Bias in Epidemiological Studies: the big picture

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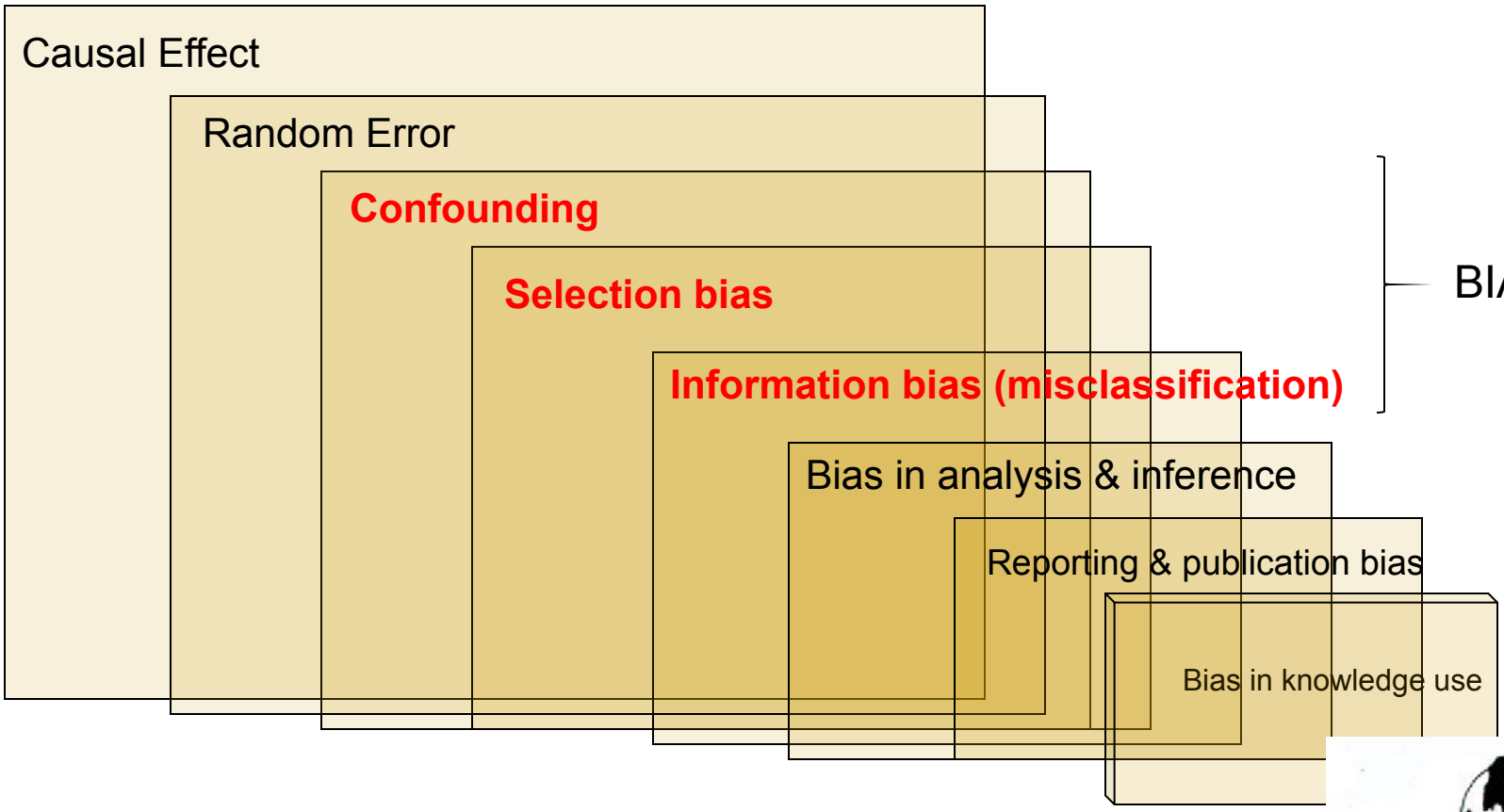
The long road to causal inference (the “big picture”)



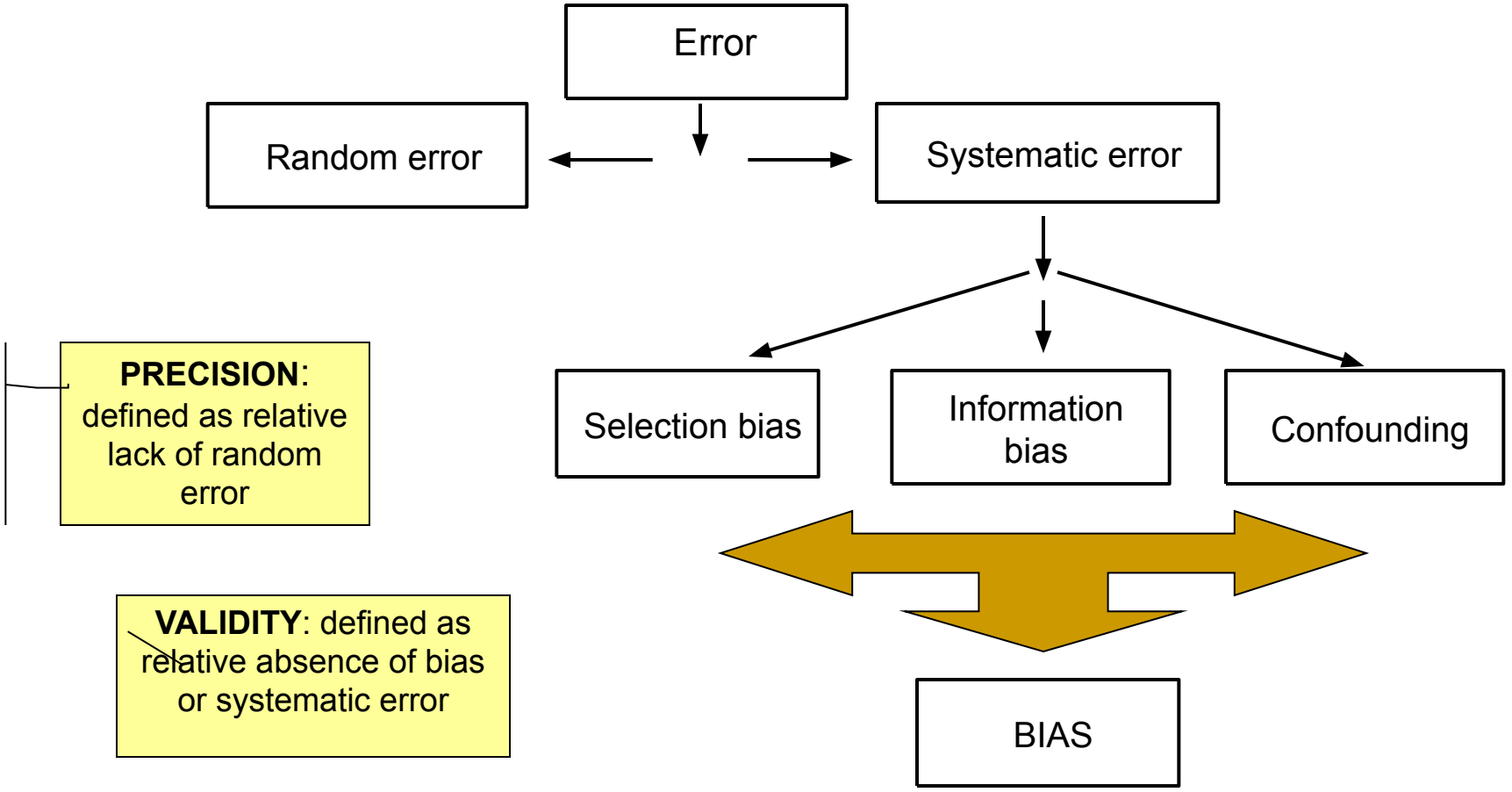
RR_{causal} “truth” [counterfactual]

the long road to causal inference…

$RR_{association}$

Adapted from: Maclure, M, Schneeweis S. Epidemiology 2001;12:114-122.

Errors in epidemiological inference



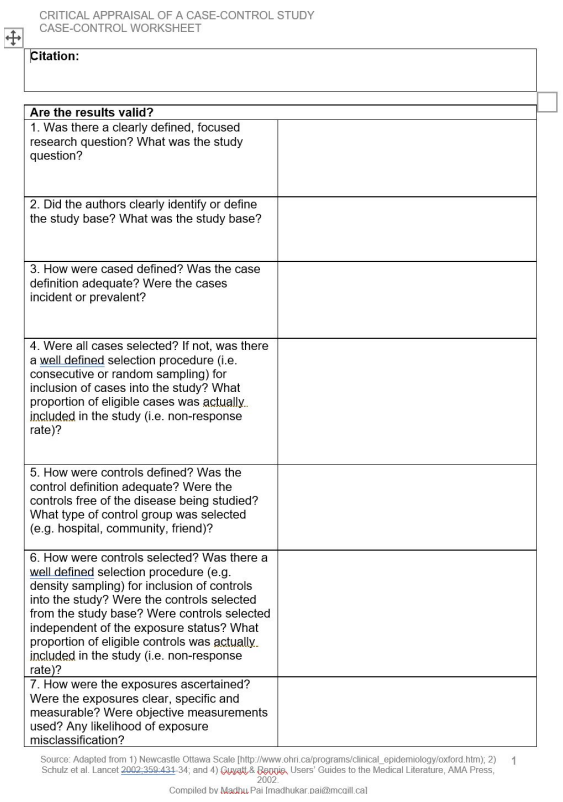
"Bias is any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth" – Sackett (1979)

"Bias is systematic deviation of results or inferences from truth." [Porta, 2008]

The key biases we look for when we read a paper, depends on the study design

- Sources of bias in RCTs:
  - Improper randomization
  - Lack of blinding
  - Attrition
- Sources of bias in case-control studies
  - How were cases and controls selected?
  - Was information collected using same methods in both cases and controls?
  - Was confounding addressed?

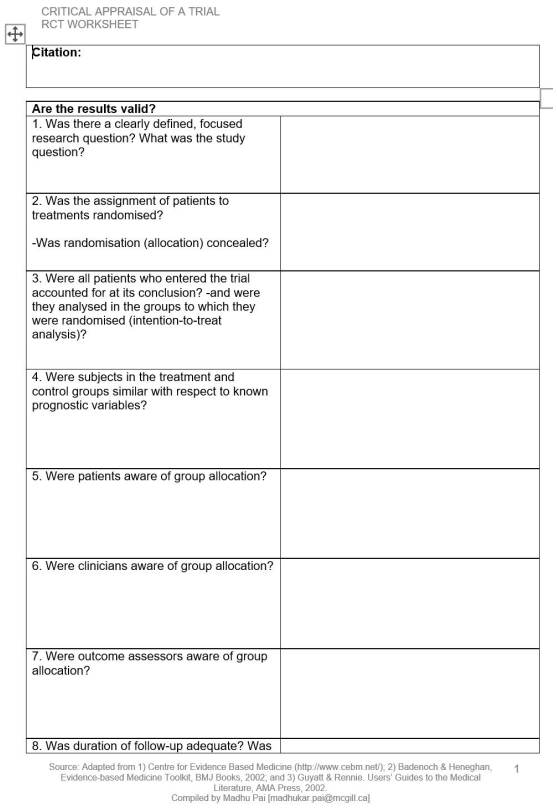
We have critical appraisal worksheets for each study design



CRITICAL APPRAISAL OF A CASE-CONTROL STUDY
CASE-CONTROL WORKSHEET

Citation:	
Are the results valid?	
1. Was there a clearly defined, focused research question? What was the study question?	
2. Did the authors clearly identify or define the study base? What was the study base?	
3. How were cased defined? Was the case definition adequate? Were the cases incident or prevalent?	
4. Were all cases selected? If not, was there a well defined selection procedure (i.e. consecutive or random sampling) for inclusion of cases into the study? What proportion of eligible cases was actually included in the study (i.e. non-response rate)?	
5. How were controls defined? Was the control definition adequate? Were the controls free of the disease being studied? What type of control group was selected (e.g. hospital, community, friend)?	
6. How were controls selected? Was there a well defined selection procedure (e.g. density sampling) for inclusion of controls into the study? Were the controls selected from the study base? Were controls selected independent of the exposure status? What proportion of eligible controls was actually included in the study (i.e. non-response rate)?	
7. How were the exposures ascertained? Were the exposures clear, specific and measurable? Were objective measurements used? Any likelihood of exposure misclassification?	

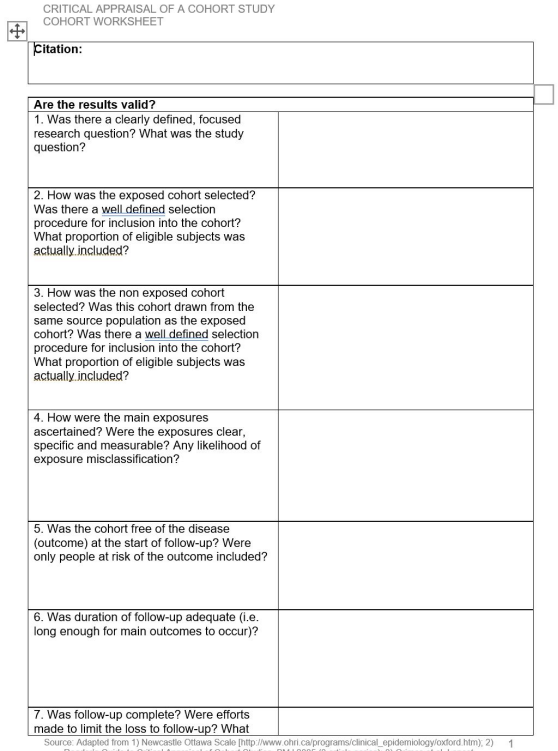
Source: Adapted from 1) Newcastle Ottawa Scale [http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm); 2) Schulz et al. Lancet 2002;359:431-34; and 4) Guyatt & Rennie. Users' Guides to the Medical Literature, AMA Press, 2002.
Compiled by Madhu Pai [madhukar.pai@mcgill.ca]



CRITICAL APPRAISAL OF A TRIAL
RCT WORKSHEET

Citation:	
Are the results valid?	
1. Was there a clearly defined, focused research question? What was the study question?	
2. Was the assignment of patients to treatments randomised? -Was randomisation (allocation) concealed?	
3. Were all patients who entered the trial accounted for at its conclusion? -and were they analysed in the groups to which they were randomised (intention-to-treat analysis)?	
4. Were subjects in the treatment and control groups similar with respect to known prognostic variables?	
5. Were patients aware of group allocation?	
6. Were clinicians aware of group allocation?	
7. Were outcome assessors aware of group allocation?	
8. Was duration of follow-up adequate? Was	

Source: Adapted from 1) Centre for Evidence Based Medicine (http://www.cebm.net/); 2) Badenoch & Heneghan, Evidence-based Medicine Toolkit, BMJ Books, 2002, and 3) Guyatt & Rennie. Users' Guides to the Medical Literature, AMA Press, 2002.
Compiled by Madhu Pai [madhukar.pai@mcgill.ca]



CRITICAL APPRAISAL OF A COHORT STUDY
COHORT WORKSHEET

Citation:	
Are the results valid?	
1. Was there a clearly defined, focused research question? What was the study question?	
2. How was the exposed cohort selected? Was there a well defined selection procedure for inclusion into the cohort? What proportion of eligible subjects was actually included?	
3. How was the non exposed cohort selected? Was this cohort drawn from the same source population as the exposed cohort? Was there a well defined selection procedure for inclusion into the cohort? What proportion of eligible subjects was actually included?	
4. How were the main exposures ascertained? Were the exposures clear, specific and measurable? Any likelihood of exposure misclassification?	
5. Was the cohort free of the disease (outcome) at the start of follow-up? Were only people at risk of the outcome included?	
6. Was duration of follow-up adequate (i.e. long enough for main outcomes to occur)?	
7. Was follow-up complete? Were efforts made to limit the loss to follow-up? What	

Source: Adapted from 1) Newcastle Ottawa Scale [http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm); 2) Reader's Guide to Critical Appraisal of Cohort Studies. BMJ 2005 (3 article series); 3) Grimes et al. Lancet 2002;359:341-45; and 4) Guyatt & Rennie. Users' Guides to the Medical Literature, AMA Press, 2002.
Compiled by Madhu Pai [madhukar.pai@mcgill.ca]

https://www.teachepi.org/teaching-resources/worksheets/

Every single epidemiological study will have bias: we can try and reduce the amount & adjust for it in our analyses

Selection Bias

@EpiEllie

COVID-19 Antibody Seroprevalence in Santa Clara County, California

Eran Bendavid[1], Bianca Mulaney[2], Neeraj Sood[3], Soleil Shah[2], Emilia Ling[2], Rebecca Bromley-Dulfano[2], Cara Lai[2], Zoe Weissberg[2], Rodrigo Saavedra-Walker[4], Jim Tedrow[5], Dona Tversky[6], Andrew Bogan[7], Thomas Kupiec[8], Daniel Eichner[9], Ribhav Gupta[10], John P.A. Ioannidis[1,10], Jay Bhattacharya[1]

Version 2, April 27, 2020
(revised in response to comments received. This remains a preliminary report of the work.)

