

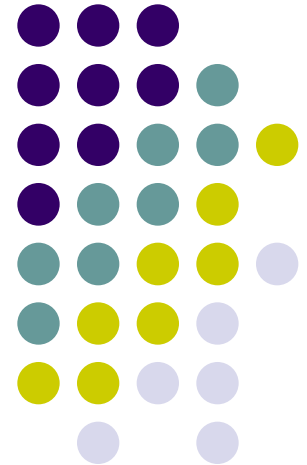
# Confounding in health research

## Part 1: Definition and conceptual issues

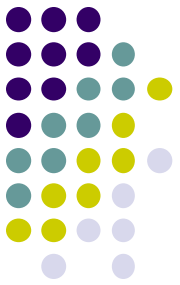
**Madhukar Pai, MD, PhD**  
**Assistant Professor of Epidemiology**  
**McGill University**  
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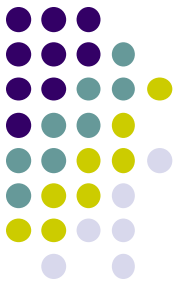
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# Why is confounding so important in epidemiology?



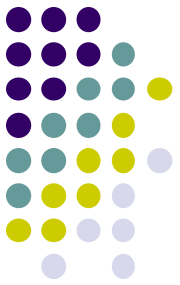
- BMJ Editorial: “The scandal of poor epidemiological research” [16 October 2004]
  - *“Confounding, the situation in which an apparent effect of an exposure on risk is explained by its association with other factors, is **probably the most important cause of spurious associations in observational epidemiology.**”*



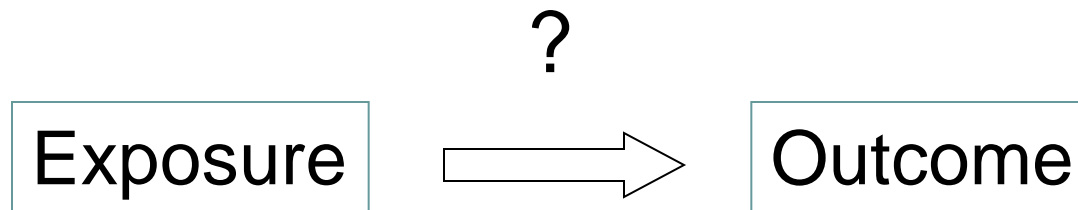
# Overview

- Causality is the central concern of epidemiology
- Confounding is the central concern with establishing causality
- Confounding can be understood using at least 4 overlapping approaches
- A strong understanding of various approaches to confounding and its control is essential for all those who engage in health research

# Causality (etio-gnosis): the central concern of epidemiology



- Most fundamental application of epidemiology: to identify etiologic (causal) associations between exposure(s) and outcome(s)



# Contradictory causal claims have greatly tarnished the reputation of epidemiology

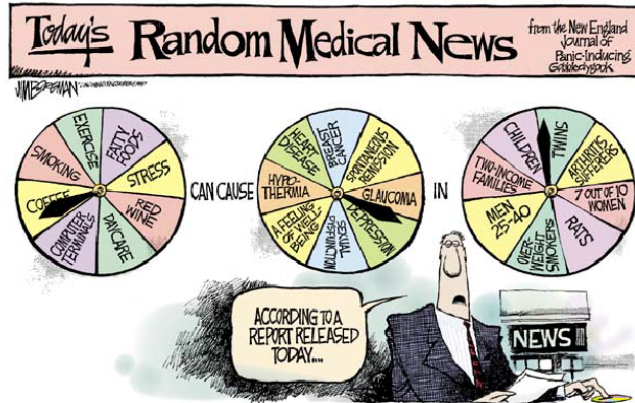
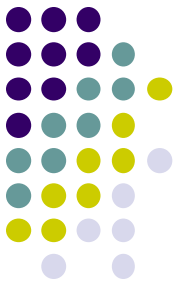


Figure 3: New England Journal of Panic-Inducing Gobbledygook.  
Source: Jim Borgman, The Cincinnati Enquirer (27 April 1997, E4).

## SPECIAL NEWS REPORT

### Epidemiology Faces Its Limits

The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty

The news about health risks comes thick and fast these days, and it seems almost constitutionally contradictory. In January of last year, for instance, a Swedish study found a significant association between residential radon exposure and lung cancer. Three months later, it was pesticide residues. The *Journal of the National Cancer Institute* published a study in April reporting—contrary to previous, less powerful studies—that the presence of DDT metabolites in the bloodstream seemed to have no effect on the risk of breast cancer. In October, it was abortion and breast cancer. Maybe yes. Maybe no. In January of this year it was electromagnetic fields (EMF) from power lines. This time a study of electric utility workers in the United States suggested a possible link between EMF and brain cancer but—contrary to a study a year ago in *Canada and France*—no link between EMF



Anxiety epidemic. Protesting risks that may—or may not—be real.

on the press for its reporting of epidemiology, and even on the public "for its unrealistic expectations" of what modern medical research can do for their health. But many epidemiologists interviewed by *Science* say the problem also lies with the very nature of epidemiologic studies—in particular those that try to isolate causes of noninfectious disease, known variously as "observational" or "risk-factor" or "environmental" epidemiology.

The predicament of these studies is a simple one: Over the past 50 years, epidemiologists have succeeded in identifying the more conspicuous determinants of diseases—smoking, for instance, which can increase the risk of developing lung cancer by as much as 3000%. Now they are left to search for subtler links between diseases and environmental causes or lifestyles. And that leads to the Catch-22 of modern epidemiology.

On the one hand, these subtle risks...

Rothman, editor of the journal *Epidemiology*: "We're pushing the edge of what can be done with epidemiology."

With epidemiology stretched to its limits or beyond, says Dimitrios Trichopoulos, head of the epidemiology department at the Harvard School of Public Health, studies will inevitably generate false positive and false negative results "with disturbing frequency." Most epidemiologists are aware of the problem, he adds, "and tend to avoid causal inferences on the basis of isolated studies or even groups of studies in the absence of compelling biomedical evidence. However, exceptions do occur, and their frequency appears to be increasing." As Trichopoulos explains, "Objectively the problems are not more than they used to be, but the pressure is greater on the profession, and the number who practice it is greater."

As a result, journals today are full of studies suggesting that a little risk is not nothing at all. The findings are often touted in press releases by the journals that publish them or by the researchers' institutions, and newspapers and other media often report the claims uncritically (see box on p. 166). And so the anxiety pendulum swings at an ever more dizzying rate. "We are fast becoming a nuisance to society," says Trichopoulos. "Shouldn't take us seriously anymore, and

The New York Times Magazine

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Do We Really Know What Makes Us Healthy?

By GARY TAUBES

Published: September 16, 2007

Once upon a time, women took estrogen only to relieve the hot flashes, sweating, vaginal dryness and the other discomforting symptoms of menopause. In the late 1960s, thanks in part to the efforts of Robert Wilson, a Brooklyn

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- It's not too late to see the revival of "Gypsy."
- Don't miss Vanessa Redgrave in "The Year of Magical Thinking."

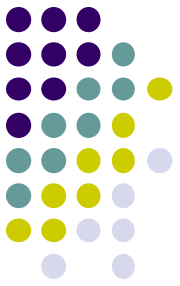
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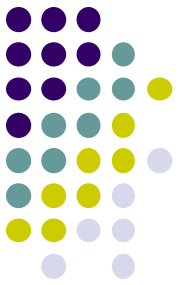
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**Question: Do you want to reduce  
your risk of Alzheimer's?**



Answer: be dutiful and conscientious about your  
601 coursework!

# Here is why...



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updated 6:46 p.m. EDT, Mon October 1, 2007

## Goal-driven achievers less prone to Alzheimer's

### STORY HIGHLIGHTS

- People who see
- Purposeful pers
- Some achievers

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TEXT SIZE - +

CHICAGO, Illinois (AP) -- A surprising study of elderly people suggests that those who see themselves as self-disciplined, organized achievers have a lower risk for developing Alzheimer's disease than people who are less conscientious.

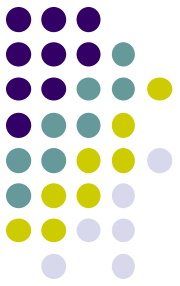


A purposeful personality may somehow protect the brain, perhaps by increasing neural connections that can act as a reserve against mental decline, said study co-author Robert Wilson of Rush University Medical Center in Chicago, Illinois.

Astoundingly, the brains of some of the dutiful people in the study were examined after their deaths and were found to have lesions that would meet accepted criteria for Alzheimer's -- even though these people had shown no signs of dementia.

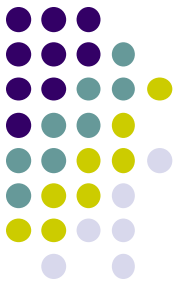
When the researchers took into account a combination of risk factors, including smoking, inactivity and limited social connections, they still found that the dutiful people had a 54 percent lower risk of Alzheimer's compared to people with the lowest scores for conscientiousness.

# Confounding: a central concern with etiologic research



- Confounding is one of the most important issues with establishing causality in epidemiologic research
- Spurious causal claims may often be due to unaddressed confounding
- Most of us intuitively understand confounding, even if we have never formally studied it!

# Who has higher wound infection rates: junior or senior surgeons?



## Anti-snake venom: too much is fatal?

Tropical Medicine and International Health

doi:10.1111/j.1365-3156.2005.01535.x

VOLUME 11 NO 1 PP 22-30 JANUARY 2006

### Clinical predictors of in-hospital mortality in patients with snake bite: a retrospective study from a rural hospital in central India

Shripakash Kalantri<sup>1,2</sup>, Amandeep Singh<sup>1</sup>, Rajnish Joshi<sup>1,2</sup>, Samuel Malamba<sup>2</sup>, Christine Ho<sup>2</sup>, Joseph Ezoua<sup>2</sup> and Maureen Morgan<sup>2</sup>

<sup>1</sup> Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram, India

<sup>2</sup> Division of Epidemiology, University of California at Berkeley, Berkeley CA, USA

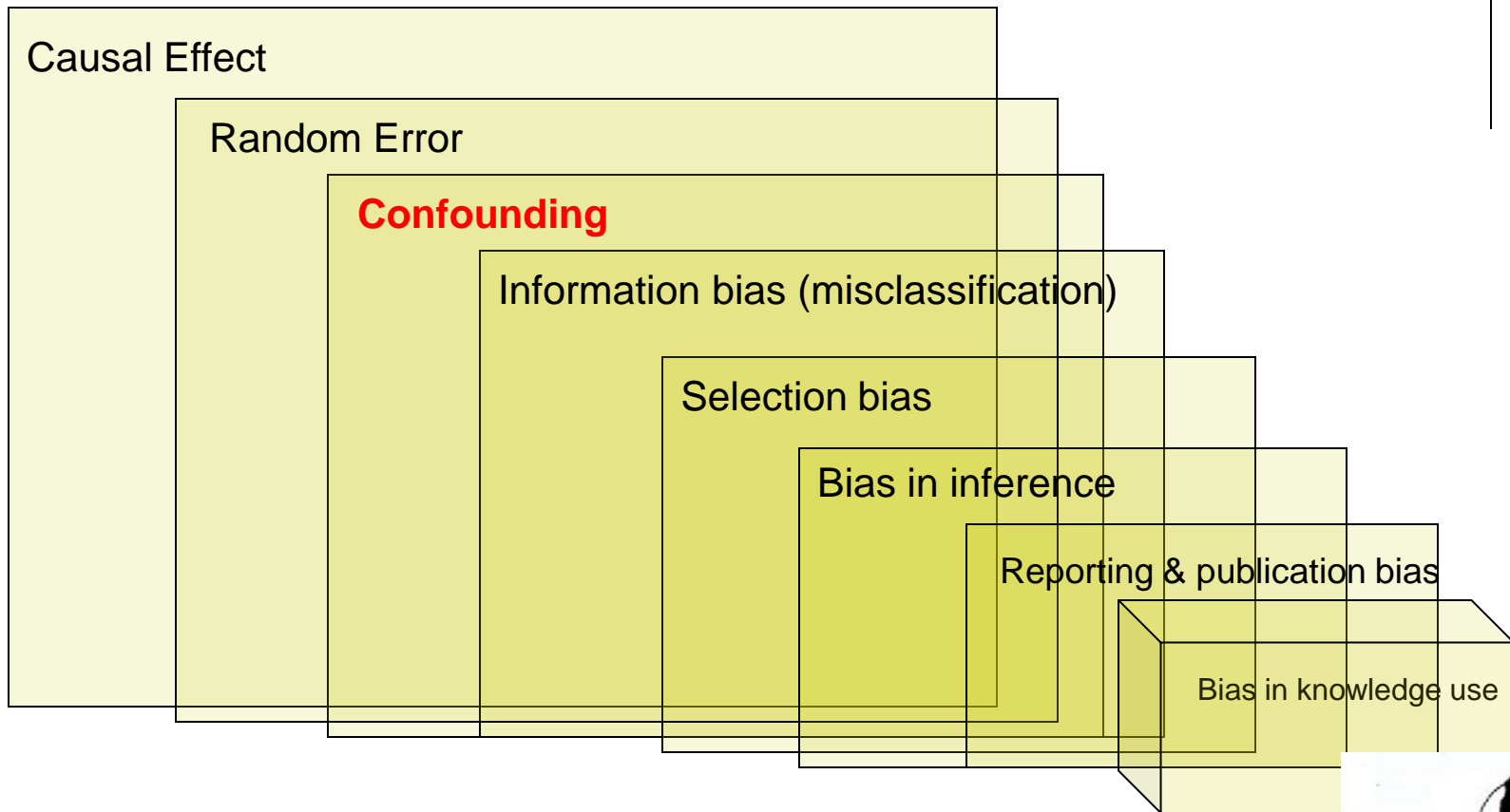
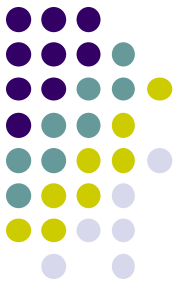
#### Summary

**OBJECTIVE** To determine the association between selected admission risk factors and in-hospital mortality in patients admitted with venomous snake bite to a rural tertiary care hospital in central India. **METHODS** Retrospective cohort study of patients aged 12 years or older admitted to a rural hospital in central India between January 2000 and December 2003 with venomous snake bites. The primary endpoint was in-hospital mortality. We used Cox proportional-hazards regression analysis to evaluate the association between risk factors (home-to-hospital distance, bite-to-hospital time, vomiting, neurotoxicity, urine albumin, serum creatinine concentration and whole-blood clotting time) and in-hospital mortality.

**RESULTS** Two hundred and seventy-seven patients [mean age 32 (SD 12) years; 188 men (68%)] were admitted with venomous snake bite, 29 patients (11%) died. The probability of survival at day 7 was 83%. Vomiting [hazard ratio 6.51 (95% CI 1.94–21.77),  $P \leq 0.002$ ], neurotoxicity [hazard ratio 3.15 (95% CI 1.45–6.83),  $P = 0.004$ ] and admission serum creatinine concentration [hazard ratio 1.35 (95% CI 1.17–1.56),  $P \leq 0.001$ ] were associated with higher risk of death in the adjusted analysis.

**CONCLUSIONS** In our rural hospital setting, the overall mortality rate was 11 per 100 cases of snake bite. Vomiting, neurotoxicity and serum creatinine are significant predictors of mortality among inpatients with snake bite. These predictors can help clinicians assess prognosis of their patients more accurately and parsimoniously and also serve as useful signposts for clinical decision-making.

