Department of Pharmacy & Pharmacology

Confounding

Corinne de Vries

Outline

- Confounding in epidemiology
  - Effect modification
  - Confounding by indication
  - Protopathic bias
- Ways to address confounding and effect modification in study design and analysis

Risk estimate <>1 and causality


HAINES, COHEN & NELSON
INVESTMENT FIRM
DEPT. OF RUMOR RESEARCH AND VERIFICATION

Risk estimate <>1 and causality

Chance?

Risk estimate <>1 and causality

Chance?

yes

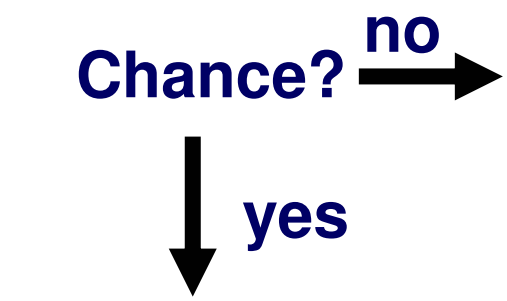
Risk estimate <>1 and causality

Chance?

yes

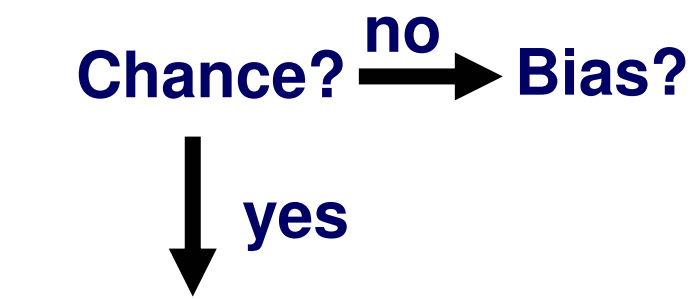
Not causal

Risk estimate <>1 and causality



Not causal

Risk estimate <>1 and causality



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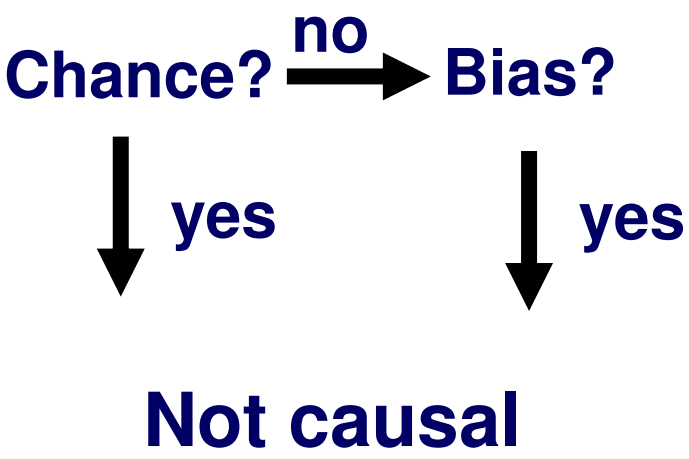

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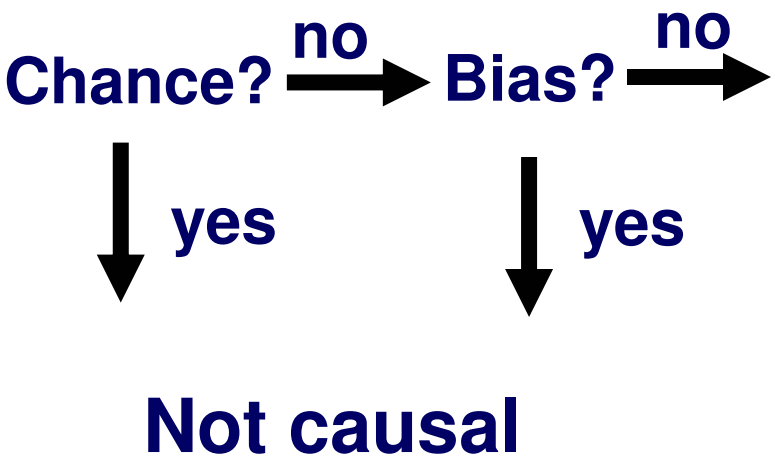

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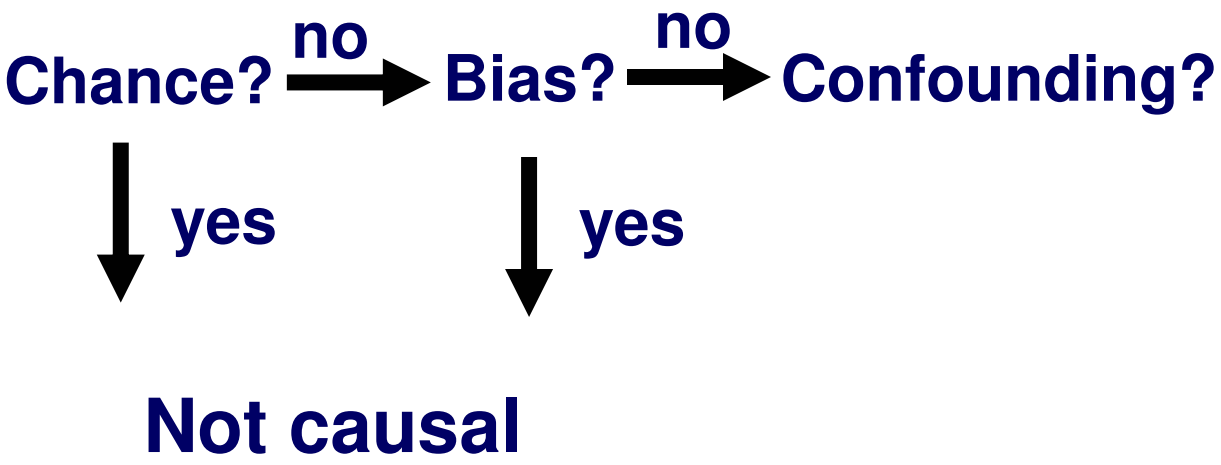
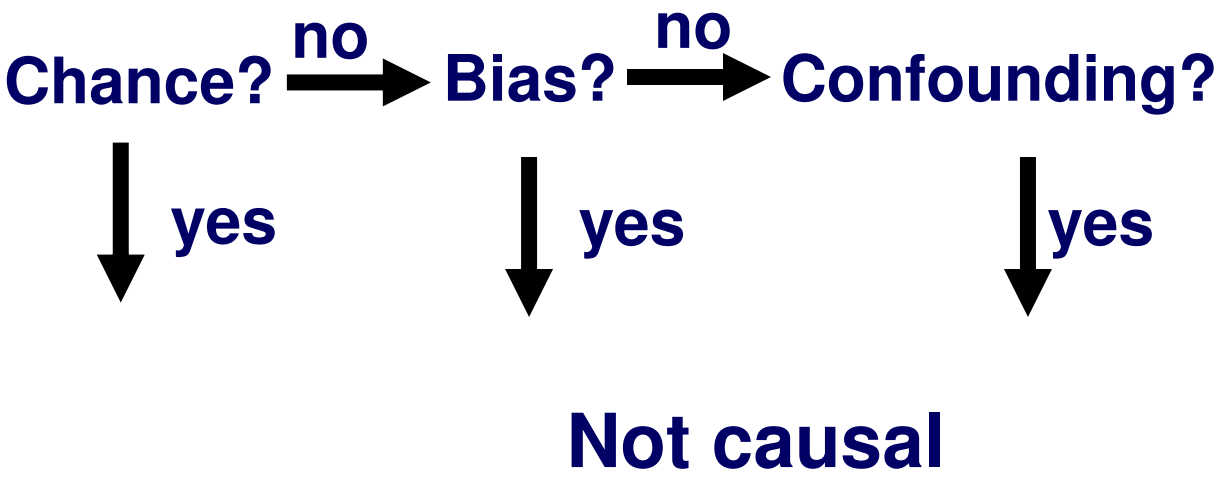


Of all men’s miseries the
bitterest is this,
to know so much and to have
control over nothing.

Herodotus

Risk estimate <>1 and causality



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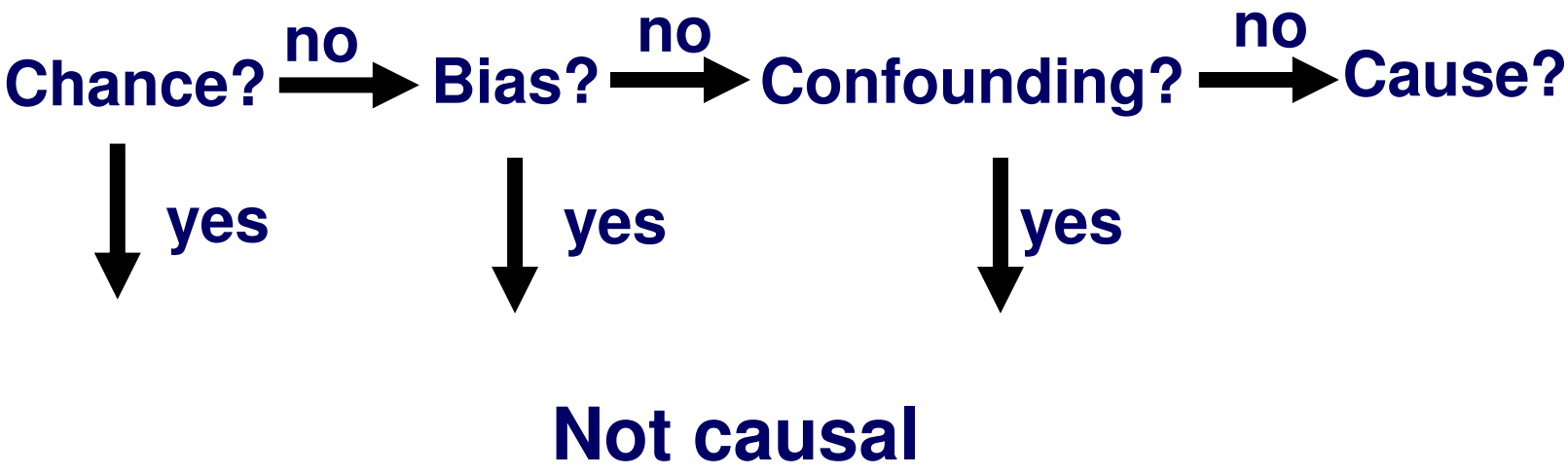
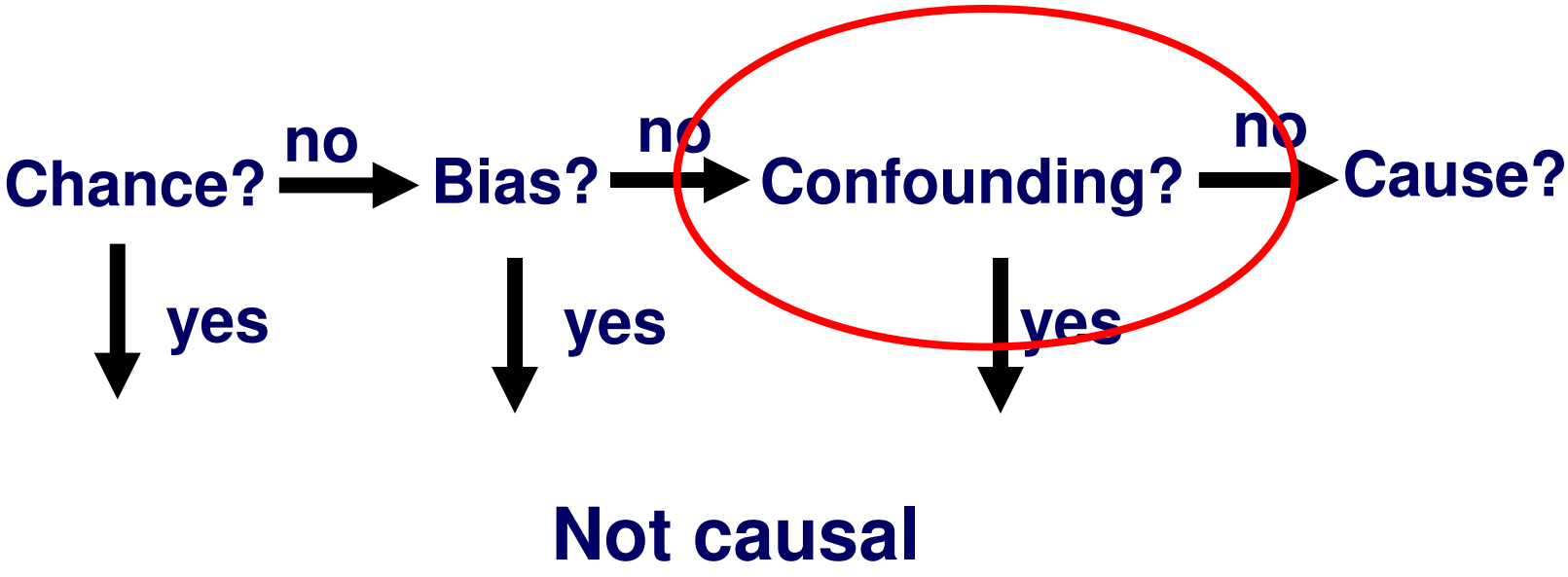