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

Potential for selection bias:

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

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

Coronavirus: Nearly 15% India's population may have antibodies, shows private lab data

Thyrocare conducted 60,000 antibody tests across 600 locations over 20 days.

A health worker in a protective gear takes a blood sample from a woman. | REUTERS/Navesh Chitrakar

Antibody Velumani. @velumania · Jul 17

#AntibodyTesting after 53,000 tests. Data Pincode wise, of >200 cases reported.15% positive for Abs,means 18 crs already silently, immunised in India (approx 10,000 per death). Too good to believe. Hope, kits do not have high false positives. @ICMRDELHI @MoHFW_INDIA #KeepMasked

110092	NEW DELHI	37.7	500043	HYDERABAD	21.3	801503	PATNA	14.1
500002	HYDERABAD	37.3	500076	HYDERABAD	21.2	422009	NASHIK	14.0
400612	THANE	36.7	122001	GURGAON	20.8	842001	MUZAFFARPUR	13.8
400086	MUMBAI	36.7	400026	MUMBAI	20.4	500072	HYDERABAD	13.4
110085	NEW DELHI	35.7	508207	NALGONDA	20.2	382443	AHMEDABAD	12.8
400009	MUMBAI	35.6	411046	PUNE	19.9	500090	K.V.RANGAREDDY	11.4
110009	NEW DELHI	33.3	800014	PATNA	19.6	800001	PATNA	11.2
110034	NEW DELHI	32.9	500047	HYDERABAD	19.0	403401	SOUTH GOA	11.0
400025	MUMBAI	32.2	380060	AHMEDABAD	18.9	422003	NASHIK	10.9
400055	MUMBAI	31.4	400703	THANE	18.8	500007	HYDERABAD	10.6
500060	K.V.RANGAREDDY	30.6	560100	BANGALORE	18.4	800013	PATNA	10.4
400705	NAVI MUMBAI	28.1	122002	GURGAON	18.4	500004	HYDERABAD	9.6
600034	CHENNAI	27.3	380058	AHMEDABAD	18.1	854105	KATIHAR	8.7
400012	MUMBAI	26.9	400706	THANE	17.6	395009	SURAT	8.7
400019	MUMBAI	26.5	400051	MUMBAI	17.5	506001	WARANGAL	7.7
395006	SURAT	26.4	500008	K.V.RANGAREDDY	17.4	831001	EAST SINGHBHUM	7.4
400097	MUMBAI	25.7	400050	MUMBAI	17.1	500074	HYDERABAD	7.2
421306	THANE	24.2	500062	HYDERABAD	17.0	410209	NAVI MUMBAI	5.6
201301	GAUTAM BUDDHA	23.7	122004	GURGAON	16.8	500032	K.V.RANGAREDDY	5.0
110025	NEW DELHI	23.5	800004	PATNA	16.4	517501	CHITTOOR	5.0
500036	HYDERABAD	23.5	500045	HYDERABAD	16.4	402107	ALIBAUG	4.9
396191	VALSAD	23.3	500084	K.V.RANGAREDDY	16.4	500097	HYDERABAD	3.8
500026	HYDERABAD	23.3	380015	AHMEDABAD	16.3	600028	CHENNAI	3.3
844101	VAISHALI	22.9	500073	HYDERABAD	15.8	123501	MAHENDRAGARH	1.9
400077	MUMBAI	21.7	395010	SURAT	15.7	410501	PUNE	1.5
421301	THANE	21.7	700039	SOUTH 24 PARGANAS	15.6	583275	BELLARY	0.9
700020	KOLKATA	21.7	500018	K.V.RANGAREDDY	15.2	402201	MUMBAI	0.7

69 407 596

"We have not chosen whom to test, we have only tested those who wanted it. 80% was the requirement of the corporates, 15 percent was the requirement of residential societies and 5% was the demand of individuals."

https://scroll.in/latest/968224/coronavirus-nearly-15-indias-population-may-have-antibodies-shows-private-lab-data

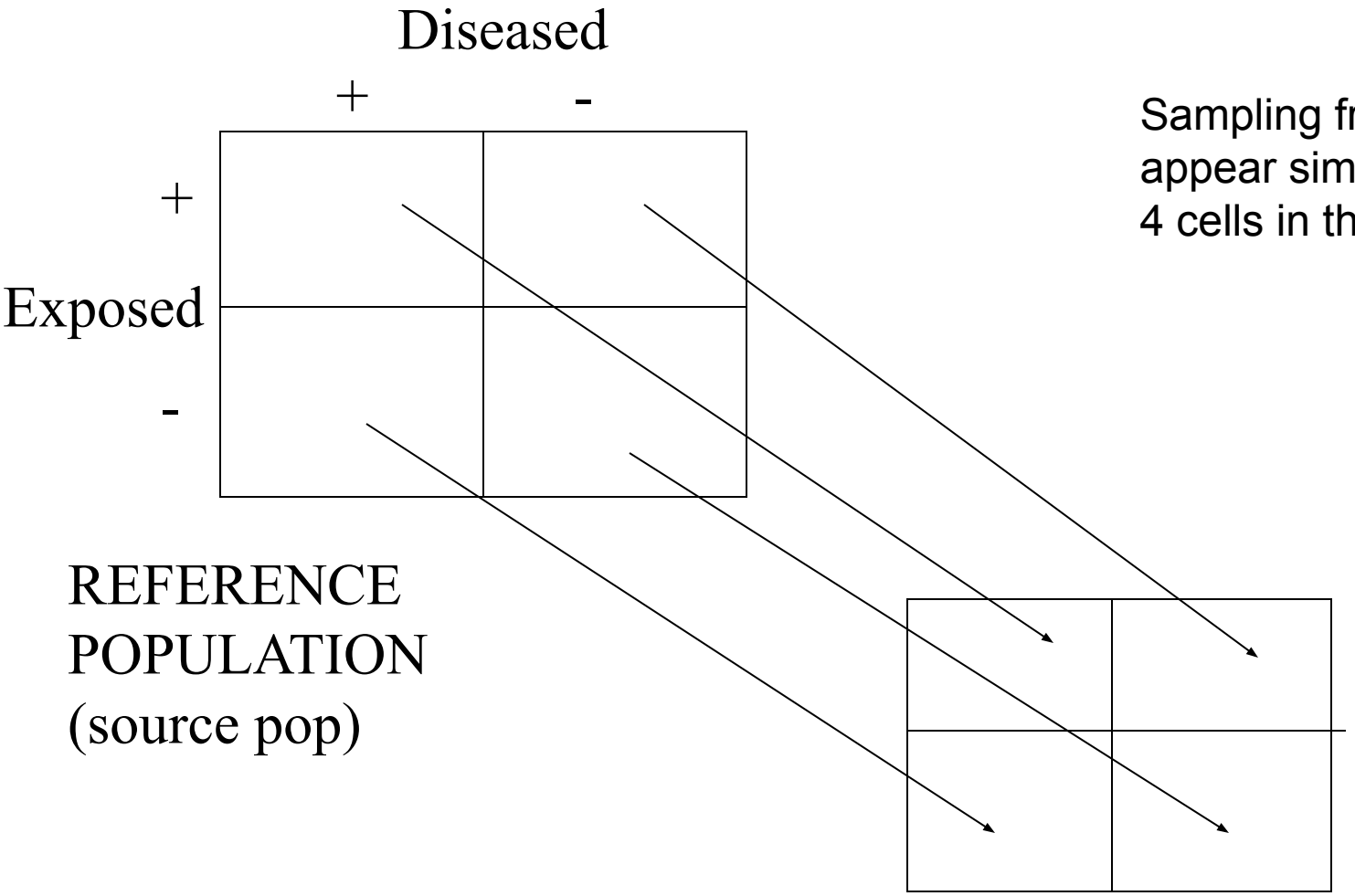
Now lets define selection bias

- "Distortions that result from procedures used to select subjects and from factors that influence participation in the study."
  - Porta M. A dictionary of epidemiology. Oxford, 2008.

- Defining feature:
  - Selection bias occurs at:
    - the stage of recruitment of participants
    - and/or during the process of retaining them in the study
  - Difficult to correct in the analysis, although one can do sensitivity analyses

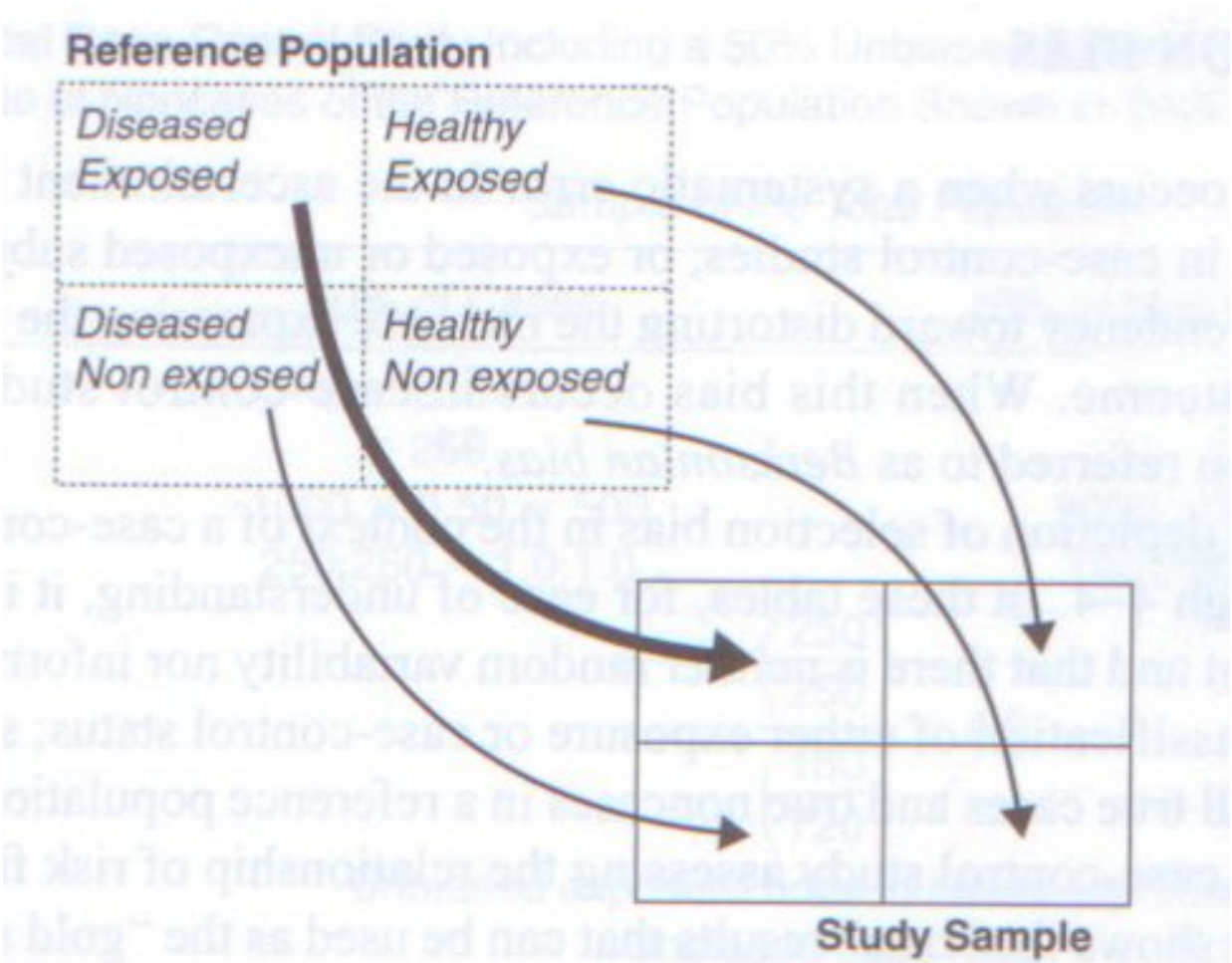
Who gets picked for a study, who refuses, who agrees, who stays in a study, and whether these issues end up producing a "skewed" sample that differs from the target [i.e. biased study base].

Unbiased Sampling



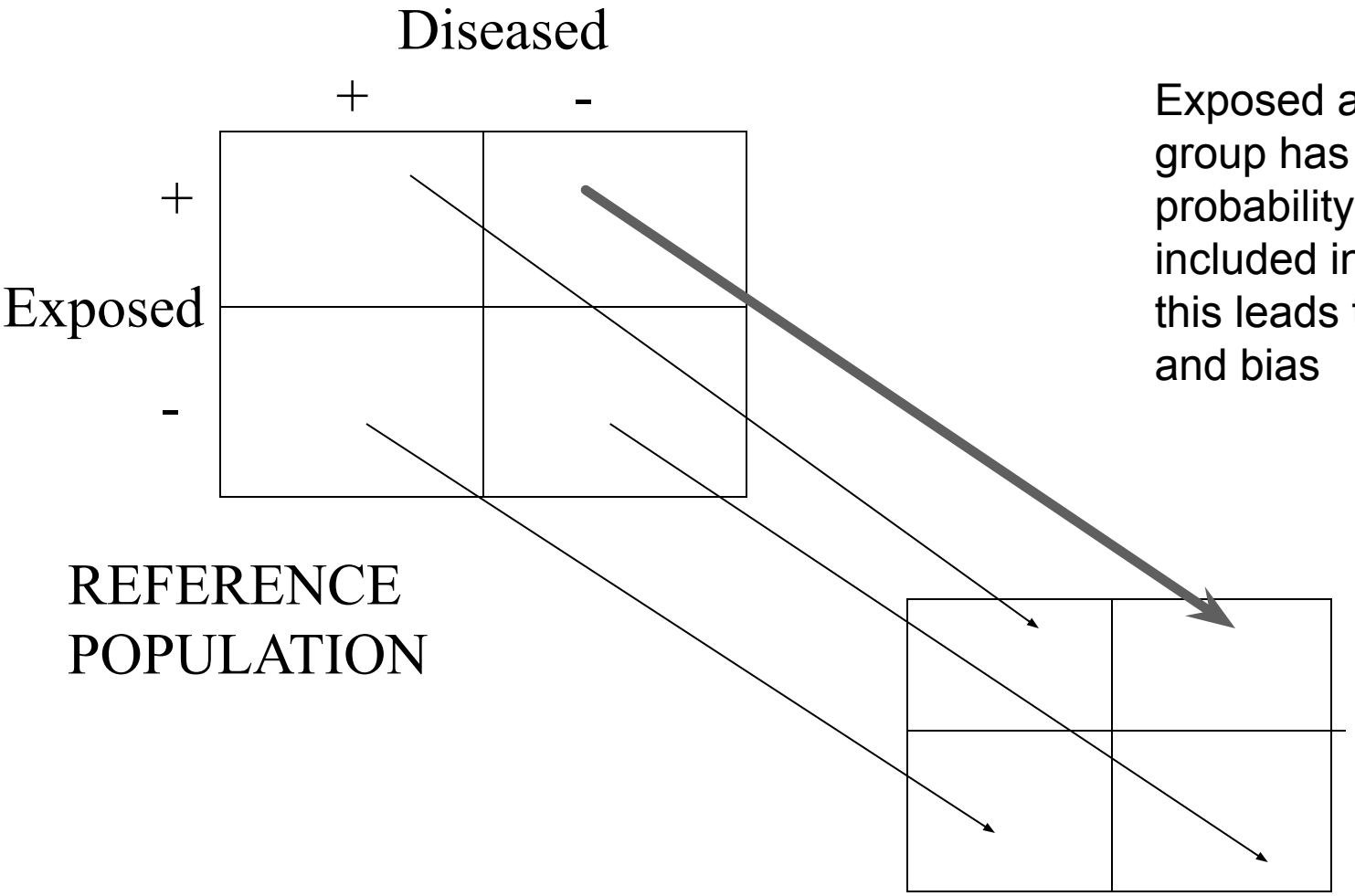
Sampling fractions
appear similar for all
4 cells in the 2 x 2 table

