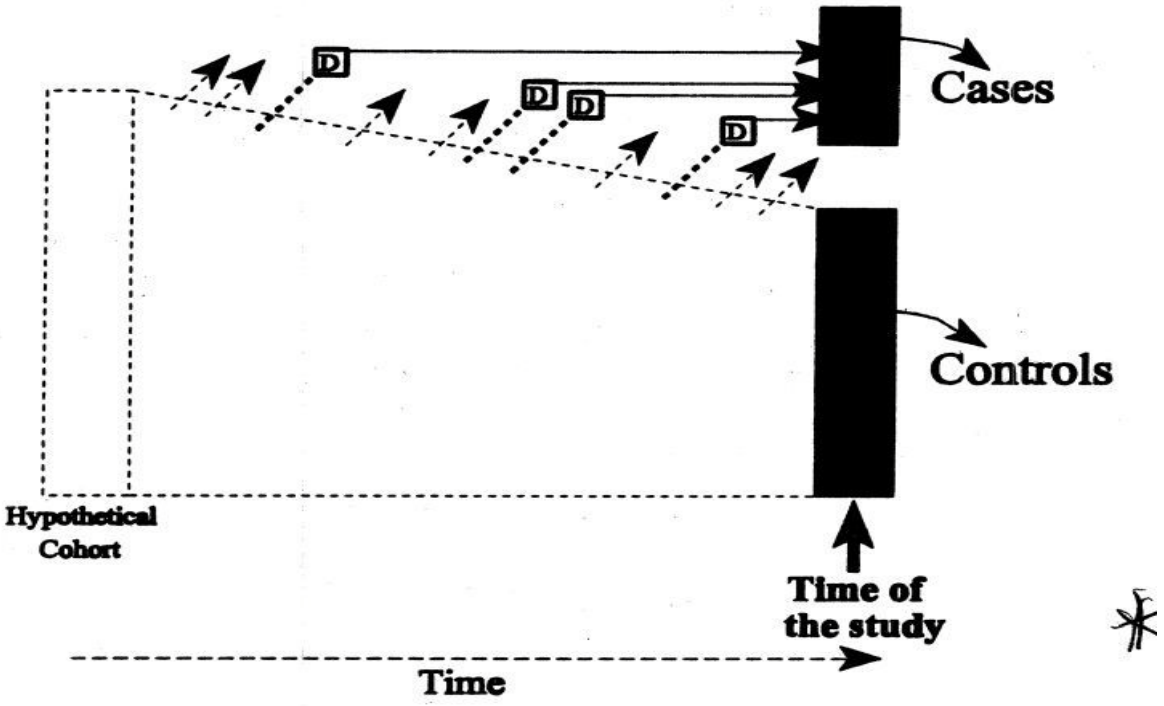


Figure 1–18 Hypothetical case-based case-control study, assuming that cases and controls are selected from a hypothetical cohort, as in Figure 1–13. The case group is assumed to include all cases that occurred in that hypothetical cohort up to the time when the study is conducted ("D" with horizontal arrows ending at the "case" bar): that is, they are assumed to be all alive and available to participate in the study; controls are selected from among those without the disease of interest (noncases) at the time when the cases are identified and assembled. Broken diagonal lines with arrows represent losses to follow-up.

Incident and prevalent cases can be included

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Case-control study: cumulative sampling of controls

Potential survival bias due to selection of cases and controls at the end of the risk period:

Only cases that survive long enough are included in the study (their exposures may have changed over time)

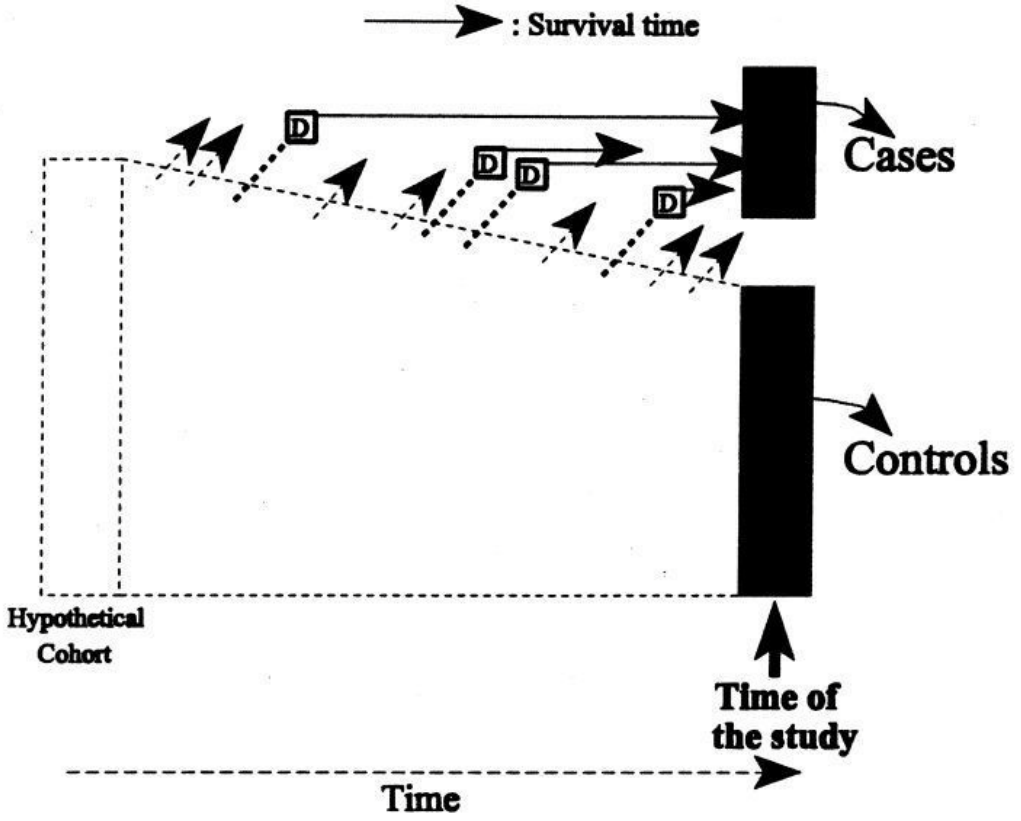


Figure 1–19 Survival bias in a case-based case-control study carried out "cross-sectionally": only cases with long survival after diagnosis (best prognosis) are included in the case group. In this hypothetical example, the horizontal lines starting in the cases' "D" boxes represent survival times; note that only two of the four cases are included in the study. Broken diagonal lines with arrows represent losses to follow-up.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Cumulative sampling design: example

Case–Control Study of Blood Lead Levels and Attention Deficit Hyperactivity Disorder in Chinese Children

Hui-Li Wang,[1] Xiang-Tao Chen,[1,2] Bin Yang,[3] Fang-Li Ma,[4] Shu Wang,[1] Ming-Liang Tang,[1] Ming-Gao Hao,[5] and Di-Yun Ruan[1]

BACKGROUND: Attention deficit/hyperactivity disorder (ADHD) and lead exposure are high-prevalence conditions among children.

OBJECTIVE: Our goal was to investigate the association between ADHD and blood lead levels (BLLs) in Chinese children, adjusting for known ADHD risk factors and potential confounding variables.

METHODS: We conducted a pair-matching case–control study with 630 ADHD cases and 630 non-ADHD controls 4–12 years of age, matched on the same age, sex, and socioeconomic status. The case and control children were systematically evaluated via structured diagnostic interviews, including caregiver interviews, based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., revised criteria (DSM-IV-R). We evaluated the association between BLLs and ADHD using the Pearson chi-square test for categorical variables and the Student *t*-test for continuous data. We then performed conditional multiple variables logistic regression analyses with backward stepwise selection to predict risk factors for ADHD.

RESULTS: There was a significant difference in BLLs between ADHD cases and controls. ADHD cases were more likely to have been exposed to lead during childhood than the non-ADHD control subjects, with adjustment for other known risk factors [children with BLLs ≥ 10 μg/dL vs. ≤ 5 μg/dL; OR = 6.0; 95% confidence interval (CI) = 4.10–8.77, $p < 0.01$; 5–10 μg/dL vs. ≤ 5 μg/dL, OR = 4.9; 95% CI = 3.47–6.98, $p < 0.01$]. These results were not modified by age and sex variables.

CONCLUSIONS: This was the largest sample size case–control study to date to study the association between BLLs and ADHD in Chinese children. ADHD may be an additional deleterious outcome of lead exposure during childhood, even when BLLs are < 10 μg/dL.

KEY WORDS: attention deficit hyperactivity disorder, blood lead levels, case–control study. *Environ Health Perspect* 116:1401–1406 (2008). doi:10.1289/ehp.11400 available via *http://dx.doi.org/* [Online 5 June 2008]

ADHD subjects were consecutively recruited from children coming for initial or follow-up assessment from October 2003 to August 2007 in two pediatric Clinics [Note: prevalent cases are included]

The non-ADHD controls were randomly selected from computerized lists of outpatients admitted for acute upper respiratory infection at the same two pediatric medical clinics during the same period

Case-control study: case-cohort (case-base) sampling of controls ("initially at risk")

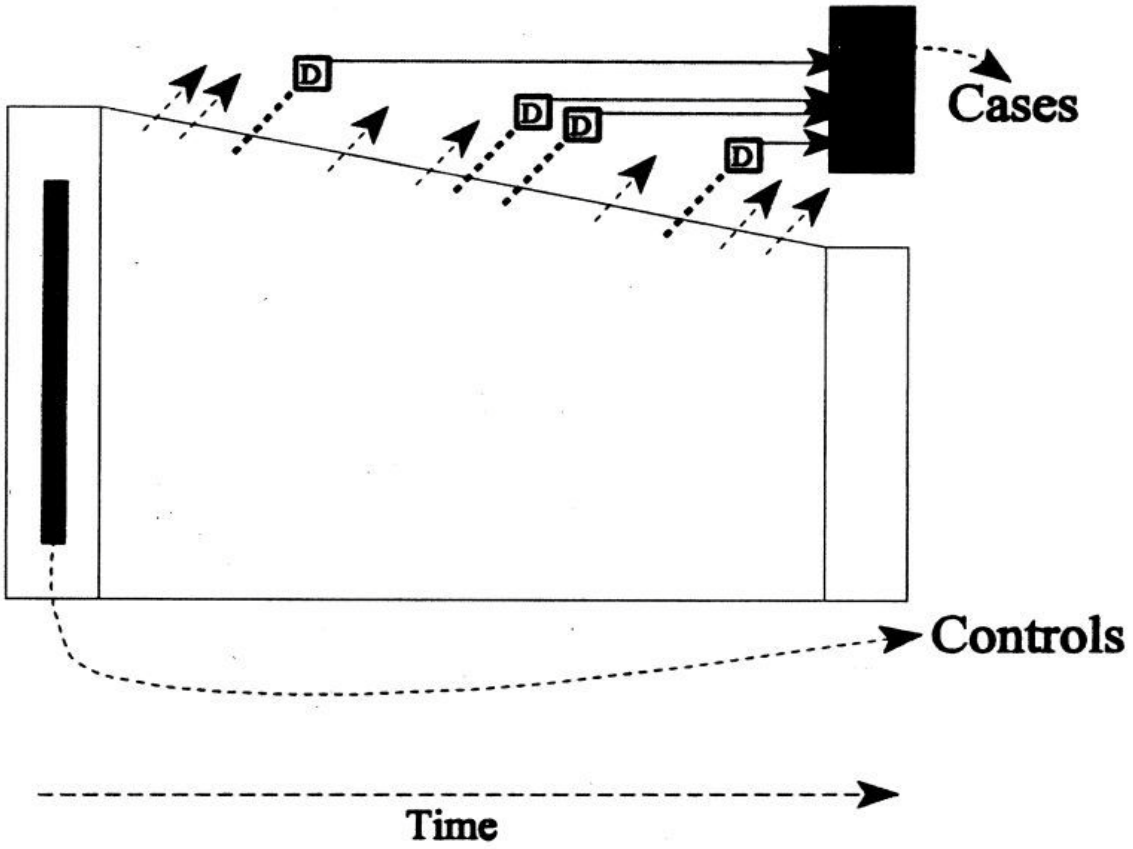


Figure 1–20 Case-control study in which the controls are selected from the baseline cohort (case-cohort study). Cases are represented by "D" boxes. Broken diagonal lines with arrows represent losses to follow-up.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Case-cohort design