# Confounding is one of the key biases in identifying causal effects



$RR_{\text{causal}}$   
“truth”



$RR_{\text{association}}$



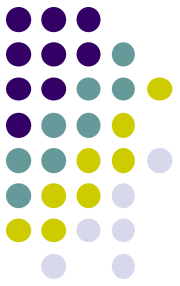
# Confounding: 4 ways to understand it!



1. “Mixing of effects”
2. “Classical” approach based on *a priori* criteria
3. Collapsibility and data-based criteria
4. “Counterfactual” and non-comparability approaches

# First approach:

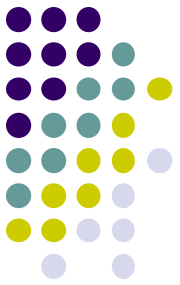
## Confounding: mixing of effects



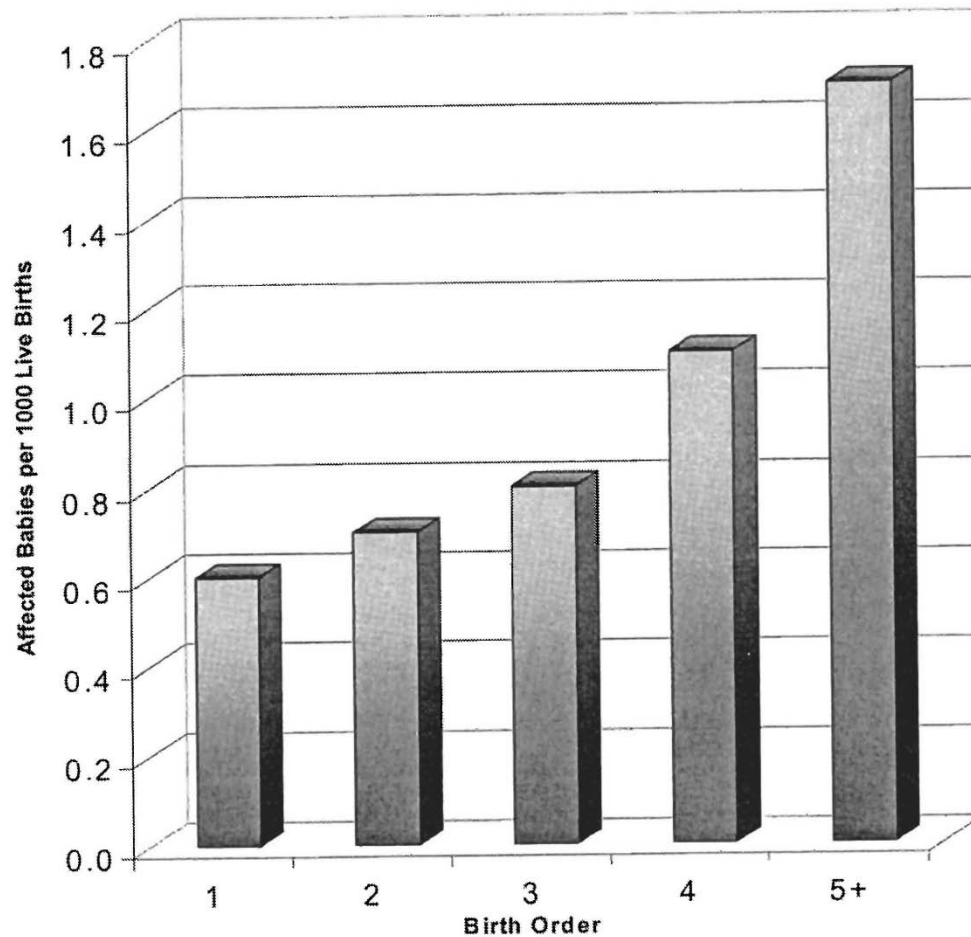
- “Confounding is confusion, or mixing, of effects; the effect of the exposure is mixed together with the effect of another variable, leading to bias” - Rothman, 2002

*Latin: “confundere” is to mix together*

# Example



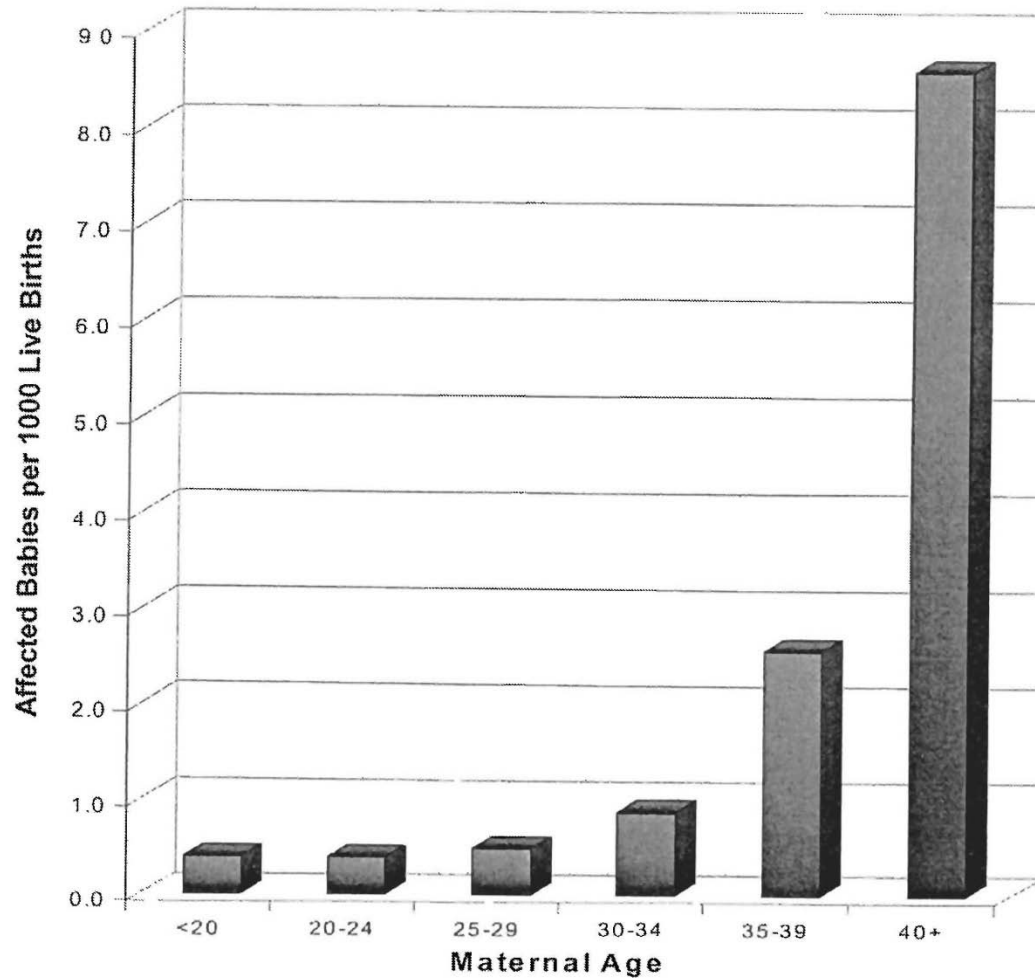
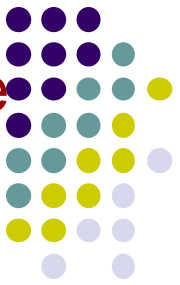
## Association between birth order and Down syndrome



Data from Stark and Mantel (1966)

Source: Rothman 2002

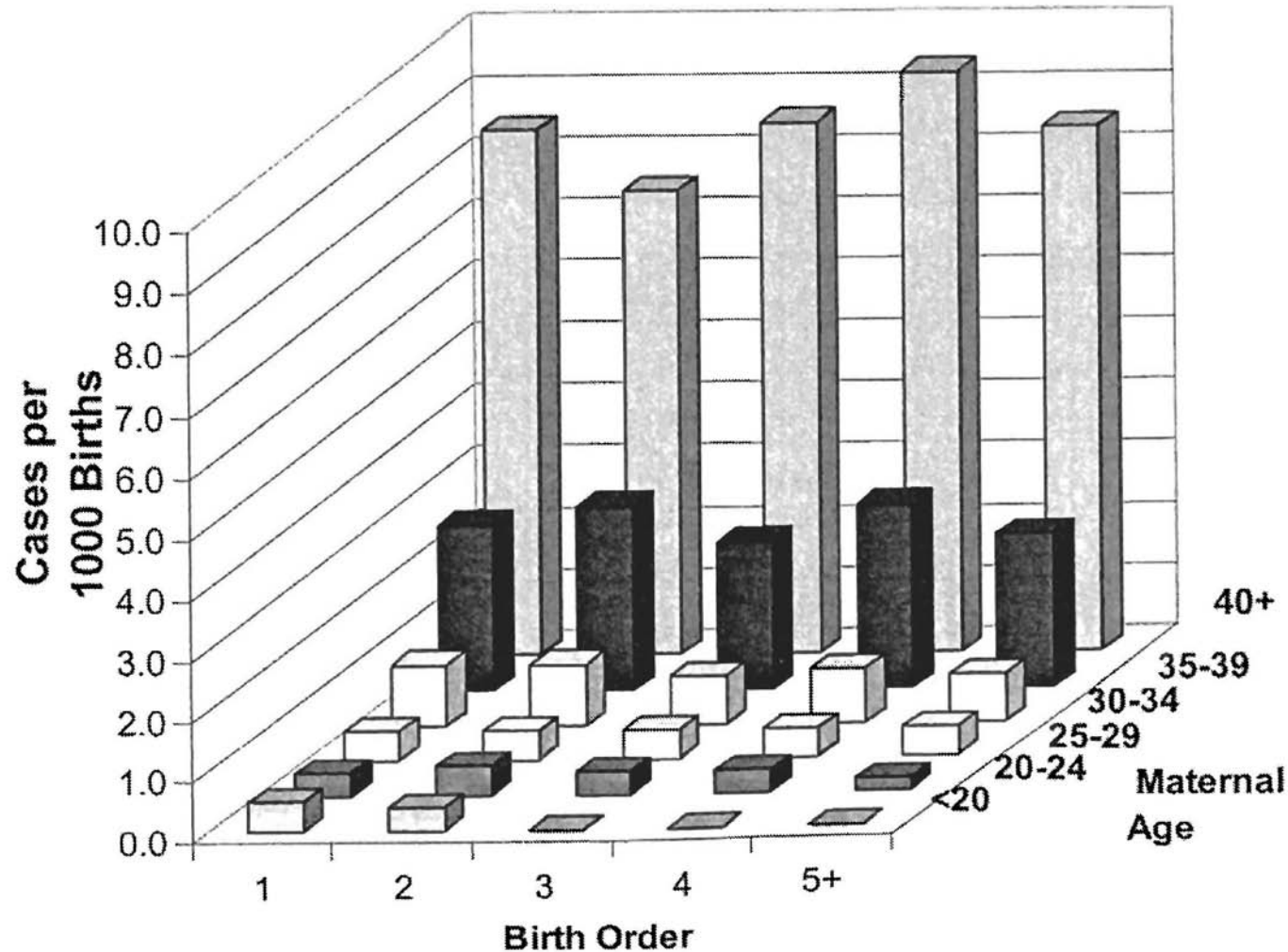
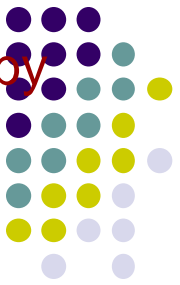
# Association between maternal age and Down syndrome



Data from Stark and Mantel (1966)

Source: Rothman 2002

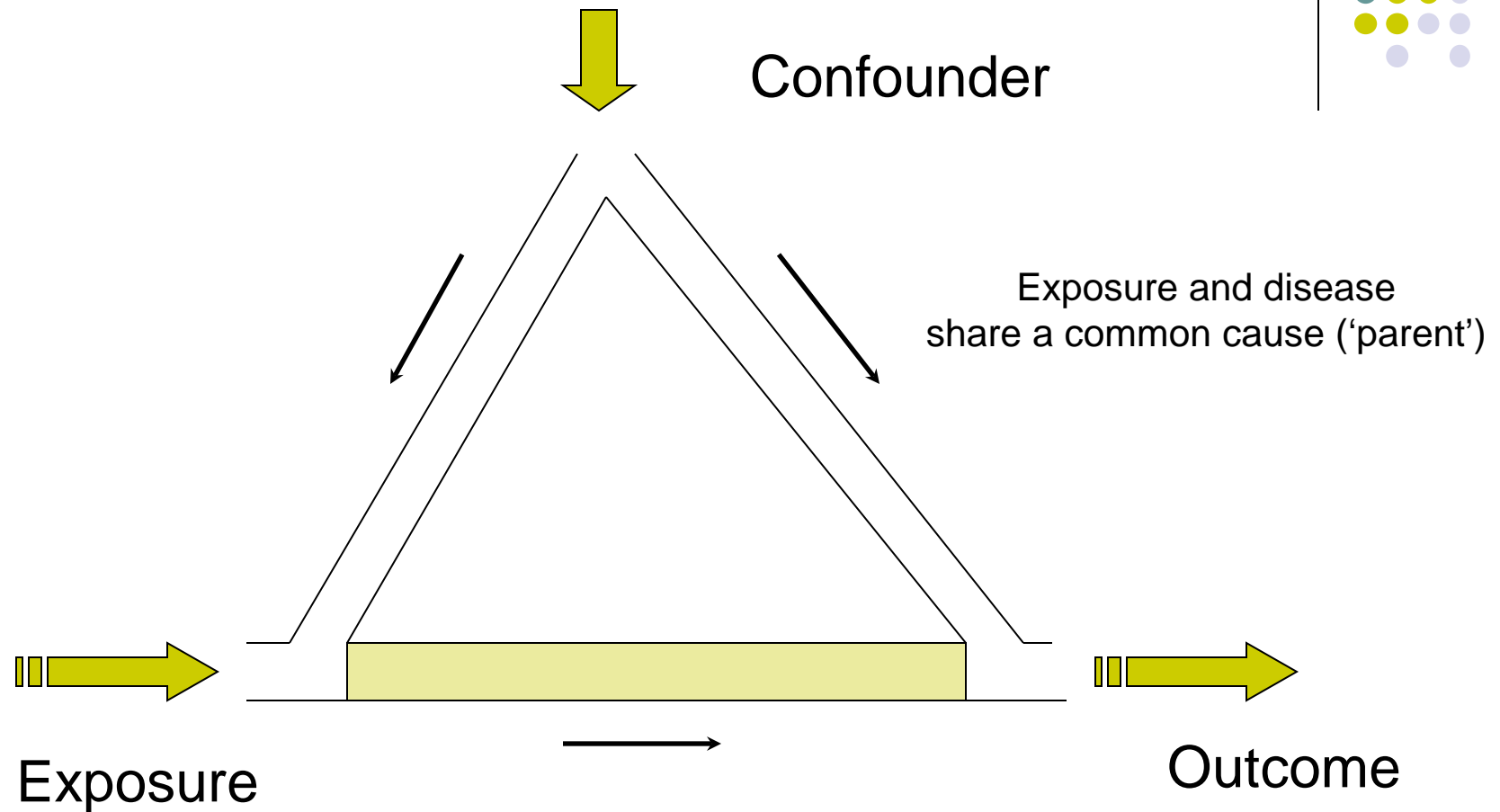
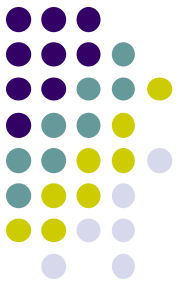
# Association between maternal age and Down syndrome, stratified by birth order



Data from Stark and Mantel (1966)