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



Szklo & Nieto. Epidemiology: Beyond the Basics. 2007

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



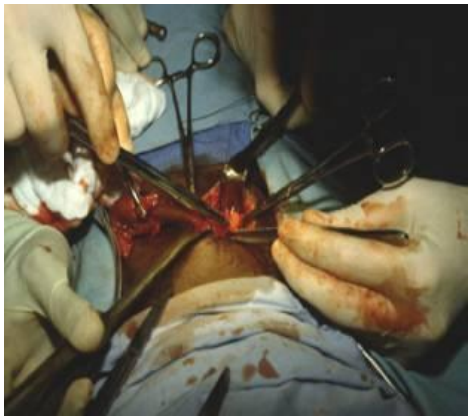
Exposed and healthy group has a higher probability of being included in the study: this leads to imbalance and bias

Selection bias in randomized controlled trials

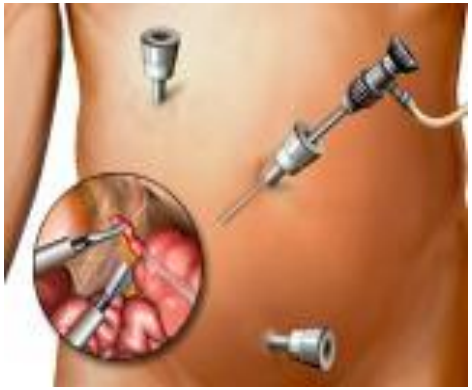
- Examples:
  - Bias due to lack of allocation concealment
    - RCT on thrombolysis with alternating day allocation
    - RCT comparing open versus laparoscopic appendectomy

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

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



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



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

Selection bias in cohort studies

- Sources:
  - Bias due to a non-representative “unexposed” group
    - Key question: aside from the exposure status, are the exposed and unexposed groups comparable?
  - Bias due to non-response
    - More likely if non-response is linked to exposure status (e.g. smokers less likely to respond in a study on smoking and cancer)
  - Bias due to attrition (withdrawals and loss to follow up)

Healthy User and Healthy Continuer Bias: HRT and CHD

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

Michels et al. Circulation. 2003;107:1830

Selection bias in case-control studies

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

Selection bias in case-control studies

630 THE NEW ENGLAND JOURNAL OF MEDICINE March 12, 1981

COFFEE AND CANCER OF THE PANCREAS

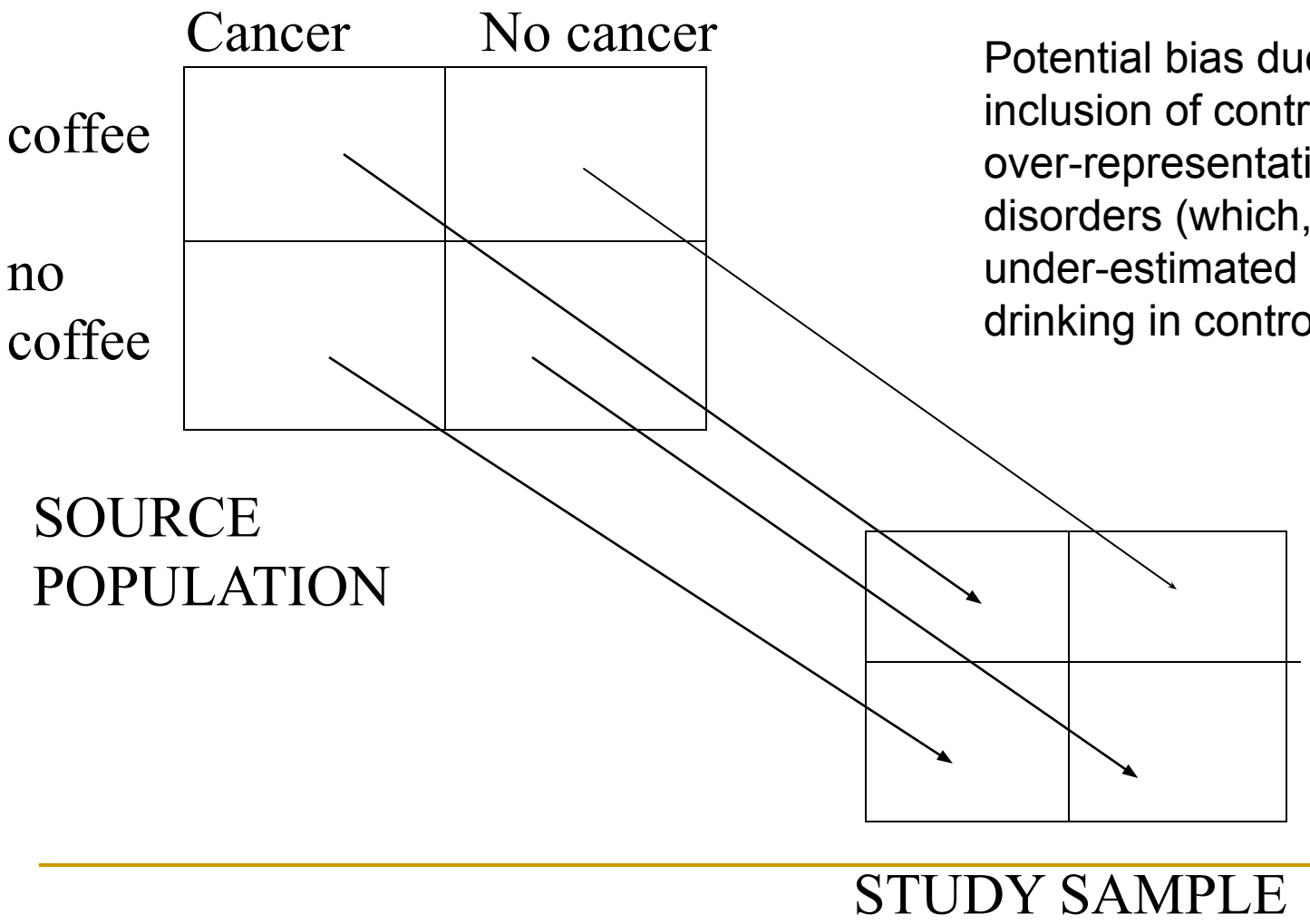
BRIAN MACMAHON, M.D., STELLA YEN, M.D., DIMITRIOS TRICHOPOULOS, M.D., KENNETH WARREN, M.D., AND GEORGE NARDI, M.D.

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

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

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

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



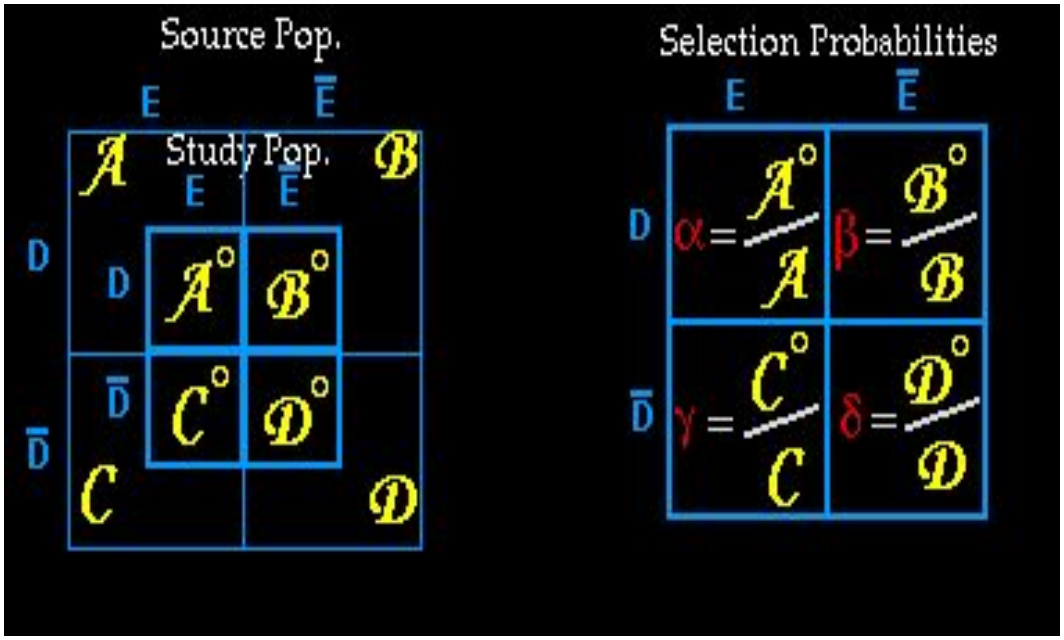
Potential bias due to inclusion of controls with over-representation of GI disorders (which, in turn, under-estimated coffee drinking in controls)

Selection bias in cross-sectional studies

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

Can selection bias be “fixed”?

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



Information Bias

@EpiEllie

Measurement error: a fact of life

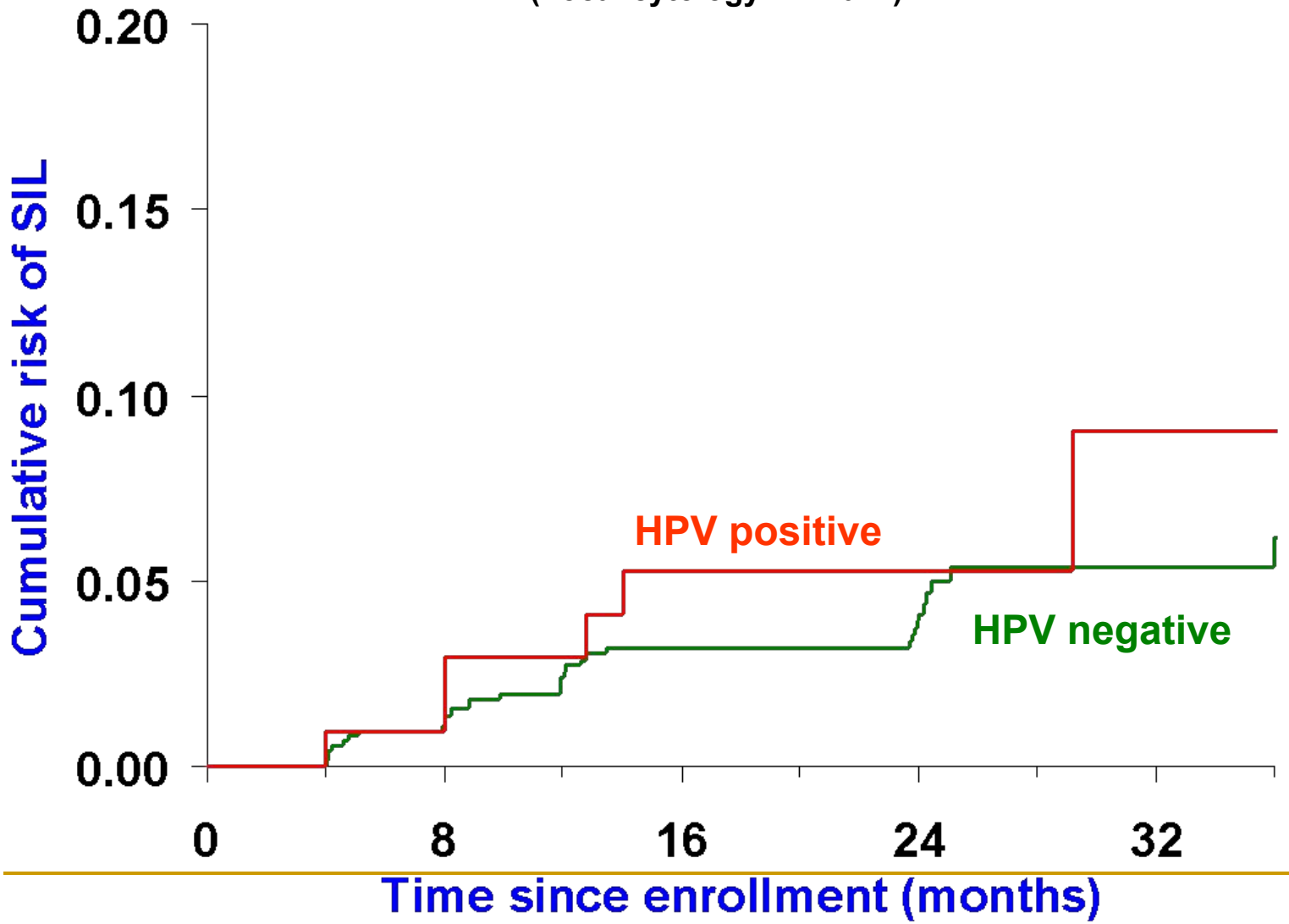
- Measurement error in the ascertainment of:
  - Exposure
  - Outcome/disease
  - Covariates (e.g. confounders)

- Measurement error leads to misclassification bias:
  - Non-differential misclassification bias
  - Differential misclassification bias

Misclassification of exposure in laboratory studies

Example: Cumulative incidence of squamous intraepithelial lesions (SIL) among women with a normal Pap smear at entry

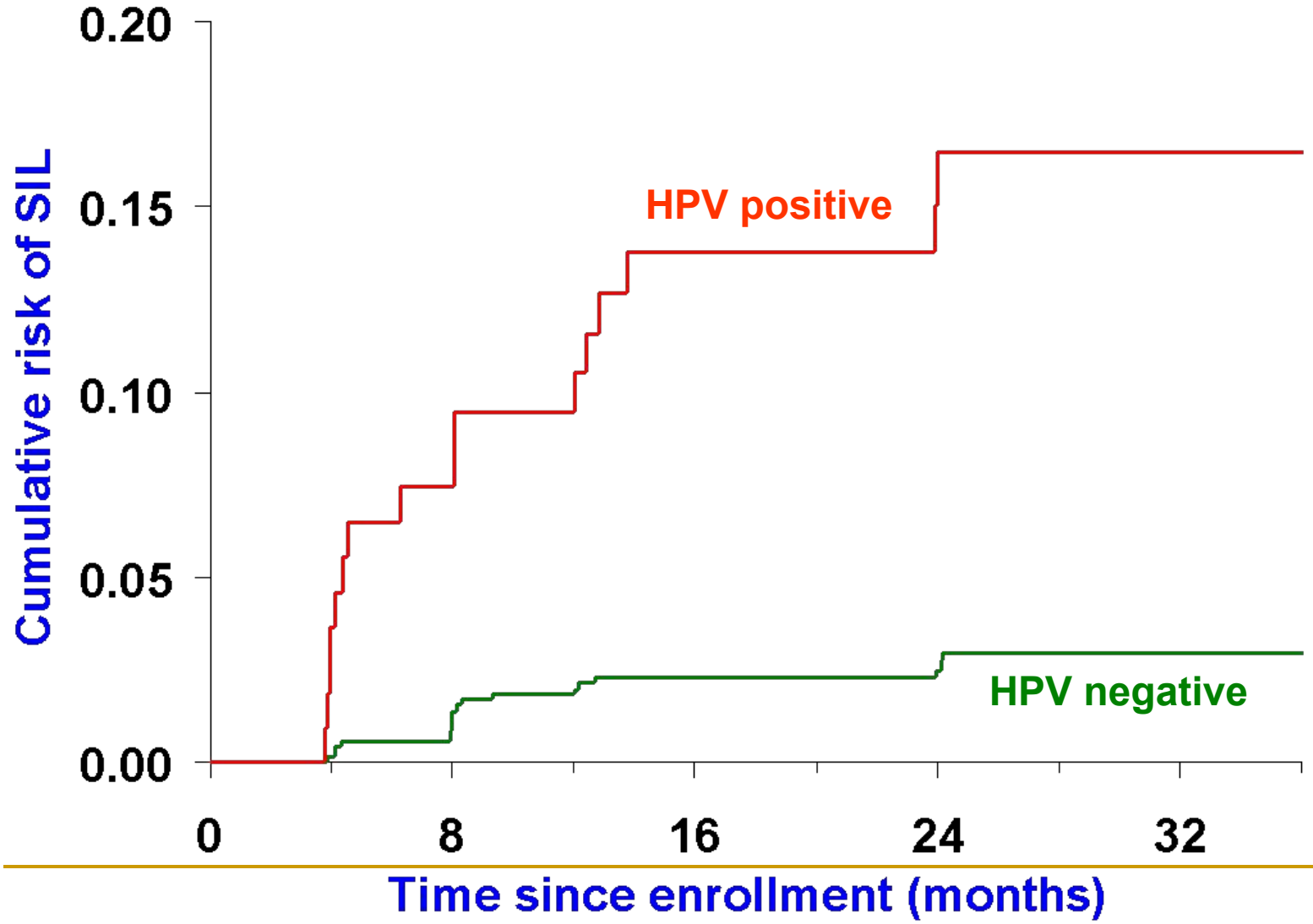
(Local cytology in Brazil)



Source: Eduardo Franco, McGill Univ.

Franco et al., PAJPH 1999; Ludwig-McGill Cohort (Follow-up data as of August 1997)

Example; Cumulative incidence of SIL among women with a normal Pap smear at entry
(Review cytology in Montreal)



Source: Eduardo Franco, McGill Univ.