Risk estimate <>1 and causality

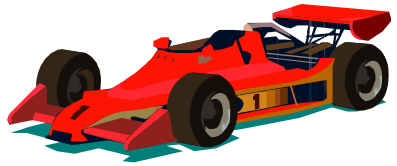


Confounding

- Suppose red cars have RR=2 of crashing.
- Suppose sports cars have RR=2 of being red.
- Do red cars crash because they are sports cars, or do sports cars crash because they are red?

Let's stratify by car type:

- Suppose red sports cars have RR=2 of crashing compared with other colours of sports cars.



- Suppose red non-sports cars have RR=2 of crashing compared with other colours of non-sports cars.

Can we now agree this is causal…?

Can we now agree this is causal…?

- However, suppose red ceased to be fashionable 7 years ago.

- Do red cars crash because they are old, or do old cars crash because they are red?

A confounder…

- is a risk factor for the disease and is correlated with the exposure.

- It results in a distorted risk estimate simply because of the mixture of people in the study population.

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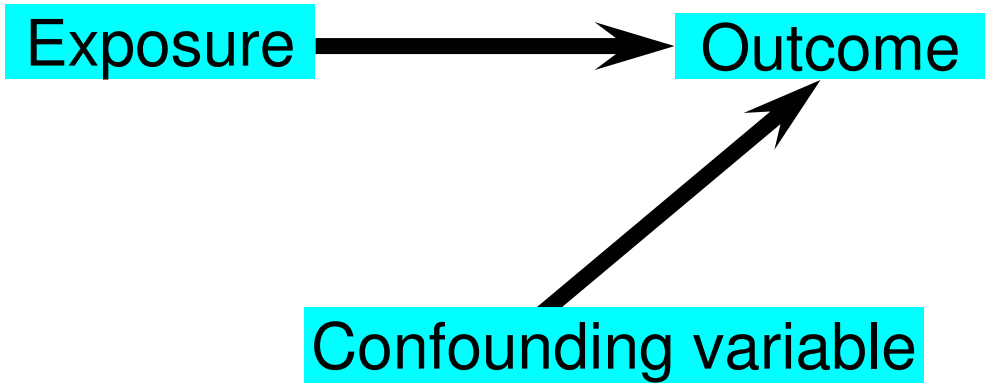
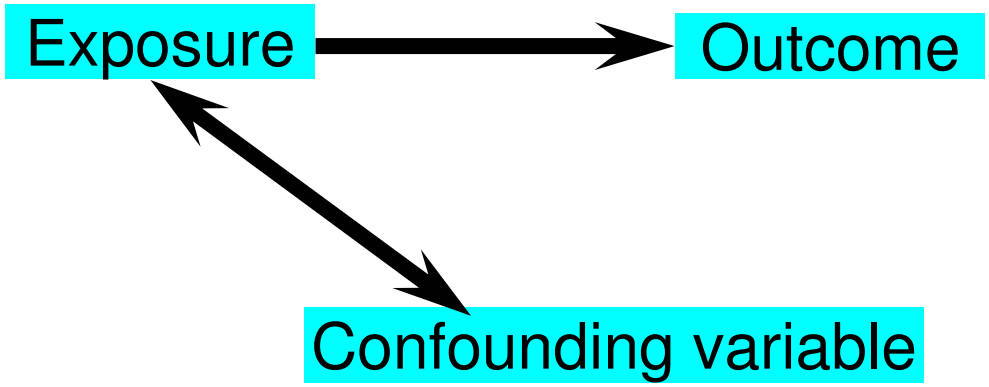
Criteria for confounders

- Associated with the disease independent of exposure



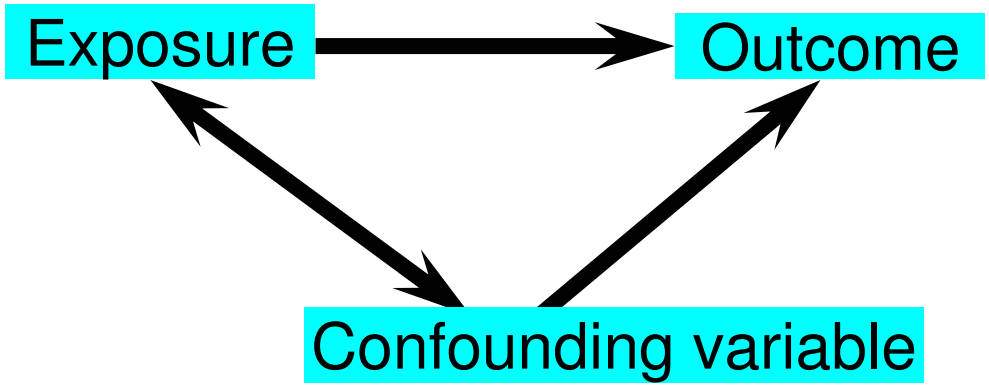
Criteria for confounders

- Associated with the disease independent of exposure
- Associated with the exposure independent of the disease