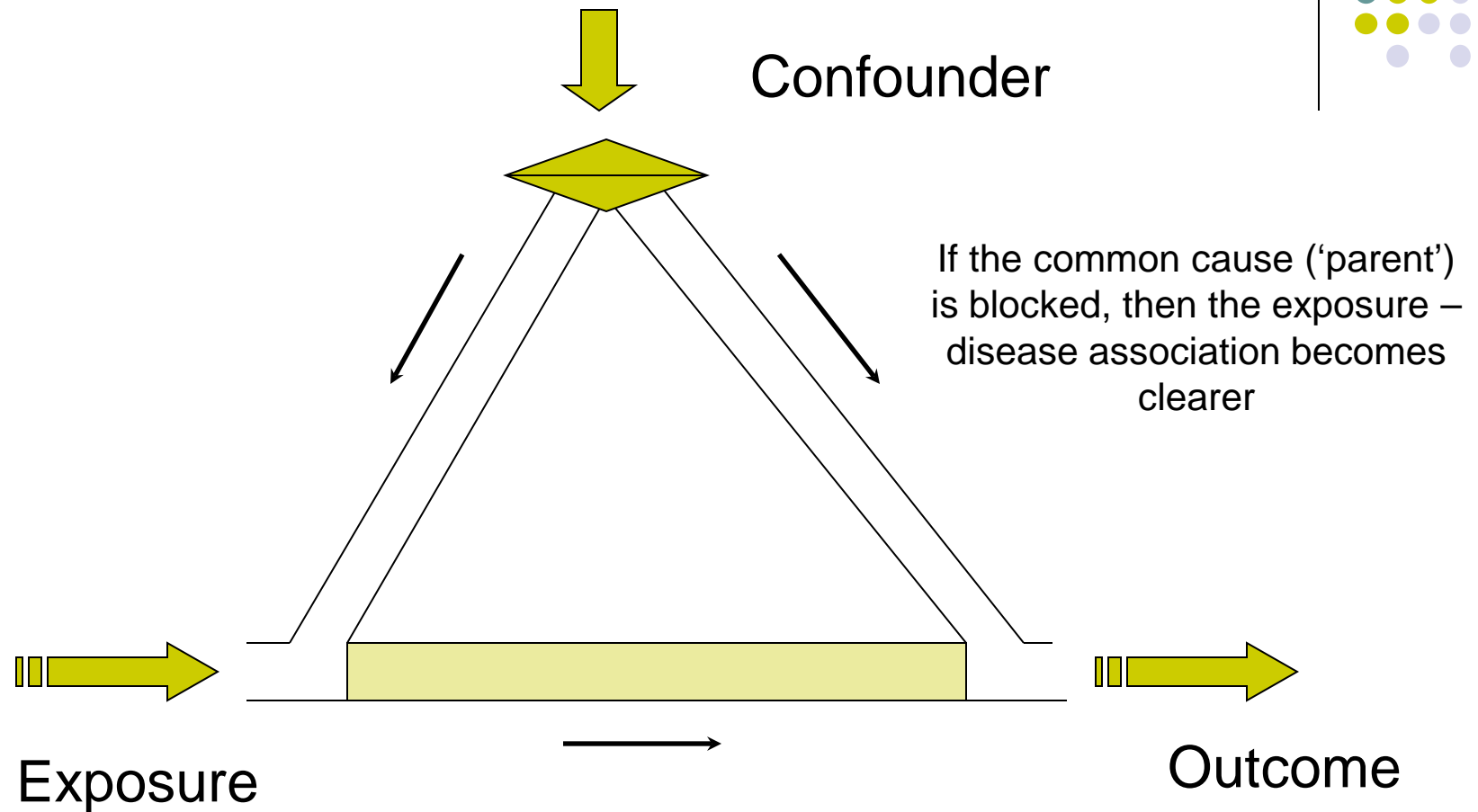
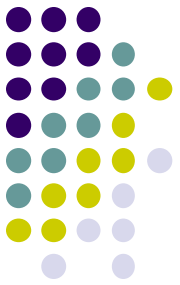
Source: Rothman 2002

# Mixing of Effects: the water pipes analogy



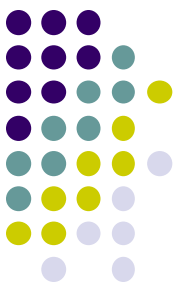
Mixing of effects – cannot separate the effect of exposure from that of confounder

# Mixing of Effects: “control” of the confounder



Successful “control” of confounding (adjustment)

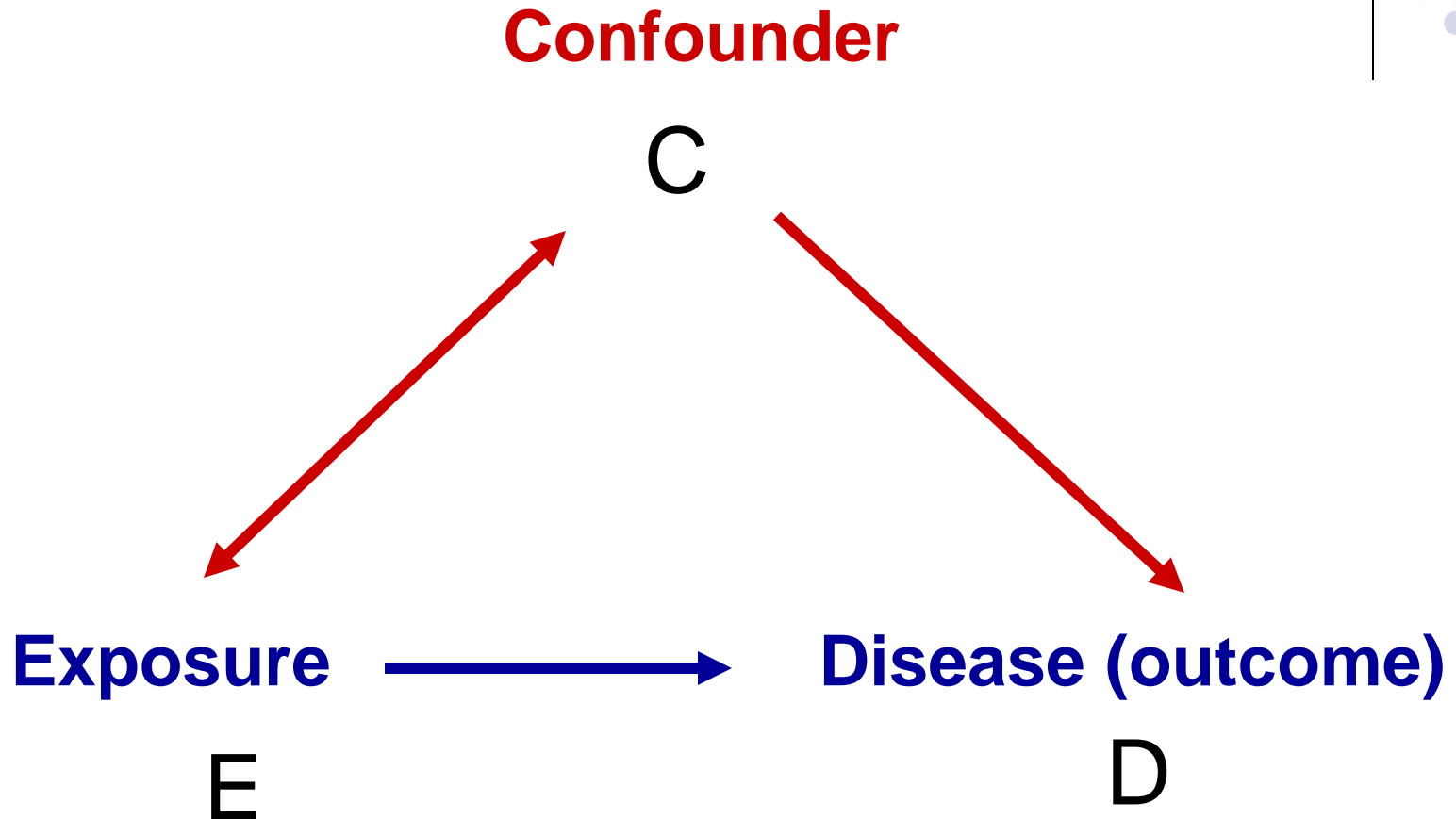
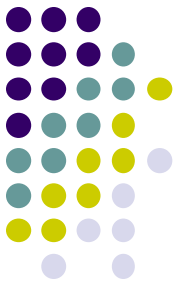
# Second approach: “Classical” approach based on *a priori* criteria



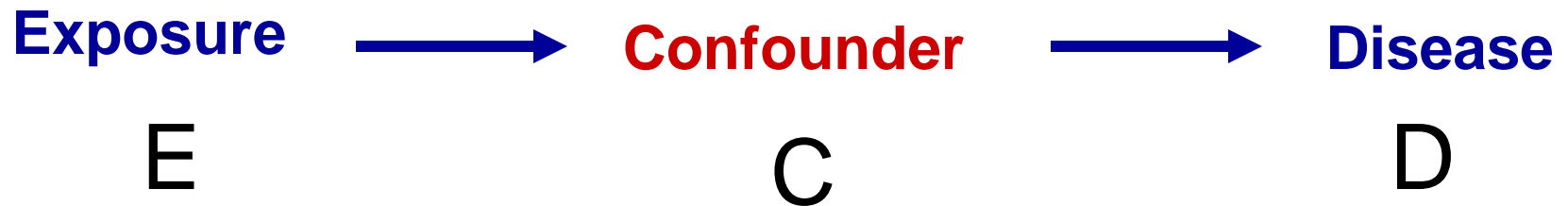
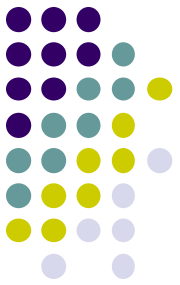
“Bias of the estimated effect of an exposure on an outcome due to the presence of a common cause of the exposure and the outcome” – Porta 2008

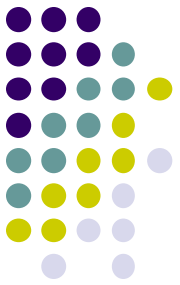
- A factor is a confounder if 3 criteria are met:
  - a) a confounder must be causally or noncausally associated with the exposure in the source population (study base) being studied;
  - b) a confounder must be a causal risk factor (or a surrogate measure of a cause) for the disease in the unexposed cohort; and
  - c) a confounder must not be an intermediate cause (in other words, a confounder must not be an intermediate step in the causal pathway between the exposure and the disease)

# Confounding Schematic

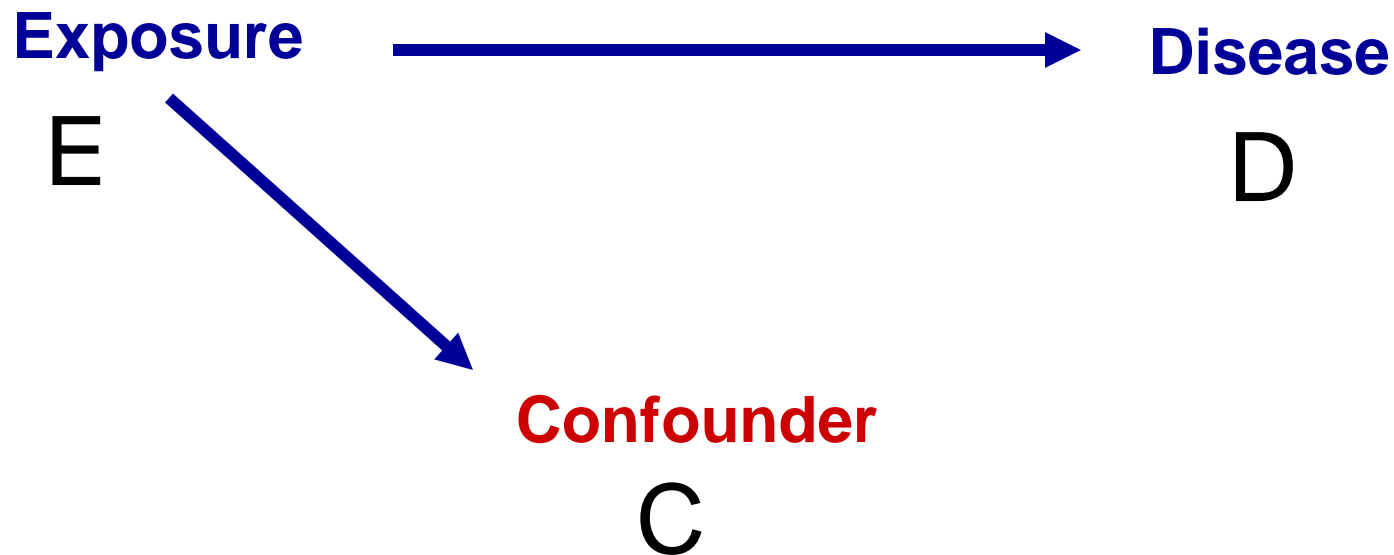


# Intermediate cause

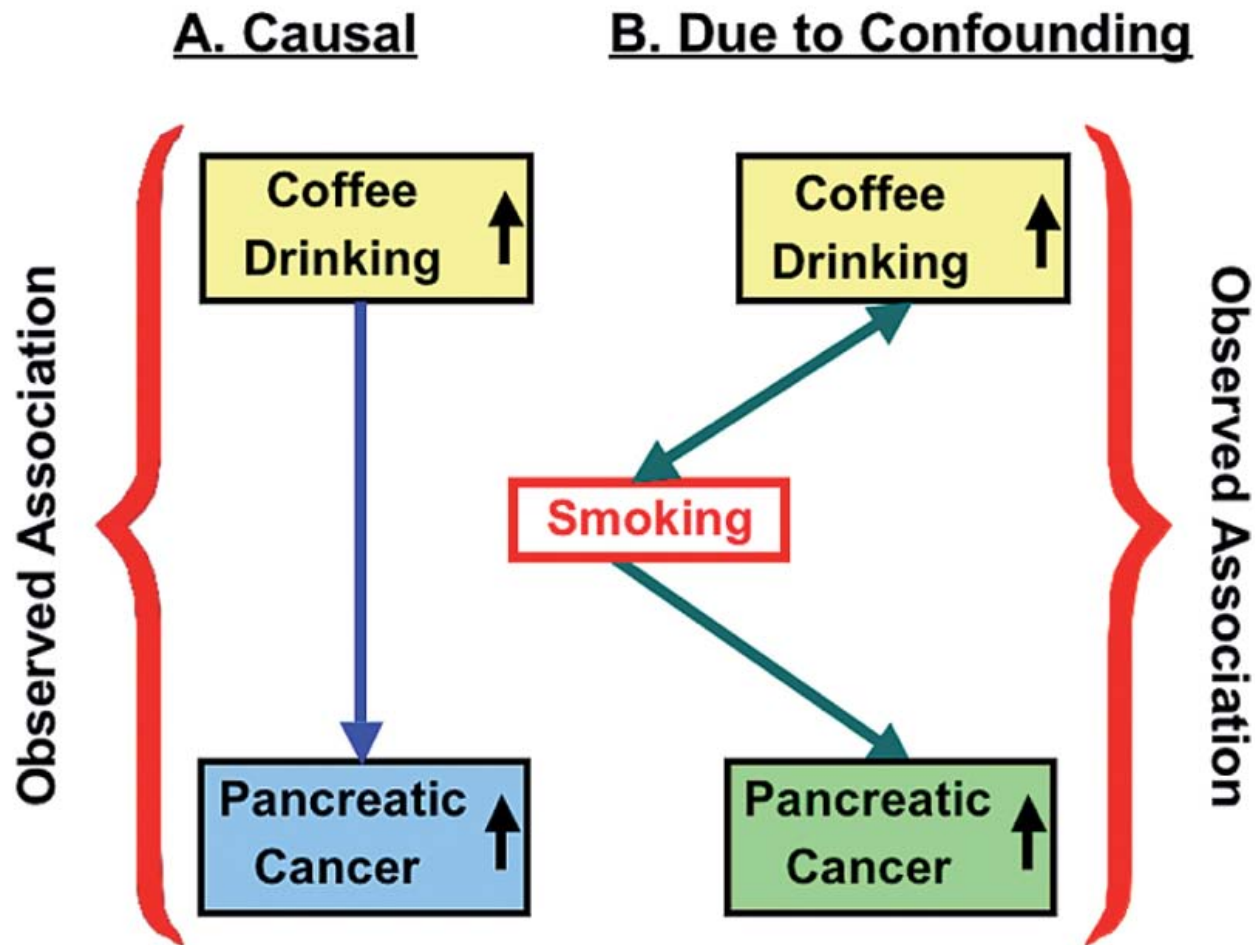
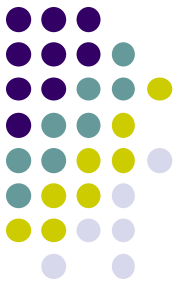