- Selection of cases
  - Because of the cohort nature of this design, it should be possible to include all the cases (or an appropriate random sample of them)
- Selection of controls
  - All or random sample from among those in the baseline cohort
    - Same set of controls can be used for several case-control studies (for various outcomes)
  - This does include some who later become cases
    - Special analytic techniques (specifically a variation of the Cox proportional hazards model) are used

Case-cohort design: example

European Journal of Epidemiology (2007) 22:173–181
DOI 10.1007/s10654-006-9099-5

PERINATAL EPIDEMIOLOGY

Oral clefts and life style factors – A case–cohort study based on prospective Danish data

Camilla Bille[1,8], Jorn Olsen[2], Werner Vach[3], Vibeke Kildegaard Knudsen[4], Sjurdur Frodi Olsen[4], Kirsten Rasmussen[5], Jeffrey C. Murray[1,6], Anne Marie Nybo Andersen[7] & Kaare Christensen[1]

Abstract. This study examines the association between oral clefts and first trimester maternal lifestyle factors based on prospective data from the Danish National Birth Cohort. The cohort includes approximately 100,000 pregnancies. In total 192 mothers gave birth to child with an oral cleft during 1997–2003. Information on risk factors such as smoking, alcohol consumption, tea, coffee, cola, and food supplements was obtained during pregnancy for these and 828 randomly selected controls. We found that first trimester maternal smoking was associated with an increased risk of oral clefts (odds ratio (OR): 1.50; 95% confidence interval (CIs): 1.05, 2.14). Although not statistically significant, we also saw associations with first trimester consumption of alcohol (OR: 1.11; CIs: 0.79, 1.55), tea (OR: 1.31; CIs: 0.93, 1.86), and drinking more than 1 l of cola per week (OR: 1.40; CIs: 0.92, 2.12). Furthermore supplementation with ≥400 mcg folic acid daily during the entire first trimester (OR: 0.75; CIs: 0.46, 1.22) suggested an inverse associated with oral clefts, similar to our results on coffee drinking. No effects were found for smaller doses of folic acid, vitamin A, B6 or B12 in this study. The present study found an association between oral clefts and smoking and, although not conclusive, supports an association of oral cleft with alcohol.

Cases were identified through 2 sources: (1) maternally reported oral clefts in post pregnancy interviews in the birth cohort ; and (2) a discharge diagnosis of oral clefts or an ICD-10 code for reconstructive surgery on lips or palate in The National Patient Register.

Controls were selected randomly among participants at baseline (the first interview) in the birth cohort.

Case-control study: incidence density sampling of those "currently at risk" (nested case-control study)

Also called "risk set" or "density" sampling of controls who are "currently at risk"

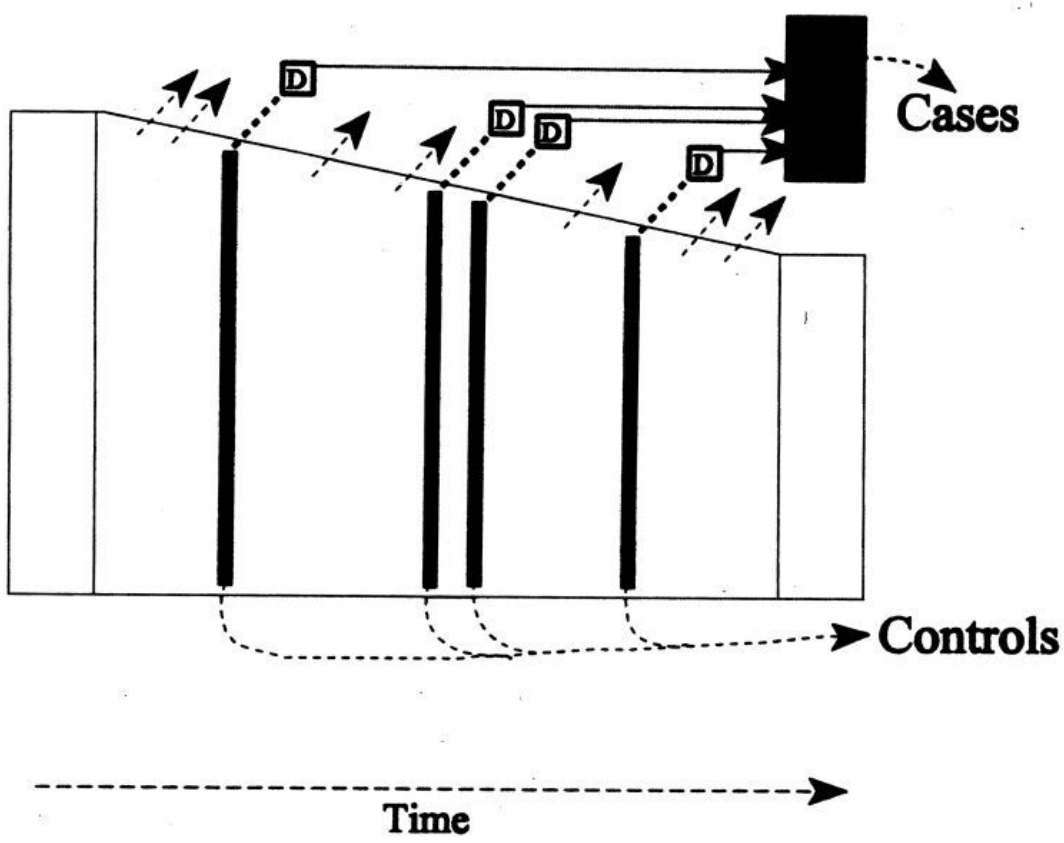


Figure 1–21 Nested case-control study in which the controls are selected at each time when a case occurs (incidence density sampling). Cases are represented by "D" boxes. Broken diagonal lines with arrows represent losses to follow-up.

Szklo & Nieto. Epidemiology: beyond the basics. Aspen Publishers, 2000

Nested case control study

- Selection of cases
  - Because of the cohort nature of this design, it should be possible to include all the new cases (or an appropriate random sample of them) – important to include only incident cases (not prevalent cases)
- Selection of controls
  - Each control is randomly sampled from the cohort at risk at the time a case is defined (currently at risk)
  - This strategy is called “incidence density sampling” or “risk-set sampling”
  - This is the equivalent of matching cases and controls on length of person-time follow-up—and needs the use of “matched data” analyses (matching on time)
  - Controls may end up as cases later on and that is fine
  - The same control may get selected (by chance) for more than one case during the follow-up and that is fine

Nested case-control: example

Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study

David J Graham, David Campen, Rita Hui, Michele Spence, Craig Cheetham, Gerald Levy, Stanford Shoor, Wayne A Ray

Summary

Background Controversy has surrounded the question about whether high-dose rofecoxib increases or naproxen decreases the risk of serious coronary heart disease. We sought to establish if risk was enhanced with rofecoxib at either high or standard doses compared with remote non-steroidal anti-inflammatory drug (NSAID) use or celecoxib use, because celecoxib was the most common alternative to rofecoxib.

Methods We used data from Kaiser Permanente in California to assemble a cohort of all patients age 18–84 years treated with a NSAID between Jan 1, 1999, and Dec 31, 2001, within which we did a nested case-control study. Cases of serious coronary heart disease (acute myocardial infarction and sudden cardiac death) were risk-set matched with four controls for age, sex, and health plan region. Current exposure to cyclo-oxygenase 2 selective and non-selective NSAIDs was compared with remote exposure to any NSAID, and rofecoxib was compared with celecoxib.

Findings During 2 302 029 person-years of follow-up, 8143 cases of serious coronary heart disease occurred, of which 2210 (27·1%) were fatal. Multivariate adjusted odds ratios versus celecoxib were: for rofecoxib (all doses), 1·59 (95% CI 1·10–2·32, p=0·015); for rofecoxib 25 mg/day or less, 1·47 (0·99–2·17, p=0·054); and for rofecoxib greater than 25 mg/day, 3·58 (1·27–10·11, p=0·016). For naproxen versus remote NSAID use the adjusted odds ratio was 1·14 (1·00–1·30, p=0·05).

Interpretation Rofecoxib use increases the risk of serious coronary heart disease compared with celecoxib use. Naproxen use does not protect against serious coronary heart disease.

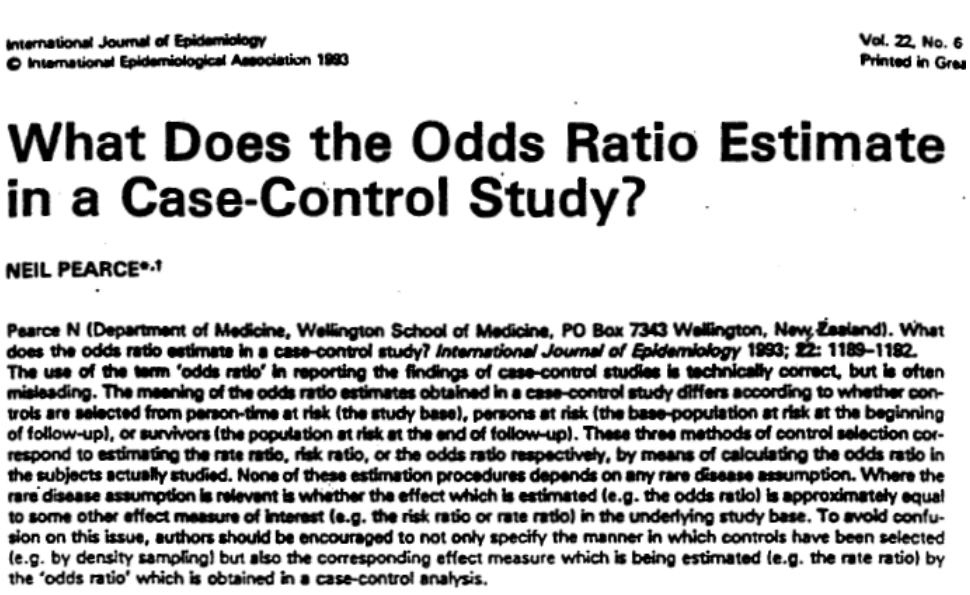
We assembled a cohort of NSAID-treated patients to undertake a nested case-control study. From Jan 1, 1999, to Dec 31, 2001, we identified all individuals age 18–84 years who filled at least one prescription for a COX2 selective (celecoxib or rofecoxib) or non-selective (all other) NSAID. Those with at least 12 months of health plan coverage before the date of that first NSAID prescription were entered into the cohort if they had no diagnoses of cancer, renal failure, liver failure, severe respiratory disease, organ transplantation, or HIV/AIDS during the screening interval. We followed up cohort members from this entry date until the end of the study period (December, 2001) or until occurrence of an acute myocardial infarction or death, whichever came first.