Franco et al., PAJPH 1999; Ludwig-McGill Cohort (Follow-up data as of August 1997)

With better tests for HPV, the association between HPV and cervical cancer became stronger

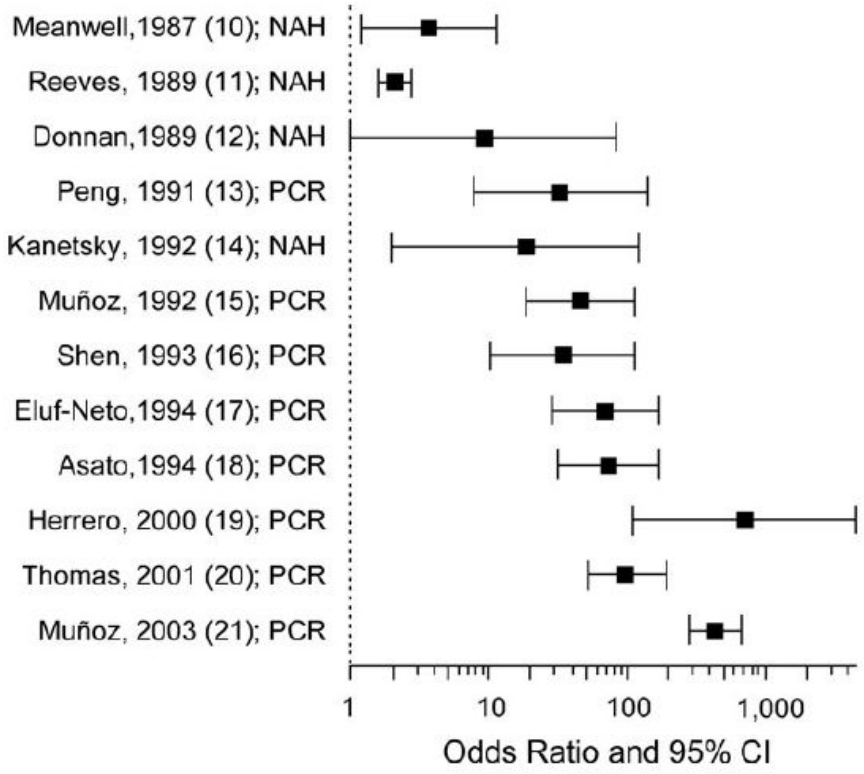


Figure 2. Odds ratios and 95% confidence intervals for the association between human papillomavirus (HPV) infection (via HPV DNA detection) and invasive cervical cancer risk in successive molecular epidemiologic studies (mostly case-control) (from top to bottom, references 10–21). CI, confidence interval; NAH, nonamplified hybridization; PCR, polymerase chain reaction.

"Studies are ordered by year of publication, which underscores the transition from nonamplified hybridization techniques to detect HPV DNA, prevailing in the 1980s, to the new era of amplified target detection via polymerase chain reaction (PCR) protocols. The graph shows that the magnitude of the association increased substantially, from 2- to 5-fold risk increases in the early studies to triple digits in the most recent investigations."

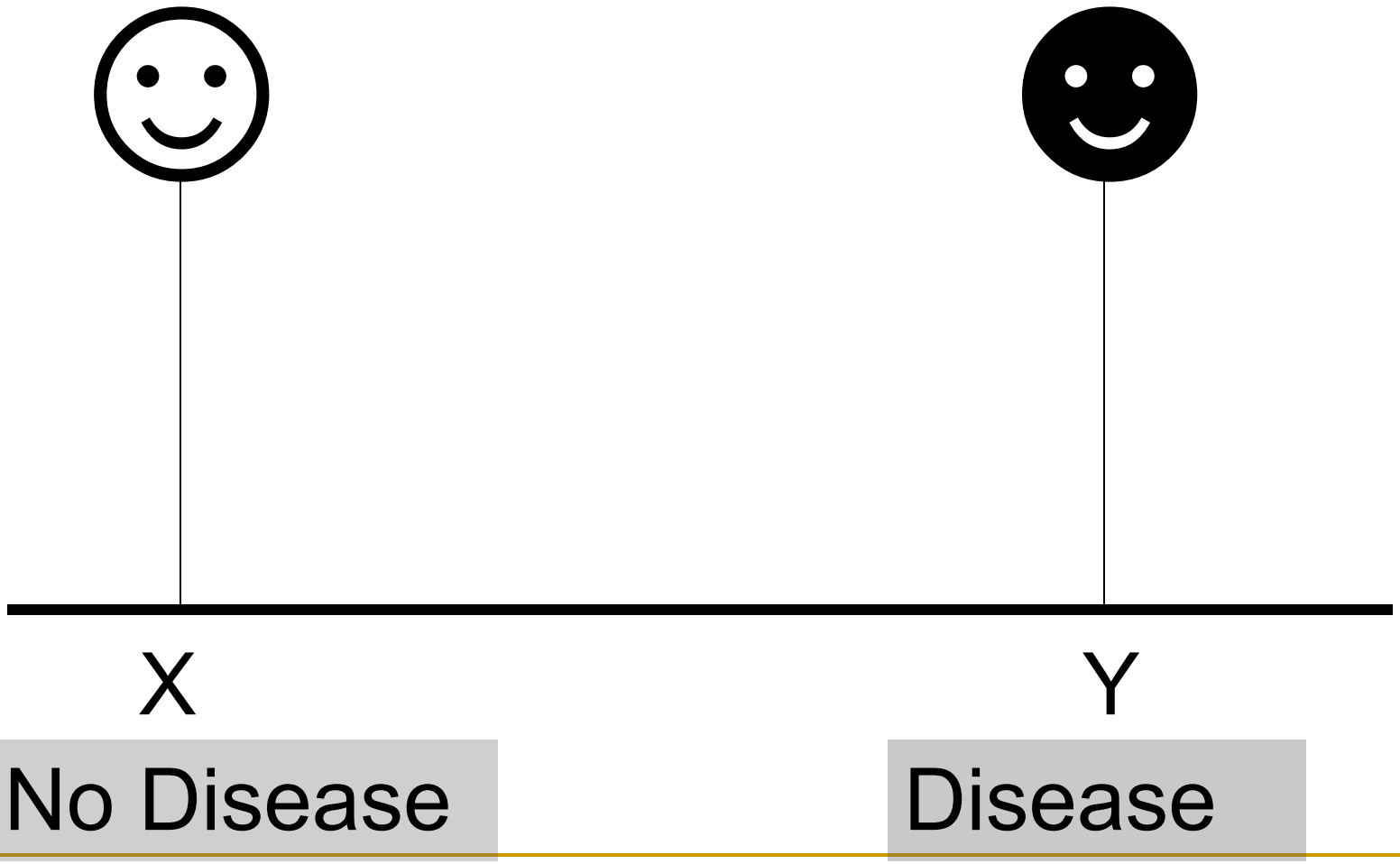
American Journal of Epidemiology 2010 171(2):164-168;

What is information bias?

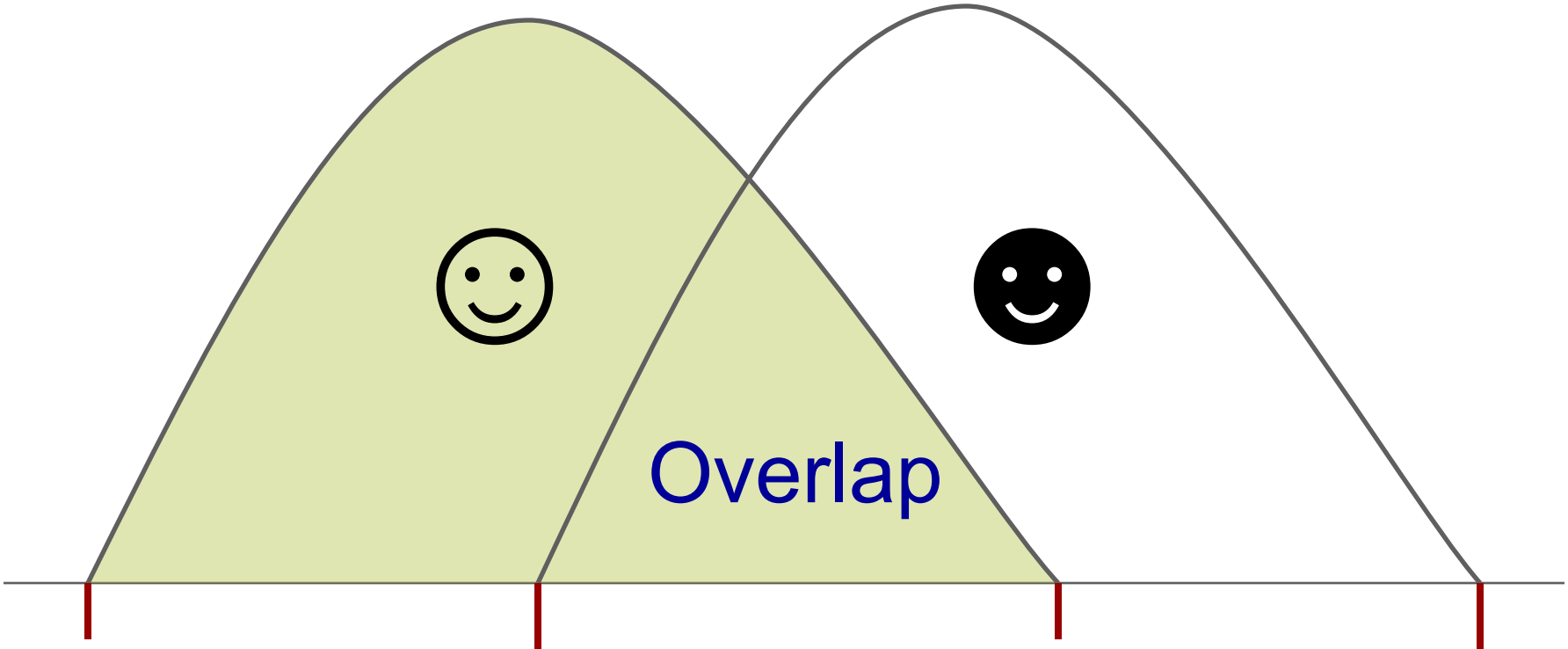
- "Bias in an estimate arising from measurement errors"
  - Porta M. A dictionary of epidemiology. Oxford, 2008.

- Defining feature:
  - Information bias occurs at the stage of data collection
  - Misclassification of exposure and/or outcome status is the main source of error, and this, in turn, has the potential to bias the effect estimate

The ideal measurement tool (i.e. a diagnostic test) = no misclassification



Variations in test results



Range of Variation in Disease free

Range of Variation in Diseased

If we used antibody tests for Covid-19, how accurate are they?

RESEARCH

Check for updates

FAST TRACK

Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis

Mayara Lisboa Bastos,[1,2] Gamuchirai Tavaziva,[1] Syed Kunal Abidi,[1] Jonathon R Campbell,[1,6] Louis-Patrick Haraoui,[3] James C Johnston,[4] Zhiyi Lan,[1] Stephanie Law,[5] Emily MacLean,[6] Anete Trajman,[1,2] Dick Menzies,[1,6] Andrea Benedetti,[1,6] Faiz Ahmad Khan[1,6]

The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3%.

Pooled specificities ranged from 96.6% to 99.7%.

https://www.bmj.com/content/bmj/370/bmj.m2516.full.pdf

Information bias in randomized controlled trials

- Sources:
  - Lack of blinding can cause detection bias (knowledge of intervention can influence assessment or reporting of outcomes)
    - Subjects ("participant expectation bias")
    - Investigators
    - Outcome assessors ("observer bias")
    - Data analysts
  - Key issue: how "hard" is the outcome variable?
    - Strong versus "soft" outcomes
    - Blinding is very important for soft outcomes

Vit C and common cold

Case studies of bias in real life epidemiologic studies

Bias File 5. How blind are the blind? The story of Vitamin C for common cold

Compiled by

Madhukar Pai, MD, PhD

Jay S Kaufman, PhD

http://www.teachepi.org/resources/bfiles.htm

Recall bias: example

SHORT REPORT

Recall bias, MMR, and autism

N Andrews, E Miller, B Taylor, R Lingam, A Simmons, J Stowe, P Waight

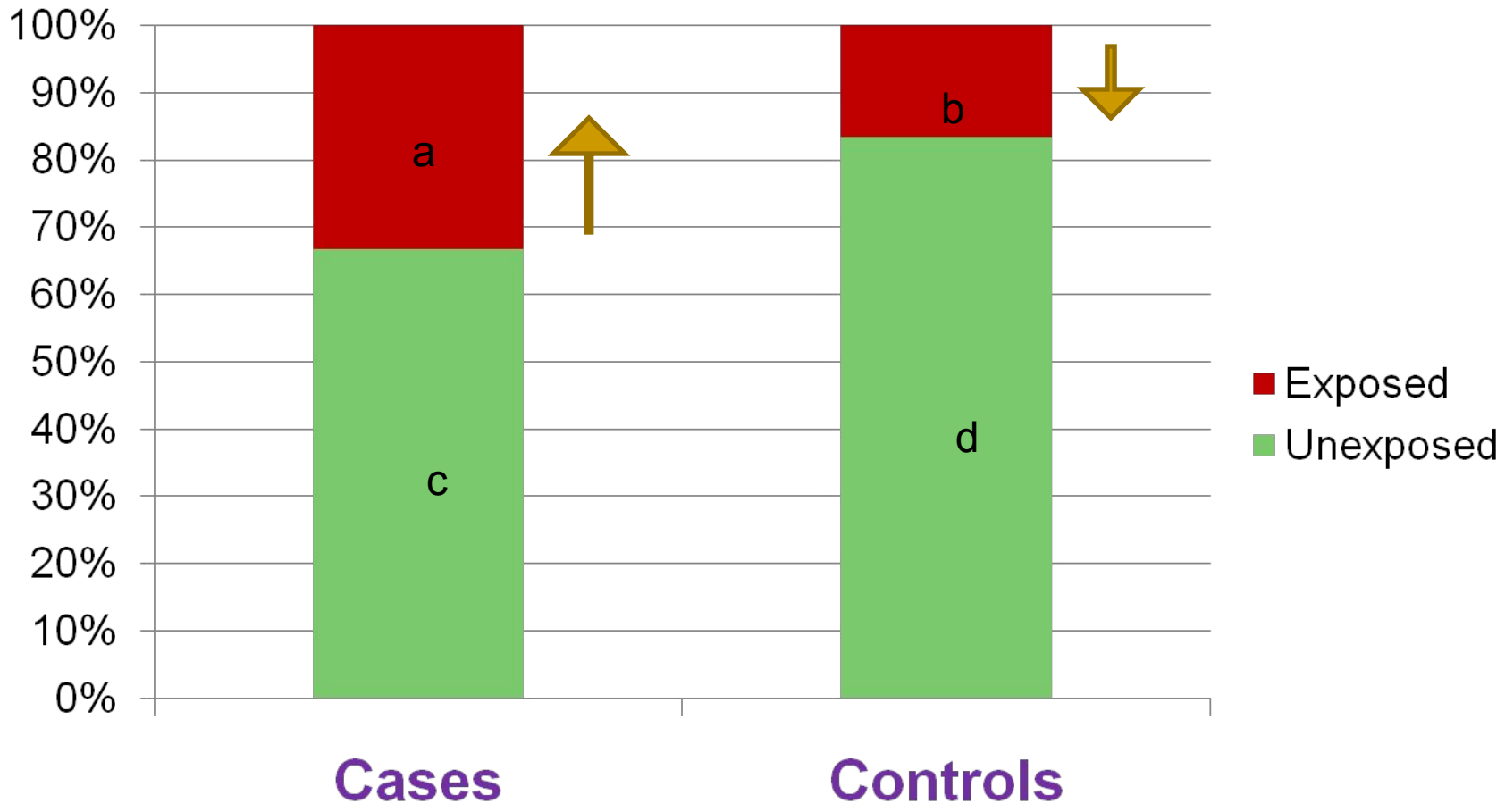
Arch Dis Child 2002;**87**:493–494

Parents of autistic children with regressive symptoms who were diagnosed after the publicity alleging a link with measles, mumps, and rubella (MMR) vaccine tended to recall the onset as shortly after MMR more often than parents of similar children who were diagnosed prior to the publicity. This is consistent with the recall bias expected under such circumstances.