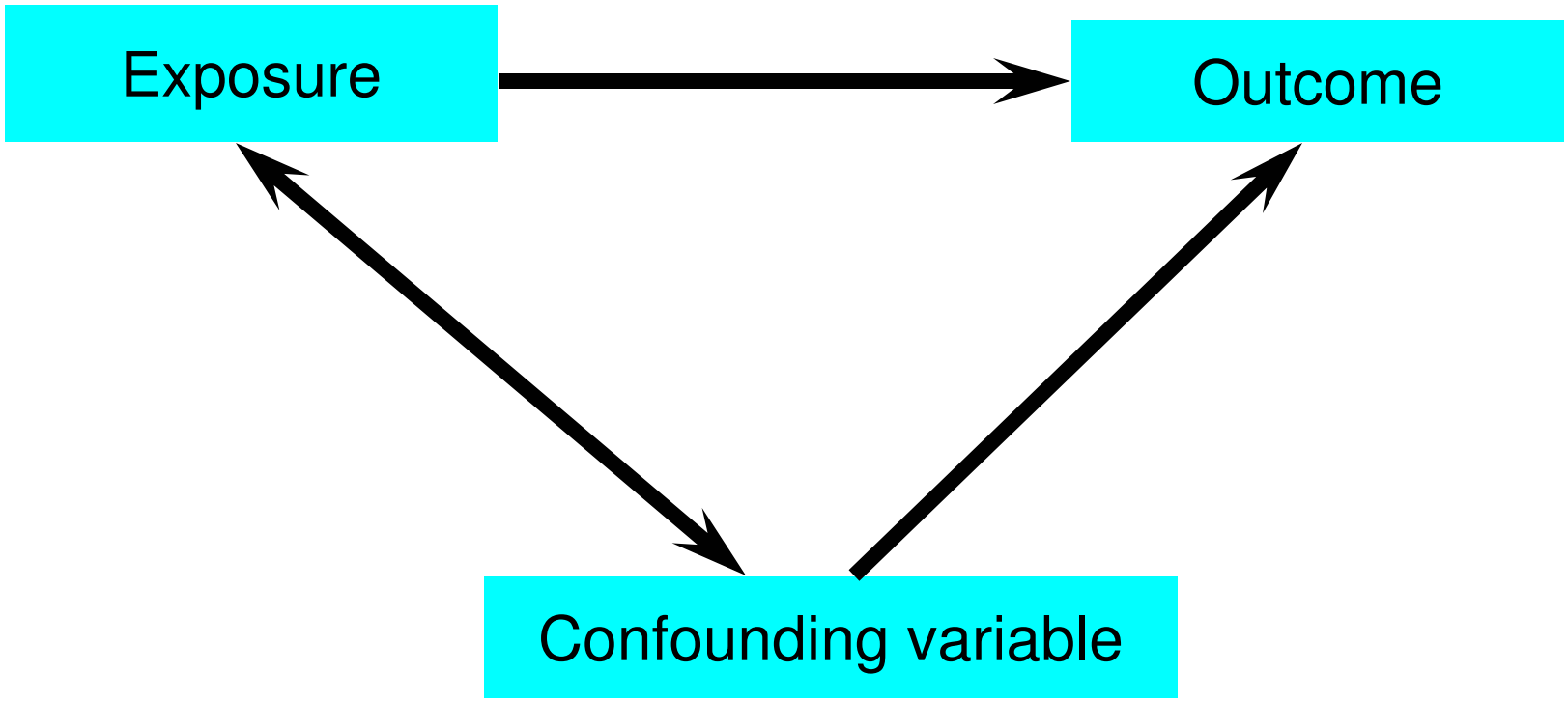


Criteria for confounders

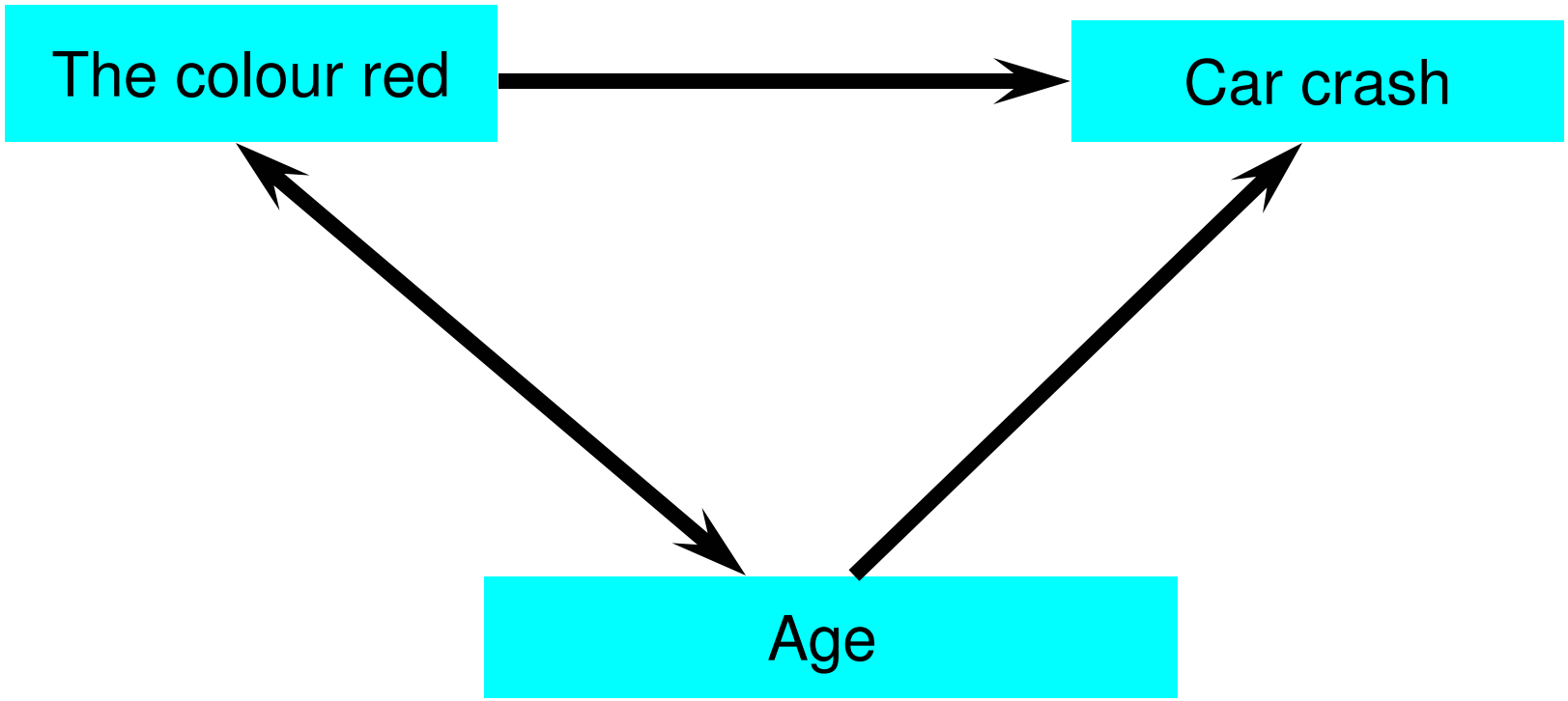
- Associated with the disease independent of exposure
- Associated with the exposure independent of the disease
- Not in the causal pathway from exposure to disease