General idea: a confounder could be a 'parent' of the exposure, but should not be a 'daughter' of the exposure

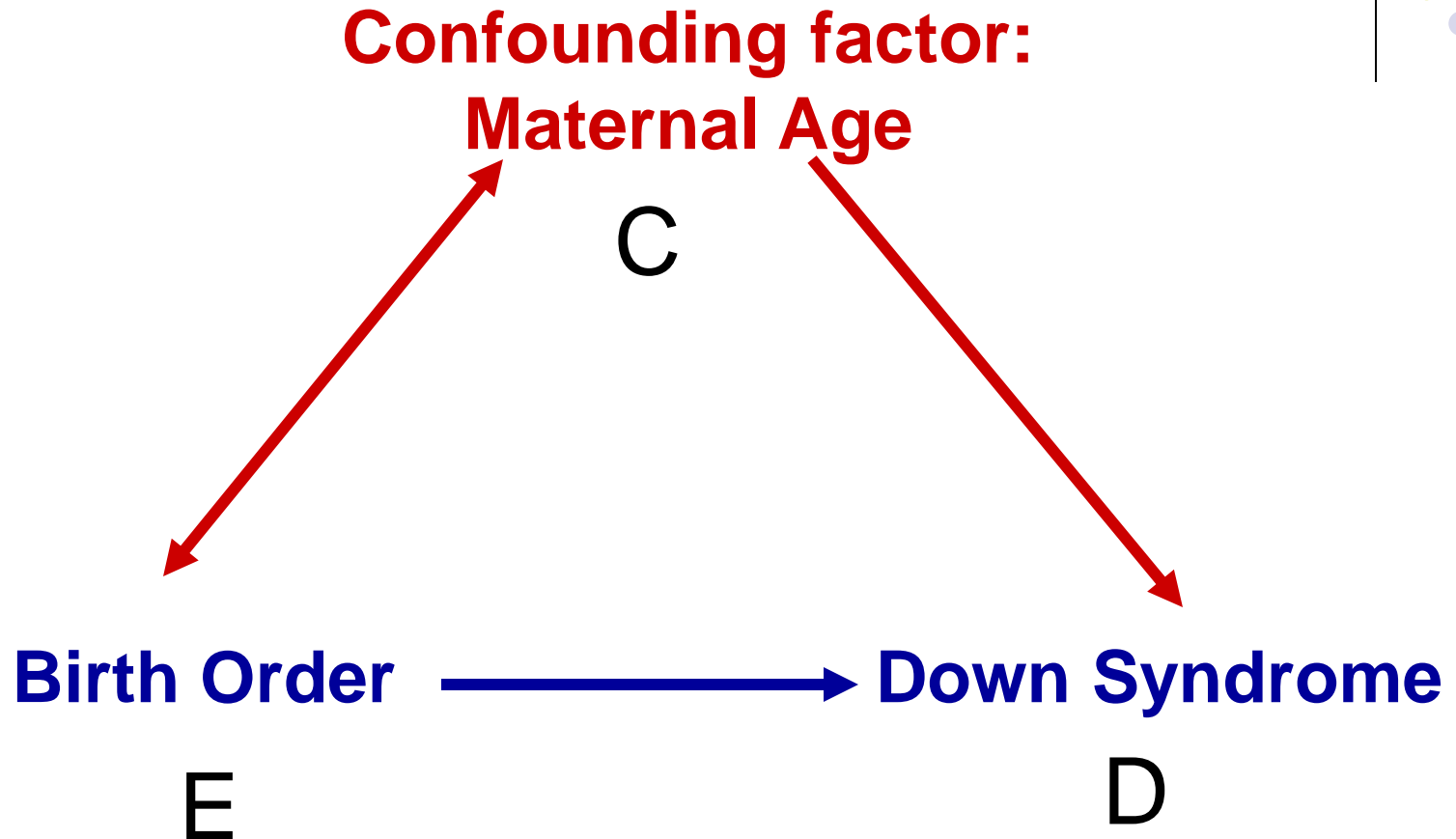
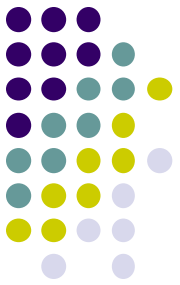


# Example of schematic (from Gordis)

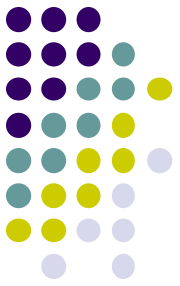


Gordis: Epidemiology, 4th Edition.  
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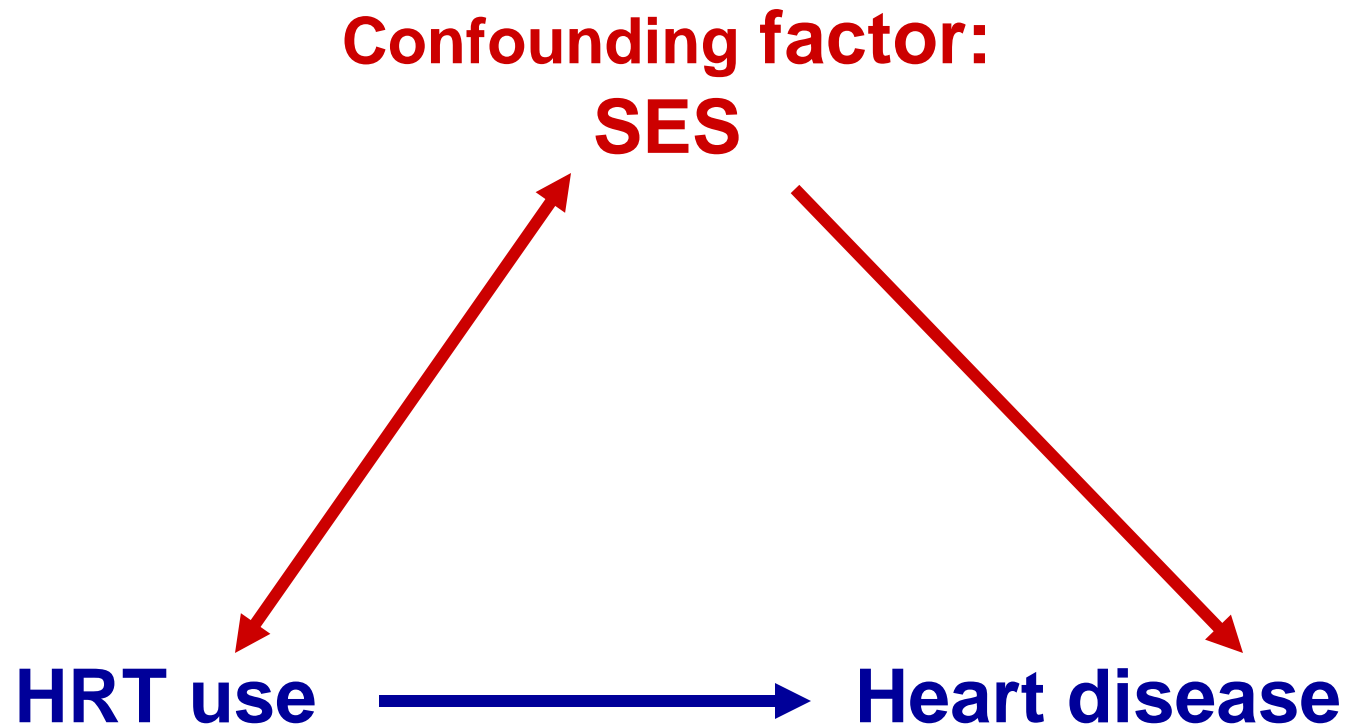
# Confounding Schematic



# Are confounding criteria met?



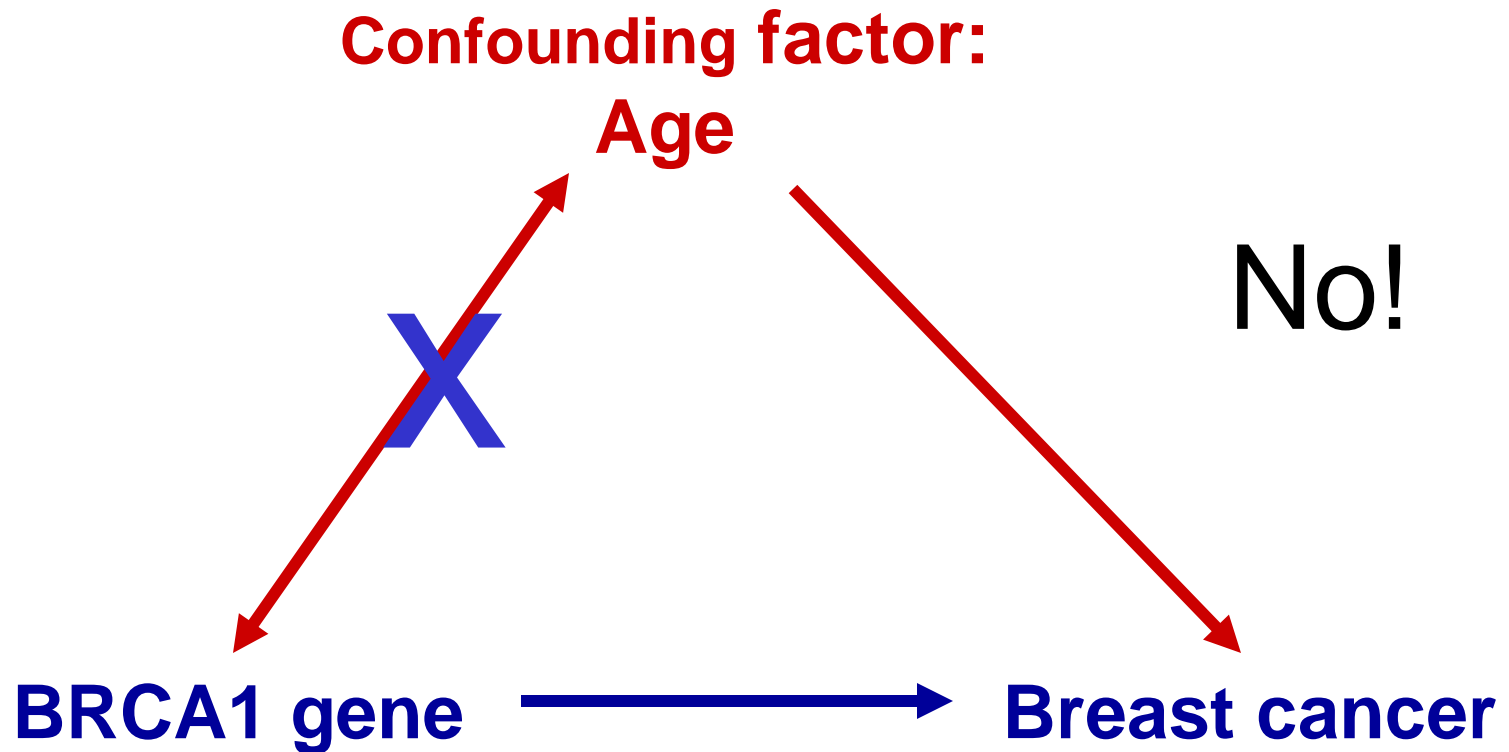
Association between HRT and heart disease



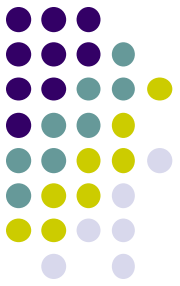
# Are confounding criteria met?



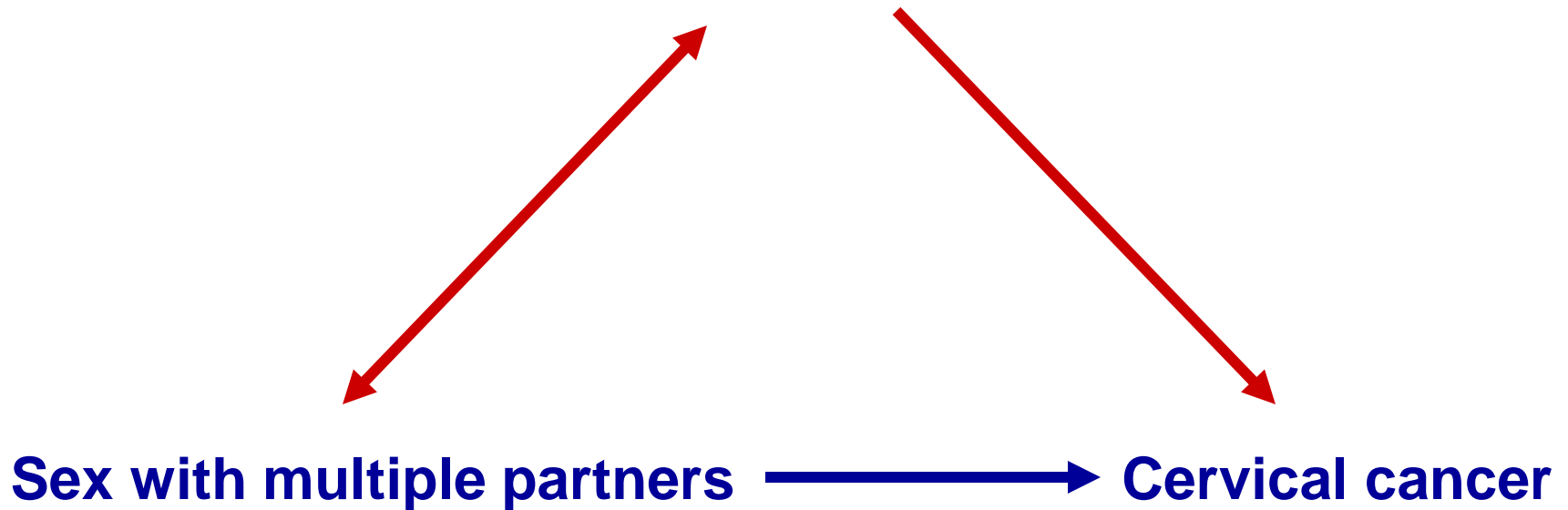
Should we adjust for age, when evaluating the association between a genetic factor and risk of breast cancer?



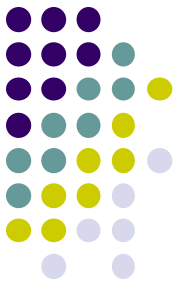
Are confounding criteria met?