The self controlled case series method[6] uses conditional Poisson regression to enable estimation of the RI using only cases by comparison of the frequency of events within and outside specified post-immunisation risk periods. In these analyses the risk periods for autism onset considered were within 2, 4, 6, and 12 months of MMR. Age was adjusted for by stratification into one month groups. In the first analysis, cases were restricted to the subset of children with core or atypical autism in whom parents reported developmental regression, with onset defined

Recall bias

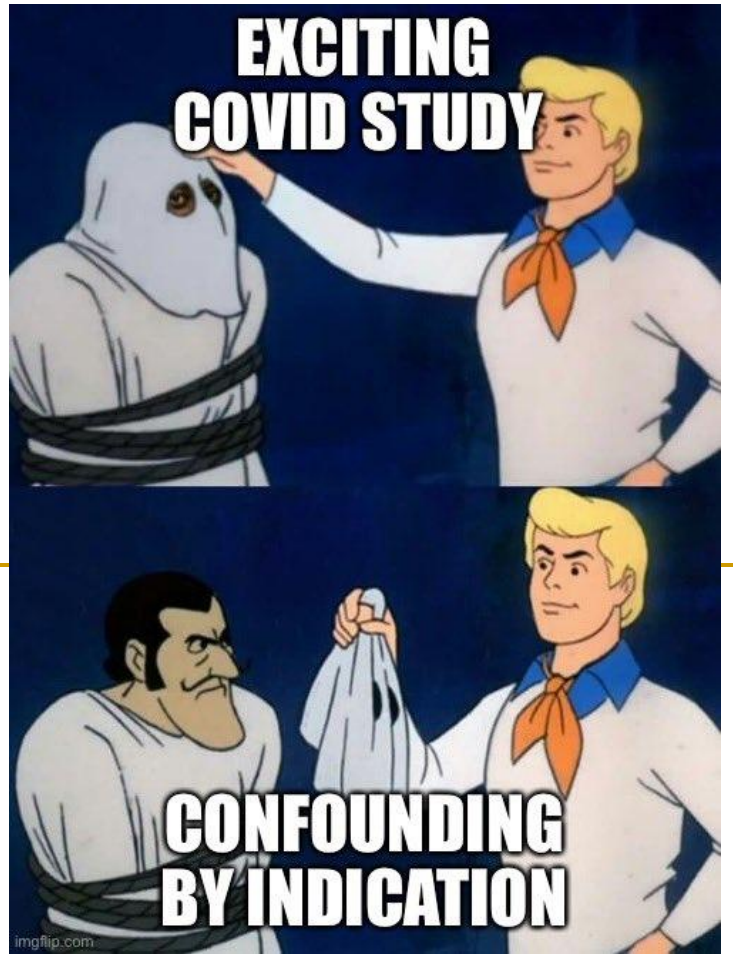
OR = ad / bc



Reducing information bias

- Use the best possible tool to measure exposure and outcomes
- Use objective (“hard”) measures as much as possible
- Use blinding as often as possible, especially for soft outcomes
- Train interviewers and perform standardization (pilot) exercises
- Use the same procedures for collecting information from cases and controls & among exposed and unexposed
- Collect data on sensitivity and specificity of the measurement tool (i.e. validation sub-studies)

Confounding



@EpiEllie

Covid-19

Smokers seem less likely than non-smokers to fall ill with covid-19

That may point towards a way of treating it

Confounding: mixing of effects

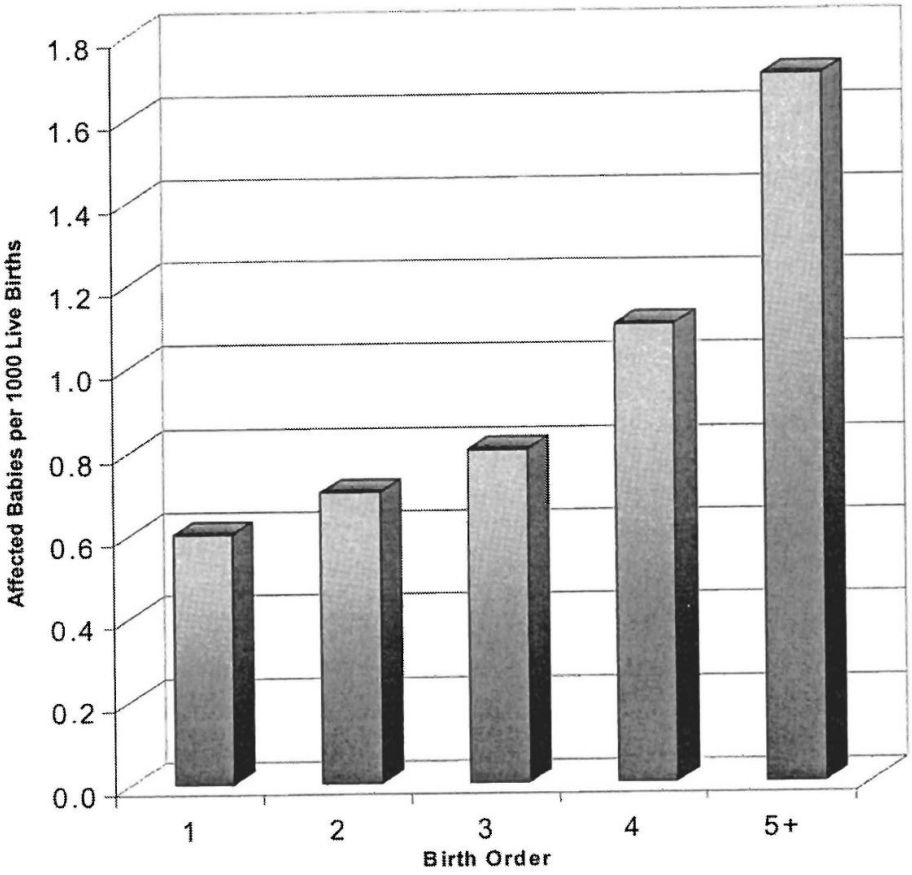
- "Confounding is confusion, or mixing, of effects; the effect of the exposure is mixed together with the effect of another variable, leading to bias" - Rothman, 2002

Latin: "confundere" is to mix together

Rothman KJ. Epidemiology. An introduction. Oxford: Oxford University Press, 2002

Example

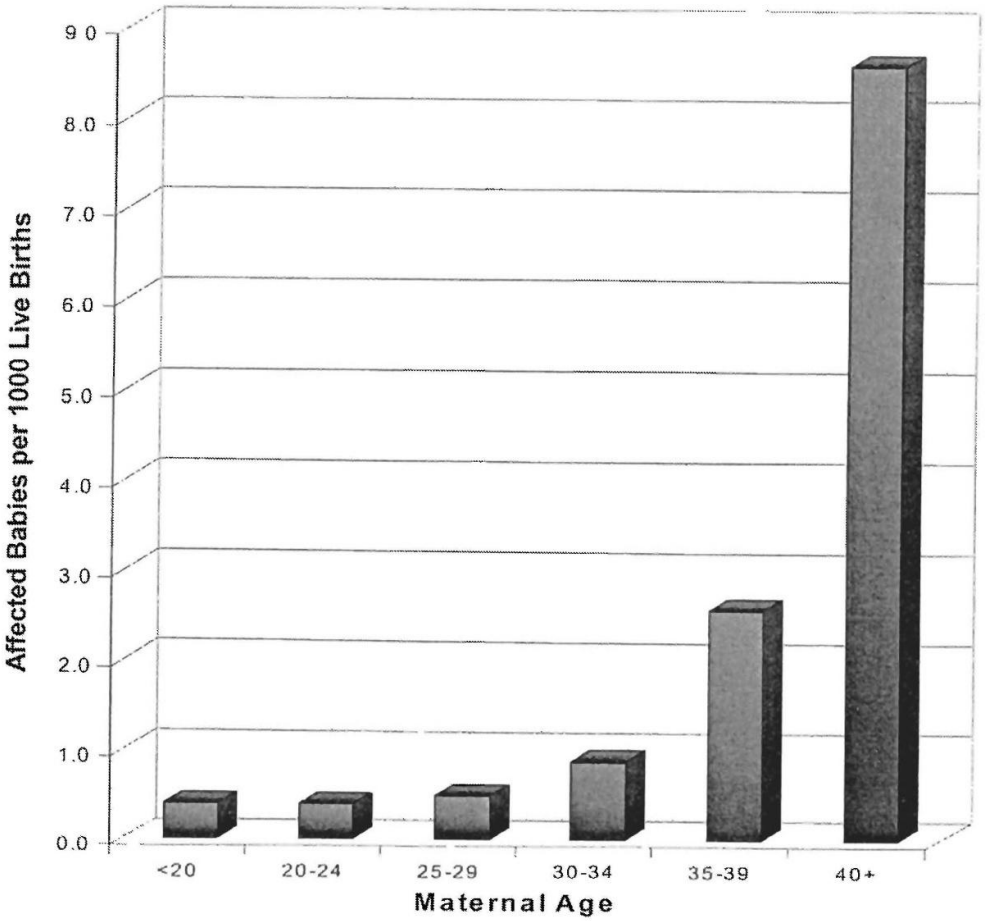
Association between birth order and Down syndrome



Data from Stark and Mantel (1966)

Source: Rothman 2002

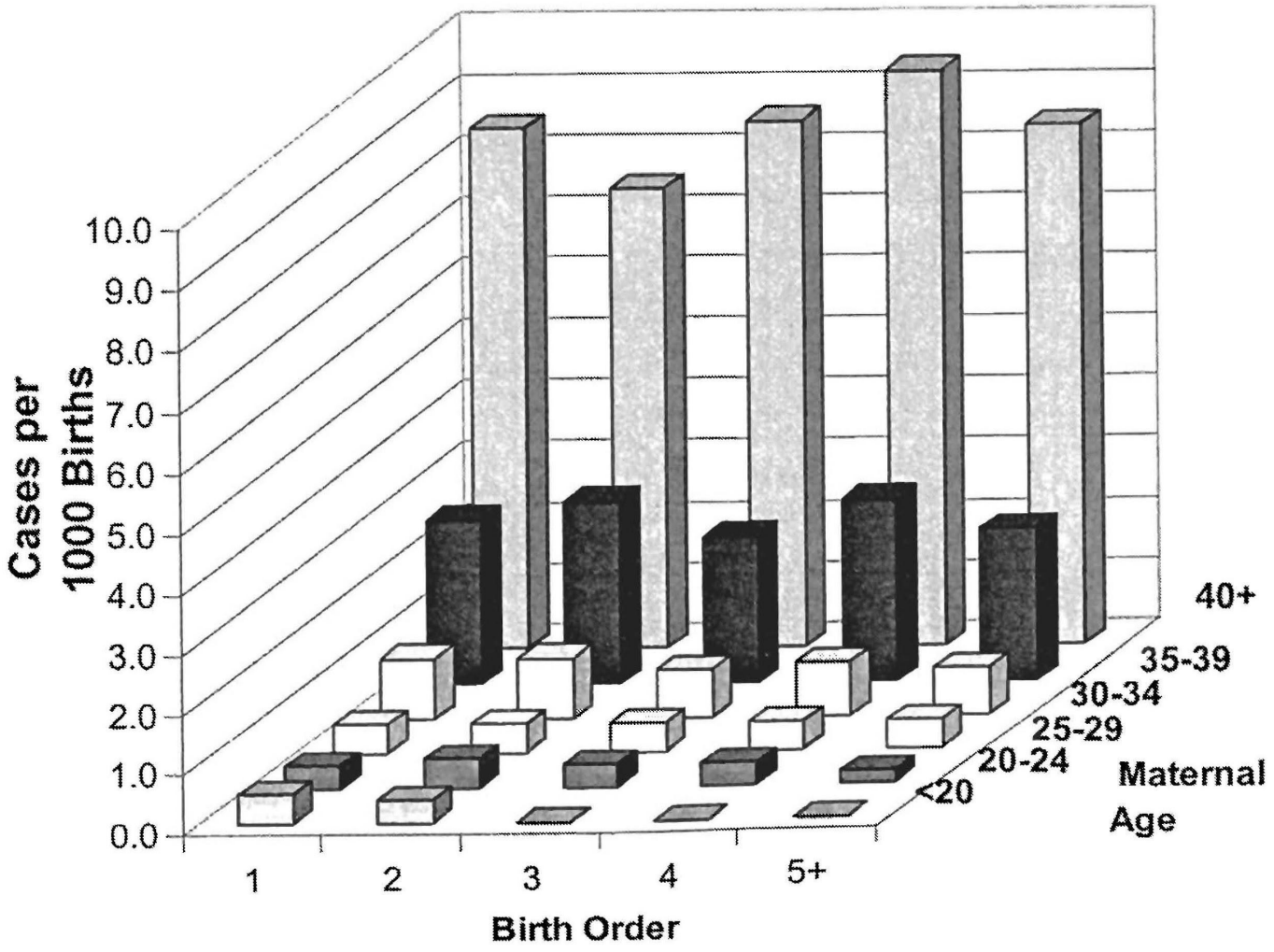
Association between maternal age and Down syndrome



Data from Stark and Mantel (1966)

Source: Rothman 2002

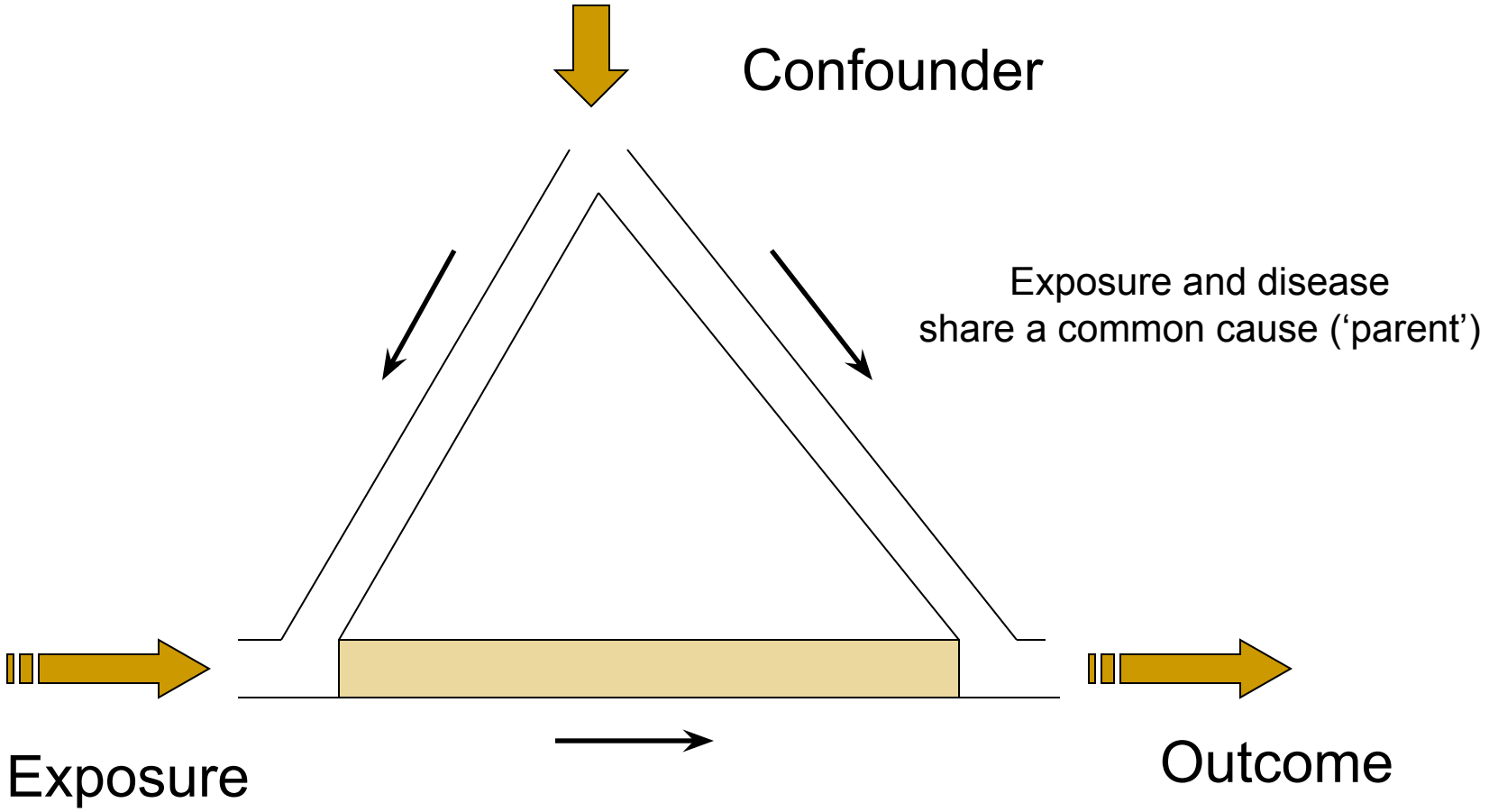
Association between maternal age and Down syndrome, stratified by birth order



Data from Stark and Mantel (1966)