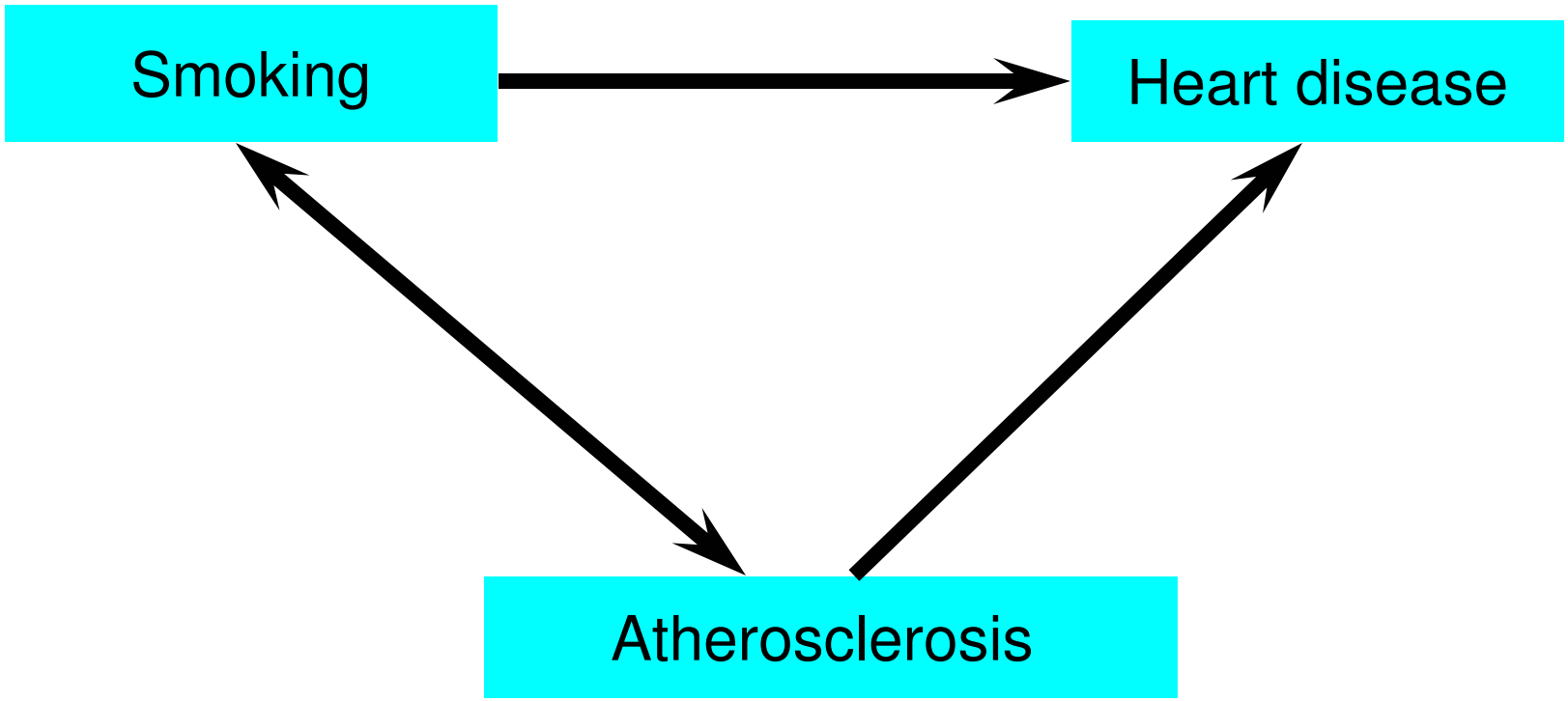
Confounding



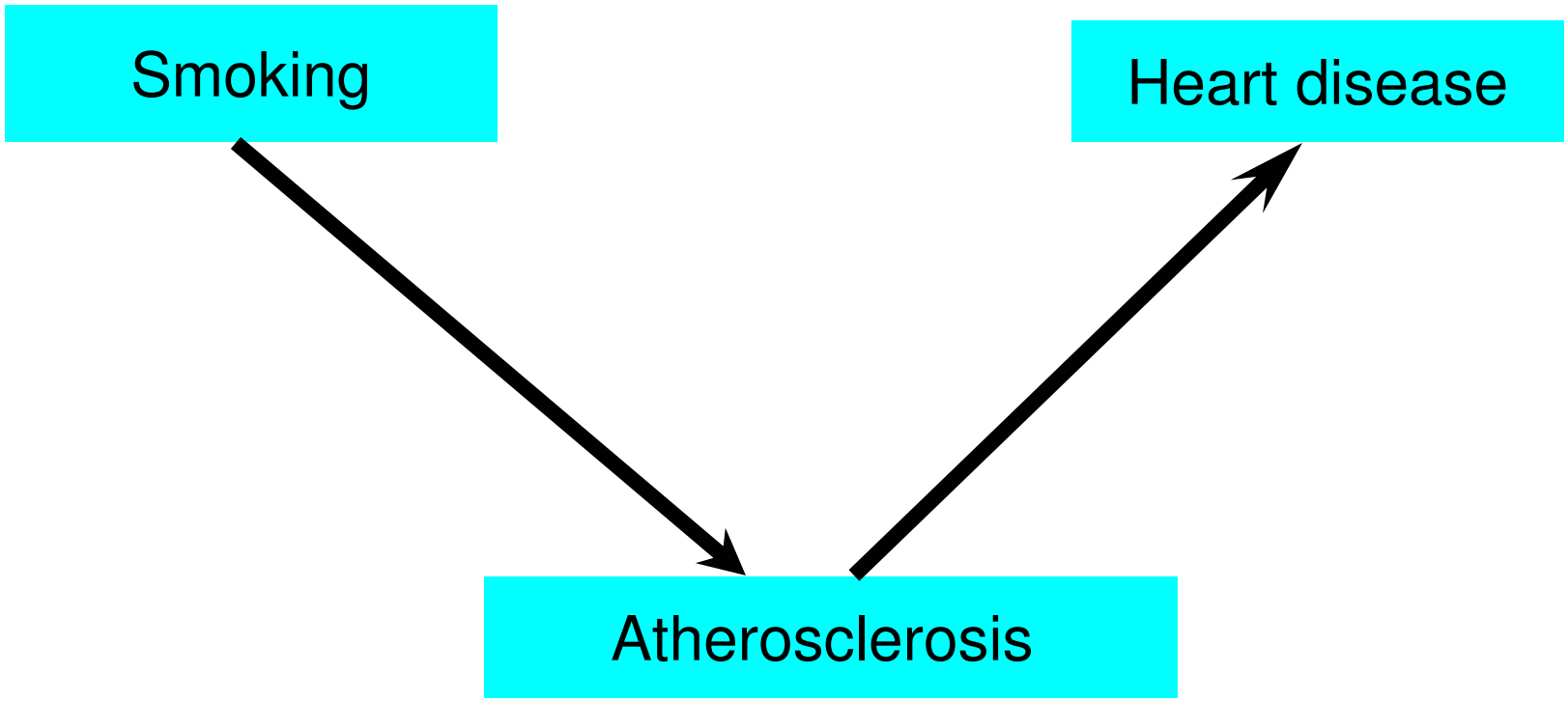
Confounding



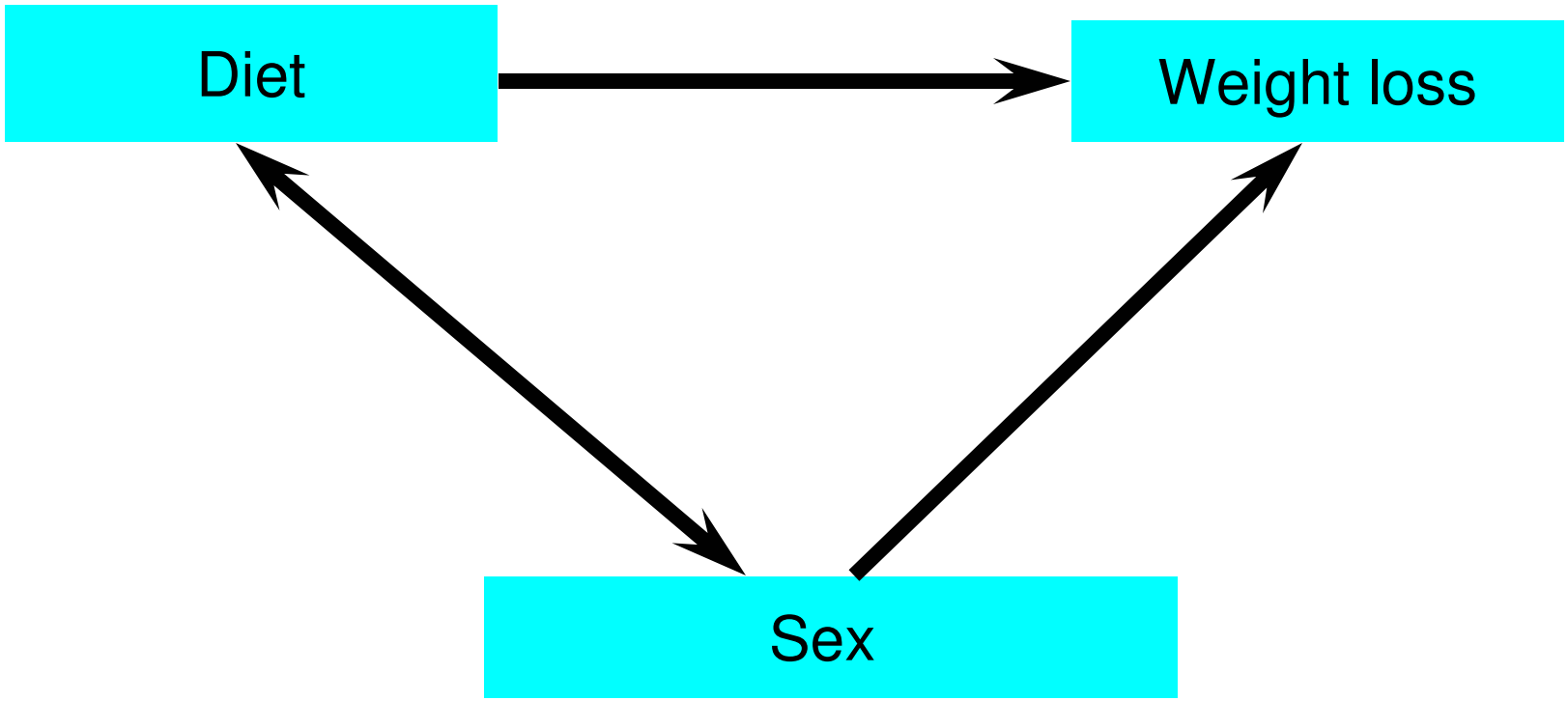
Confounding?



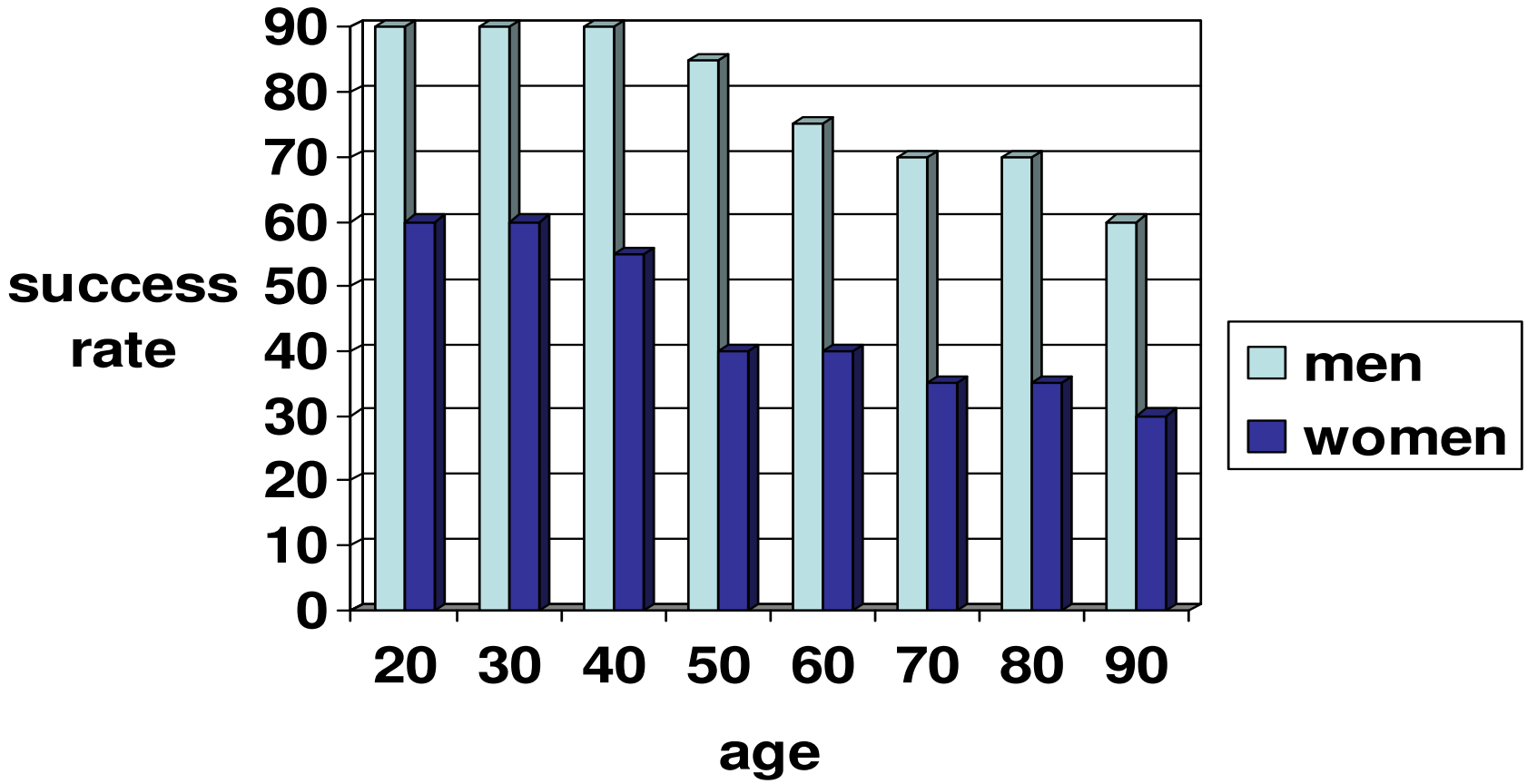
Atherosclerosis is in the causal pathway:



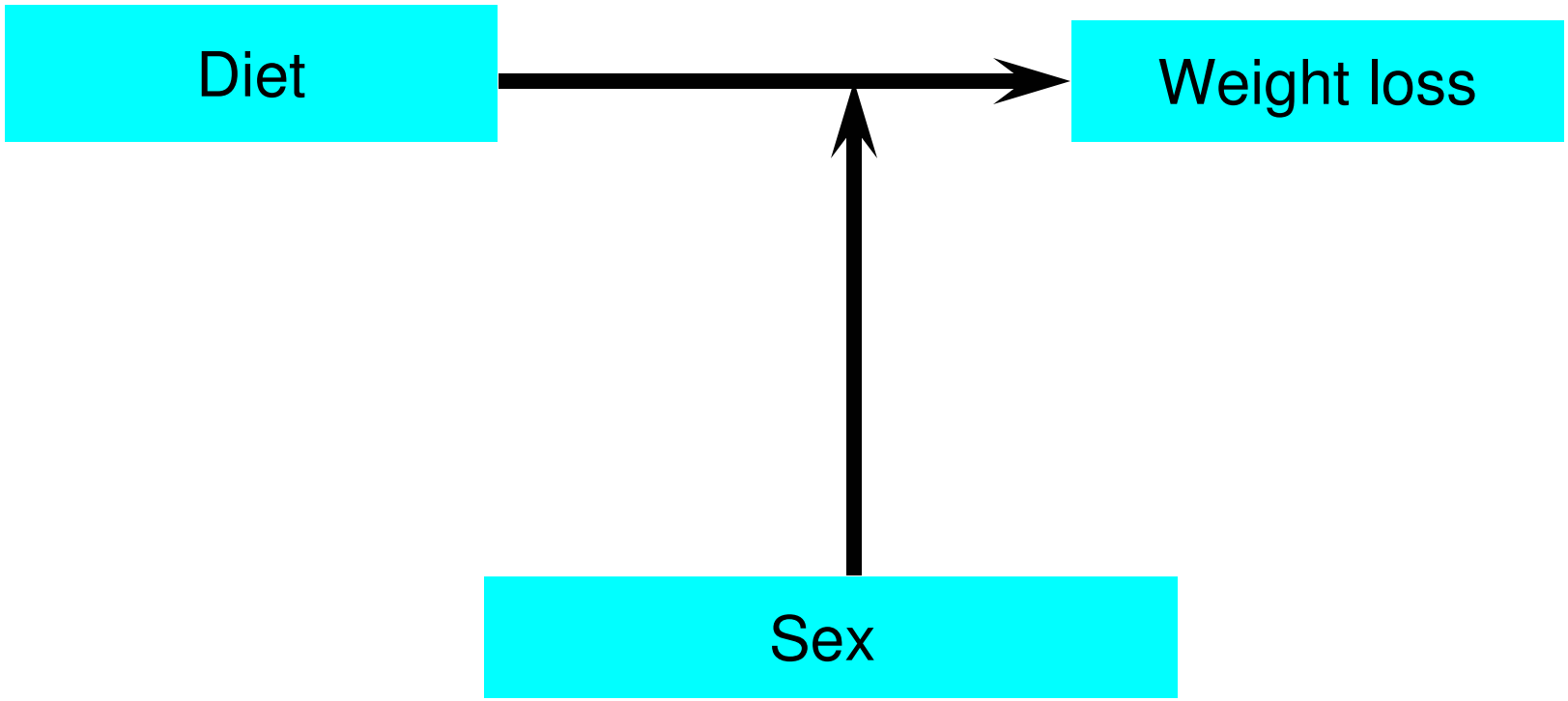
Confounding?