For every case, we randomly selected four controls from individuals under observation in the study cohort on the date of the case event (index date), and matched them for age (year of birth), sex, and health plan region (north or south).[17] A given cohort member selected as a control for a case on one date could become a control for another case occurring on a later index date, as long as he or she remained in the study cohort and was therefore also at risk of becoming a case. Thus, a control could subsequently become a case. We excluded potential cases and controls if they were not enrolled on the index date and for at least 11 of the 12 preceding months. During the study period, pharmacy benefits persisted for enrolment lapses of up to 1 calendar month.

Nested case control design vs. case-cohort design

- Both are useful for studying rare outcomes
- Case-cohort design
  - Is an unmatched variant of the nested case control
  - Selects controls as a subcohort (random sample) of the original cohort—advantages of this design arise from this use of random sampling
- Nested-case control design
  - Selects controls matched on time (of case diagnosis) to cases
  - Its advantages arise from its control (by matching) of time

What effect measures do the 3 designs actually estimate?



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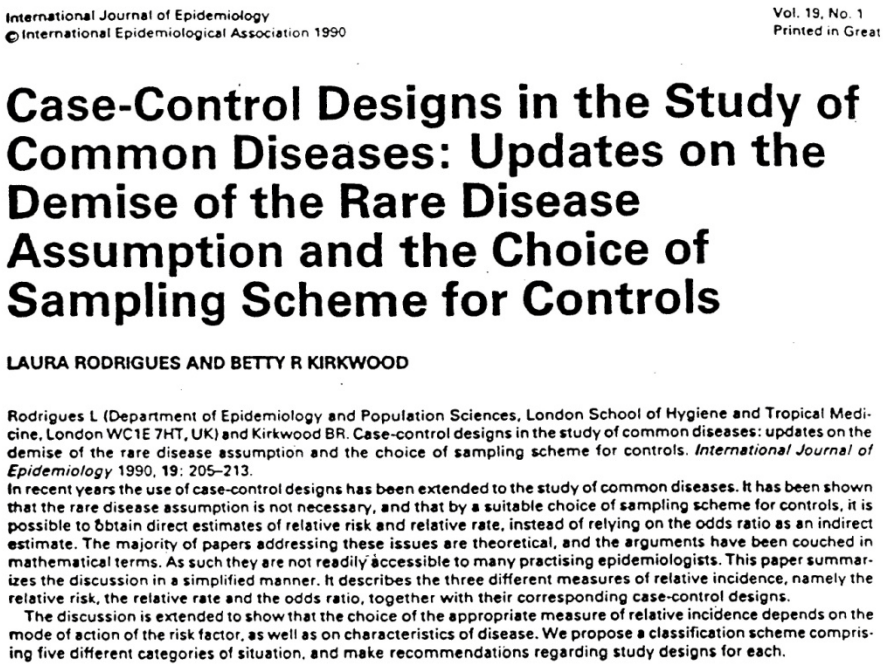
What Does the Odds Ratio Estimate in a Case-Control Study?

NEIL PEARCE*,†

Pearce N (Department of Medicine, Wellington School of Medicine, PO Box 7343 Wellington, New Zealand). What does the odds ratio estimate in a case-control study? *International Journal of Epidemiology* 1993; 22: 1189–1192.
The use of the term 'odds ratio' in reporting the findings of case-control studies is technically correct, but is often misleading. The meaning of the odds ratio estimates obtained in a case-control study differs according to whether controls are selected from person-time at risk (the study base), persons at risk (the base-population at risk at the beginning of follow-up), or survivors (the population at risk at the end of follow-up). These three methods of control selection correspond to estimating the rate ratio, risk ratio, or the odds ratio respectively, by means of calculating the odds ratio in the subjects actually studied. None of these estimation procedures depends on any rare disease assumption. Where the rare disease assumption is relevant is whether the effect which is estimated (e.g. the odds ratio) is approximately equal to some other effect measure of interest (e.g. the risk ratio or rate ratio) in the underlying study base. To avoid confusion on this issue, authors should be encouraged to not only specify the manner in which controls have been selected (e.g. by density sampling) but also the corresponding effect measure which is being estimated (e.g. the rate ratio) by the 'odds ratio' which is obtained in a case-control analysis.



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Case-Control Designs in the Study of Common Diseases: Updates on the Demise of the Rare Disease Assumption and the Choice of Sampling Scheme for Controls

LAURA RODRIGUES AND BETTY R KIRKWOOD

Rodrigues L (Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK) and Kirkwood BR. Case-control designs in the study of common diseases: updates on the demise of the rare disease assumption and the choice of sampling scheme for controls. *International Journal of Epidemiology* 1990, 19: 205–213.
In recent years the use of case-control designs has been extended to the study of common diseases. It has been shown that the rare disease assumption is not necessary, and that by a suitable choice of sampling scheme for controls, it is possible to obtain direct estimates of relative risk and relative rate, instead of relying on the odds ratio as an indirect estimate. The majority of papers addressing these issues are theoretical, and the arguments have been couched in mathematical terms. As such they are not readily accessible to many practising epidemiologists. This paper summarizes the discussion in a simplified manner. It describes the three different measures of relative incidence, namely the relative risk, the relative rate and the odds ratio, together with their corresponding case-control designs.
The discussion is extended to show that the choice of the appropriate measure of relative incidence depends on the mode of action of the risk factor, as well as on characteristics of disease. We propose a classification scheme comprising five different categories of situation, and make recommendations regarding study designs for each.

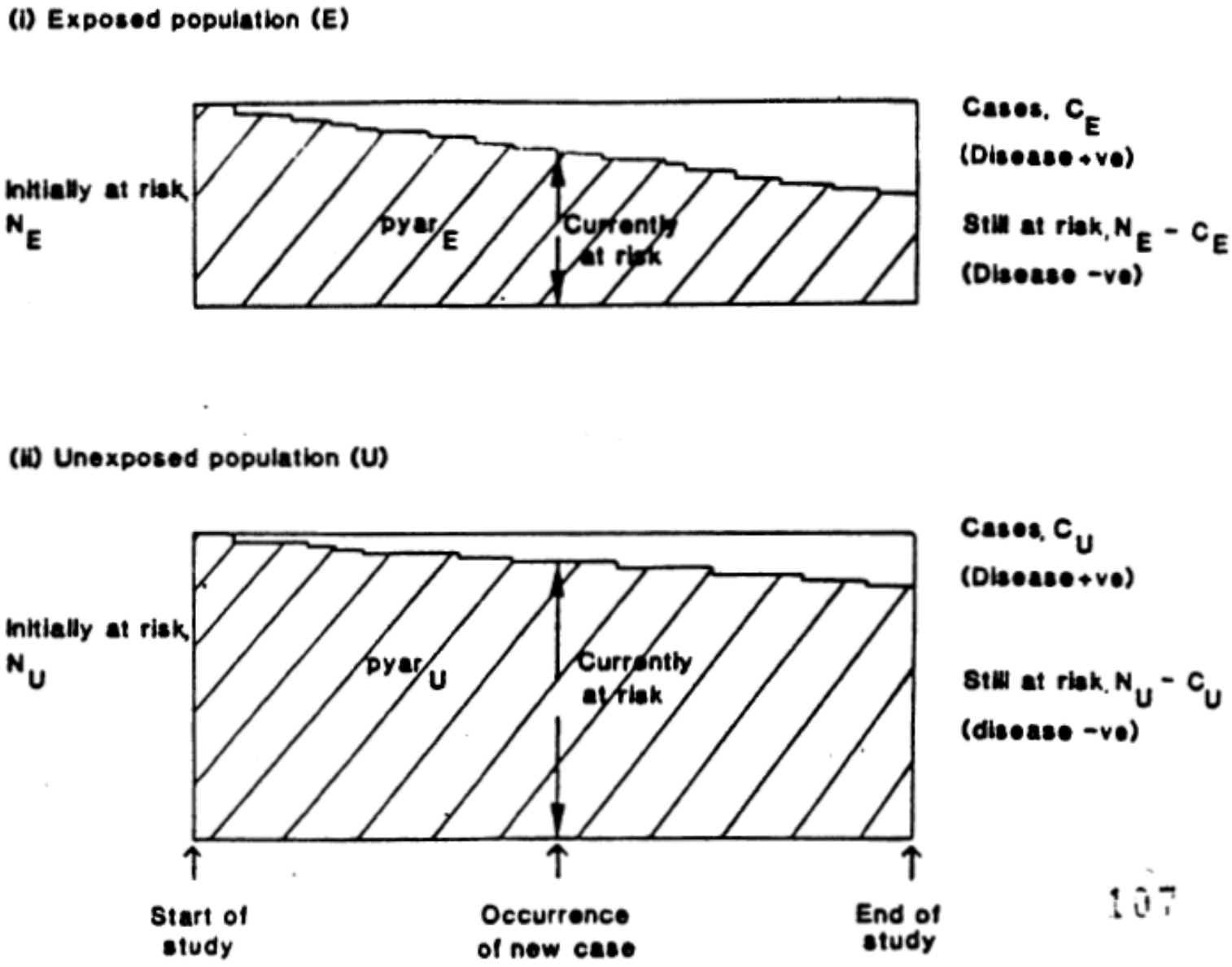
In earlier times, researchers thought that an OR from a case-control study would be equivalent to the RR in a cohort study, provided the disease was rare (rare disease assumption). Later, it became obvious that this assumption was not really necessary, especially if density sampling was done

What effect measure do the various designs actually estimate?

Sampling design	Controls sampled from	Definition	Effect measure that is estimated
Cumulative sampling (traditional case control study)	People disease-free throughout the study period ("survivors" at the end of the follow-up [prevalent cases])	$\frac{C_E / N_E - C_E}{C_U / N_U - C_U}$	Odds ratio (OR), which may numerically equal CIR if rare disease assumption holds
Case-base or case-cohort or case-referent	The baseline cohort (regardless of future disease status)	$\frac{C_E / N_E}{C_U / N_U}$	Cumulative incidence ratio (CIR) [does not need rare disease assumption]
Risk set sampling or incidence density sampling (nested case-control)	People currently at risk - in the risk set at the time an incident case occurs in the study base	$\frac{C_E / Pyar_E}{C_U / Pyar_U}$	Incidence density ratio (IDR) [does not need rare disease assumption] [this design is the gold standard among case-control designs!]

Adapted from Rodrigues et al. IJE 1990 [see next slide for graphic & notation]

Adapted from Rodrigues et al. IJE 1990



Notation for Table on previous slide

Most case-control studies do not discuss what their ORs estimate

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Practice of Epidemiology

What Do Case-Control Studies Estimate? Survey of Methods and Assumptions in Published Case-Control Research

Mirjam J. Knol, Jan P. Vandenbroucke, Pippa Scott, and Matthias Egger

Received for publication December 7, 2007; accepted for publication June 18, 2008.