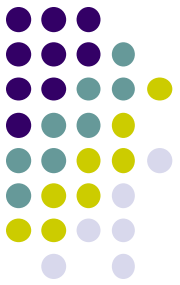
**Confounding factor:  
HPV**



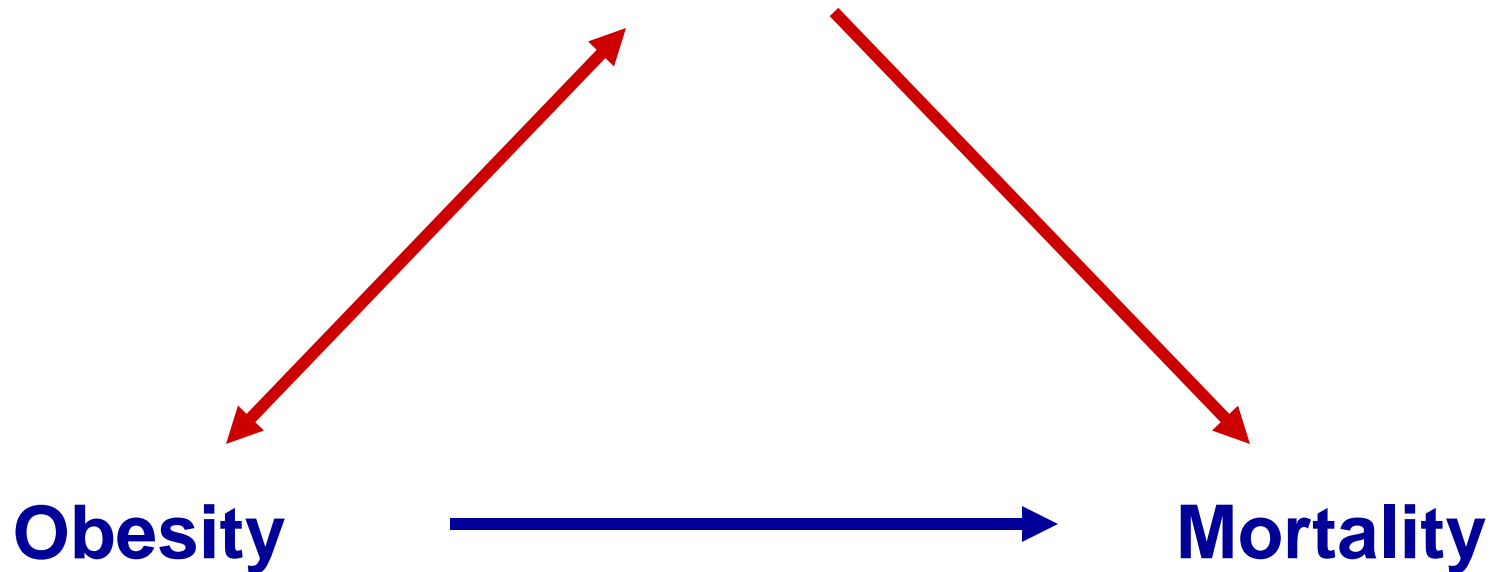
# What if this was the underlying causal mechanism?



Are confounding criteria met?

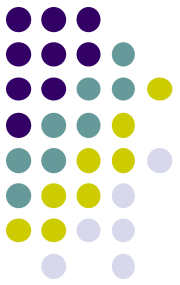


**Confounding factor:  
Hypertension**

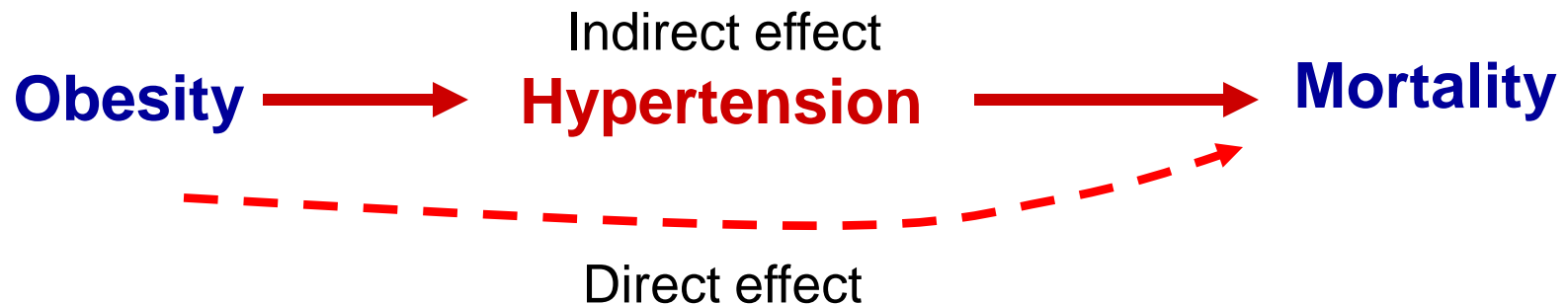
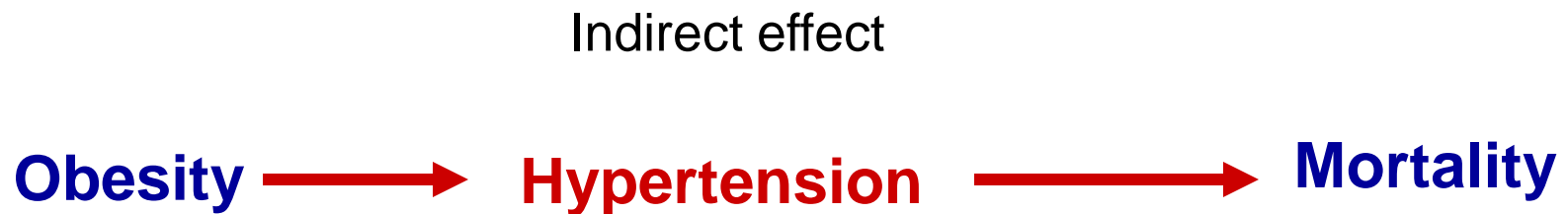


# What if this was the underlying causal mechanism?



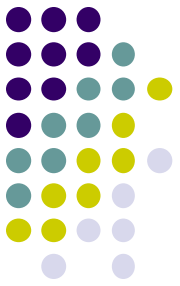


# Direct vs indirect effects

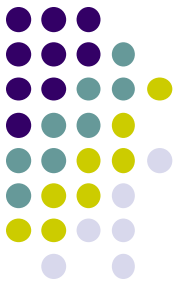


Direct effect is portion of the total effect that does not act via an intermediate cause

# Confounding



Think3D



Analytic Perspective

Open Access

## Teaching: the role of active manipulation of three-dimensional scatter plots in understanding the concept of confounding

Cora MC Busstra\*<sup>1</sup>, Rob Hartog<sup>2</sup> and Pieter van 't Veer<sup>1</sup>

### Exercise 'A 3D view to confounding'

The exercises below are part of a larger module in which students study confounding. The module uses interactive animations of three-dimensional scatter plots to illustrate the concept of confounding.

#### Explanation:

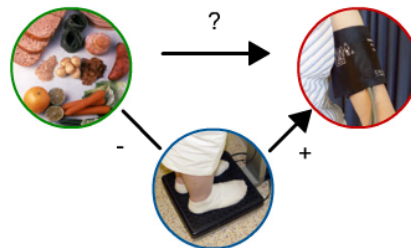
The total module consists of three parts, each describing the results of a (hypothetical) study on fiber intake and blood pressure. Body weight is taken into account because this is a risk factor for blood pressure and therefore might confound the association between fiber intake and blood pressure.

In the first part, there is no association between body weight and fiber intake in the study. Guided by several questions the student had to conclude that body weight was not a confounder. In the second part, fiber intake was negatively associated with body weight. In that study, body weight is a confounder. The demo on this site shows the introduction to this part together with two of the questions. The third part of the module describes a study in which fiber intake is positively associated with body weight, in that study body weight is also a confounder.

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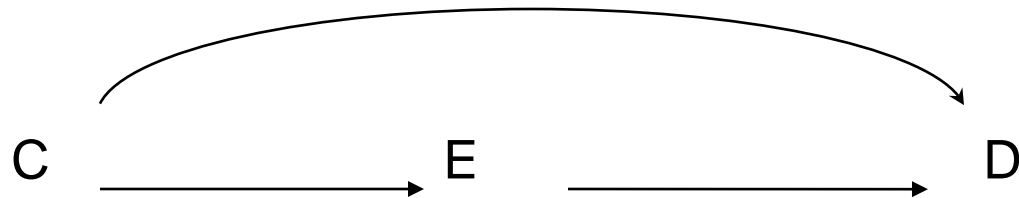
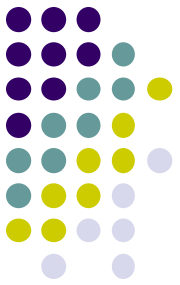
#### Confounding: Study 2

Another research group conducted a similar study but in a different population. In this population subjects with high fiber intake tend to be more health conscious and also have lower body weight, i.e. fiber intake is inversely associated with body weight.



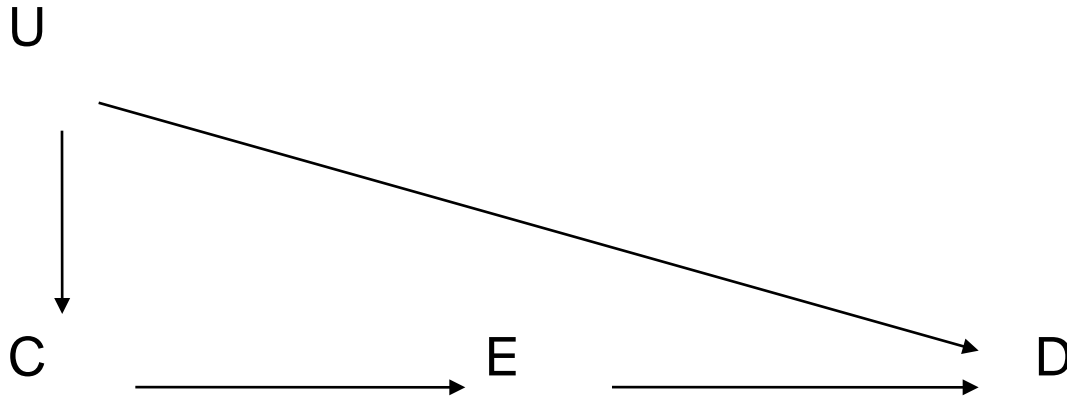
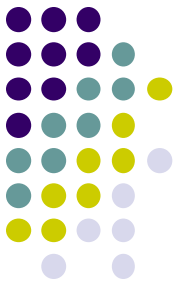
View the animation of this study in a 3D plot ([animation 2](#)). Study the plot and the projections in this plot (take your time). After that go to the next question.

# Simple causal graphs



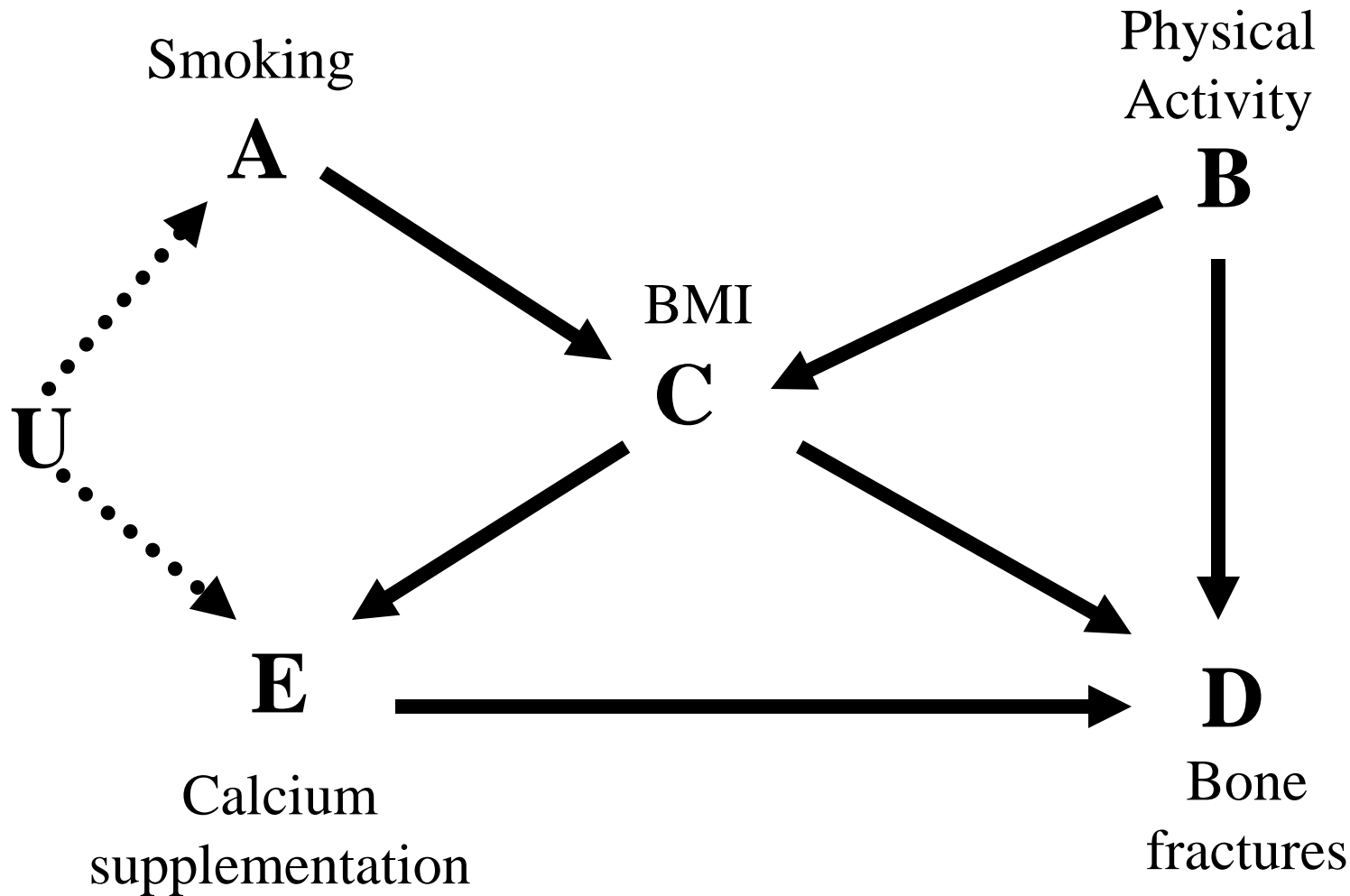
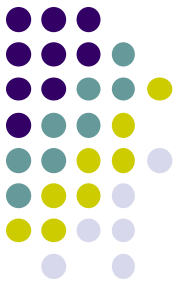
Maternal age (C) can confound the association between multivitamin use (E) and the risk of certain birth defects (D)

# Complex causal graphs



History of birth defects (C) may increase the chance of periconceptional vitamin intake (E). A genetic factor (U) could have been the cause of previous birth defects in the family, and could again cause birth defects in the current pregnancy

# More complicated causal graphs!



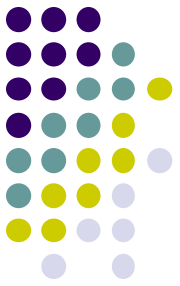
## A decorative graphic consisting of a grid of colored dots in the bottom right corner. The dots are arranged in a roughly rectangular shape, with colors including dark purple, teal, yellow, and light purple. The dots are of varying sizes and are scattered across the bottom right area of the page.

 = Significant Delay



A PowerPoint diagram meant to portray the complexity of American strategy in Afghanistan!