Diet and weight loss



Sex is an effect modifier:



Effect modifier

- Effect modification occurs when the effect of the exposure is different in different groups of the population
- A factor that modifies the effect of a putative causal factor under study
- There is no average ‘true value’

	cases	controls
exposed	60	80
unexposed	140	720

OR =

	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

TOTAL	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

Stratified by sex

MEN	cases	controls
exposed	20	40
unexposed	80	360

TOTAL	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

Stratified by sex

MEN	cases	controls
exposed	20	40
unexposed	80	360

OR = (20*360) / (80*40) = 2.25

TOTAL	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

Stratified by sex

MEN	cases	controls
exposed	20	40
unexposed	80	360

OR = (20*360) / (80*40) = 2.25

WOMEN	cases	controls
exposed	40	40
unexposed	60	360

TOTAL	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

Stratified by sex

MEN	cases	controls
exposed	20	40
unexposed	80	360

OR = (20*360) / (80*40) = 2.25

WOMEN	cases	controls
exposed	40	40
unexposed	60	360

OR = (40*360) / (60*40) = 6.00

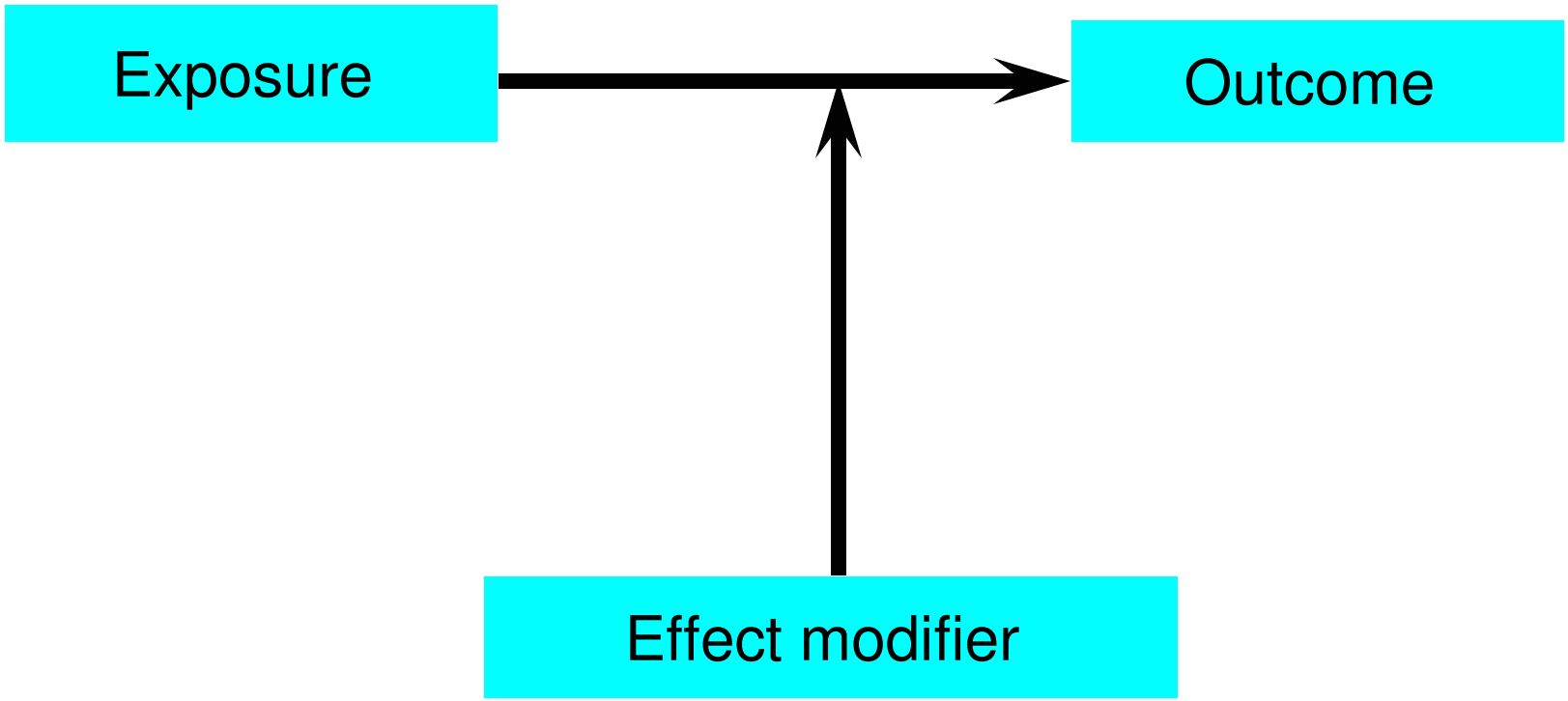
TOTAL	cases	controls
exposed	60	80
unexposed	140	720

OR = (60*720) / (140*80) = 3.86

Effect modifier

- Effect modification occurs when the effect of the exposure is different in different groups of the population
- A factor that modifies the effect of a putative causal factor under study
- There is no average ‘true value’
- Examples can be sex, genetics, age
- Results are usually best presented stratified

Effect modification



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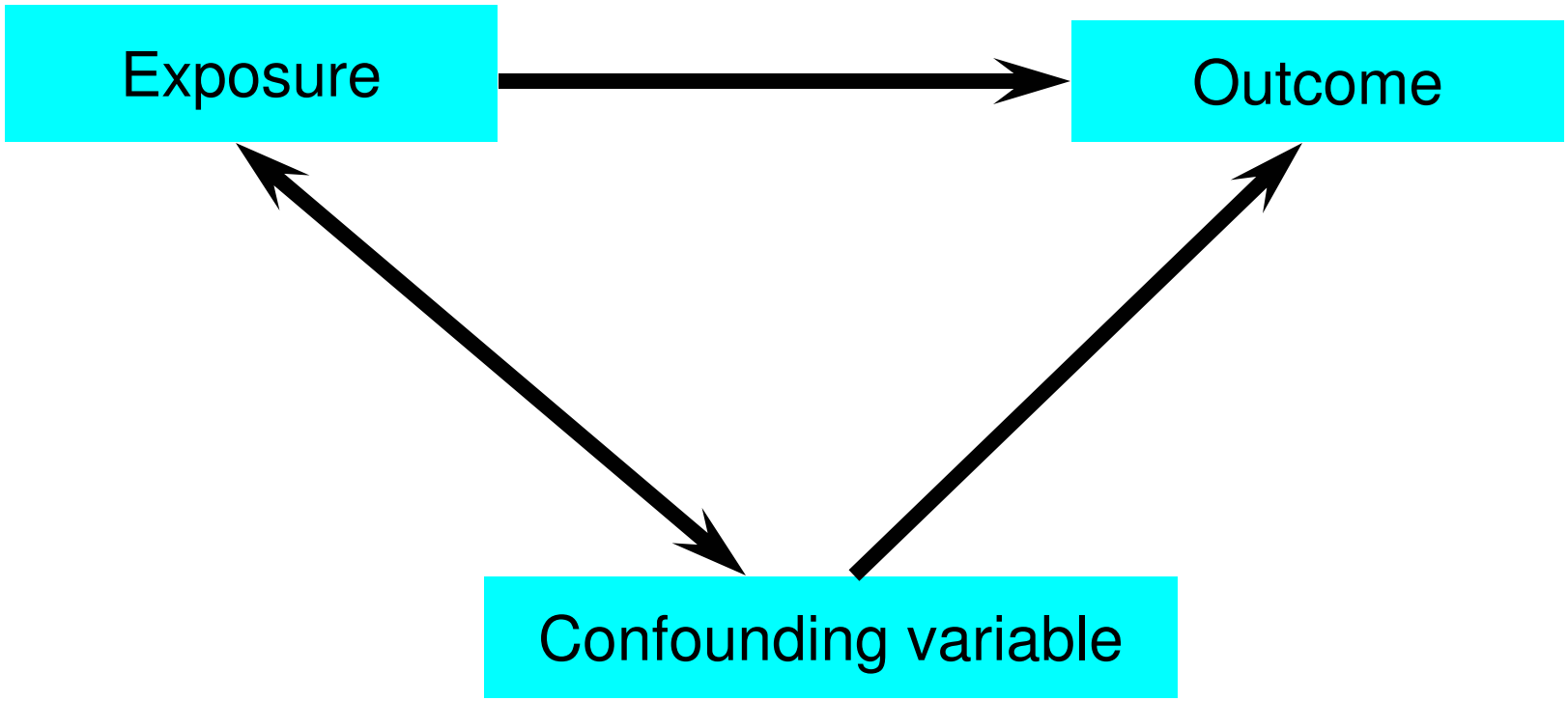