Source: Rothman 2002

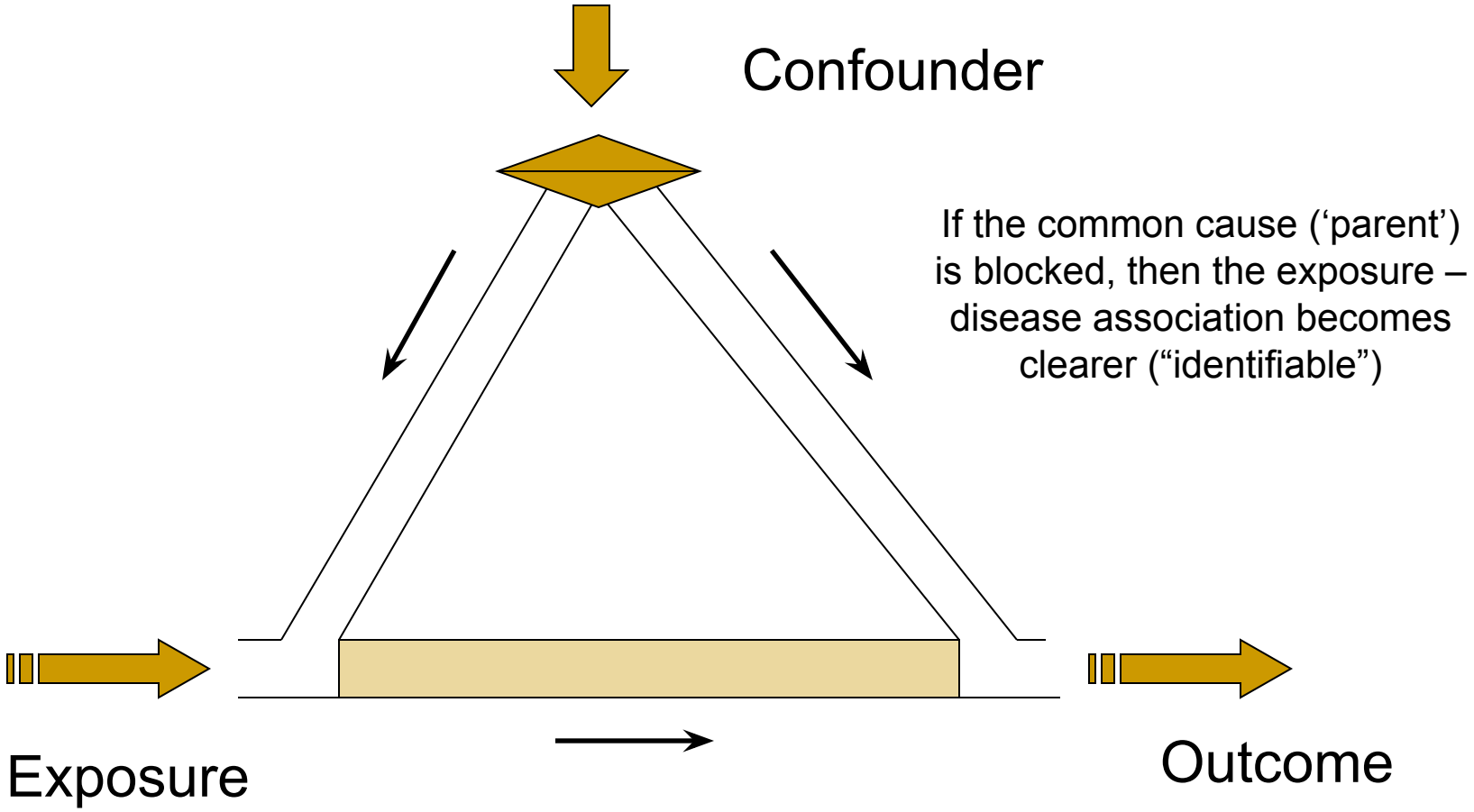
Mixing of Effects: the water pipes analogy



Mixing of effects – cannot separate the effect of exposure from that of confounder

Adapted from Jewell NP. Statistics for Epidemiology. Chapman & Hall, 2003

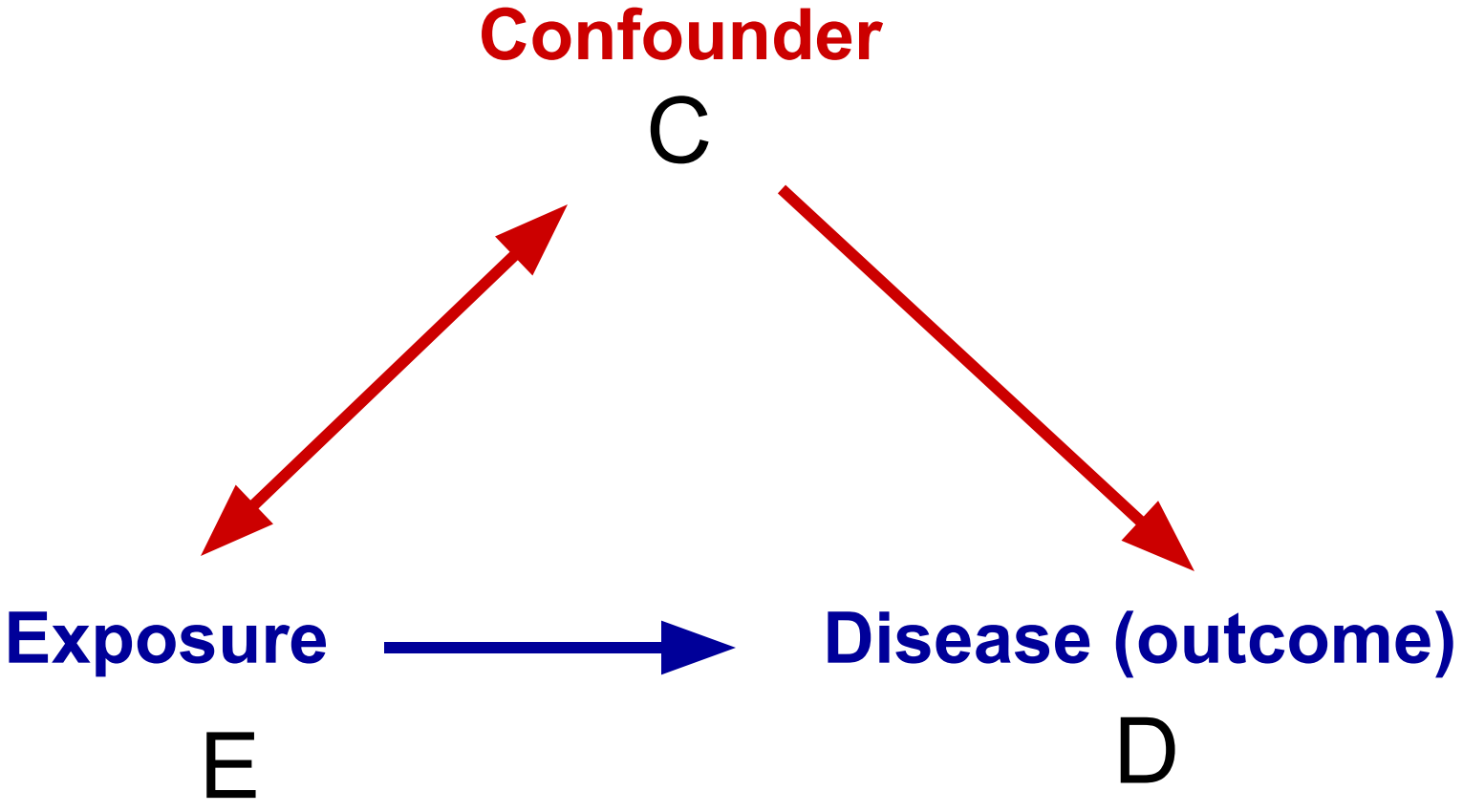
Mixing of Effects: "control" of the confounder



Successful "control" of confounding (adjustment)

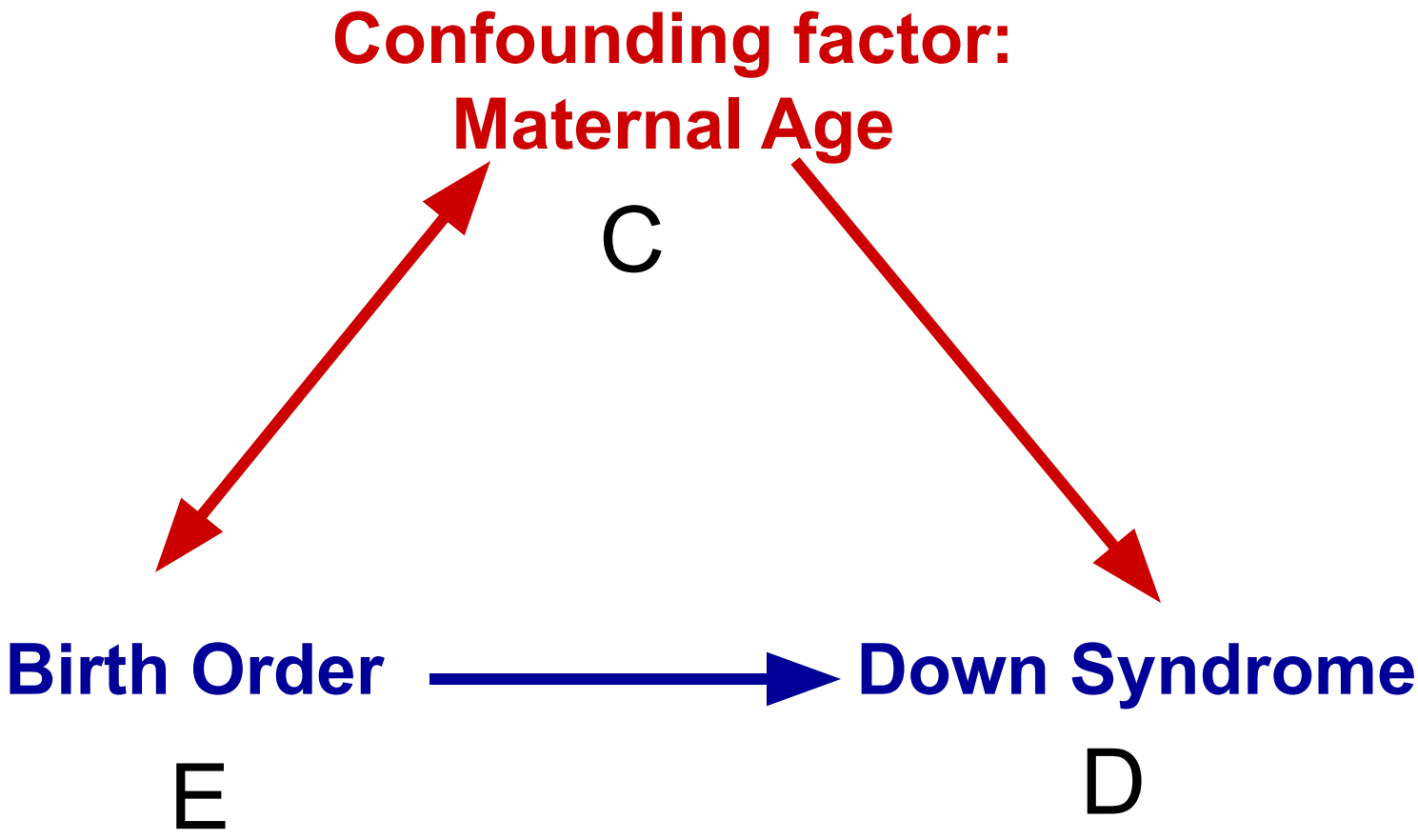
Adapted from: Jewell NP. Statistics for Epidemiology. Chapman & Hall, 2003

So, a confounder is a parent of exposure & outcome



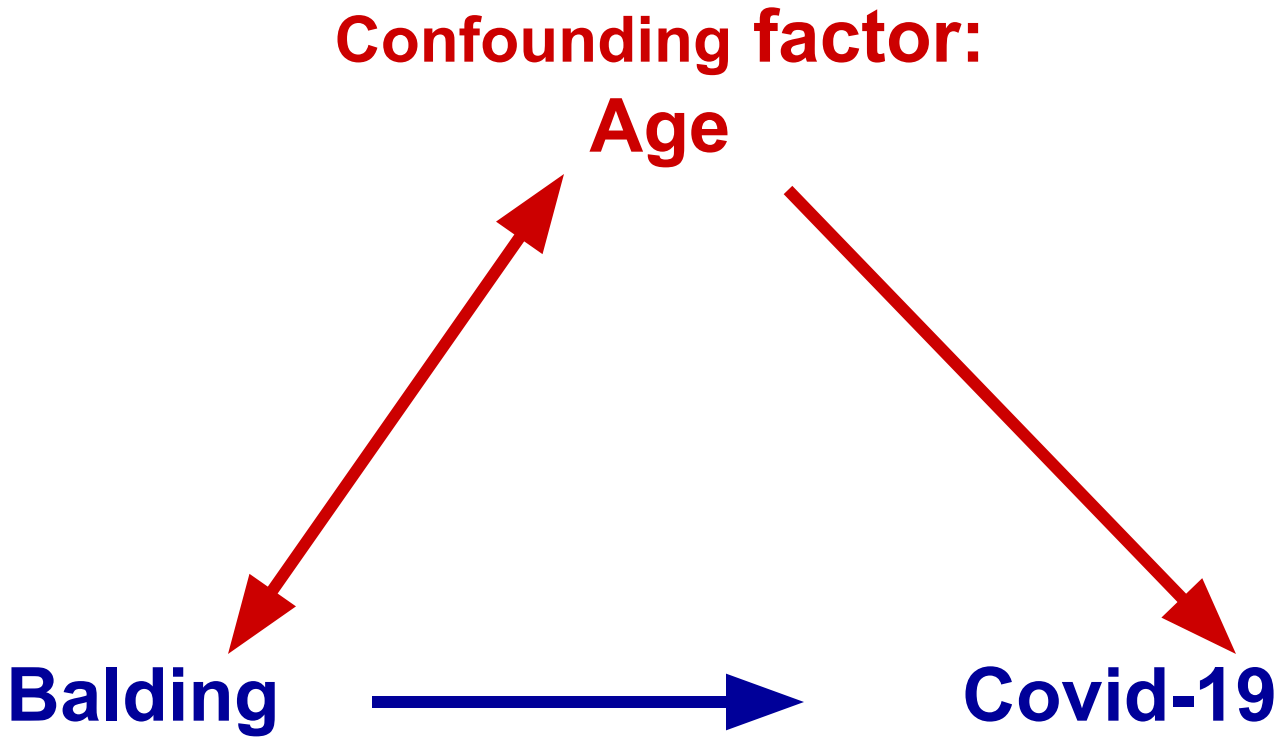
Szklo M, Nieto JF. Epidemiology: Beyond the basics. Aspen Publishers, Inc., 2000.
Gordis L. Epidemiology. Philadelphia: WB Saunders, 4th Edition.

Confounding Schematic



Are confounding criteria met?

Association between balding and Covid19

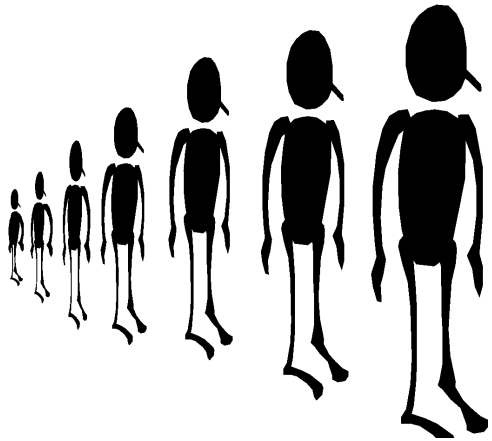


Counterfactual model explains how confounding occurs

- Ideal "causal contrast" between exposed and unexposed groups:
  - "A causal contrast compares disease frequency under *two* exposure distributions, but in *one* target population during *one* etiologic time period"
  - If the ideal causal contrast is met, the observed effect is the "causal effect"

Maldonado & Greenland, Int J Epi 2002;31:422-29

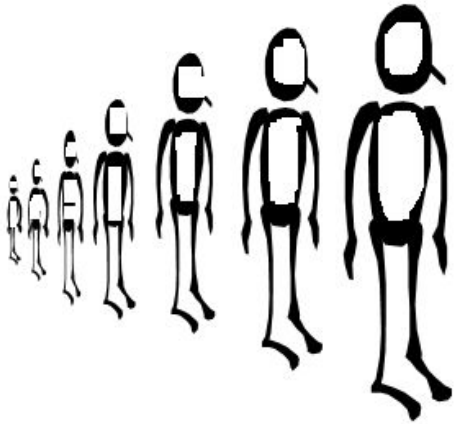
Ideal counterfactual comparison to determine causal effects



Exposed cohort

I_{exp}

"Initial conditions" are identical in the exposed and unexposed groups – because they are the same population!