To evaluate strategies used to select cases and controls and how reported odds ratios are interpreted, the authors examined 150 case-control studies published in leading general medicine, epidemiology, and clinical specialist journals from 2001 to 2007. Most of the studies (125/150; 83%) were based on incident cases; among these, the source population was mostly dynamic (102/125; 82%). A minority (23/125; 18%) sampled from a fixed cohort. Among studies with incident cases, 105 (84%) could interpret the odds ratio as a rate ratio. Fifty-seven (46% of 125) required the source population to be stable for such interpretation, while the remaining 48 (38% of 125) did not need any assumptions because of matching on time or concurrent sampling. Another 17 (14% of 125) studies with incident cases could interpret the odds ratio as a risk ratio, with 16 of them requiring the rare disease assumption for this interpretation. The rare disease assumption was discussed in 4 studies but was not relevant to any of them. No investigators mentioned the need for a stable population. The authors conclude that in current case-control research, a stable exposure distribution is much more frequently needed to interpret odds ratios than the rare disease assumption. At present, investigators conducting case-control studies rarely discuss what their odds ratios estimate.

Types of controls in case control studies

- Population controls
- Hospital or disease registry controls
- Controls from a medical practice
- Friend controls
- Relative controls

Epidemiology 2

Compared to what? Finding controls for case-control studies

David A Grimes, Kenneth F Schulz

Lancet 2005; 365: 1429–33

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Use of control (comparison) groups is a powerful research tool. In case-control studies, controls estimate the frequency of an exposure in the population under study. Controls can be taken from known or unknown study populations. A known group consists of a defined population observed over a period, such as passengers on a cruise ship. When the study group is known, a sample of the population can be used as controls. If no population roster exists, then techniques such as random-digit dialling can be used. Sometimes, however, the study group is unknown, for example, motor-vehicle crash victims brought to an emergency department, who may come from far away. In this situation, hospital controls, neighbourhood controls, and friend, associate, or relative controls can be used. In general, one well-selected control group is better than two or more. When the number of cases is small, the ratio of controls to cases can be raised to improve the ability to find important differences. Although no ideal control group exists, readers need to think carefully about how representative the controls are. Poor choice of controls can lead to both wrong results and possible medical harm.

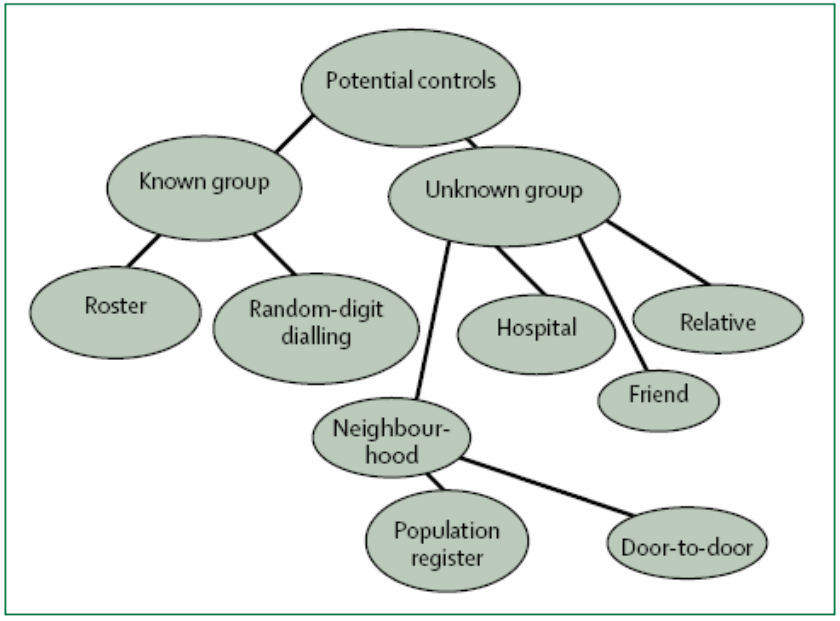

Figure 2: Choosing controls with known and unknown group of study participants

Population controls

- When a population roster (sampling frame) is available, the selection of population controls is simplest.
  - Census lists (available in some states and other countries)
  - Birth certificates
  - Electoral rolls (other countries)
- Some possible approaches when no roster is available:
  - Random digit dialing
  - Neighborhood controls

Population controls

Mobile phone use and risk of acoustic neuroma: results of the Interphone case–control study in five North European countries

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There is public concern that use of mobile phones could increase the risk of brain tumours. If such an effect exists, acoustic neuroma would be of particular concern because of the proximity of the acoustic nerve to the handset. We conducted, to a shared protocol, six population-based case–control studies in four Nordic countries and the UK to assess the risk of acoustic neuroma in relation to mobile phone use. Data were collected by personal interview from 678 cases of acoustic neuroma and 3553 controls. The risk of acoustic neuroma in relation to regular mobile phone use in the pooled data set was not raised (odds ratio (OR) = 0.9, 95% confidence interval (CI): 0.7–1.1). There was no association of risk with duration of use, lifetime cumulative hours of use or number of calls, for phone use overall or for analogue or digital phones separately. Risk of a tumour on the same side of the head as reported phone use was raised for use for 10 years or longer (OR = 1.8, 95% CI: 1.1–3.1). The study suggests that there is no substantial risk of acoustic neuroma in the first decade after starting mobile phone use. However, an increase in risk after longer term use or after a longer lag period could not be ruled out.

British Journal of Cancer (2005) **93,** 842–848. doi:10.1038/sj.bjc.6602764 www.bjcancer.com

Cases were identified through neurosurgery, neuropathology, oncology, neurology and otorhinolaryngology centres in the study areas. Lists of cases were also obtained from the appropriate population-based cancer registries to ensure completeness of ascertainment. Eligible cases were individuals diagnosed with acoustic neuroma between 1 September 1999 and 31 August 2004 (the exact dates within this period vary by centre) at ages 20–69 years in the Nordic countries, 18–59 in Southeast England, and 18–69 in the Northern UK, and resident in the study region at the time of diagnosis.

Controls in the Nordic centres were randomly selected from the population register for each study area, frequency matched to cases on age, sex and region. In the UK, where there is no such accessible population register, controls were randomly selected from general practitioners' practice lists. Controls were subject to the same age and residence criteria as cases and had never been diagnosed with a brain tumour.

Population controls

Prone sleep position and the sudden infant death syndrome in King County, Washington: A case-control study

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From the Department of Pediatrics, University of Washington, the Seattle–King County Department of Public Health, and the King County Medical Examiner's Office, Seattle, Washington

Objective: **To determine whether the prone sleep position was associated with an increased risk of the sudden infant death syndrome (SIDS).**
Study design: **Population-based case-control study.**
Participants: **Case subjects were infants who died of SIDS in King County, Washington. Control subjects were randomly selected infants born in King County. Up to four control subjects were matched on date of birth to each case subject.**
Methods: **During the study period, November 1992 through October 1994, sleep-position data were collected on infants who died of SIDS by the King County Medical Examiner's Office during their investigation of the deaths. Parents of infants chosen as control subjects were contacted by telephone, and sleep position information was obtained. Infants who usually slept on their abdomen were classified as sleeping prone; those who usually slept on the side or back were categorized as sleeping nonprone. The adjusted odds ratio for prone sleep position as a risk factor for SIDS was calculated with conditional logistic regression after control for race, birth weight, maternal age, maternal marital status, household income, and maternal cigarette smoking during pregnancy.**
Results: **Sleep position data were collected on 47 infants with SIDS (77% of eligible infants) and 142 matched control subjects; 57.4% of infants who died of SIDS usually slept prone versus 24.6% of control subjects ($p < 0.00001$). The unadjusted odds ratio for prone sleep position as a risk factor for SIDS was 4.69 (95% confidence interval: 2.17, 10.17). After control for potentially confounding variables, the adjusted odds ratio for prone sleep position was 3.12 (95% confidence interval: 1.08, 9.03).**
Conclusion: **Prone sleep position was significantly associated with an increased risk of SIDS among a group of American infants. (J Pediatr 1996;128:626-30)**

A case-control study was conducted from Nov. 1, 1992, through Oct. 31, 1994. Case subjects were infants who were King County residents and who died in King County, and in whom a diagnosis of SIDS was confirmed by death-scene investigation and postmortem examination. Control subjects were living babies born and residing in King County. To maximize the chances of detecting a difference in sleep position if one existed, we selected up to four infants as control subjects for each SIDS case subject, with matching based on the date of birth.

Once a diagnosis of SIDS was supported by autopsy, a list of the names of all children born in King County on the same day as the case infant was generated from birth certificate files. With the use of a random number table, 10 potential control subjects were sequentially selected. Attempts were made to contact the parents of the selected infants for a telephone interview. The potential control subject was excluded

(J Pediatr 1996; 128:626-30)

Advantages and disadvantages of population controls

Population controls have both advantages and disadvantages. Random sampling should provide representative controls, and extrapolation of results to the study group is easily justified. On the other hand, population controls can be inappropriate when cases have not been completely identified in the population or when substantial numbers of potential controls cannot be reached—eg, those on holiday. Moreover, population controls could be less motivated to take part in research than individuals in a health-care setting, such as hospitalised patients.[15]

Grimes & Schulz. Lancet 2005

Neighborhood controls

Advantages of neighbourhood controls include no need for a roster and that many confounding factors are accounted for—eg, socioeconomic status, climate, etc). On the other hand, canvassing neighbourhoods is expensive[21] and using homes rather than people as the sampling unit is a problem shared with random-digit dialling. Non-response can pose challenges. In one report, an average of nine household contacts was needed for one successful control,[20] although in our experience this ratio can be as much as 150/1. Multiunit buildings require identification of all units and then gain of access. This challenge is not unique to urban settings;

Grimes & Schulz. Lancet 2005

Random digit dialing controls

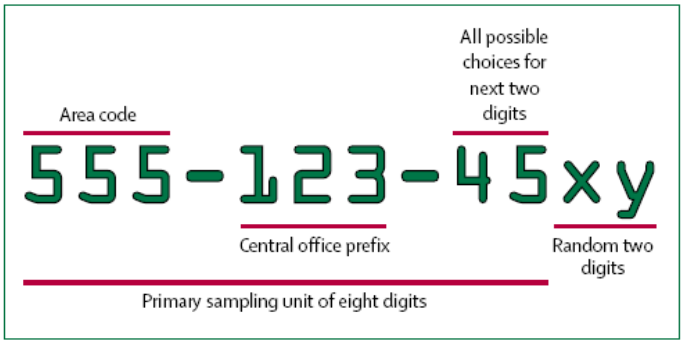


Figure 3: **Random-digit dialling for controls**[17]
Primary sampling unit included eight-digit numbers: all known area codes and three-digit central-office prefixes in the county, plus all combinations of next two digits. For all these eight-digit numbers randomly chosen, a computer generated the two final digits, creating a ten-digit number to be called.

It attempts to sample residential telephone numbers equally while keeping calls to commercial numbers to a minimum. The strategy reaches both new numbers and unlisted numbers not available through directories. Although it provides a random sample of telephone numbers, a random sample of potential controls is the real goal. Not all people have telephones; those without tend to be of lower socioeconomic status. Moreover, some individuals have more than one telephone number (eg, home plus cellular telephone), which could be related to higher socioeconomic status. Such people have an increased likelihood of being contacted. Some telephone numbers are used by more than one potential control. Individuals who are reluctant to respond to telephone enquiries differ from those who readily agree to participate.[18] For example, young women are less likely to be found by random-digit dialling than are others.[19] Although these quirks of telephone coverage might lead to bias,[15] control groups selected this way are largely representative of the reference population.[17]

Grimes & Schulz. Lancet 2005

Advantages and disadvantages of hospital controls

Hospital controls have been widely used—and criticised—in case-control studies. They have several appealing features: convenience, low-cost to identify and interview, comparable information quality as cases, motivation to participate, and comparable health-care-seeking behaviour.[15] However, the disadvantages are notable. Use of hospital controls assumes that they are representative of the background rate of exposure among people in the study group that produced the cases, meaning that the exposure is unrelated to the disease leading to hospitalisation of the control. The best way to avoid this pitfall is to exclude as controls those whose admission diagnosis is likely to be related to the exposure of interest. For example, in a hospital-based

Grimes & Schulz. Lancet 2005

Disadvantages of hospital controls (cont.)

community. Different diseases can have different catchment areas for a hospital; control diagnoses should have the same catchment area as the cases.