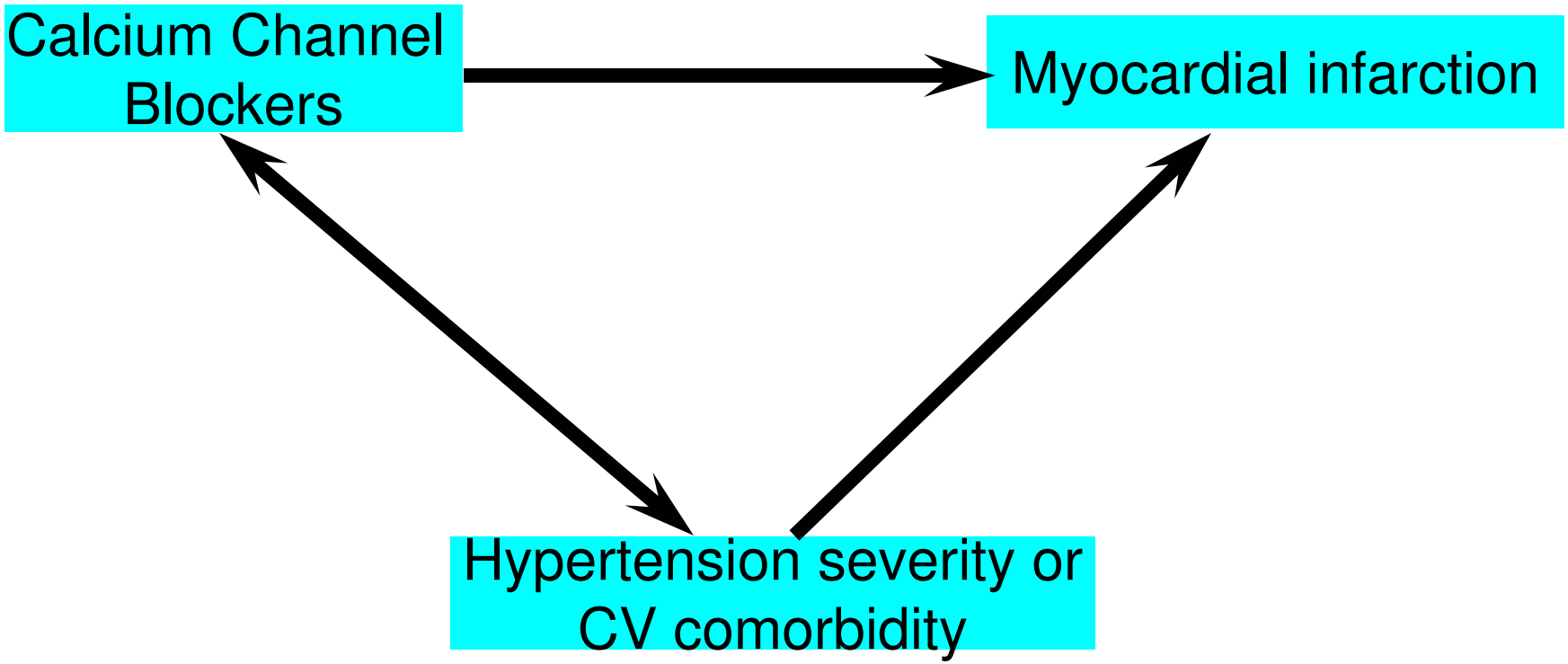
Confounding by indication

- The clinical condition that determines drug selection is linked to the outcome

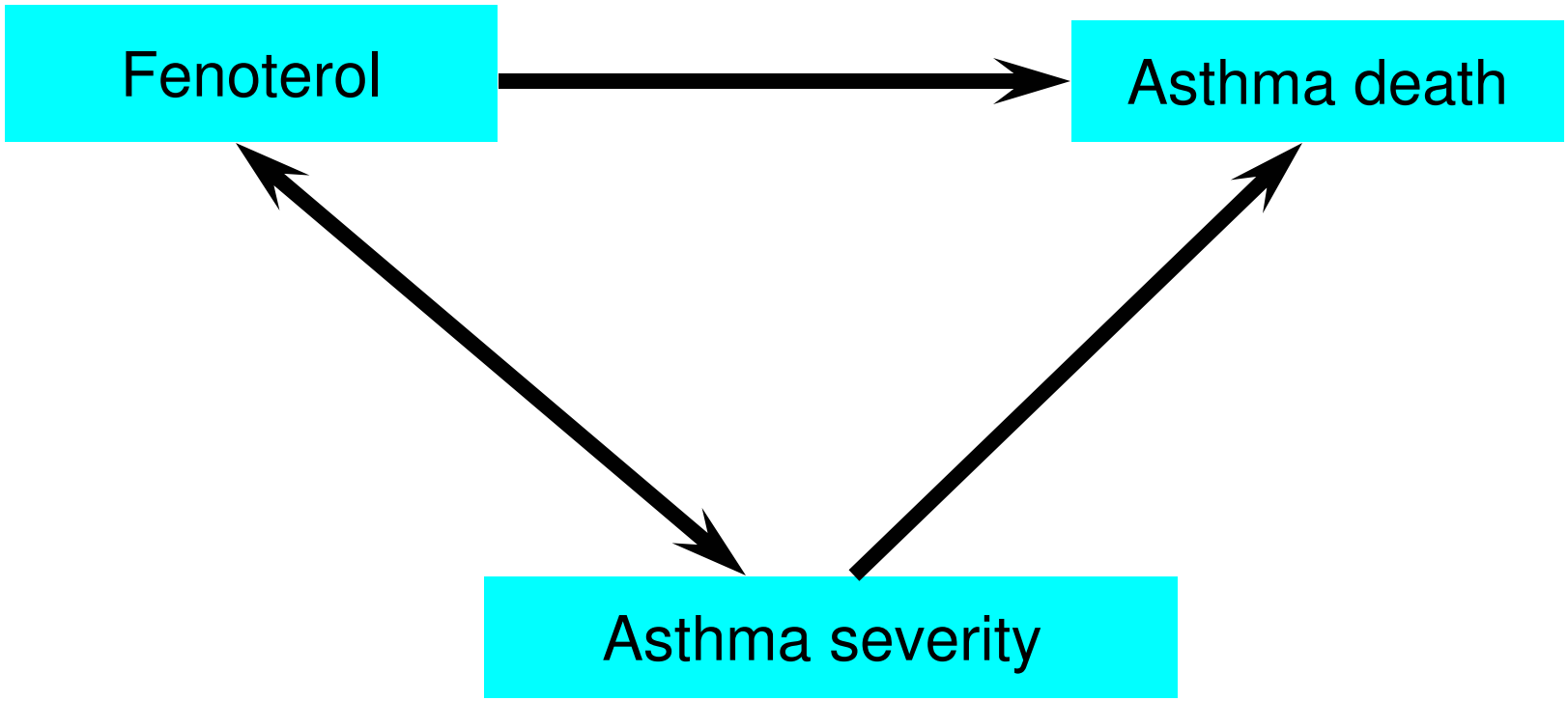
Confounding by indication

- The clinical condition that determines drug selection is linked to the outcome
- Perceived high risk or poor outcome is an indication for the intervention

Confounding by indication



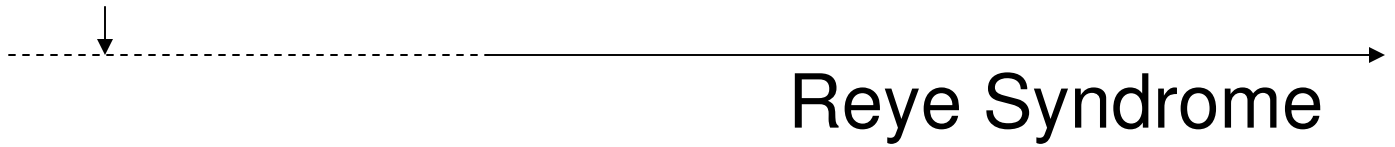
Confounding by indication



PROTOPATHIC BIAS

The first symptoms of the outcome of interest are the reasons for the prescription of the drug **and** the outcome of interest