Counterfactual, unexposed cohort

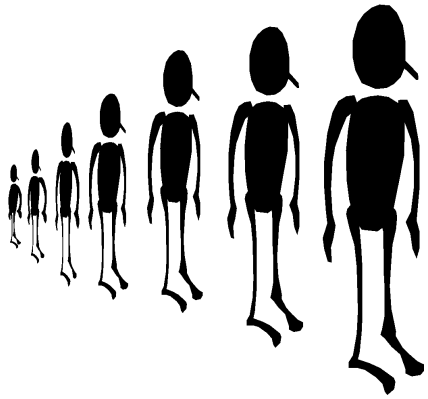
I_{unexp}

$$RR_{causal} = I_{exp} / I_{unexp}$$

"A causal contrast compares disease frequency under *two* exposure distributions, but in *one* target population during *one* etiologic time period"

Maldonado & Greenland, Int J Epi 2002;31:422-29

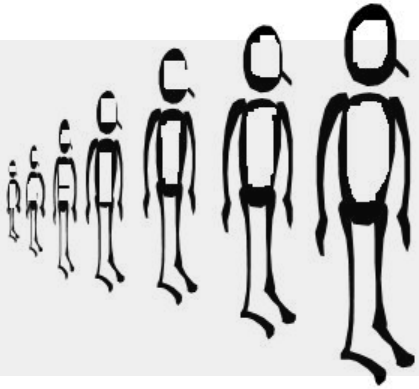
What happens actually?



Exposed cohort

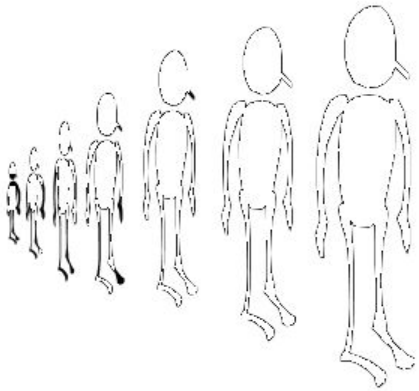
I_{exp}

counterfactual state is not observed



Counterfactual, unexposed cohort

I_{unexp}

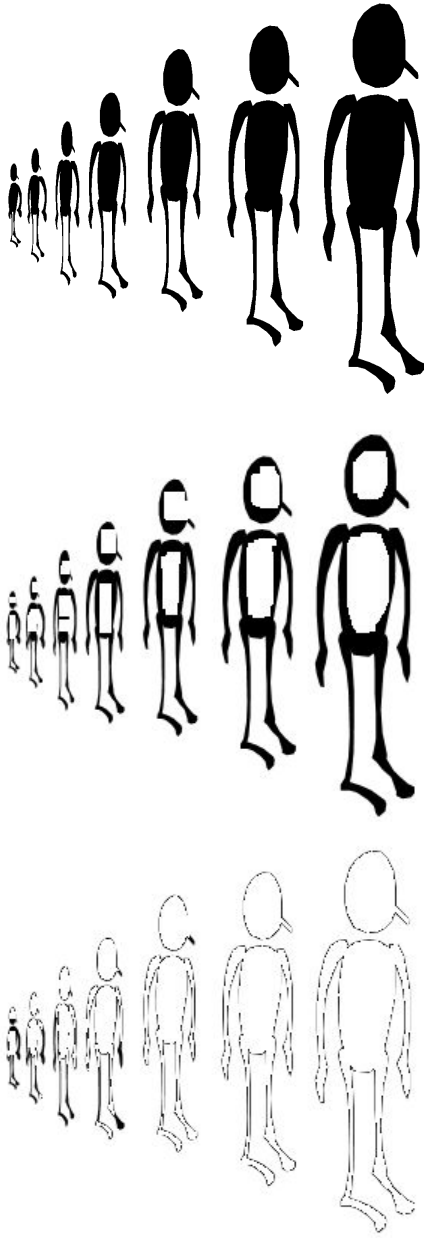


Substitute, unexposed cohort

$I_{substitute}$

A substitute will usually be a population other than the target population during the etiologic time period - INITIAL CONDITIONS MAY BE DIFFERENT

Counterfactual definition of confounding



$$RR_{causal} =/= RR_{assoc}$$

Exposed cohort

Counterfactual, unexposed cohort

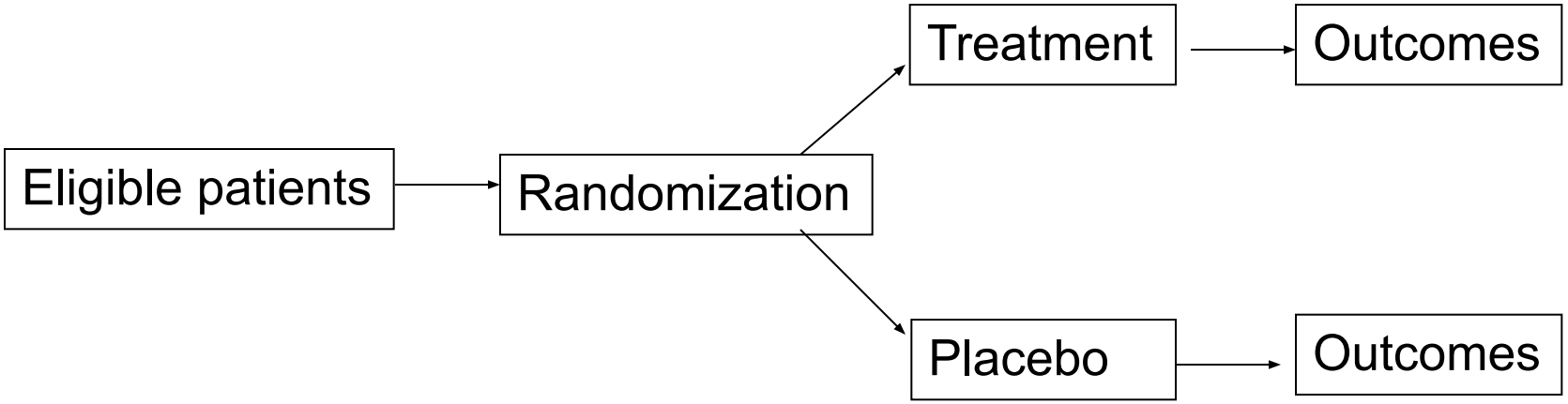
Substitute, unexposed cohort

"Confounding is present if the substitute population imperfectly represents what the target would have been like under the counterfactual condition"

"An association measure is *confounded* (or biased due to confounding) for a causal contrast if it does not equal that causal contrast because of such an imperfect substitution"

Maldonado & Greenland, Int J Epi 2002;31:422-29

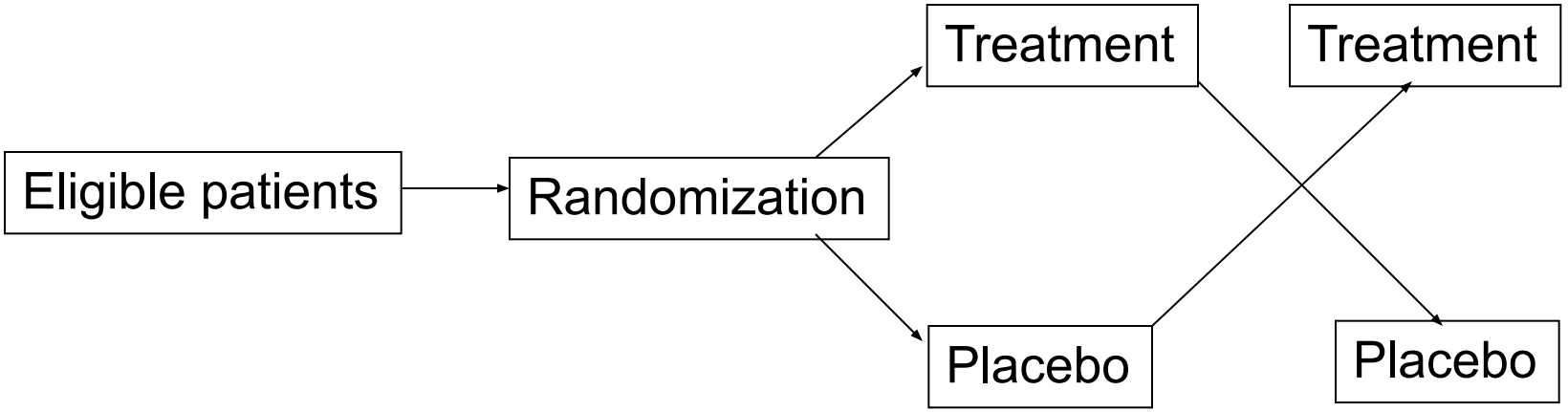
Simulating the counter-factual comparison:
Experimental Studies: RCT



Randomization helps to make the groups “comparable” (i.e. similar initial conditions) with respect to known and unknown confounders

Therefore confounding is unlikely at randomization - time t_0

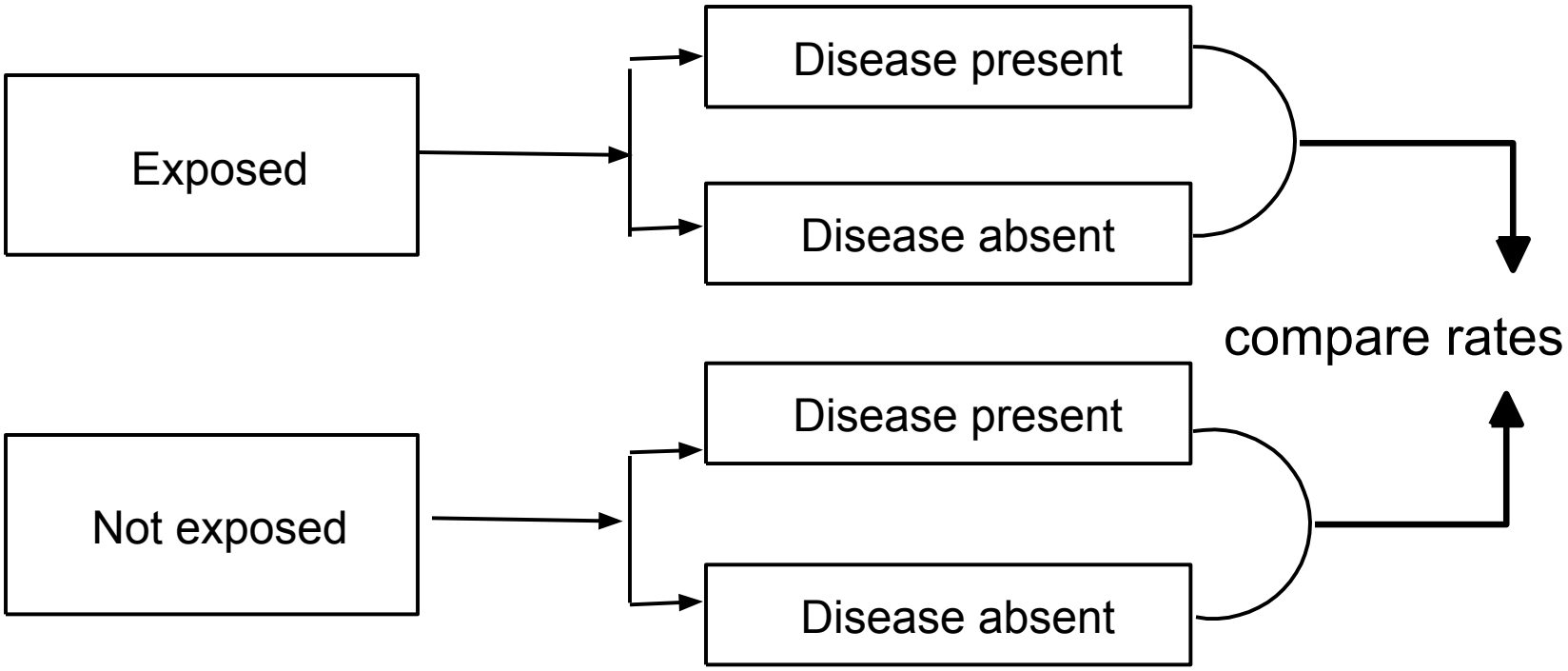
Simulating the counter-factual comparison:
Experimental Studies: Cross-over trials



Although cross-over trials come close to the ideal of counterfactual comparison, they do not achieve it because a person can be in only one study group at a time; variability in other exposures across time periods can still introduce confounding (Rothman, 2002)

Simulating the counter-factual comparison:
Observational Studies

In observational studies, because exposures are not assigned randomly, attainment of exchangeability is impossible – "initial conditions" are likely to be different and the groups may not be comparable



PRESENT ⟶ FUTURE

Confounding is ALWAYS a concern with observational designs!

Example: Does male circumcision reduce risk of HIV?

HIV and male circumcision—a systematic review with assessment of the quality of studies

N Siegfried, M Muller, J Deeks, J Volmink, M Egger, N Low, S Walker, and P Williamson

Lancet Infect Dis 2005; 5: 165–73

NS and JV are at the South African Cochrane Centre, Medical Research Council, South Africa; NS is currently a Nuffield Medical Fellow at The University of Oxford, Oxford, UK; JV is also at the Primary Health Care Directorate, University of Cape Town, Cape Town, South Africa; MM is at the Institute for Maritime Technology, Simon's Town, South Africa; JD is at the Centre for Statistics in Medicine, Institute of Health Sciences,

This Cochrane systematic review assesses the evidence for an interventional effect of male circumcision in preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. The review includes a comprehensive assessment of the quality of all 37 included observational studies. Studies in high-risk populations consisted of four cohort studies, 12 cross-sectional studies, and three case-control studies; general population studies consisted of one cohort study, 16 cross-sectional studies, and one case-control study. There is evidence of methodological heterogeneity between studies, and statistical heterogeneity was highly significant for both general population cross-sectional studies (χ^2=132·34; degrees of freedom [df]=15; p<0·00001) and high-risk cross-sectional studies (χ^2=29·70; df=10; p=0·001). Study quality was very variable and no studies measured the same set of potential confounding variables. Therefore, conducting a meta-analysis was inappropriate. Detailed quality assessment of observational studies can provide a useful visual aid to interpreting findings. Although most studies show an association between male circumcision and prevention of HIV, these results may be limited by confounding, which is unlikely to be adjusted for.

Observational studies had major limitations, especially confounding

Confounders considered in the Cochrane review

Panel: **Potential confounding factors**

Age
Location of study (eg, rural, urban)
Religion
Education, occupation, and socioeconomic status
Sexual behaviour (eg, measured by age at first intercourse, number of sexual partners, contact with sex workers)
Any STIs
Condom use
Migration status
Travel to different countries
Other possible exposures (eg, injections, blood transfusions, homosexual intercourse)

Siegfried N et al. Lancet Infect Dis 2005

In 2005, first RCT gets published

Open access, freely available online PLOS MEDICINE

Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial

Bertran Auvert[1,2,3,4*], **Dirk Taljaard**[5], **Emmanuel Lagarde**[2,4], **Joëlle Sobngwi-Tambekou**[2], **Rémi Sitta**[2,4], **Adrian Puren**[6]

1 Hôpital Ambroise-Paré, Assitance Publique—Hôpitaux de Paris, Boulogne, France, **2** INSERM U 687, Saint-Maurice, France, **3** University Versailles Saint-Quentin, Versailles, France, **4** IFR 69, Villejuif, France, **5** Progressus, Johannesburg, South Africa, **6** National Institute for Communicable Disease, Johannesburg, South Africa

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

Author Contributions: BA designed the study with DT, EL, and AP. DT and AP were responsible for operational aspects, including laboratory and field work and in-country administration of the study. BA monitored the study with input from EL and wrote the paper with input from all authors. BA analyzed the data with RS, with inputs from JST. RS conducted the interim analysis.

Academic Editor: Steven Deeks, San Francisco General Hospital, San Francisco, California, United States of America.

Citation: Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, et al. (2005) Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLoS Med 2(11): e298.

Received: June 29, 2005
Accepted: September 26, 2005
Published: October 25, 2005

DOI:
10.1371/journal.pmed.0020298

ABSTRACT

Background

Observational studies suggest that male circumcision may provide protection against HIV-1 infection. A randomized, controlled intervention trial was conducted in a general population of South Africa to test this hypothesis.

Methods and Findings

A total of 3,274 uncircumcised men, aged 18–24 y, were randomized to a control or an intervention group with follow-up visits at months 3, 12, and 21. Male circumcision was offered to the intervention group immediately after randomization and to the control group at the end of the follow-up. The grouped censored data were analyzed in intention-to-treat, univariate and multivariate, analyses, using piecewise exponential, proportional hazards models. Rate ratios (RR) of HIV incidence were determined with 95% CI. Protection against HIV infection was calculated as 1 − RR. The trial was stopped at the interim analysis, and the mean (interquartile range) follow-up was 18.1 mo (13.0–21.0) when the data were analyzed. There were 20 HIV infections (incidence rate = 0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to an RR of 0.40 (95% CI: 0.24%–0.68%; $p < 0.001$). This RR corresponds to a protection of 60% (95% CI: 32%–76%). When controlling for behavioural factors, including sexual behaviour that increased slightly in the intervention group, condom use, and health-seeking behaviour, the protection was of 61% (95% CI: 34%–77%).