Admission rate bias can also cause difficulties.[4,24] For example, if women wearing an intrauterine device are more likely to be admitted for treatment of salpingitis than are women with salpingitis but no device, this difference would exaggerate the apparent odds ratio of salpingitis associated with intrauterine device use.[25]

Several reports suggest that hospital controls might not be representative of the study group. Hospital controls can resemble cases more than do population controls,[26,27] and others have noted substantial differences between hospital and population controls in weight, smoking patterns, and burden of illness (affecting the probability of hospitalisation).[28]

Grimes & Schulz. Lancet 2005

Composition of a hospital control series

- Suggestions
  - Exclude from the control series any conditions likely to be related to the exposure:
    - Example: exclude controls with diseases likely to be associated with NSAIDS in a study of NSAIDS and colorectal cancer
    - In practice: choose controls with many diseases just in case the assumption about the independence of the control disease to exposure is wrong
  - A prior history of disease should not exclude control subjects unless this condition also applies to the cases
  - Patients with any disease that can't be easily distinguished from the study disease should be excluded as controls in order to reduce misclassification bias

Panel 2: **Introduction of bias through poor choice of controls**

Cases	Control selection	Non-representativeness	Selection bias
Colorectal cancer patients admitted to hospital	Patients admitted to hospital with arthritis	Controls probably have high degrees of exposure to NSAIDs	Would spuriously **reduce** the estimate of effect (odds ratio)
Colorectal cancer patients admitted to hospital	Patients admitted to hospital with peptic ulcers	Controls probably have low degrees of exposure to NSAIDs	Would spuriously **increase** the estimate of effect (odds ratio)

NSAIDs=non-steroidal anti-inflammatory drugs.

Grimes & Schulz. Lancet 2005

Controls from a medical practice

- Controls from a medical practice may be more appropriate that hospital controls in studies at urban health center
- Would these controls come from a primary or secondary base? What must one assume for this to be the proper base?
- How could the study base principle be violated by the use of medical practice controls?
- Example: A study of the relationship between coffee and pancreatic cancer

Bias in case-control studies

Selection bias

- Huge concern in case-control studies
  - Which control group is chosen?
  - How are controls actually recruited?
  - Are controls from the same study base that gave rise to the cases?
  - Are controls chosen independent of the exposure?

Selection bias in case-control studies

Coffee and cancer of the pancreas.

MacMahon B, et al

- Questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee.
- Controls included patients with gastro-intestinal disorders
- There was a weak positive association between pancreatic cancer and cigarette smoking, but 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 approximately 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% confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7)
- Conclusion: coffee use might account for a substantial proportion of the cases of this disease in the United States.

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

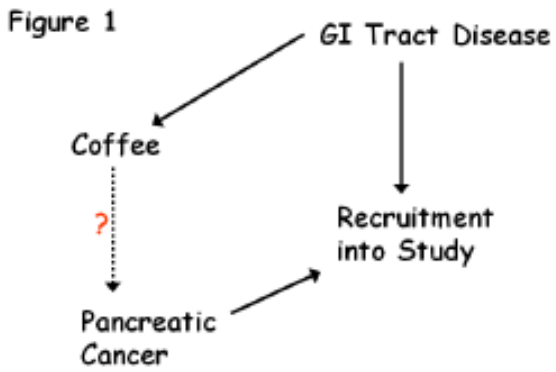
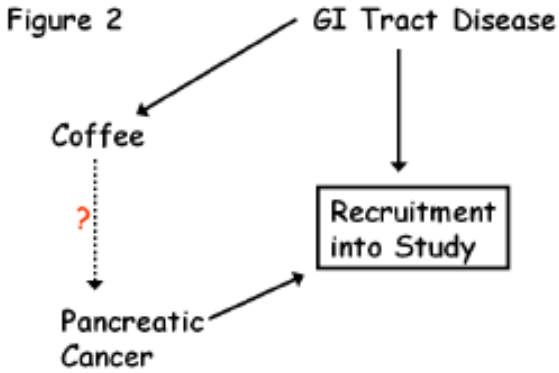
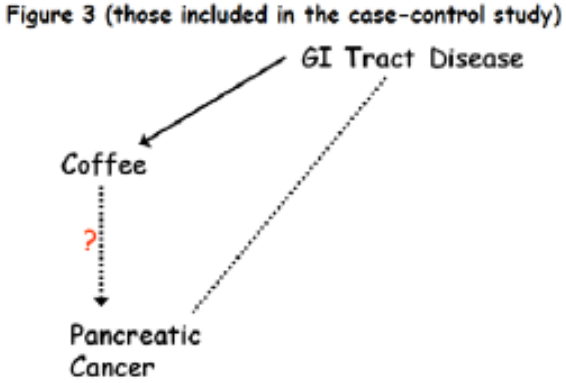


Figure 1 as a directed arc from "GI tract disease" t



something else: a GI tract disease. Therefore, rest
hospitalized the cases induces a negative correlati



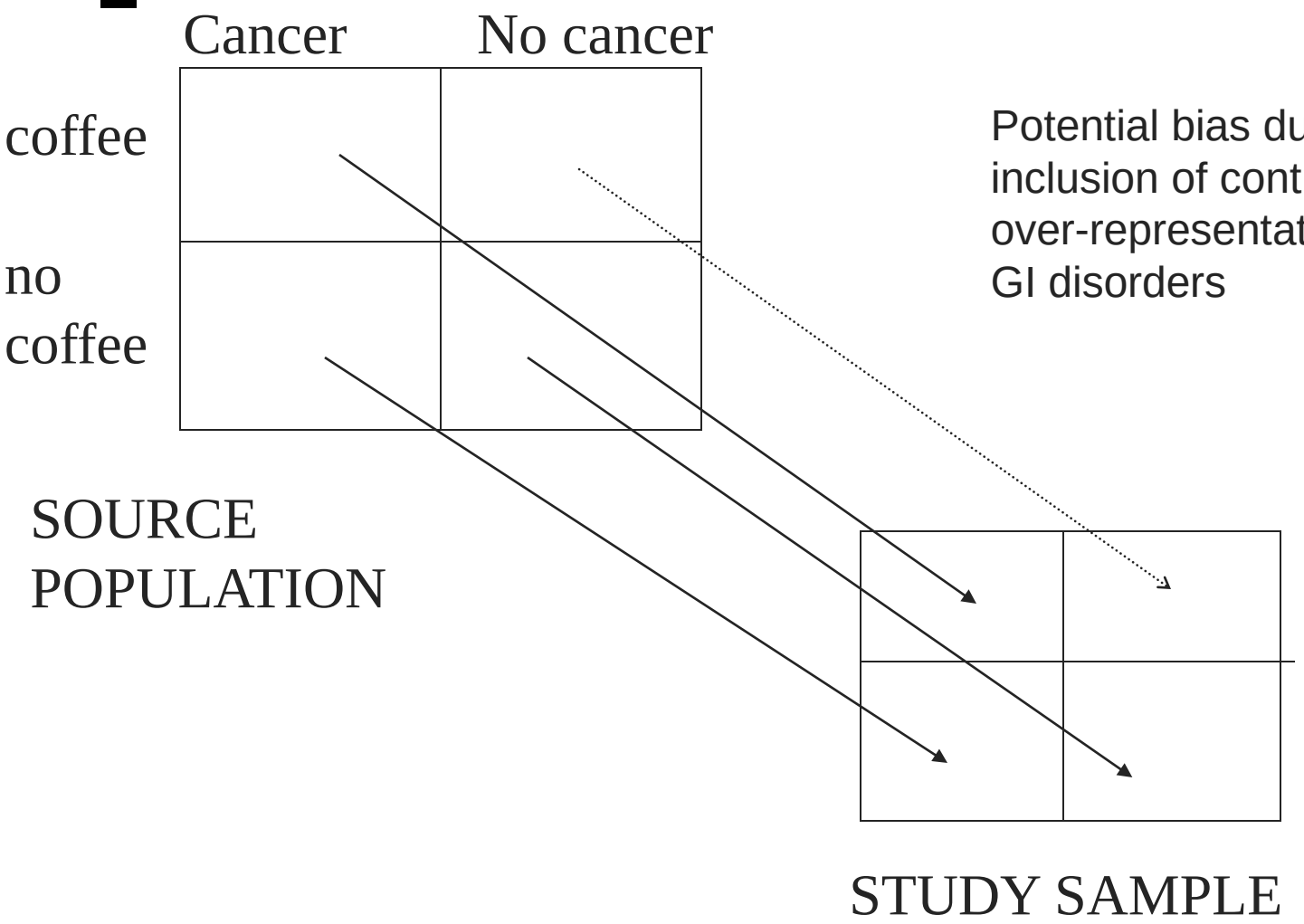
Controls in the MacMahon study were selected from a group of patients hospitalized by the same physicians who had diagnosed and hospitalized the cases' disease. The idea was to make the selection process of cases and controls similar.

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.

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



Potential bias due to inclusion of controls with over-representation of GI disorders

Direction of bias

		Case	Control
Exposure	Yes	a	b
	No	c	d

OR = ad / bc

If controls have an unusually low prevalence of exposure, then b will tend to be small -- this will bias the OR away from 1 (over-estimate the OR)

Coffee and cancer of the pancreas: Use of population-based controls

- Gold et al. *Cancer* 1985

	Case	Control
Coffee: ≥1 cup day	84	82
No coffee	10	14

OR= (84/10) / (82/14) = 1.4 (95% CI, 0.55 - 3.8)

Results of the MacMahon study were not replicated
When population-based controls were used, the effect was not significant

For a more in-depth analysis of this case study, see B-File #2

Bias File 2. Should we stop drinking coffee? The story of coffee and pancreatic cancer

Another example of selection bias (due to inclusion of friend controls)

Friends or work associates of cases sometimes serve as controls. This approach has both critics and supporters. An advantage is generation of a control group similar to the cases in several important respects—such as socioeconomic status and education. However, asking cases to name potential controls is the antithesis of random selection. Those named might be more gregarious and sociable than other potential controls, leading to the controls not being representative.[15] On the other hand, in hidden populations for which socially unacceptable behaviours are being studied, eg, drug abuse, friend controls have been suggested to be convenient and unlikely to introduce selection bias. In one study, drug misusers were asked to nominate a friend who was a drug misuser (a new case) and another friend who had never been involved with drugs (a control). This chain referral or snowball technique concluded that cases and controls came from the same population.[29]

Grimes & Schulz. Lancet 2005

Selection bias (friend controls)

- **Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study.**

  Reingold AL, Broome CV, Gaventa S, Hightower AW.