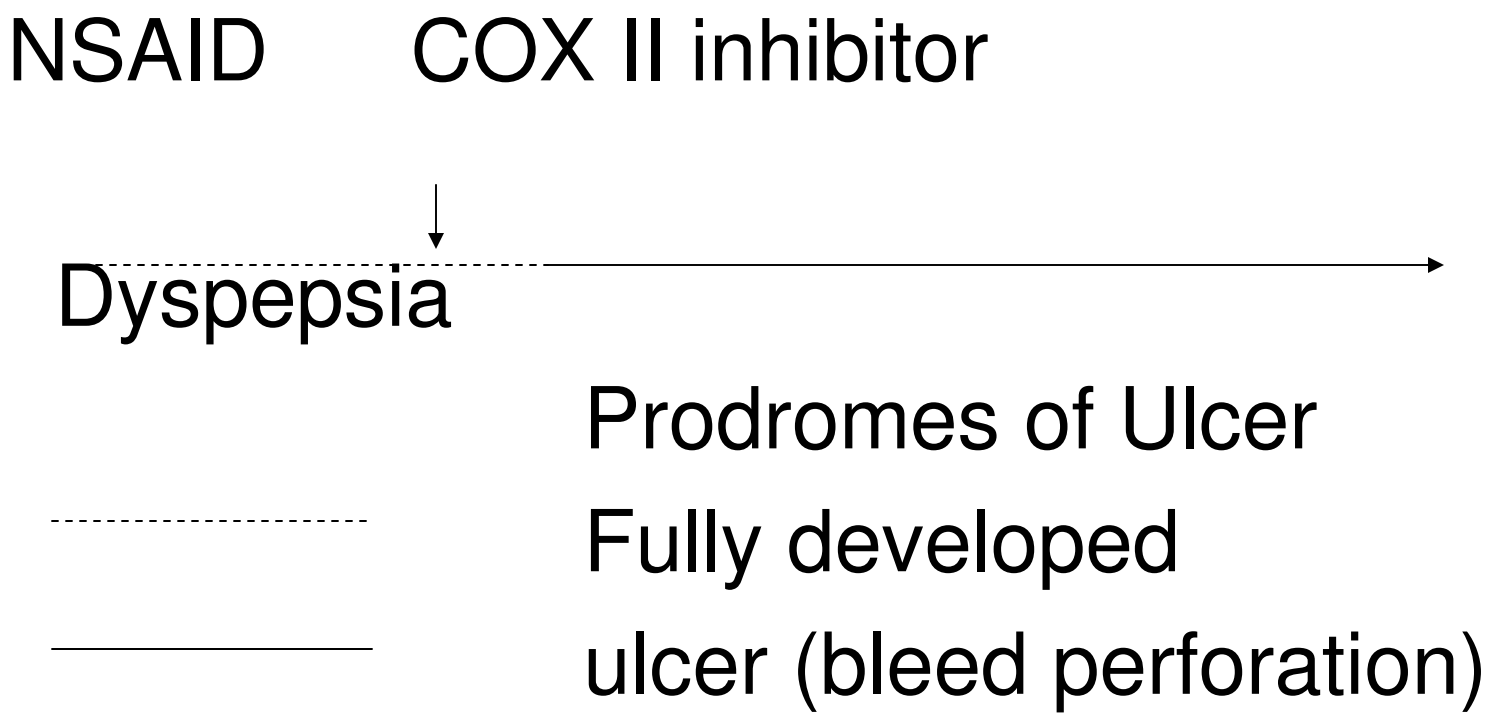
ASA

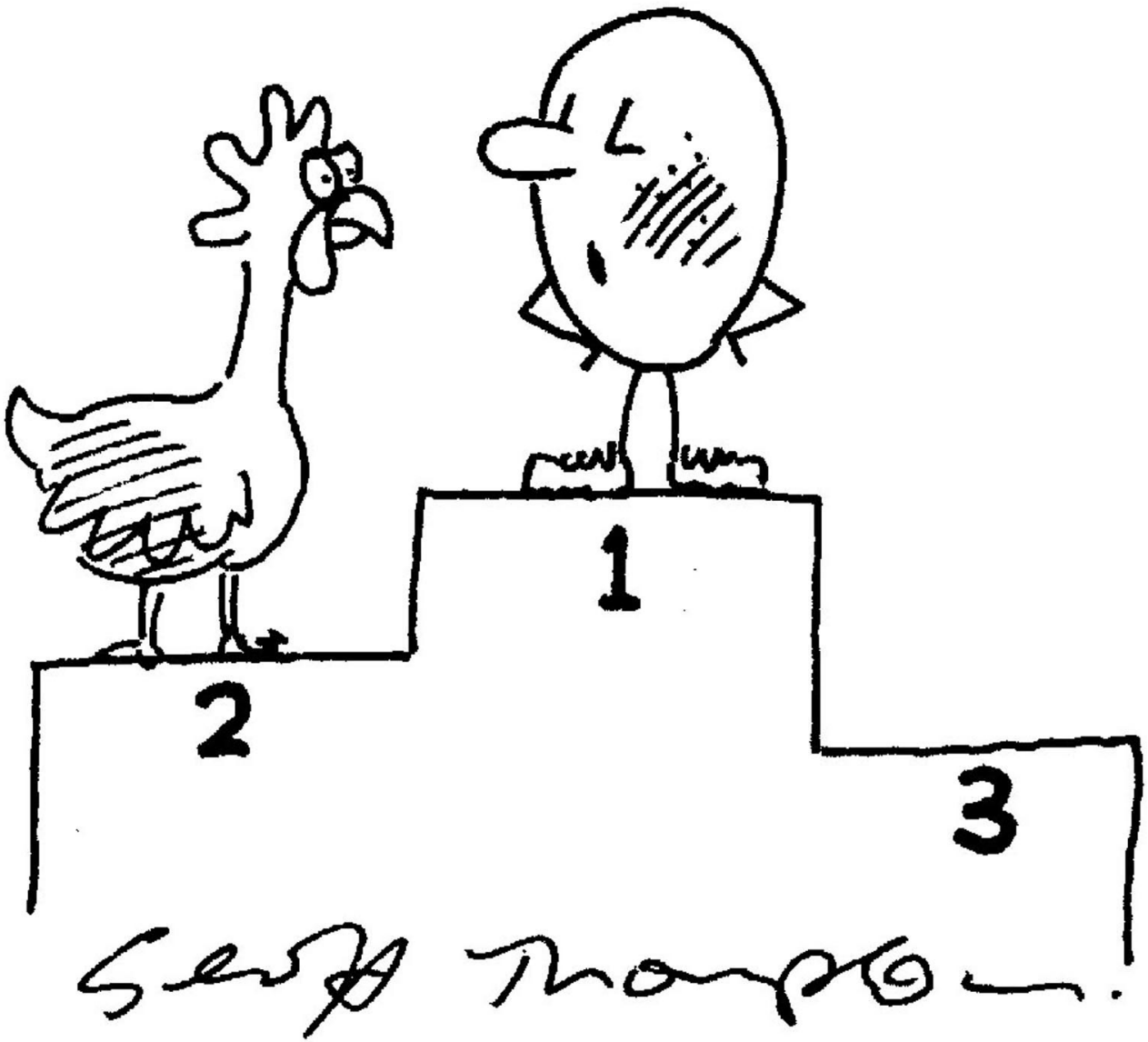


Prodrome

Fully Symptomatic Disease

PROTOPATHIC BIAS





"I hope we're not going to have
the same old argument."

How to address confounding

- Get your facts first, and then you can distort them as much as you please

Mark Twain

How to address confounding

- Get your facts first, and then you can distort them as much as you please

  Mark Twain

- The trouble with facts is that there are so many of them

  Samuel McChord Crothers

How to address confounding

- Find out whether determinants of treatment choice are associated with the outcome

We often assume that

- Doctors do a history
- Doctors perform a physical exam
- Doctors think
- Doctors have an arsenal of several drugs from which they choose the most appropriate according to the patients clinical condition

Oxford levels of evidence

- Class 0 RCTs
- Class 0a non-randomised / non blinded trials
- Class 1 Cohort studies
- Class 2 Case-control studies
- Class 3 Case series
- Class 4 Case reports

Doctor's levels of belief

- Class 0 Things I believe
- Class 0a Things I believe despite the available data
- Class 1 RCTs that agree with what I believe
- Class 2 other prospectively collected data
- Class 3 expert opinion
- Class 4 RCTs that don't agree with what I believe
- Class 5 What you believe and I don't

BMJ 2004;329:1473

How to address confounding

- Find out whether determinants of treatment choice are associated with the outcome
  - Cannot be done staying behind a computer screen
  - Might be misleading if obtained from (academic) super-specialists
  - Might vary in different countries

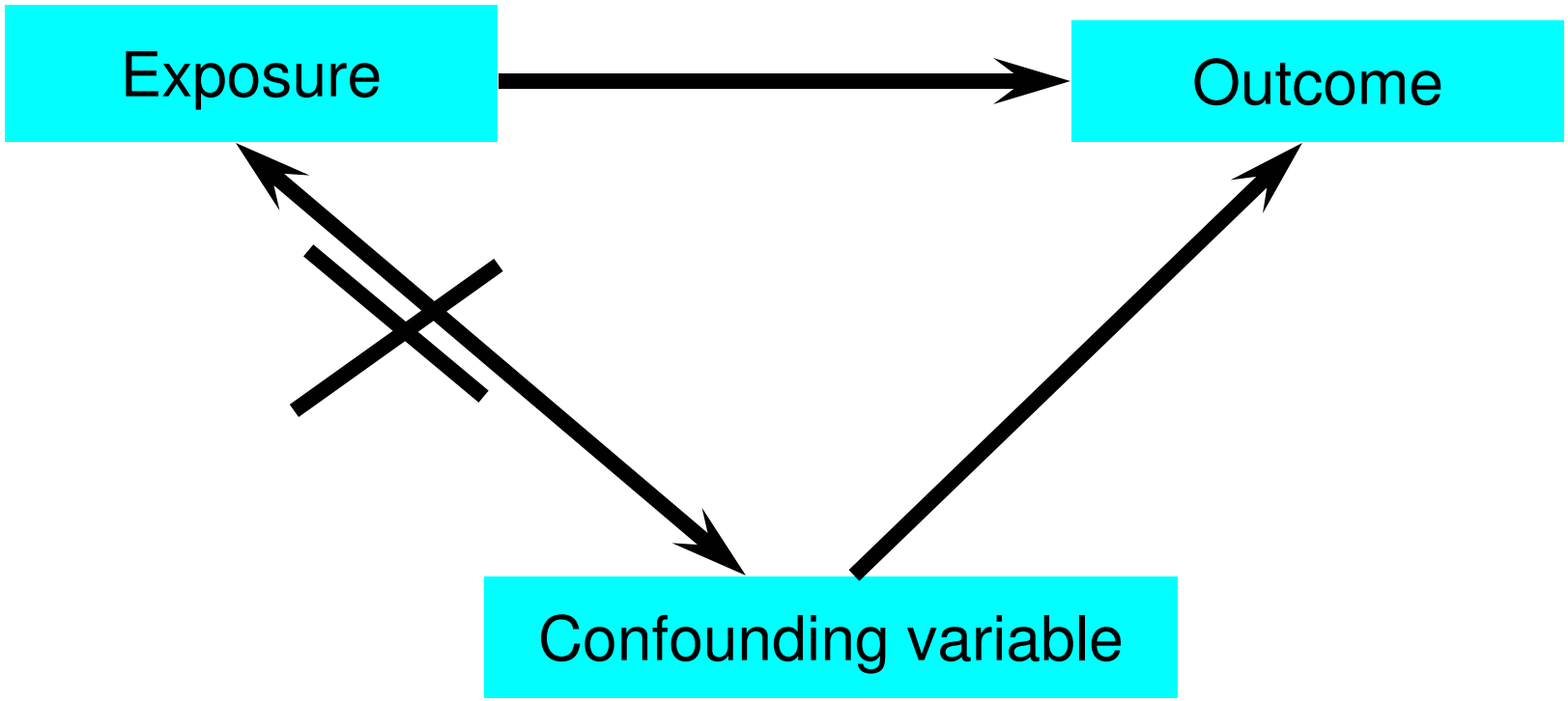
How to address confounding

- Find out whether determinants of treatment choice are associated with the outcome
- Random allocation
- Restriction
- Stratification
- Matching
- Mathematical modelling

restriction

- In/exclusion of subjects based on status of confounders
- E.g. include men only
- Advantages:
  - Eliminates confounding

Confounding



restriction

- In/exclusion of subjects based on status of confounders
- E.g. include men only
- Nested study
- Advantages:
  - Eliminates confounding
  - Easy and intuitive
- Disadvantages:
  - Limits generalisability