# Confounding



**THINK N-D!**

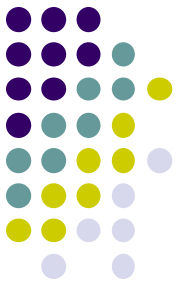
# Third approach: Collapsibility and data-based approaches



- According to this definition, a factor is a confounding variable if
  - a) the effect measure is homogeneous across the strata defined by the confounder and
  - b) the crude and common stratum-specific (adjusted) effect measures are unequal (this is called “lack of collapsibility”)
- Usually evaluated using 2x2 tables, and simple stratified analyses to compare crude effects with adjusted effects

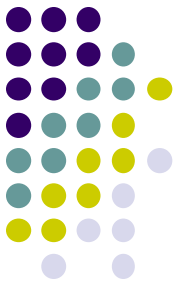
“Collapsibility is equality of stratum-specific measures of effect with the crude (collapsed), unstratified measure” Porta, 2008, Dictionary

# Crude vs. Adjusted Effects



- **Crude**: does not take into account the effect of the confounding variable
- **Adjusted**: accounts for the confounding variable(s) (what we get by pooling stratum-specific effect estimates)
  - Generating using methods such as Mantel-Haenszel estimator
  - Also generated using multivariate analyses (e.g. logistic regression)
- Confounding is likely when:
  - $RR_{\text{crude}} \neq RR_{\text{adjusted}}$
  - $OR_{\text{crude}} \neq OR_{\text{adjusted}}$

# Hormone replacement therapy and cardiovascular disease

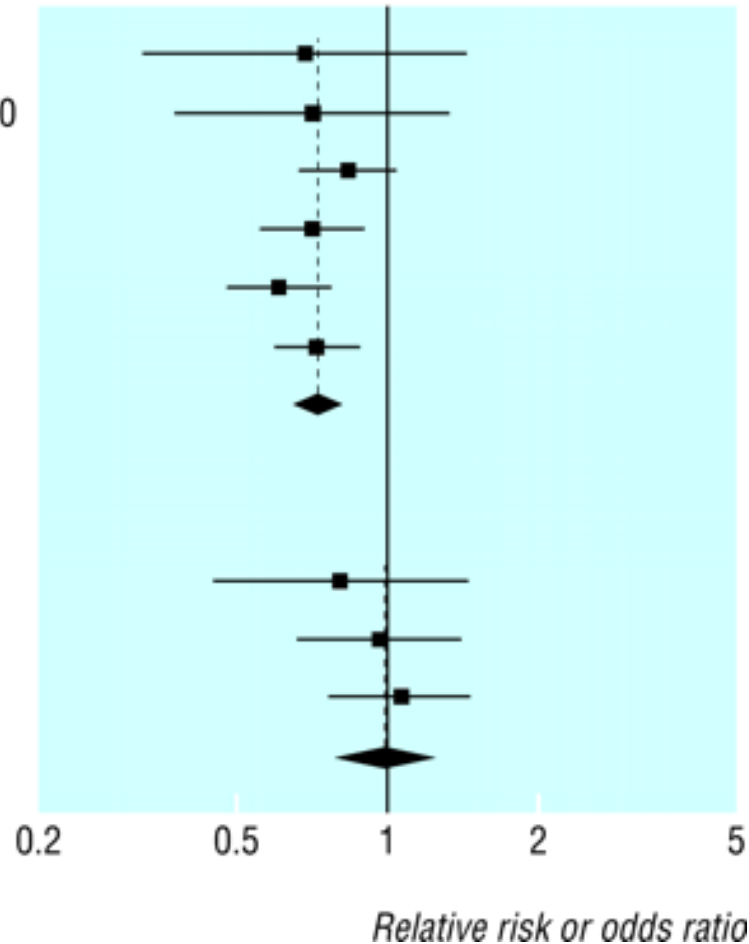


## Not adjusted for socioeconomic status

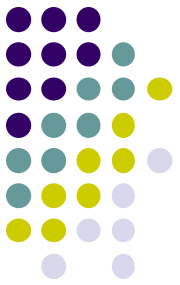
Pfeffer et al 1978  
Hernandez Avila et al 1990  
Mann et al 1994  
Heckbert et al 1997  
Grodstein et al 2000  
Varas-Lorenzo et al 2000  
Combined

## Adjusted for socioeconomic status

Rosenberg et al 1993  
Sidney et al 1997  
Sourander et al 1998  
Combined



For a more in-depth analysis of this case study, see B-File #1

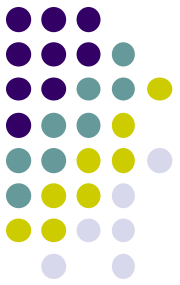


# THE **B** FILES

**Case studies of bias in real life epidemiologic studies**

Bias File 1. The Rise and Fall of Hormone Replacement Therapy

# Stratified Analysis



Crude


$OR_{Crude}$

Crude 2 x 2 table

Calculate Crude OR (or RR)

Stratify by Confounder

Stratum 1

Stratum 2



$OR_1$

$OR_2$

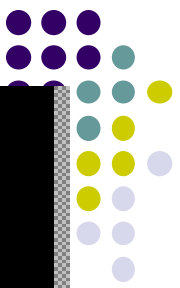
Calculate OR's  
for each stratum

If stratum-specific OR's are similar,  
calculate adjusted RR (e.g. MH)

If Crude OR  $\neq$  Adjusted OR,  
confounding is likely

If Crude OR = Adjusted  
OR, confounding is  
unlikely

# Stratified Analysis: Example



TCX exposure status (E)

Lung Cancer status (D)

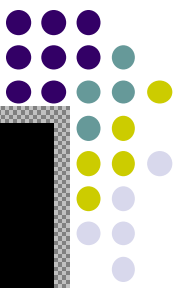
Chemical Workers	TCX	no TCX	Total
LC	27	14	41
No LC	48	67	115
Total	75	81	156

Ten-year risks for LC

TCX:  $27/75 = 0.36$

no TCX:  $14/81 = 0.17$

$$\hat{RR} = 0.36/0.17 = 2.1$$



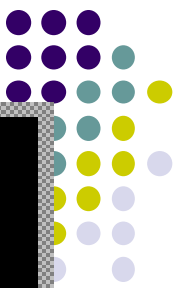
Chemical Workers	TCX	no TCX	Total
LC	27	14	41
No LC	48	67	115
Total	75	81	156

$$\hat{RR} = 2.1$$

Other Variables? SMK history

Do TCX exposed smoke more than TCX unexposed?

If yes, that may explain the increased risk of 2.1.



Chemical Workers	TCX	no TCX	Total	$\hat{RR} = 2.1$
LC	27	14	41	
No LC	48	67	115	
Total	75	81	156	

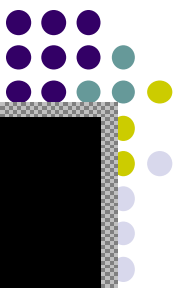
non-smokers

	TCX	no TCX	Total
LC	1	2	3
No LC	24	48	72
Total	25	50	75

smokers

	TCX	no TCX	Total
LC	26	12	38
No LC	24	19	43
Total	50	31	81

**We say we are “controlling for smoking” and smoking is a “control variable”.**



Chemical Workers	TCX	no TCX	Total
LC	27	14	41
No LC	48	67	115
Total	75	81	156

$$\hat{RR} = 2.1$$

non-smokers

smokers

	TCX	no TCX	Total
LC	1	2	3
No LC	24	48	72
Total	25	50	75

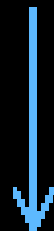
	TCX	no TCX	Total
LC	26	12	38
No LC	24	19	43
Total	50	31	81

$$\hat{RR} = 1.0 \quad \text{No Association}$$

$$\hat{RR} = 1.3$$

Ignore smoking history:

$$\hat{RR} = 2.1$$



Control for smoking history:

$$\hat{RR} = 1.0$$

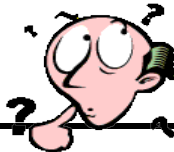

No Association

$$\hat{RR} = 1.3$$

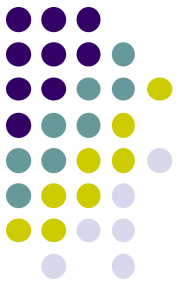
Persons exposed to TCX smoke more  
than those persons not exposed to TCX!  
Smoking history is a confounder.

# Examples: crude vs adjusted RR



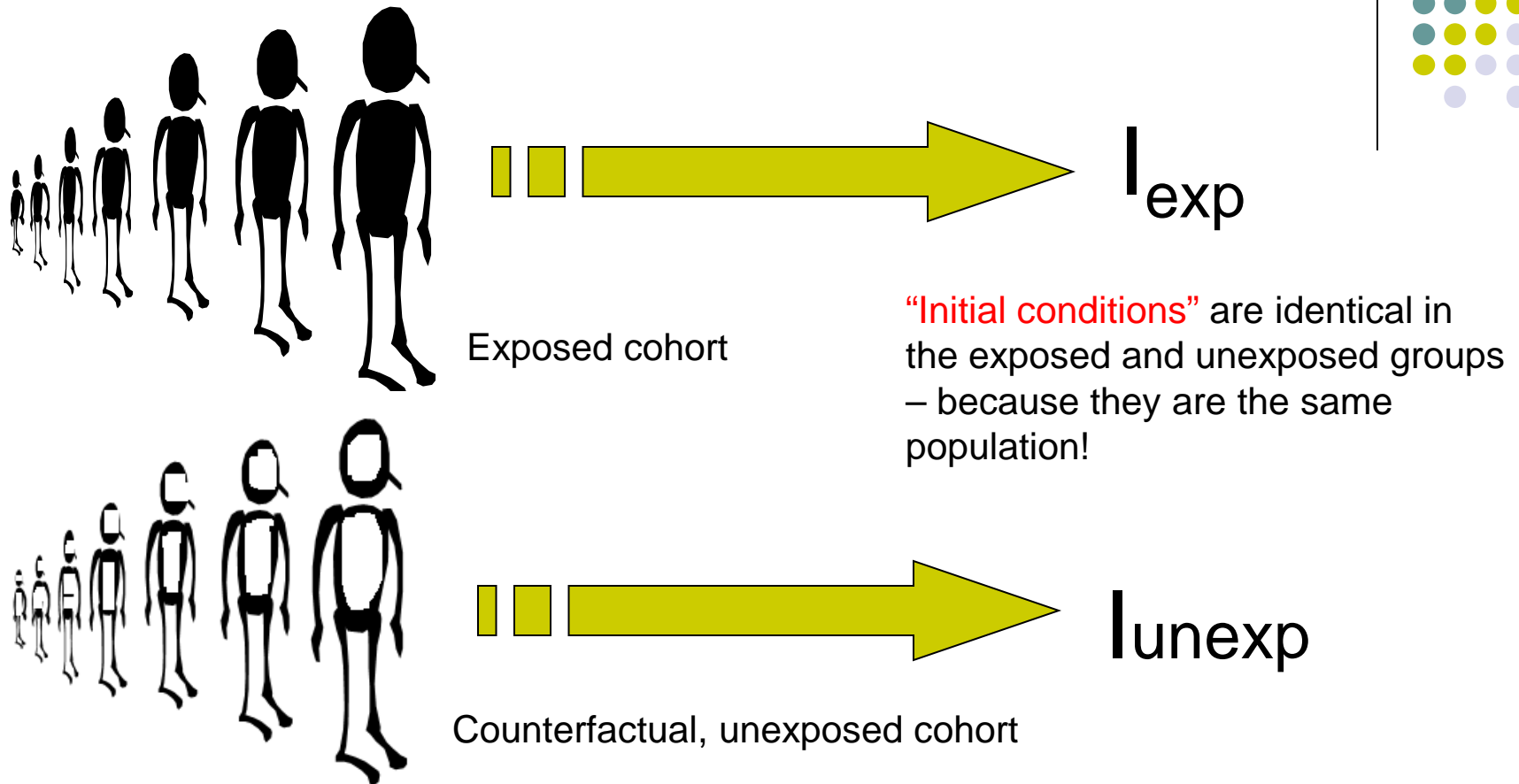
Study	Crude RR	Stratum1 RR	Stratum2 RR	Adjusted RR	Confounding?
1	6.00	3.20	3.50	3.30	YES
2	2.00	1.02	1.10	1.08	YES
3	1.10	2.00	2.00	2.00	YES
4	0.56	0.50	0.60	0.54	NO
5	4.20	4.00	4.10	4.04	NO
6	1.70	0.03	3.50		

# Fourth approach: Causality: counterfactual model



- 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”

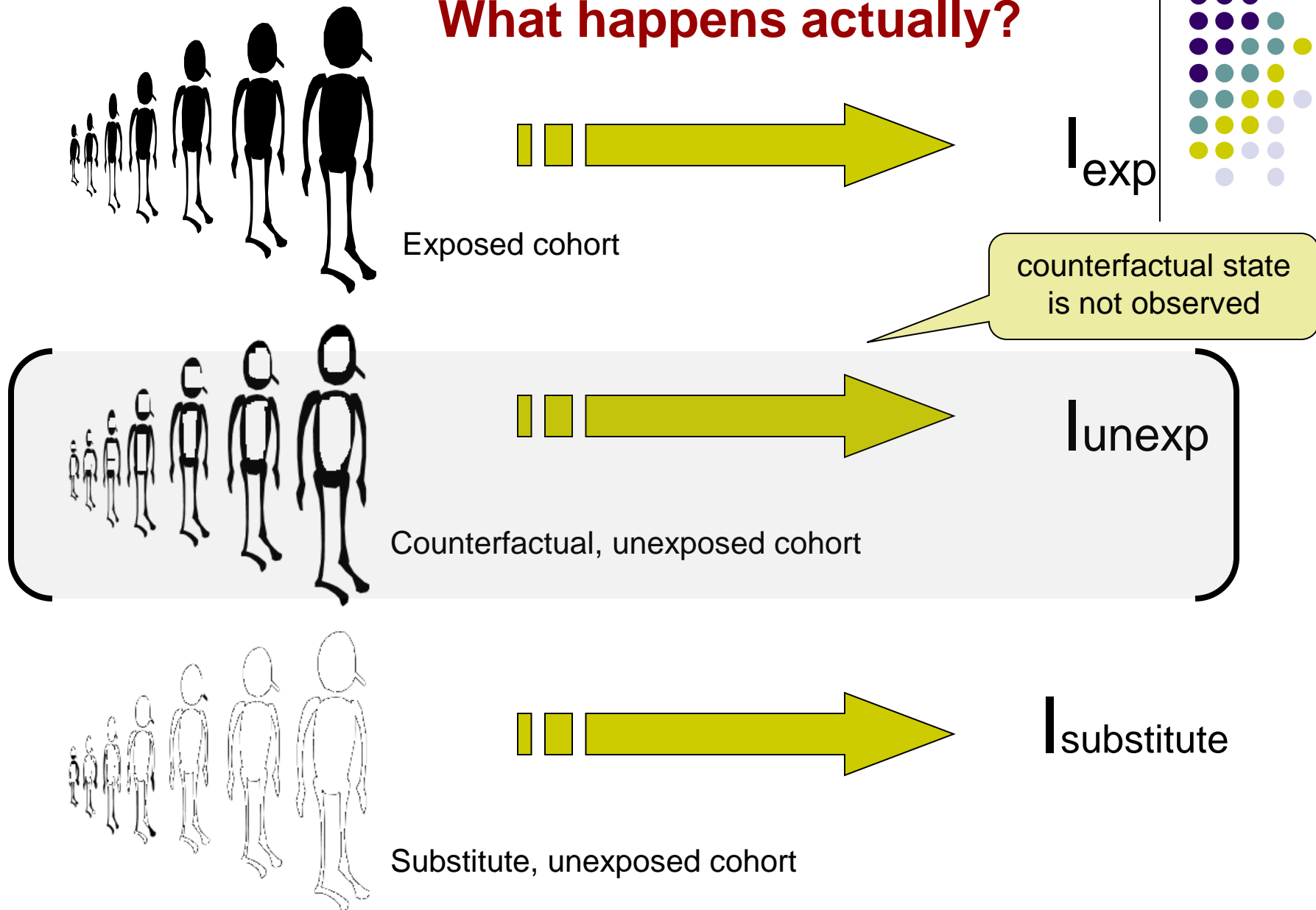
# Ideal counterfactual comparison to determine causal effects