- For assessment of current risk factors for developing toxic shock syndrome (TSS) during menstruation, a case-control study was performed
- Cases with onset between 1 January 1986 and 30 June 1987 were ascertained in six study areas with active surveillance for TSS
- Age-matched controls were selected from among each patient's friends and women with the same telephone exchange
- Of 118 eligible patients, 108 were enrolled, as were 185 "friend controls" and 187 telephone exchange-matched controls

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41

Selection bias (friend controls)

- Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study

- **Results:**
  - OR when both control groups were combined = 29
  - OR when friend controls were used = 19
  - OR when neighborhood controls were used = 48

- Why did use of friend controls produce a lower OR?
  - Friend controls were more likely to have used tampons than were neighborhood controls (71% vs. 60%)

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41

Direction of bias

		Case		Control
Exposure	Yes	a	⟺	b
	No	c		d

OR = ad / bc

If cases and controls share similar exposures (e.g. friend controls), then a and b will tend to be nearly the same -- this will bias the OR towards 1 (towards null)

Relative/spouse controls

Relatives share many traits with cases. When genetic factors are deemed to be confounding, relatives have been used to control for this bias.[15] Many other exposures will be similar—eg, siblings are likely to have diet, environment, lifestyle, and socioeconomic status in common as well. For example, when siblings serve as controls, the potential effect of family size cannot be examined.[15] Some researchers have concluded that as long as the exposure-specific risks remain stable over time, use of relatives as controls does not distort the results.[30]

Grimes & Schulz. Lancet 2005

Use of partners/spouses as controls

OPEN ACCESS Freely available online PLOS MEDICINE

Travel-Related Venous Thrombosis: Results from a Large Population-Based Case Control Study (MEGA Study)

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1 Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands, 2 Department of Medical Statistics, Leiden University Medical Center, Leiden, Netherlands, 3 Thrombosis and Haemostasis Research Center, Department of Haematology, Leiden University Medical Center, Leiden, Netherlands

Funding: This research was supported by the Netherlands Heart Foundation (NHS 98.113) and the Dutch Cancer Foundation (RUL 99/1992). SCC is employed on the WRIGHT Project, which is being carried out under the auspices of the World Health Organization and funded jointly by the United Kingdom government and the European Commission. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Citation: Cannegieter SC, Doggen CJM, van Houwelingen HC, Rosendaal FR (2006) Travel-related venous thrombosis: Results from a large population-based case control study (MEGA study). PLoS Med 3(8): e307. DOI: 10.1371/journal.pmed.0030307

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Published: August 22, 2006

ABSTRACT

Background

Recent studies have indicated an increased risk of venous thrombosis after air travel. Nevertheless, questions on the magnitude of risk, the underlying mechanism, and modifying factors remain unanswered.

Methods and Findings

We studied the effect of various modes and duration of travel on the risk of venous thrombosis in a large ongoing case-control study on risk factors for venous thrombosis in an unselected population (MEGA study). We also assessed the combined effect of travel and prothrombotic mutations, body mass index, height, and oral contraceptive use.

Since March 1999, consecutive patients younger than 70 y with a first venous thrombosis have been invited to participate in the study, with their partners serving as matched control individuals. Information has been collected on acquired and genetic risk factors for venous thrombosis. Of 1,906 patients, 233 had traveled for more than 4 h in the 8 wk preceding the event. Traveling in general was found to increase the risk of venous thrombosis 2-fold (odds ratio [OR] 2.1; 95% confidence interval [CI] 1.5–3.0). The risk of flying was similar to the risks of traveling by car, bus, or train. The risk was highest in the first week after traveling. Travel by car, bus, or train led to a high relative risk of thrombosis in individuals with factor V Leiden (OR 8.1; 95% CI 2.7–24.7), in those who had a body mass index of more than 30 kg/m^2 (OR 9.9; 95% CI 3.6–27.6), in those who were more than 1.90 m tall (OR 4.7; 95% CI 1.4–15.4), and in those who used oral contraceptives (estimated OR > 20). For air travel these synergistic findings were more apparent, while people shorter than 1.60 m had an increased risk of thrombosis after air travel (OR 4.9; 95% CI 0.9–25.6) as well.

Use of siblings as controls

6 Freeman J, McGowan Jr JE. Risk factors for nosocomial infection. *J Infect Dis* 1978;**138**:811–9
7 Kollef MH. Time to get serious about infection prevention in the ICU. *Chest* 2006;**130**:1293–6

Does breast feeding provide protection against acute appendicitis? A case-control study

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TROPICAL DOCTOR 2008; 38: 235–236
DOI: 10.1258/td.2008.070404

SUMMARY Breast feeding stimulates a more tolerant lymphoid tissue at the base of the appendix and this could provide protection against acute appendicitis. Two studies

Methods and patients

The study population consisted of 243 children and adolescents who underwent surgery for suspected appendicitis at our hospitals – Instituto Materno Infantil Professor Fernando Figueira (IMPI) and Hospital da Restauracao (HR) – in Recife, northeast Brazil between 1 August 2006 and 30 March 2007. The 200 of these who did have histologically confirmed appendicitis were recruited to the study, matched by 200 familial controls (i.e. a sibling of the same gender and age within three years without a history of appendicitis). All the mothers were interviewed during the hospital stay. The study was approved by the ethics committee at the IMIP. We asked mothers how and for how long were their children – those with and those without appendicitis – fed milk during the first year of life and if they were breast feed only, given a mixture of breast and bottle or bottle feed only.

The sample size was based on the assumption that a 15% difference in the prevalence of breast feeding between the two groups would be clinically significant. The SPSS 12.0 for Windows (SPSS, Inc, Chicago, IL, USA) was used for the analysis of data. Quantitative data were expressed as means $\pm$ standard deviation (SD). Differences in continuous variables were analysed by the Mann-Whitney *U*-test or Student's *t*-test. Differences in categorical variables were assessed with the Fisher's exact test and the chi-squared test with Yate's correction: a P value <0.05 was considered statistically significant.

Results

This analysis included completed interview data from the mothers of 400 children – 200 cases and 200 controls. The

If cases are dead, what about controls?

- Main argument for choosing dead controls is to enhance comparability
- Dead people are not in the study base for cases, since death will preclude the occurrence of any further disease
- Choosing dead controls may misrepresent the exposure distribution in the study base if the exposure causes or prevents death in a substantial number of people
- If live controls are used for dead cases, then proxy respondents can be used for live controls as well

Rothman 2002

If cases are dead, what about controls?

Case–control study of suicide in Karachi, Pakistan*

Murad Moosa Khan, Sadia Mahmud, Mehtab S. Karim, Mohammad Zaman and Martin Prince

Background
In recent years suicide has become a major public health problem in Pakistan.

Aims
To identify major risk factors associated with suicides in Karachi, Pakistan.

Method
A matched case–control psychological autopsy study. Interviews were conducted for 100 consecutive suicides, which were matched for age, gender and area of residence with 100 living controls.

Results
Both univariate analysis and conditional logistic regression model results indicate that predictors of suicides in Pakistan are psychiatric disorders (especially depression), marital status (being married), unemployment, and negative and stressful life events. Only a few individuals were receiving treatment at the time of suicide. None of the victims had been in contact with a health professional in the month before suicide.

Conclusions
Suicide in Pakistan is strongly associated with depression, which is under-recognised and under-treated. The absence of an effective primary healthcare system in which mental health could be integrated poses unique challenges for suicide prevention in Pakistan.

Declaration of interest
None. Funding detailed in Acknowledgements.

We studied the first 100 consecutive suicides during the study period.

Controls were matched to suicide victims with respect to age (+2 years), gender and area of residence. They were identified in the immediate vicinity of 20 houses in the same street. When a suitable control could not be identified in the same street, the next streets were visited until a suitable control was identified.

For both dead cases and live controls, close relatives were interviewed (psychological ‘autopsy’).

Brit J Psych 2008

Number of control groups and number of controls

- Usually one control group (that is most reflective of the study base)
  - If two are used, then might pose problems if results are divergent
- Number of controls:
  - Usually 1:1
  - Can increase up to 1:4 to gain precision (does not improve validity)
  - Beyond 1:4, the added value is marginal

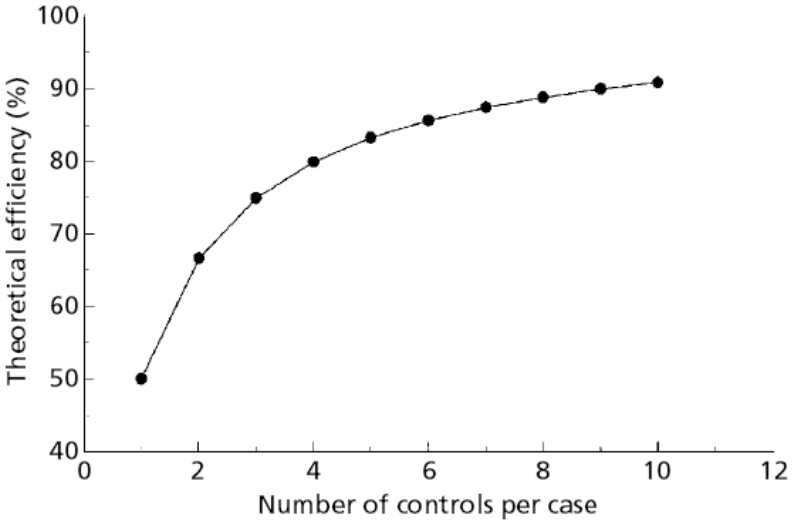
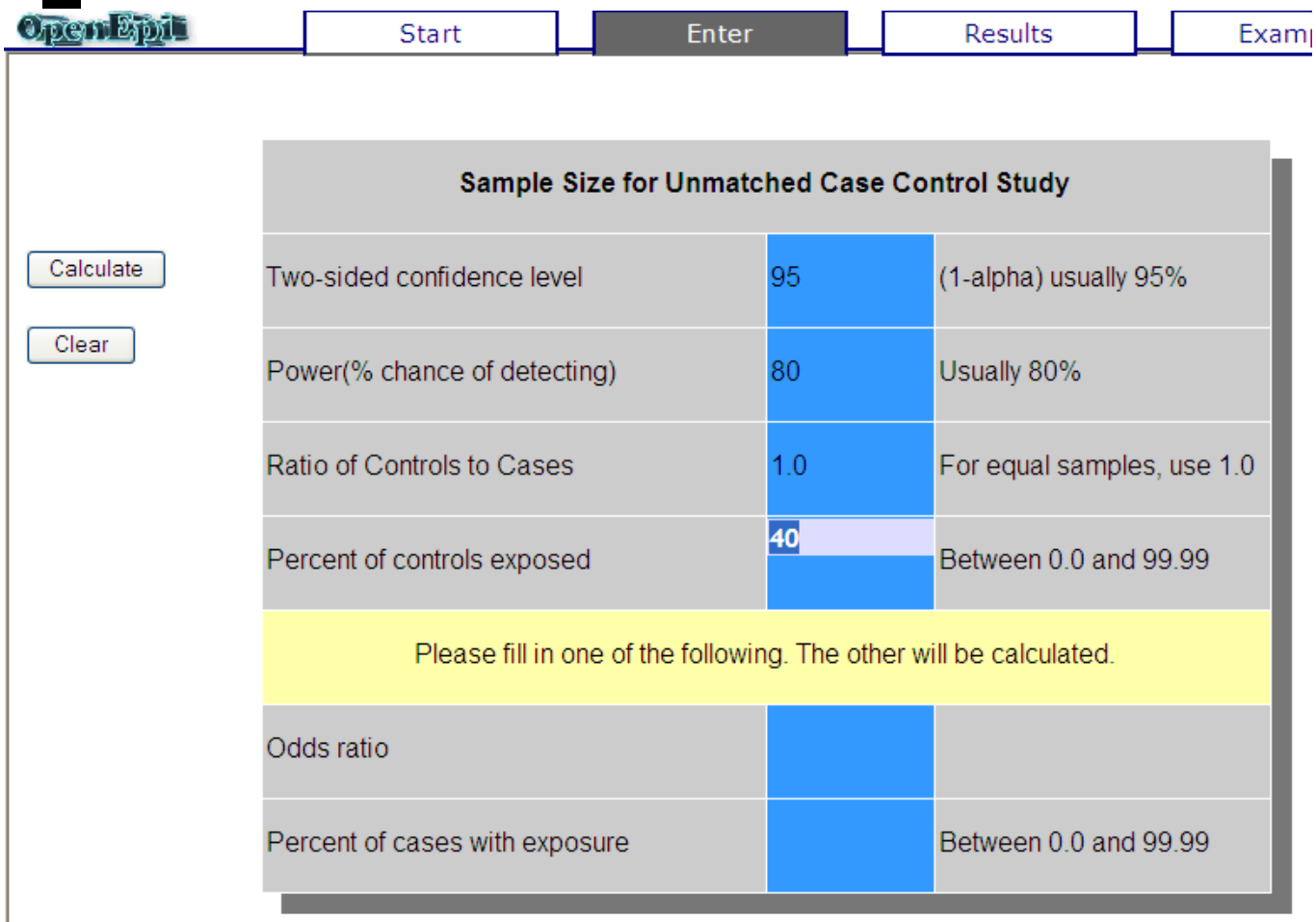