Conclusion

Male circumcision provides a degree of protection against acquiring HIV infection, equivalent to what a vaccine of high efficacy would have achieved. Male circumcision may provide an important way of reducing the spread of HIV infection in sub-Saharan Africa. (Preliminary and partial results were presented at the International AIDS Society 2005 Conference, on 26 July 2005, in Rio de Janeiro, Brazil.)

First RCT showed a big effect – 60% protection!

First RCT: comparability of the randomized groups

Table 2. Baseline Characteristics of HIV-Negative Men Enrolled in the Trial

Background Characteristics		Control $n = 1,582$	Intervention $n = 1,546$
Age	Less than or equal to 21 y	52.4%	48.6%
	More than 21 y	47.6%	51.4%
Primary level of education completed		98.4%	98.3%
Religion	African traditional	47.0%	51.6%
	Protestant or Catholic	11.1%	11.9%
	Other religion	41.8%	36.5%
Ethnic group	Sotho	47.3%	49.0%
	Zulu	38.1%	32.8%
	Other	14.6%	18.2%
Drank alcohol in the past month		41.9%	42.2%
Reported sexual behaviour			
Have had first sexual experience		90.5%	91.8%
Median (IQR) age at first sex (years)[a]		16.6 (15.2–18.4)	16.8 (15.4–18.5)
Median (IQR) number of lifetime sex partners[b]		4 (2–7)	4 (3–7)
Used a condom at first sex[b]		13.4%	15.2%
Ever used a condom[b]		81.2%	82.3%
At-risk behaviour[c,d]		46.7%	46.8%
Married or living as married[d]		1.8%	1.8%
Mean (IQR) number of non-spousal partners[e]		1.4 (0–2)	1.4 (0–2)
At least one sexual partnership with only one sexual contact[e]		29.8%	30.7%
Mean (IQR) number of sexual contacts[e]		8.0 (0–8)	8.7 (1–8)
Attended a clinic for a health problem related to the genital area[e]		10.0%	9.6%

Randomization resulted in highly comparable distribution of potential confounders; so confounding is not an issue (at baseline)

Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial

Ronald H Gray, Godfrey Kigozi, David Serwadda, Frederick Makumbi, Stephen Watya, Fred Nalugoda, Noah Kiwanuka, Lawrence H Moulton, Mohammad A Chaudhary, Michael Z Chen, Nelson K Sewankambo, Fred Wabwire-Mangen, Melanie C Bacon, Carolyn F M Williams, Pius Opendi, Steven J Reynolds, Oliver Laeyendecker, Thomas C Quinn, Maria J Wawer

Summary

Background Ecological and observational studies suggest that male circumcision reduces the risk of HIV acquisition in men. Our aim was to investigate the effect of male circumcision on HIV incidence in men.

Methods 4996 uncircumcised, HIV-negative men aged 15–49 years who agreed to HIV testing and counselling were enrolled in this randomised trial in rural Rakai district, Uganda. Men were randomly assigned to receive immediate circumcision (n=2474) or circumcision delayed for 24 months (2522). HIV testing, physical examination, and interviews were repeated at 6, 12, and 24 month follow-up visits. The primary outcome was HIV incidence. Analyses were done on a modified intention-to-treat basis. This trial is registered with ClinicalTrials.gov, with the number NCT00425984.

Findings Baseline characteristics of the men in the intervention and control groups were much the same at enrolment. Retention rates were much the same in the two groups, with 90–92% of participants retained at all time points. In the modified intention-to-treat analysis, HIV incidence over 24 months was 0·66 cases per 100 person-years in the intervention group and 1·33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%, 95% CI 16–72; p=0·006). The as-treated efficacy was 55% (95% CI 22–75; p=0·002); efficacy from the Kaplan-Meier time-to-HIV-detection as-treated analysis was 60% (30–77; p=0·003). HIV incidence was lower in the intervention group than it was in the control group in all sociodemographic, behavioural, and sexually transmitted disease symptom subgroups. Moderate or severe adverse events occurred in 84 (3·6%) circumcisions; all resolved with treatment. Behaviours were much the same in both groups during follow-up.

Interpretation Male circumcision reduced HIV incidence in men without behavioural disinhibition. Circumcision can be recommended for HIV prevention in men.

Lancet 2007; 369: 657–66

See Editorial page 615
See Comment page 617
See Perspectives page 635
See Articles page 643
See Viewpoint page 708

Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA (Prof R H Gray MD, Prof L H Moulton PhD, M A Chaudhary PhD, M Z Chen MSc, Prof M J Wawer MD); **Rakai Health Sciences Program, Entebbe, Uganda** (G Kigozi MBChB, F Nalugoda MHS, N Kiwanuka MBChB, P Opendi MBChB); **Makerere University, Institute of Public Health, Kampala, Uganda** (D Serwadda MBChB, F Makumbi PhD, F Wabwire-Mangen PhD); **Makerere University, Mulago**

In 2007, two other RCT confirm the first RCT findings

Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Robert C Bailey, Stephen Moses, Corette B Parker, Kawango Agot, Ian Maclean, John N Krieger, Carolyn F M Williams, Richard T Campbell, Jeckoniah O Ndinya-Achola

Summary

Background Male circumcision could provide substantial protection against acquisition of HIV-1 infection. Our aim was to determine whether male circumcision had a protective effect against HIV infection, and to assess safety and changes in sexual behaviour related to this intervention.

Methods We did a randomised controlled trial of 2784 men aged 18–24 years in Kisumu, Kenya. Men were randomly assigned to an intervention group (circumcision; n=1391) or a control group (delayed circumcision, 1393), and assessed by HIV testing, medical examinations, and behavioural interviews during follow-ups at 1, 3, 6, 12, 18, and 24 months. HIV seroincidence was estimated in an intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, with the number NCT00059371.

Findings The trial was stopped early on December 12, 2006, after a third interim analysis reviewed by the data and safety monitoring board. The median length of follow-up was 24 months. Follow-up for HIV status was incomplete for 240 (8·6%) participants. 22 men in the intervention group and 47 in the control group had tested positive for HIV when the study was stopped. The 2-year HIV incidence was 2·1% (95% CI 1·2–3·0) in the circumcision group and 4·2% (3·0–5·4) in the control group (p=0·0065); the relative risk of HIV infection in circumcised men was 0·47 (0·28–0·78), which corresponds to a reduction in the risk of acquiring an HIV infection of 53% (22–72). Adjusting for non-adherence to treatment and excluding four men found to be seropositive at enrolment, the protective effect of circumcision was 60% (32–77). Adverse events related to the intervention (21 events in 1·5% of those circumcised) resolved quickly. No behavioural risk compensation after circumcision was observed.

Interpretation Male circumcision significantly reduces the risk of HIV acquisition in young men in Africa. Where appropriate, voluntary, safe, and affordable circumcision services should be integrated with other HIV preventive interventions and provided as expeditiously as possible.

Lancet 2007; 369: 643–56

See Editorial page 615
See Comment page 617
See Articles page 657
See Viewpoint page 708

Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago, IL, USA (Prof R C Bailey PhD, Prof R T Campbell PhD); **Department of Medical Microbiology** (I Maclean PhD), **Community Health Sciences and Medicine** (Prof S Moses M D), **UNIM Project, Kisumu, Kenya and Department of Community Health Sciences** (K Agot PhD), **University of Manitoba, Winnipeg, Canada; RTI International, Research Triangle Park, NC, USA** (C B Parker DrPh); **Department of Urology, University of Washington School of Medicine, Seattle, WA, USA** (Prof J N Krieger MD); **Division**

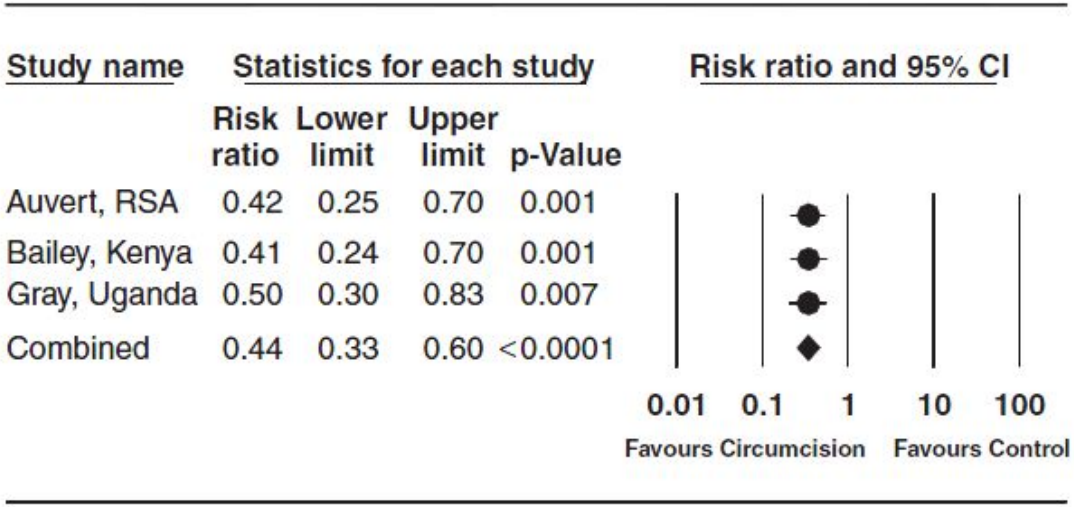
DOI: 10.1111/j.1468-1293.2008.00596.x
HIV Medicine (2008), 9, 332–335

VIEWPOINTS ON HIV RESEARCH

Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11 050 men*

E Mills,[1] C Cooper,[2] A Anema[1] and G Guyatt[3]

[1]*St Paul's Hospital, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada,* [2]*Division of Infectious Diseases, Ottawa Hospital, University of Ottawa, ON, Canada and* [3]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada*



Meta-analysis of 3 RCTs in 2008

UNAIDS endorsed this intervention in 2007

UNAIDS — JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

World Health Organization

Press release

EMBARGOED: Wednesday, 28 March, 12.00 GMT, 14.00 CET

WHO AND UNAIDS ANNOUNCE RECOMMENDATIONS FROM EXPERT MEETING ON MALE CIRCUMCISION FOR HIV PREVENTION

Paris, 28 March 2007 -- In response to the urgent need to reduce the number of new HIV infections globally, the World Health Organization (WHO) and the UNAIDS Secretariat convened an international expert consultation to determine whether male circumcision should be recommended for the prevention of HIV infection.

Based on the evidence presented, which was considered to be compelling, experts attending the consultation recommended that male circumcision now be recognized as an additional important intervention to reduce the risk of heterosexually acquired HIV infection in men. The international consultation, which was held from 6-8 March 2007 in Montreux, Switzerland, was attended by participants representing a wide range of stakeholders, including governments, civil society, researchers, human rights and women's health advocates, young people, funding agencies and implementing partners.

"The recommendations represent a significant step forward in HIV prevention", said Dr Kevin De Cock, Director, HIV/AIDS Department, World Health Organization. "Countries with high rates of heterosexual HIV infection and low rates of male circumcision now have an additional intervention which can reduce the risk of HIV infection in heterosexual men. Scaling up male circumcision in such countries will result in immediate benefit to individuals. However, it will be a number of years before we can expect to see an impact on the epidemic from such investment."

There is now strong evidence from three randomized controlled trials undertaken in Kisumu, Kenya, Rakai District, Uganda and Orange Farm, South Africa that male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 60%. This evidence supports the findings of numerous observational studies that have also suggested that the geographical correlation long described between lower HIV prevalence and high rates of male circumcision in some countries in Africa, and more recently elsewhere, is, at least in part, a causal association. Currently, an estimated 665 million men, or 30 % of men worldwide, are estimated to be circumcised

Control of confounding:

- Control at the design stage
  - Randomization
  - Restriction
  - Matching
- Control or ‘adjustment’ at the analysis stage
  - Conventional approaches
    - Stratified analyses
    - Multivariate analyses

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

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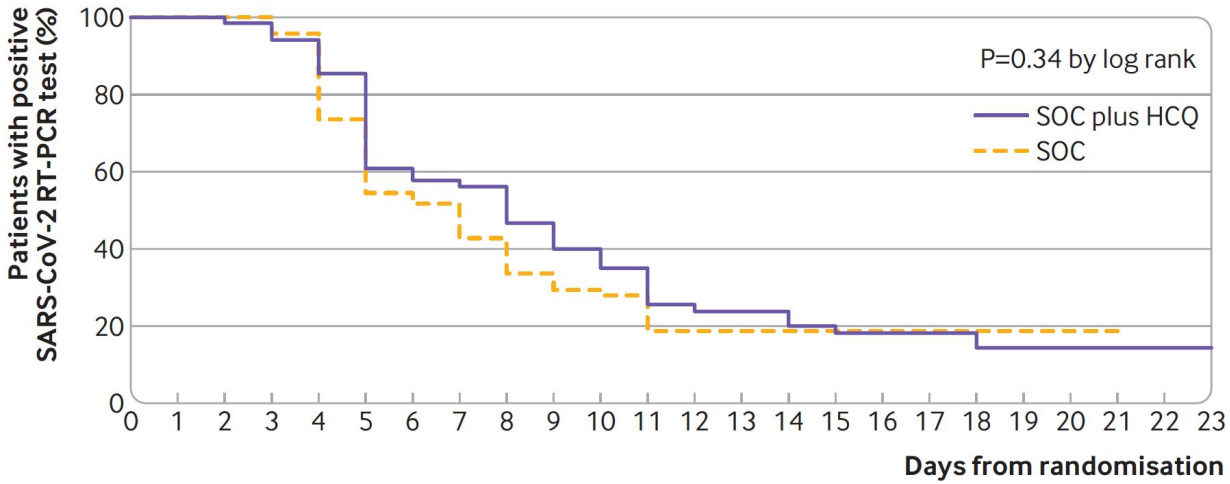

SOC plus HCQ	75	75	70	68	65	59	39	37	36	28	23	19	14	13	13	10	7	5	5	4	4	4	3	1
SOC	75	75	73	73	69	50	37	35	29	23	20	18	12	12	10	3	1	1	1	1	1	1		

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

In our analysis, we adjusted for likely confounders, including age, race and ethnic group, body-mass index, diabetes, underlying kidney disease, chronic lung disease, hypertension, baseline vital signs, Pao2 :Fio2 , and inflammatory markers of the severity of illness. Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding remains.

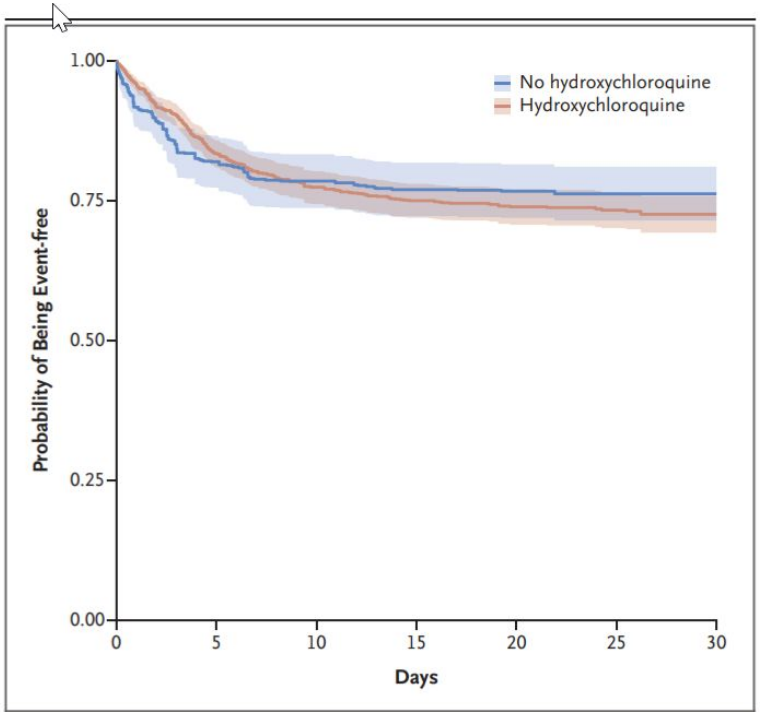

Figure 2. Freedom from Composite End Point of Intubation or Death.
The shaded areas represent pointwise 95% confidence intervals.

https://www.nejm.org/doi/pdf/10.1056/NEJMoa2012410?articleTools=true