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

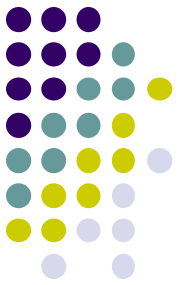
“A causal contrast compares disease frequency under *two* exposure distributions, but in *one* target population during *one* etiologic time period”

# What happens actually?



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

# What happens actually?



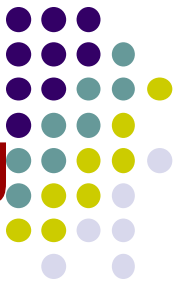
$$RR_{\text{causal}} = I_{\text{exp}} / I_{\text{unexp}}$$

IDEAL

$$RR_{\text{assoc}} = I_{\text{exp}} / I_{\text{substitute}}$$

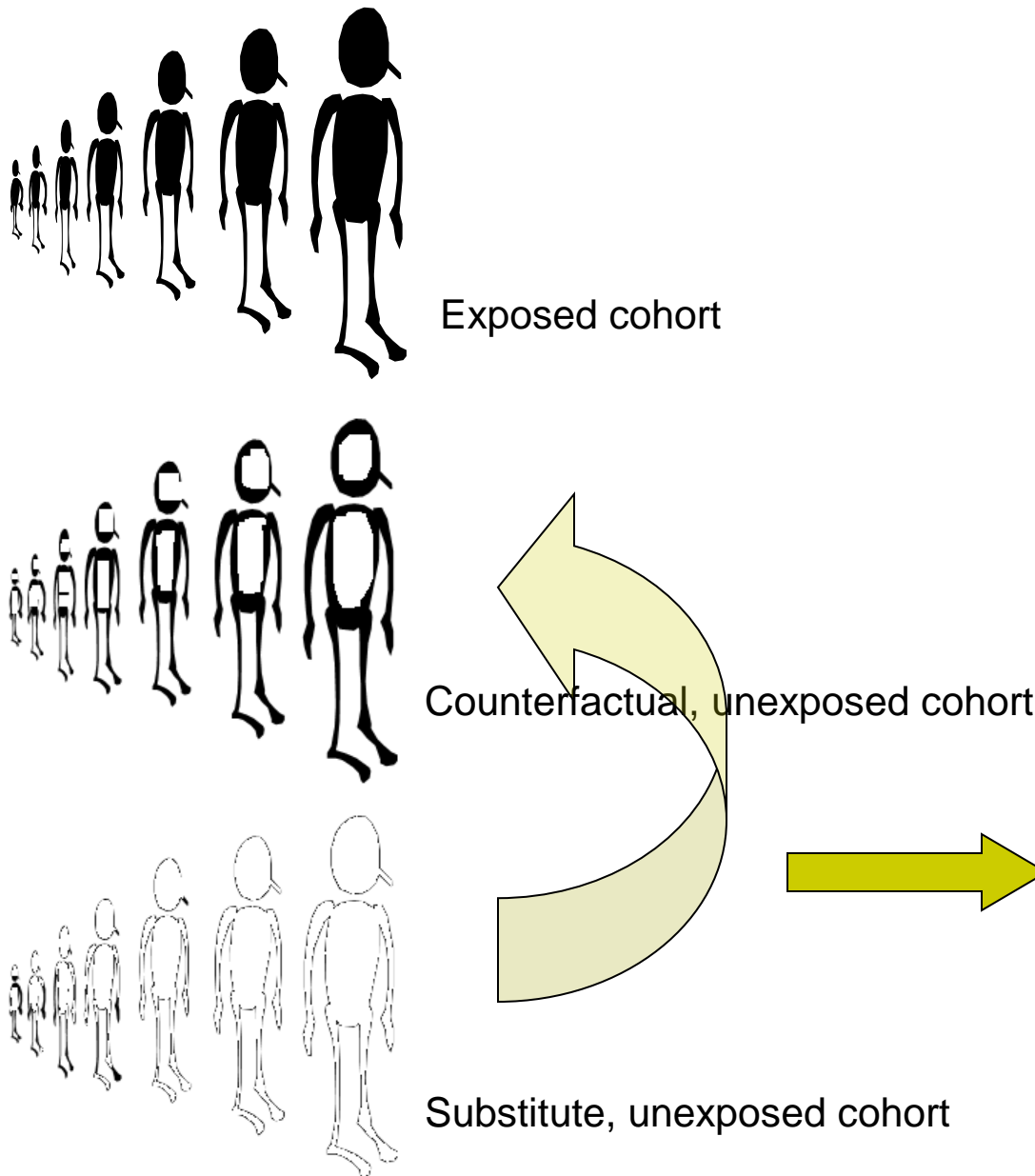
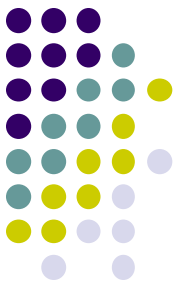
ACTUAL

# Counterfactual definition of confounding



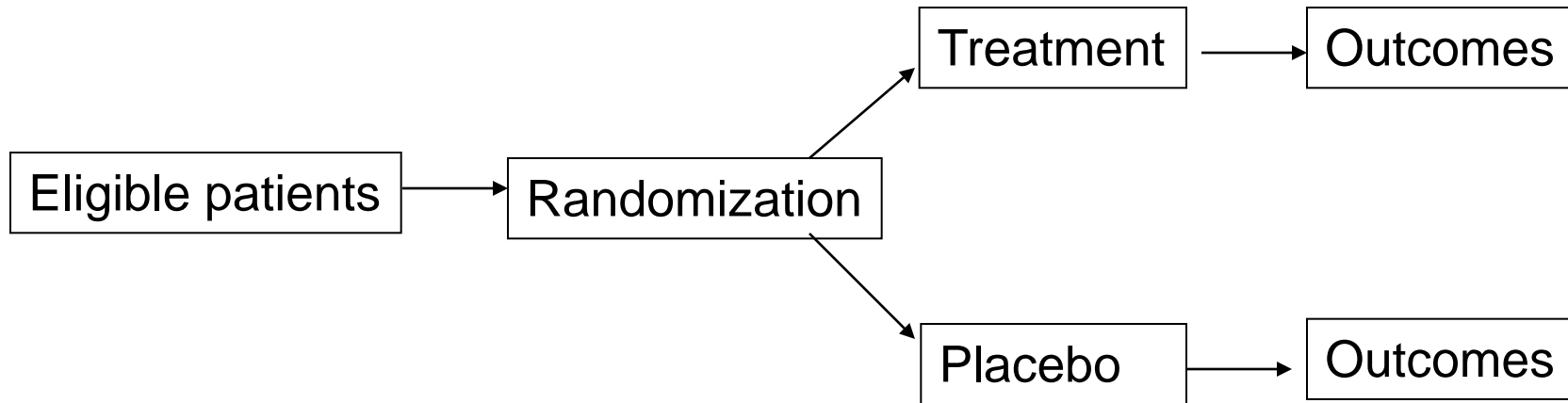
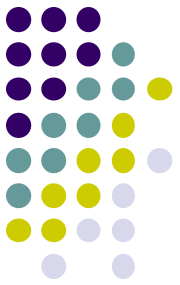
- “*Confounding* is present if the substitute population imperfectly represents what the target would have been like under the counterfactual condition”
- “An association measure is *confounded* (or biased due to confounding) for a causal contrast if it does not equal that causal contrast because of such an imperfect substitution”

$$RR_{\text{causal}} \neq RR_{\text{assoc}}$$



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

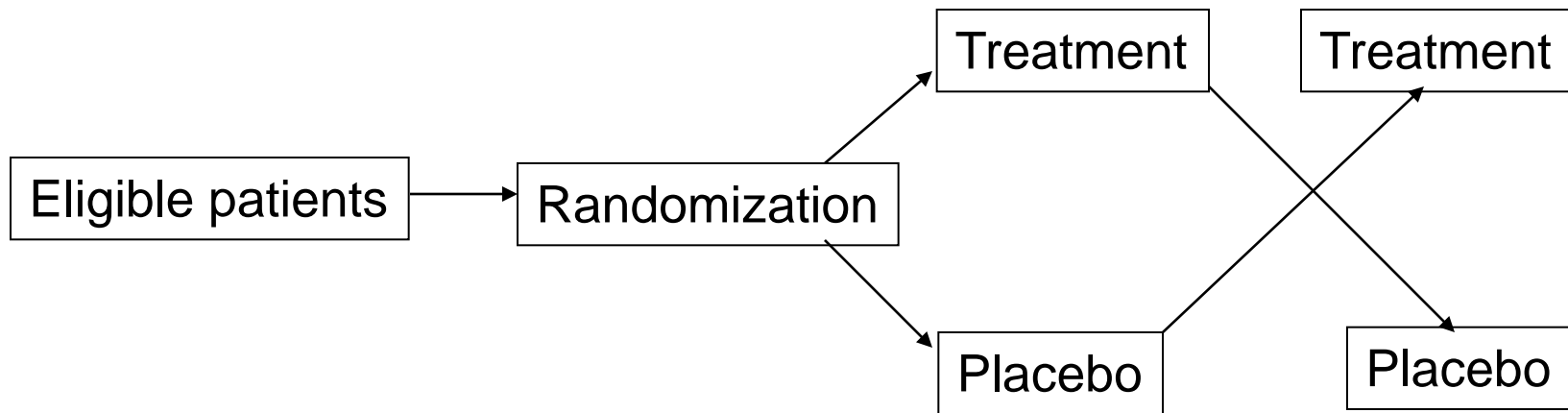
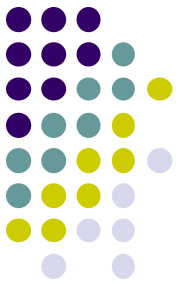
# Simulating the counter-factual comparison: Experimental Studies: RCT



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

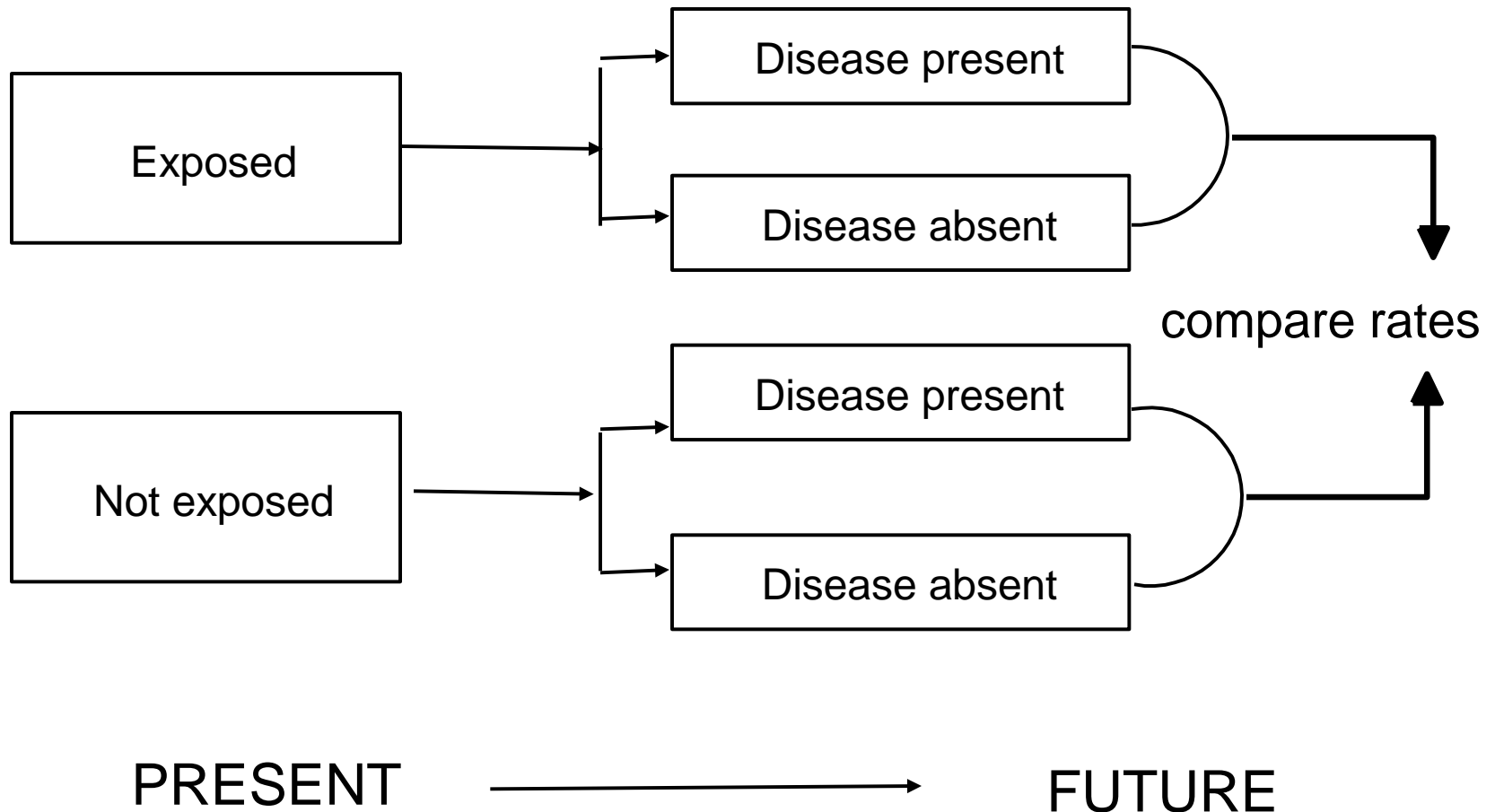


Although cross-over trials come close to the ideal of counterfactual comparison, they do not achieve it because a person can be in only one study group at a time; variability in other exposures across time periods can still introduce confounding (Rothman, 2002)

# Simulating the counter-factual comparison: Observational Studies

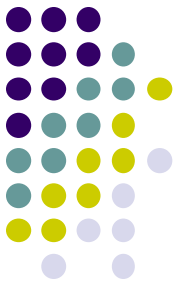


In observational studies, because exposures are not assigned randomly, attainment of exchangeability is impossible – “initial conditions” are likely to be different and the groups may not be comparable



Confounding is ALWAYS a concern with observational designs!

# Confounding in observational studies vs randomized trials



- Two case studies:
  - Male circumcision and HIV
  - Aspirin to reduce cardiovascular mortality

# Example: Does male circumcision reduce risk of HIV?

## Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis

Helen A. Weiss, Maria A. Quigley and Richard J. Hayes

**Objective:** To systematically review studies of male circumcision and the risk of HIV-1 infection in men in sub-Saharan Africa, and to summarize the findings in a meta-analysis.

**Design:** A meta-analysis of observational studies.

**Methods:** A systematic literature review was carried out of studies published up to April 1999 that included circumcision as a risk factor for HIV-1 infection among men in sub-Saharan Africa. A random effects meta-analysis was used to calculate a pooled relative risk (RR) and 95% confidence interval (CI) for all studies combined, and stratified by type of study population. Further analyses were conducted among those studies that adjusted for potential confounding factors.

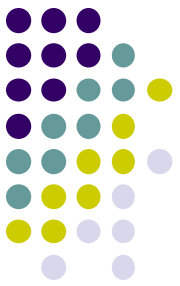
**Results:** Twenty-seven studies were included. Of these, 21 showed a reduced risk of HIV among circumcised men, being approximately half that in uncircumcised men (crude RR = 0.52, CI 0.40–0.68). In 15 studies that adjusted for potential confounding factors, the association was even stronger (adjusted RR = 0.42, CI 0.34–0.54). The association was stronger among men at high risk of HIV (crude RR = 0.27; adjusted RR = 0.29, CI 0.20–0.41) than among men in general populations (crude RR = 0.93; adjusted RR = 0.56, CI 0.44–0.70).