Figure 2 Relationship between efficiency and the number of controls per case in a matched pair study.

Disability & Rehab , 2000 ; v o l . 22, n o . 6. 259± 265

Sample size calculation



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Research article

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Selection bias: neighbourhood controls and controls selected from those presenting to a Health Unit in a case control study of efficacy of BCG revaccination

Odimariles MS Dantas*[1], Ricardo AA Ximenes[2,3], Maria de Fatima PM de Albuquerque[4,5], Ulisses R Montarroyos[5], Wayner V de Souza[5], Patrícia Varejão[2] and Laura C Rodrigues[6]

Abstract

Background: In most case control studies the hardest decision is the choice of the control group, as in the ideal control group the proportion exposed is the same as in the population that produced the cases.

Methods: A comparison of two control groups in a case control study of the efficacy of BCG revaccination. One group was selected from subjects presenting to the heath unit the case attended for routine prevention and care; the second group was selected from the neighbourhood of cases. All Health Units from which controls were selected offered BCG revaccination. Efficacy estimated in a randomized control trial of BCG revaccination was used to establish that the neighbourhood control group was the one that gave unbiased results.

Results: The proportion of controls with scars indicating BCG revaccination was higher among the control group selected from Health Unit attenders than among neighbourhood controls. This excess was not removed after control for social variables and history of exposure to tuberculosis, and appears to have resulted from the fact that people attending the Health Unit were more likely to have been revaccinated than neighbourhood controls, although we can not exclude an effect of other unmeasured variables.

Conclusion: In this study, controls selected from people presenting to a Health Unit overrepresented exposure to BCG revaccination. Had the results from the HU attenders control group been accepted this would have resulted in overestimation of vaccine efficacy. When the exposure of interest is offered in a health facility, selection of controls from attenders at the facility may result in over representation of exposure in controls and selection bias.

When two control groups are used

BMC Medical Research Methodology 2007, **7:**11

- Cases were people with newly diagnosed TB, recruited in Health Units that offered TB treatment
- Controls were Health Unit controls, selected from those attending the Health Unit that cases used for routine medical care before their diagnosis of TB.
- Second control group was selected from the neighbourhood of cases using a systematic approach, starting from the address of the case

Table 1: Presence of 2 BCG scars and two BCG vaccinations in the vaccination card in Health Unit and neighbourhood controls

	Cases	Health Unit Controls	Neighbourhood Controls
BCG Scar			
One	75 (44.4%)	180 (32.7%)	213 (44.7%)
Two	94 (55.6%)	371 (67.3%)	264 (55.3%)
Vaccination card			
One	28 (33.7%)	36 (20.9%)	81 (38.9%)
Two	55 (63.3%)	136 (79.1%)	127 (61.1%)
		VE (95%CI)	
Vaccine efficacy		39% (2 to 62)	8% (-77 to 52)

* Based on scar, matched and adjusted for year of birth, sex, known tuberculosis contact, water supply and income of the head of the family.

A higher proportion of Health Unit attender controls had two BCG scars at examination and two BCG vaccinations in the vaccination cards than neighbourhood controls (Table); as consequence (adjusted) vaccine efficacy was 8% for population controls and 39% for Health Unit controls.

Multiple BCG vaccinations and tuberculosis

Health Unit [HU] Controls

		Case	Control
Exposure [BCG revaccination]	Yes	a	b ↑
	No	c	d

Neighbourhood Controls

		Case	Control
Exposure [BCG revaccination]	Yes	a	b
	No	c	d

When HU controls were used, prevalence of exposure was higher because people attending HU were more likely to get revaccinated

This would lead to over-estimation of BCG vaccine efficacy (OR will be much lower than 1)

Information bias in case-control studies

Sources:

- Poor recall of past exposures (poor memory; can happen with both cases and controls; so, non-differential)
- Differential recall between cases and controls (“recall bias” or “exposure identification bias” or “exposure suspicion bias”)
  - Cases have a different recall than controls
- Differential exposure ascertainment (influenced by knowledge of case status)
  - Interviewer/observer bias (cases are probed or interviewed or investigated differently than controls)

Poor recall versus recall bias

Journal of Exposure Science and Environmental Epidemiology (2009) 19, 369–381

www.nature.com/jes

Recall bias in the assessment of exposure to mobile phones

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[g] *Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Victoria, Australia*
[h] *B.C. Cancer Agency, Vancouver, British Columbia, Canada*
[i] *INRS-Institut Armand-Frappier, Université du Québec, Laval, Quebec, Canada*
[j] *University of Montreal, Montreal, Quebec, Canada*

Most studies of mobile phone use are case–control studies that rely on participants' reports of past phone use for their exposure assessment. Differential errors in recalled phone use are a major concern in such studies. INTERPHONE, a multinational case–control study of brain tumour risk and mobile phone use, included validation studies to quantify such errors and evaluate the potential for recall bias. Mobile phone records of 212 cases and 296 controls were collected from network operators in three INTERPHONE countries over an average of 2 years, and compared with mobile phone use reported at interview. The ratio of reported to recorded phone use was analysed as measure of agreement. Mean ratios were virtually the same for cases and controls: both underestimated number of calls by a factor of 0.81 and overestimated call duration by a factor of 1.4. For cases, but not controls, ratios increased with increasing time before the interview; however, these trends were based on few subjects with long-term data. Ratios increased by level of use. Random recall errors were large. In conclusion, there was little evidence for differential recall errors overall or in recent time periods. However, apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use.
Journal of Exposure Science and Environmental Epidemiology (2009) **19**, 369–381; doi:10.1038/jes.2008.27; published online 21 May 2008

Information bias: example from case-control study of risk factors for suicide in Pakistan

Table 1 ICD–10 principal diagnosis

Diagnosis	Cases (*n*=100)	Controls (*n*=100)
Moderate depressive episode (F32.1)	30	1
Severe depressive episode (F32.2)	43	0
Severe depressive episode with psychotic symptoms (F32.3)	6	2
Schizophrenia (F20)	6	2
Adjustment disorders (F43.2)	3	0
Acute stress reaction (F43.0)	6	0
Alcohol use (F10.0)	0	0
Substance abuse (F11.0)	1	0
Mental retardation (F79)	1	0
Personality disorder (F60)	1	1
No psychiatric diagnosis	4	94

Table 2 Final multivariable conditional logistic regression model

Variable	Adjusted OR (95% CI)
Educational attainment	
No formal education/primary[a]	4.9 (0.8–29.8)
Secondary and above	1.0
Marital status	
Never married	1.0
Ever married	3.6 (0.6–22.3)
Depression	
No	1.0
Yes	208.3 (11.0–3935.2)

a. Adjusted for employment status.

- Close relatives of 100 suicide cases and 100 live controls were interviewed.
- 79/100 suicide cases were found to have had depression.
- Only 3/100 controls were found to have depression (lower than the population average).
- Due to lack of blinding, quality of interviews may have been lower in controls

Brit J Psych 2008

Recall bias: example

Bias File 6. Double whammy: recall and selection bias in case-control studies of congenital malformations

What is the ideal control group in case-control studies of malformations?

- Should the control group be parents of normal children ("normal controls"), or should the control group include only parents of children with a defect other than that under study ("malformed controls")?
  - Some researchers advocated the routine use of malformed controls by suggesting that the use of normal controls will overestimate the effect (because of recall bias).
  - The rationale for using malformed controls was to balance out the issue of selective recall by parents of malformed children.
  - Because both case and control children will have some birth defect, it was felt that the issue of unequal or differential recall is addressed to some extent.

What is the ideal control group in case-control studies of malformations?

- Other experts argued that it was better to include normal controls because this enables direct comparison of the histories of infants affected by a selected birth defect with those without any apparent pathology.
- They also argued that although the use of malformed controls might appear to address the recall bias problem, two wrongs don't make a right. If cases report with bias, then finding controls who also report with bias does not necessarily fix the original bias.
- Also, the strategy of using malformed controls introduces a brand new problem of selection bias.
  - Since the controls have malformations, and if the malformations in the control group were positively associated with the study exposure, then this introduces selection bias that can underestimate the odds ratio.
  - In other words, if the study exposure was associated with the birth defects in the control group, then the exposure odds in the control group would be spuriously higher than the source population.
  - This, in turn, would bias the odds ratio towards null, because both cases and controls may end up with fairly similar exposure histories.

What is the ideal control group in case-control studies of malformations?

- So, a solution, proposed by some researchers, is to use both types of controls.
- For example, Hook suggested "as the use of normal controls biases the estimate if anything high, and use of malformed controls biases the estimate if anything low, *the optimal strategy would appear to use both types of controls*... One could safely infer that the true estimate of relative risk is at least somewhere between the two, and then with more refined analysis attempt to narrow the estimate of effect."