**Conclusion:** Male circumcision is associated with a significantly reduced risk of HIV infection among men in sub-Saharan Africa, particularly those at high risk of HIV. These results suggest that consideration should be given to the acceptability and feasibility of providing safe services for male circumcision as an additional HIV prevention strategy in areas of Africa where men are not traditionally circumcised.

© 2000 Lippincott Williams & Wilkins

*AIDS* 2000. 14:2361–2370

Many observational studies had shown a protective effect, but it was impossible to be sure



# Cochrane review in 2005: confounding was a major concern



## 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*

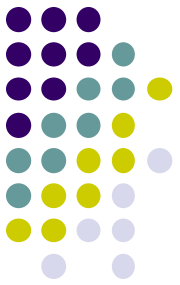
This Cochrane systematic review assesses the evidence for an interventional effect of male circumcision in preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. The review includes a comprehensive assessment of the quality of all 37 included observational studies. Studies 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 ( $\chi^2=132.34$ ; degrees of freedom [df]=15;  $p<0.00001$ ) and high-risk cross-sectional studies ( $\chi^2=29.70$ ; 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.

*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,

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)

# 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<sup>1,2,3,4\*</sup>, Dirk Taljaard<sup>5</sup>, Emmanuel Lagarde<sup>2,4</sup>, Joëlle Sobngwi-Tambekou<sup>2</sup>, Rémi Sitta<sup>2,4</sup>, Adrian Puren<sup>6</sup>

**1** Hôpital Ambroise-Paré, Assistance 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.

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**DOI:**

10.1371/journal.pmed.0020298

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### 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.

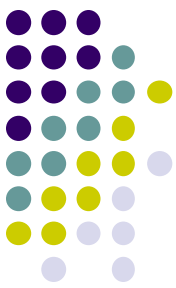
#### Methods and Findings

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  $1 - \text{RR}$ . 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%
<b>Reported sexual behaviour</b>			
Have had first sexual experience		90.5%	91.8%
Median (IQR) age at first sex (years) <sup>a</sup>		16.6 (15.2–18.4)	16.8 (15.4–18.5)
Median (IQR) number of lifetime sex partners <sup>b</sup>		4 (2–7)	4 (3–7)
Used a condom at first sex <sup>b</sup>		13.4%	15.2%
Ever used a condom <sup>b</sup>		81.2%	82.3%
At-risk behaviour <sup>c,d</sup>		46.7%	46.8%
Married or living as married <sup>d</sup>		1.8%	1.8%
Mean (IQR) number of non-spousal partners <sup>e</sup>		1.4 (0–2)	1.4 (0–2)
At least one sexual partnership with only one sexual contact <sup>e</sup>		29.8%	30.7%
Mean (IQR) number of sexual contacts <sup>e</sup>		8.0 (0–8)	8.7 (1–8)
Attended a clinic for a health problem related to the genital area <sup>e</sup>		10.0%	9.6%

Randomization resulted in highly comparable distribution of potential confounders; so confounding is not an issue!

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

Ronald H Gray, Godfrey Kigozi, David Serwadda, Frederick Makuumbi, 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  
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## 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 Ndiyo-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  
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In 2007, two other RCT confirm the first RCT findings

UNAIDS endorsed  
this intervention in  
2007



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

Study name	Statistics for each study				Risk ratio and 95% CI						
	Risk ratio	Lower limit	Upper limit	p-Value							
Auvert, RSA	0.42	0.25	0.70	0.001							
Bailey, Kenya	0.41	0.24	0.70	0.001							
Gray, Uganda	0.50	0.30	0.83	0.007							
Combined	0.44	0.33	0.60	<0.0001							
					0.01	0.1	1	10	100	Favours Circumcision	Favours Control

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.

## Meta-analysis of 3 RCTs in 2008

## Modelling studies show large benefits

## But not reaching the target groups?

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### Policy Forum

## Male Circumcision for HIV Prevention in High HIV Prevalence Settings: What Can Mathematical Modelling Contribute to Informed Decision Making?

UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention<sup>1\*</sup>

### Background

Three recent randomised controlled trials [1–3] in Kenya, South Africa, and Uganda have confirmed previous observational studies [4] and ecological experience [5] and demonstrated beyond reasonable doubt that male circumcision performed by well-trained medical professionals reduces the risk of men acquiring HIV through female-to-male transmission by approximately 60% [5,6]. Furthermore, results from the Kenyan trial indicate that the protective effects of circumcision are sustained for at least 42 mo [7], which suggests that circumcision is likely to provide life-long partial protection.

Although the evidence from the randomised trials is compelling, the longer-term population-level impact of introducing or expanding safe male circumcision services within comprehensive HIV prevention

### Summary Points

- Mathematical models can estimate the population-level impact of male circumcision on HIV incidence in high HIV prevalence settings, but different methods, assumptions, and input variables can produce conflicting results.
- UNAIDS/WHO/SACEMA recently convened experts to review the outcomes of six simulation models on key policy and programmatic decision-making questions.
- Large benefits of male circumcision among heterosexual men in low male circumcision, high HIV prevalence settings were found: one HIV infection being averted for every five to 15 male circumcisions performed, and costs to avert one HIV infection ranging from US\$150 to US\$900 using a 10-y time horizon.
- The models predicted that both premature postoperative resumption of sexual intercourse and behavioural risk compensation, if confined to newly or already circumcised men and their partners, have only small population level effects on the anticipated impact of male circumcision service scale-up on HIV incidence.
- Women benefit indirectly from reduced HIV prevalence in circumcised male partners and male circumcision service scale-up acts synergistically with other strategies to reduce HIV disease burden.
- The modelling results have informed development of a pragmatic decision-makers' programme planning tool.

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### South Africa Is Seen to Lag in H.I.V. Fight



Benedicte Kurzen/VII Mentor, for The New York Times

Even without government involvement, demand for circumcision has surged over the last year in Orange Farm, South Africa.

By CELIA W. DUGGER  
Published: July 19, 2009

ORANGE FARM, [South Africa](#) — Young men have flocked by the thousands to this clinic for circumcisions, the only one of its kind in South Africa. Each of them lies down on one of seven closely spaced surgical tables, his privacy shielded only by a green curtain.

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“Circumcision has been proven to reduce a man’s risk of contracting HIV by more than half. Yet two years after the WHO recommended the surgery, the government here still does not provide it to help fight the disease or educate the public about its benefits.”

# Another example: Confounding by indication (a huge concern with pharmacoepi studies)

## THE **B** FILES

**Case studies of bias in real life epidemiologic studies**

Bias File 7. Confounding by indication: a most stubborn bias?

Compiled by

Madhukar Pai, MD, PhD

Jay S Kaufman, PhD

# RCT on aspirin for reducing cardiovascular mortality

## FINAL REPORT ON THE ASPIRIN COMPONENT OF THE ONGOING PHYSICIANS' HEALTH STUDY

STEERING COMMITTEE OF THE PHYSICIANS' HEALTH STUDY RESEARCH GROUP\*

**Abstract** The Physicians' Health Study is a randomized, double-blind, placebo-controlled trial designed to determine whether low-dose aspirin (325 mg every other day) decreases cardiovascular mortality and whether beta carotene reduces the incidence of cancer. The aspirin component was terminated earlier than scheduled, and the preliminary findings were published. We now present detailed analyses of the cardiovascular component for 22,071 participants, at an average follow-up time of 60.2 months.

There was a 44 percent reduction in the risk of myocardial infarction (relative risk, 0.56; 95 percent confidence interval, 0.45 to 0.70;  $P < 0.00001$ ) in the aspirin group (254.8 per 100,000 per year as compared with 439.7 in the placebo group). A slightly increased risk of stroke among those taking aspirin was not statistically significant; this trend was observed primarily in the subgroup with hemorrhagic stroke (relative risk, 2.14; 95 percent confidence interval, 0.96 to 4.77;  $P = 0.06$ ). No reduction in mortality

from all cardiovascular causes was associated with aspirin (relative risk, 0.96; 95 percent confidence interval, 0.60 to 1.54).

Further analyses showed that the reduction in the risk of myocardial infarction was apparent only among those who were 50 years of age and older. The benefit was present at all levels of cholesterol, but appeared greatest at low levels. The relative risk of ulcer in the aspirin group was 1.22 (169 in the aspirin group as compared with 138 in the placebo group; 95 percent confidence interval, 0.98 to 1.53;  $P = 0.08$ ), and the relative risk of requiring a blood transfusion was 1.71.

This trial of aspirin for the primary prevention of cardiovascular disease demonstrates a conclusive reduction in the risk of myocardial infarction, but the evidence concerning stroke and total cardiovascular deaths remains inconclusive because of the inadequate numbers of physicians with these end points. (N Engl J Med 1989; 321: 129-35.)

After the trial was stopped early, all participants were then offered the opportunity to take aspirin, and the study population remained under observation. Some participants chose to take aspirin while others did not take it or stopped taking after a while.

# Observational follow-up of the same RCT population

## Self-Selected Posttrial Aspirin Use and Subsequent Cardiovascular Disease and Mortality in the Physicians' Health Study

Nancy R. Cook, ScD; Patricia R. Hebert, PhD; JoAnn E. Manson, MD;  
Julie E. Buring, ScD; Charles H. Hennekens, MD

**Background:** The randomized aspirin component of the Physicians' Health Study (PHS) was terminated early, after 5 years, primarily because of the emergence of a statistically extreme ( $P < .00001$ ) 44% reduction of first myocardial infarction (MI) among those assigned to aspirin. As a result, there were insufficient numbers of strokes or cardiovascular disease (CVD)-related deaths to evaluate these end points definitively.

**Methods:** Data on self-selected aspirin use were collected until the beta carotene component ended as scheduled after 12 years. Posttrial use of aspirin was assessed at the 7-year follow-up among 18 496 participants with no previous reported CVD. Randomized and posttrial observational results in the PHS were compared, and differences between those self-selecting aspirin and those not were examined.

**Results:** At 7 years, 59.5% of participants without CVD reported self-selected aspirin use for at least 180 d/y, and 20.8% for 0 to 13 d/y. Use was significantly associated

with family history of MI, hypertension, elevated cholesterol levels, body mass index, alcohol consumption, exercise, and use of vitamin E supplements. In multivariate analyses, self-selected aspirin use for at least 180 vs 0 to 13 d/y was associated with lower risk for subsequent MI (relative risk [RR], 0.72; 95% confidence interval [CI], 0.55-0.95), no relation with stroke (RR, 1.02; 95% CI, 0.74-1.39), and significant reductions in CVD-related (RR, 0.65; CI, 0.47-0.89) and total mortality (RR, 0.64; CI, 0.54-0.77).

**Conclusion:** These associations between self-selected aspirin use and CVD risk factors increase the likelihood of residual confounding and emphasize the need for large-scale randomized trials, such as the ongoing Women's Health Study, to detect reliably the most plausible small to moderate effects of aspirin in the primary prevention of stroke and CVD-related death.

*Arch Intern Med.* 2000;160:921-928

*Subjects who chose to take aspirin for 180 days or more (compared with nonusers) were: 1) slightly heavier, 2) slightly older, 3) about 30% more likely to have a family history of MI, 4) almost 20% more likely to be under treatment of hypertension, 5) almost 50% more likely to be under treatment to lower their cholesterol (and still had higher cholesterol levels), and 6) about 45% more likely to be daily alcohol drinkers.*

# So, major difference between RCT and observational designs

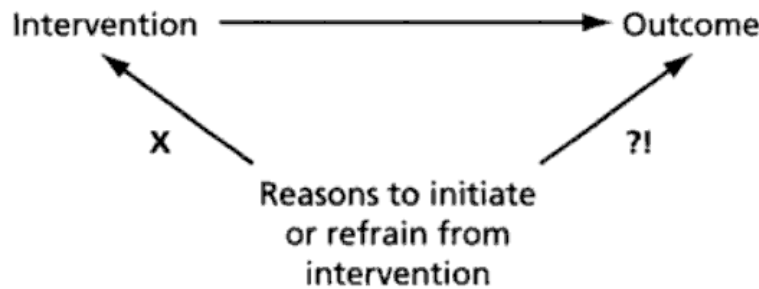


FIGURE 5.7 Major strength of a random allocation of patients to an intervention.

Randomization ensured that aspirin was not selectively offered to, for example, older males who smoke, are overweight, and have family history of cardiovascular problems. Thus, confounding by these factors is unlikely to occur.

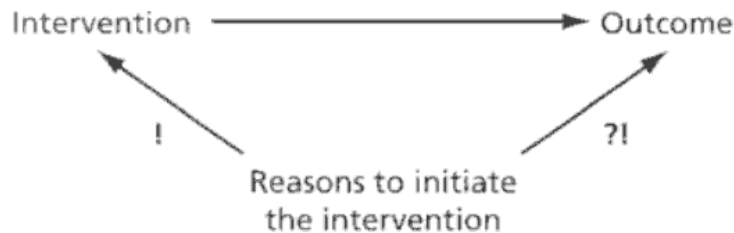


FIGURE 5.6 Reasons underlying the decision to initiate treatment are important potential confounders.

In observational studies, it is likely that aspirin users will be older, smokers, overweight, have already had cardiovascular events, and/or have comorbid conditions. These factors will result in confounding by indication because they are also associated with the outcome.

# Healthy-user bias

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*International Journal of Epidemiology* 2006;**35**:337–344  
doi:10.1093/ije/dyi274

## Evidence of bias in estimates of influenza vaccine effectiveness in seniors

Lisa A Jackson,<sup>1,2\*</sup> Michael L Jackson,<sup>1,2</sup> Jennifer C Nelson,<sup>1,3</sup> Kathleen M Neuzil<sup>4</sup> and Noel S Weiss<sup>2</sup>

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Accepted 3 November 2005

**Background** Numerous observational studies have reported that seniors who receive influenza vaccine are at substantially lower risk of death and hospitalization during the influenza season than unvaccinated seniors. These estimates could be influenced by differences in underlying health status between the vaccinated and unvaccinated groups. Since a protective effect of vaccination should be specific to influenza season, evaluation of non-influenza periods could indicate the possible contribution of bias to the estimates observed during influenza season.

**Methods** We evaluated a cohort of 72 527 persons 65 years of age and older followed during an 8 year period and assessed the risk of death from any cause, or hospitalization for pneumonia or influenza, in relation to influenza vaccination, in periods before, during, and after influenza seasons. Secondary models adjusted for covariates defined primarily by diagnosis codes assigned to medical encounters.

**Results** The relative risk of death for vaccinated persons compared with unvaccinated persons was 0.39 [95% confidence interval (95% CI), 0.33–0.47] before influenza season, 0.56 (0.52–0.61) during influenza season, and 0.74 (0.67–0.80) after influenza season. The relative risk of pneumonia hospitalization was 0.72 (0.59–0.89) before, 0.82 (0.75–0.89) during, and 0.95 (0.85–1.07) after influenza season. Adjustment for diagnosis code variables resulted in estimates that were further from the null, in all time periods.

**Conclusions** The reductions in risk before influenza season indicate preferential receipt of vaccine by relatively healthy seniors. Adjustment for diagnosis code variables did not control for this bias. In this study, the magnitude of the bias demonstrated by the associations before the influenza season was sufficient to account entirely for the associations observed during influenza season.

**Keywords** Influenza/prevention and control, influenza vaccines, cohort studies, bias(epidemiology), confounding factor, epidemiological

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# Readings for this module



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- Rothman text:
  - Chapters 5 and 8
- Gordis text:
  - Chapters 14 and 15
- B-File #7  
(confounding by indication)

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