TERATOLOGY 61:325–326 (2000)

Letters to the Editor

What Kind of Controls to Use in Case Control Studies of Malformed Infants: Recall Bias Versus "Teratogen Nonspecificity" Bias

Some studies have shown similar odds ratio estimates with healthy and malformed controls

Multivitamin Supplementation and Risk of Birth Defects

Martha M. Werler,[1] Catherine Hayes,[2] Carol Louik,[1] Samuel Shapiro,[1] and Allen A. Mitchell[1]

It is widely accepted that supplementation with folic acid, a B vitamin, reduces the risk of neural tube defects (NTDs). This case-control study tested the hypothesis that multivitamins reduce risks of selected birth defects other than NTDs. Infants with and without birth defects and aborted fetuses with birth defects were ascertained in the greater metropolitan areas of Boston, Philadelphia, and Toronto during 1993–1996. Mothers were interviewed within 6 months after delivery about a variety of factors, including details on vitamin use. Eight case groups were included: cleft lip with or without cleft palate, cleft palate only, conotruncal defects, ventricular septal defects, urinary tract defects, limb reduction defects, congenital hydrocephaly, and pyloric stenosis (*n*'s ranged from 31 to 186). Controls were 521 infants without birth defects (nonmalformed controls) and 442 infants with defects other than those of the cases (malformed controls). Daily multivitamin supplementation was evaluated according to gestational timing categories, including periconceptional use (28 days before through 28 days after the last menstrual period). Odds ratios (ORs) below 1.0 were observed for all case groups except cardiac defects, regardless of control type. For periconceptional use, ORs with 95% confidence intervals that excluded 1.0 were estimated for limb reduction defects using both nonmalformed controls (OR = 0.3) and malformed controls (OR = 0.2) and for urinary tract defects using both nonmalformed controls (OR = 0.6) and malformed controls (OR = 0.5). Statistically significant ORs for use that began after the periconceptional period were observed for cleft palate only and urinary tract defects. These data support the hypothesis that periconceptional vitamin supplementation may extend benefits beyond a reduction in NTD risk. However, other than folic acid's protecting against NTDs, it is not clear what nutrient or combination of nutrients might affect risk of other specific defects. *Am J Epidemiol* 1999;150:675–82.

Confounding in case-control studies

- Always an issue!
- Can be addressed at the design or analysis stage [usually both]:
  - Design:
    - Matching
      - Has to be done carefully [can introduce selection bias!]
      - If done, only match on strong confounders
      - Take matching into account in analysis (i.e. Matched OR and conditional LR)
    - Restriction
      - If the study base is restricted, then confounding can be minimized (e.g. only men)
  - Analysis:
    - Multivariable analysis
      - Logistic regression (LR) is the most natural model
        - Unconditional LR if not pair matched
        - Conditional LR if pair matched
      - Results reported as adjusted odds ratios

Confounding in case-control studies

- A key issue is to know what confounders to adjust for and why
  - Need to have expertise in content area
  - Useful to draw out a causal diagram (DAG) before analysis is done
  - Each confounder must be justified
- There is considerable inconsistency and variation in how researchers adjust for confounding

Inconsistency in adjustment: example

ORIGINAL ARTICLE

Tobacco smoking and pulmonary tuberculosis

C Kolappan, P G Gopi

Thorax 2002;**57**:964–966

See end of article for authors' affiliations

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Received 21 November 2001
Accepted for publication 31 July 2002

Background: The prevalence of tuberculosis in adult men in India is 2–4 times higher than in women. Tobacco smoking is prevalent almost exclusively among men, so it is possible that tobacco smoking may be a risk factor for developing pulmonary tuberculosis. A nested case control study was carried out to study the association between tobacco smoking and pulmonary tuberculosis.
Methods: A tuberculosis disease survey was carried out in two Panchayat unions in the Tiruvallur district of Tamil Nadu in India. Eighty five men aged 20–50 years with bacteriological tuberculosis (smear and/or culture positive) were selected as cases and 459 age matched men without tuberculosis were selected randomly as controls. Information on smoking status, type of tobacco smoked, quantity of tobacco smoked, and duration of tobacco smoking was collected from cases and controls using a questionnaire.
Results: The estimated crude odds ratio (OR) of the association between tobacco smoking and bacillary tuberculosis was 2.48 (95% confidence interval (CI) 1.42 to 4.37), p<0.001.The age adjusted OR (Mantel-Hanszel estimate) was 2.24.(95% CI 1.27 to 3.94), p<0.05. The ORs for mild (1–10 cigarettes/day), moderate (11–20/day), and heavy (>20/day) smokers were 1.75, 3.17, and 3.68, respectively (p<0.0001 test for linear trend). The ORs for smokers with <10 years, 11–20 years, and >20 years of smoking were 1.72, 2.45, and 3.23, respectively (p<0.0001 test for linear trend).
Conclusion: There is a positive association between tobacco smoking and pulmonary (bacillary) tuberculosis (OR 2.5). The association also shows a strong dose-response relationship.

Only age was adjusted for in this study

Inconsistency in adjustment: example

A case-control study of tobacco smoking and tuberculosis in India

R. Prasad, Suryakant, R. Garg, S. Singhal, R. Dawar, G. G. Agarwal[1]

Abstract:

OBJECTIVES: To evaluate the role of smoking as a risk factor for the development of pulmonary tuberculosis.

MATERIALS AND METHODS: A total of 111 sputum smear–positive patients of pulmonary tuberculosis and 333 controls matched for age and sex were interviewed according to a predesigned questionnaire.

RESULTS: The adjusted odd ratio of the association between tobacco smoking and pulmonary tuberculosis was 3.8 (95% confidence interval, 2.0 to 7.0; *P* value, <.0001). A positive relationship between pack years, body mass index and socioeconomic class was also observed.

CONCLUSION: There is a positive association between tobacco smoking and pulmonary tuberculosis.

Key words:

Diagnosis, India, smoking, tobacco, tuberculosis

Table 2: Multivariable logistic regression model for the factors associated with pulmonary tuberculosis

Variables	Matched OR (95% CI)	Adjusted OR (95% CI)	*P* value
Smoking	3.4 (2.0, 5.8)	3.8 (2.0, 7.0)	< 0.0001
Social class*			
Type V	5.3 (1.8, 16.0)	3.6 (1.0, 12.8)	0.04
Type IV	2.3 (0.8, 6.7)	1.9 (0.6, 6.4)	0.3
House type**			
Kuchcha	3.2 (1.4, 7.5)	2.8 (1.1, 7.2)	0.03
Semi-*pucca*	2.3 (1.0, 5.1)	2.3 (0.9, 5.6)	0.07
Body mass index***	4.1 (2.5, 6.8)	4.2 (2.4, 7.3)	< 0.0001

*Reference category is 'type III socioeconomic status.'; **Reference category is 'pakka house.'; ***Reference category is 'BMI > 19.4 (median value)

Overadjustment and unnecessary adjustment

Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies

Enrique F. Schisterman,[a] *Stephen R. Cole,*[b] *and Robert W. Platt*[c]

Abstract: Overadjustment is defined inconsistently. This term is meant to describe control (eg, by regression adjustment, stratification, or restriction) for a variable that either increases net bias or decreases precision without affecting bias. We define overadjustment bias as control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome. We define unnecessary adjustment as control for a variable that does not affect bias of the causal relation between exposure and outcome but may affect its precision. We use causal diagrams and an empirical example (the effect of maternal smoking on neonatal mortality) to illustrate and clarify the definition of overadjustment bias, and to distinguish overadjustment bias from unnecessary adjustment. Using simulations, we quantify the amount of bias associated with overadjustment. Moreover, we show that this bias is based on a different causal structure from confounding or selection biases. Overadjustment bias is not a finite sample bias, while inefficiencies due to control for unnecessary variables are a function of sample size.

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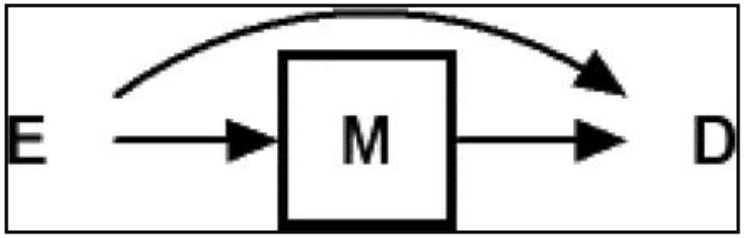
confounding[1] and selection biases[2,3] have been discussed extensively in the epidemiologic literature, the concept of "overadjustment" has had relatively little attention. The definition of overadjustment remains vague and the causal structure of this concept has not been well described.

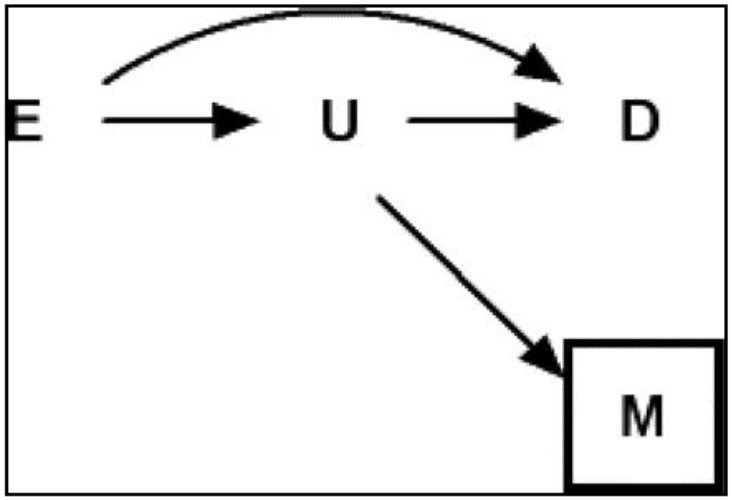
The Dictionary of Epidemiology[4] cites a seminal paper by Breslow[5] in broadly defining overadjustment as "Statistical adjustment by an excessive number of variables or parameters, uninformed by substantive knowledge (eg, lacking coherence with biologic, clinical, epidemiological, or social knowledge). It can obscure a true effect or create an apparent effect when none exists." Rothman and Greenland[6] discuss overadjustment in the context of intermediate variables: "Intermediate variables, if controlled in an analysis, would usually bias results towards the null. . . . . Such control of an intermediate may be viewed as a form of overadjustment." One also finds reference to the term overadjustment in settings with unnecessary control for variables.[7] In summary, overadjustment sometimes means control (eg, by regression

Overadjustment bias is control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome



Example: mediating role of triglycerides (M) in the association between prepregnancy body mass index (E) and preeclampsia (D)

If M is adjusted for, then the causal effect will be biased towards null



Example: adjusting for prior history of spontaneous abortion (M); an underlying abnormality in the endometrium (U) is the unmeasured intermediate caused by smoking (E), and is a cause of prior (M) and current (D) spontaneous abortion. M is a “descending” proxy for the intermediate variable U.

If U is adjusted for, the observed association between the exposure E and outcome D will typically be biased toward the null with respect to the total causal effect

Schisterman E et al. Epidemiology 2009

Content area expertise is important for evaluation of confounding

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Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology

Miguel A. Hernán,[1] Sonia Hernández-Díaz,[2] Martha M. Werler,[2] and Allen A. Mitchell[2]

Common strategies to decide whether a variable is a confounder that should be adjusted for in the analysis rely mostly on statistical criteria. The authors present findings from the Slone Epidemiology Unit Birth Defects Study, 1992–1997, a case-control study on folic acid supplementation and risk of neural tube defects. When statistical strategies for confounding evaluation are used, the adjusted odds ratio is 0.80 (95% confidence interval: 0.62, 1.21). However, the consideration of a priori causal knowledge suggests that the crude odds ratio of 0.65 (95% confidence interval: 0.46, 0.94) should be used because the adjusted odds ratio is invalid. Causal diagrams are used to encode qualitative a priori subject matter knowledge. *Am J Epidemiol* 2002;155:176–84.

Know your field!!

Readings for case-control designs

- Schulz et al. Case-control studies: research in reverse. *Lancet* 2002: 359: 431–34
- Grimes et al. Compared to what? Finding controls for case-control studies. Lancet 2005;365:1429-33
- Rothman text:
  - Page 73 to 91 [section on case-control studies]
- Gordis text:
  - Chapter 10
  - Chapter 13

Undergradese

What undergrads ask vs. what they're REALLY asking