Stratification

- Separating a sample into several sub-samples according to specified criteria

	cases	controls
exposed	85	220
unexposed	115	580

	cases	controls
exposed	85	220
unexposed	115	580

OR = (85*580) / (115*220) = 1.95

Stratified by age

YOUNG	cases	controls
exposed	10	120
unexposed	40	480

OR =

OLD	cases	controls
exposed	75	100
unexposed	75	100

OR =

TOTAL	cases	controls
exposed	85	220
unexposed	115	580

OR = (85*580) / (115*220) = 1.95

Stratified by age

YOUNG	cases	controls
exposed	10	120
unexposed	40	480

OR = (10*480) / (40*120) = 1.00

OLD	cases	controls
exposed	75	100
unexposed	75	100

OR = (75*100) / (75*100) = 1.00

TOTAL	cases	controls
exposed	85	220
unexposed	115	580

OR = (85*580) / (115*220) = 1.95

A confounder…

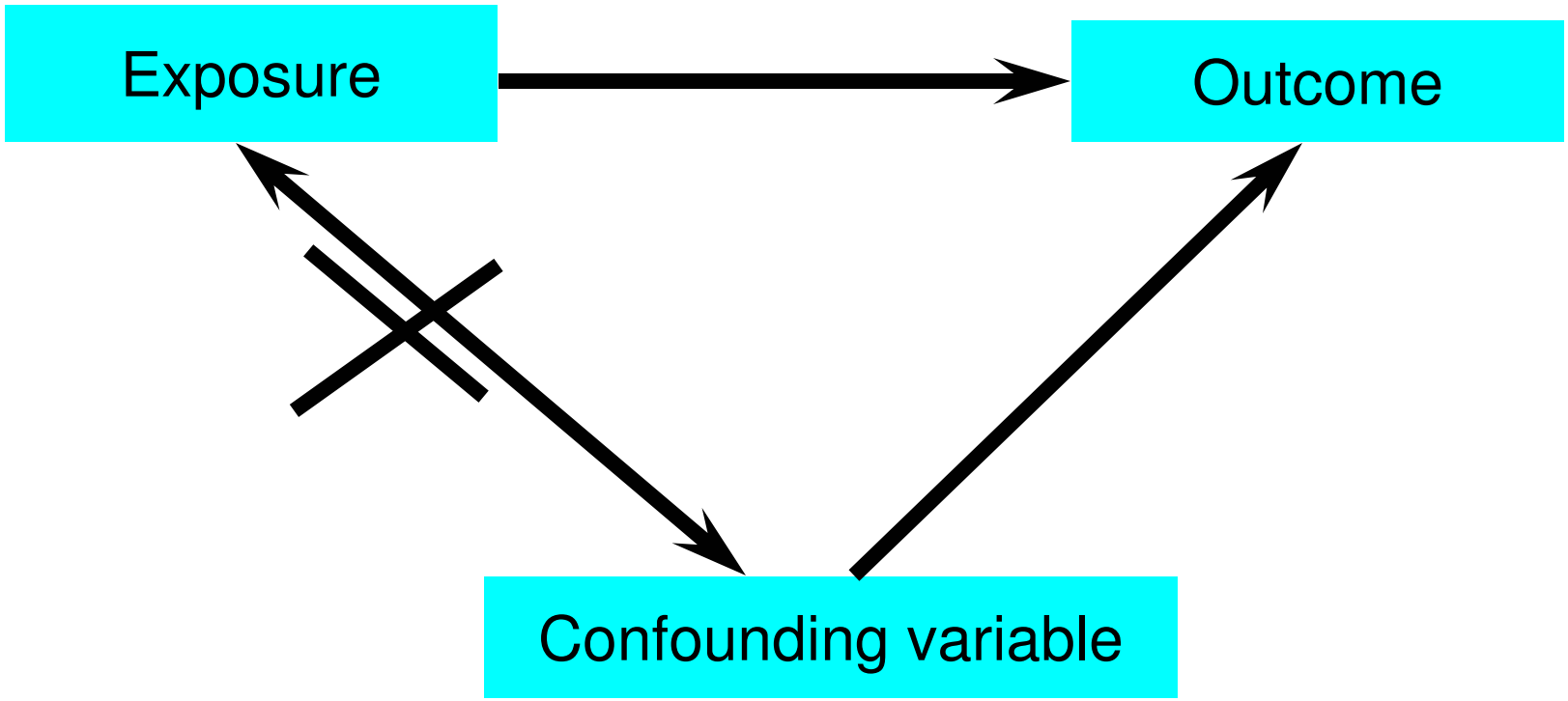
- is a risk factor for the disease and is correlated with the exposure.

- It results in a distorted risk estimate simply because of the mixture of people in the study population.

Stratification

- Separating a sample into several sub-samples according to specified criteria
- Can accommodate one, maybe two factors at a time

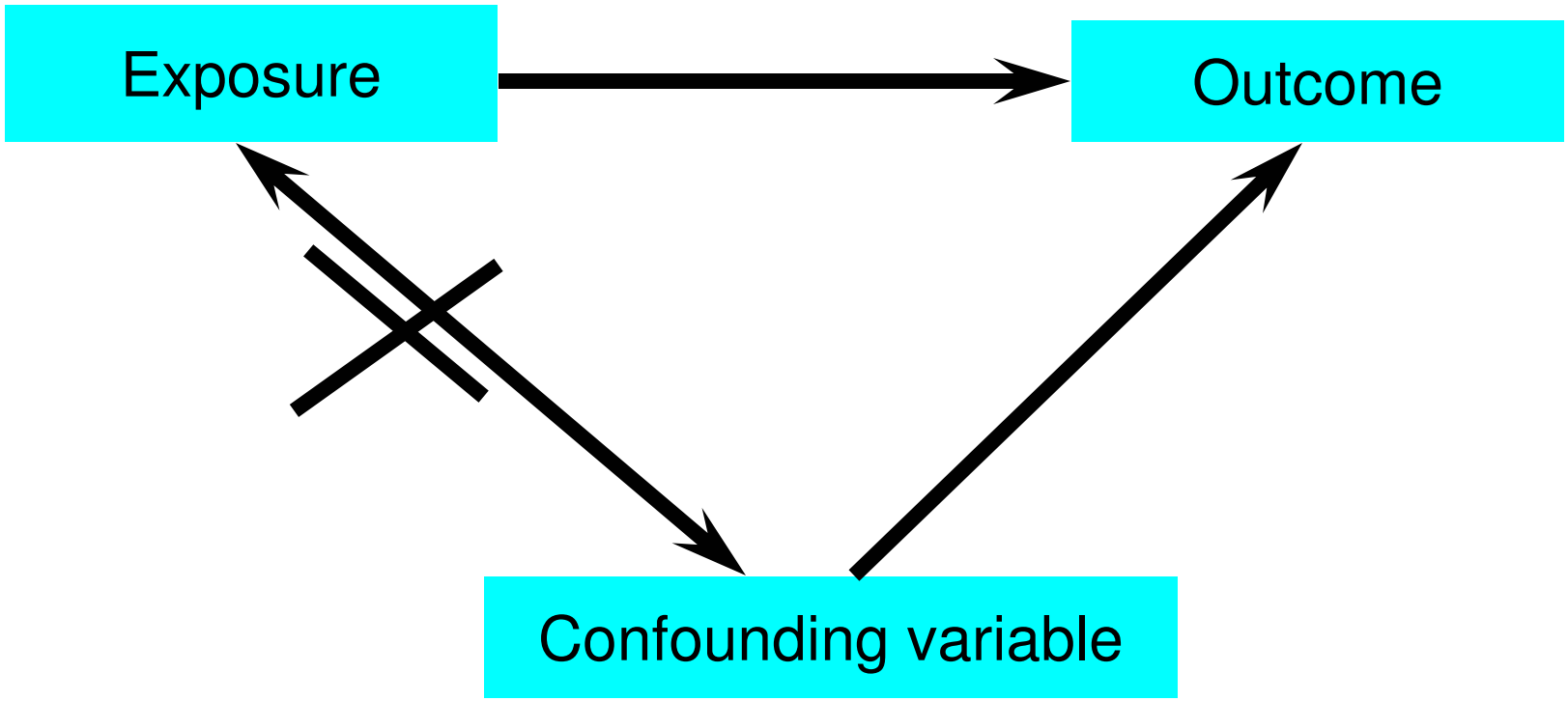
Confounding



Matching

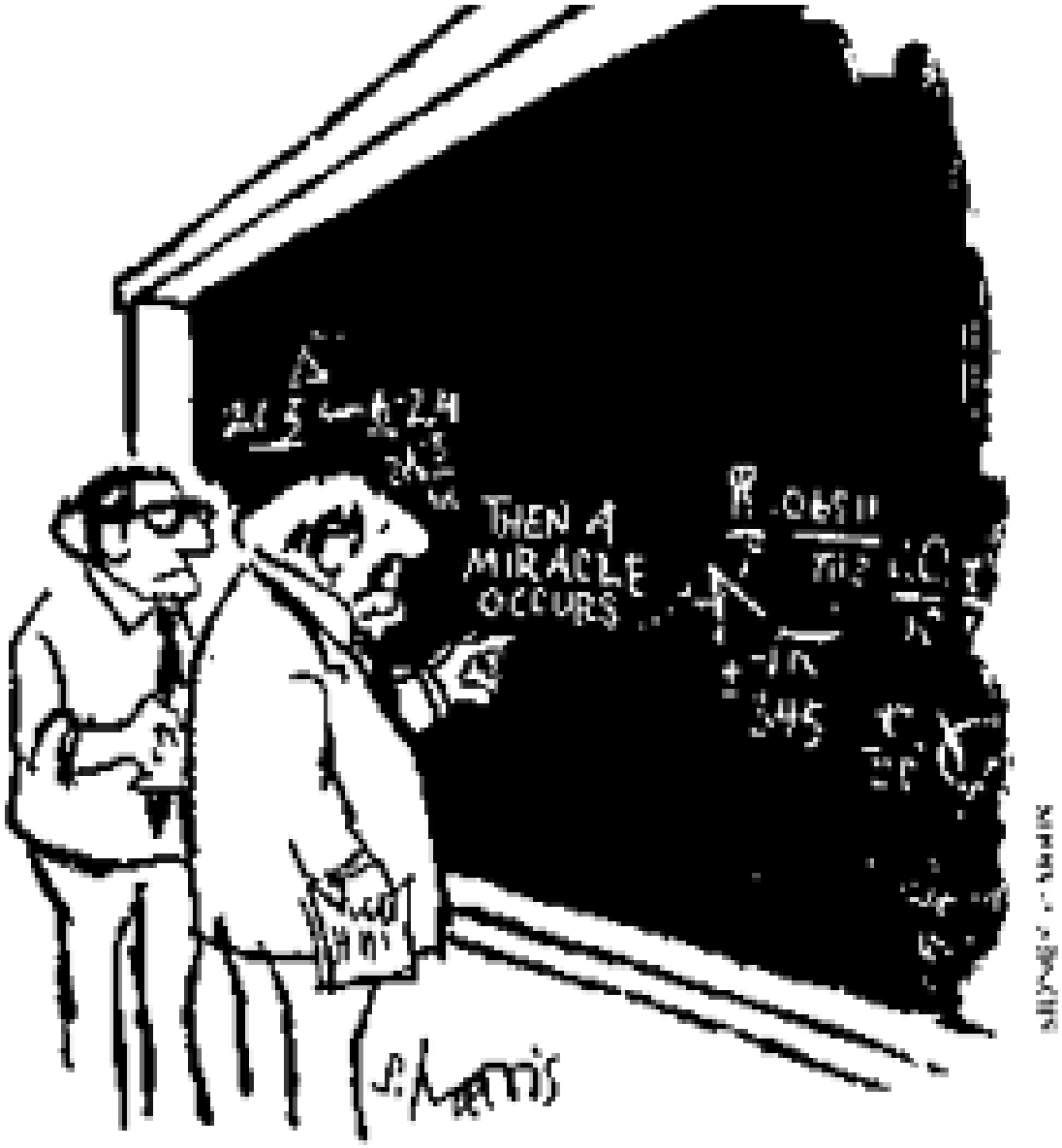
- Employment of constraints in the comparison group in order to make it more similar to the index group with respect to the distribution of one or more confounders
- Increases power
- Limits generalisability
- Risk of overmatching

Confounding



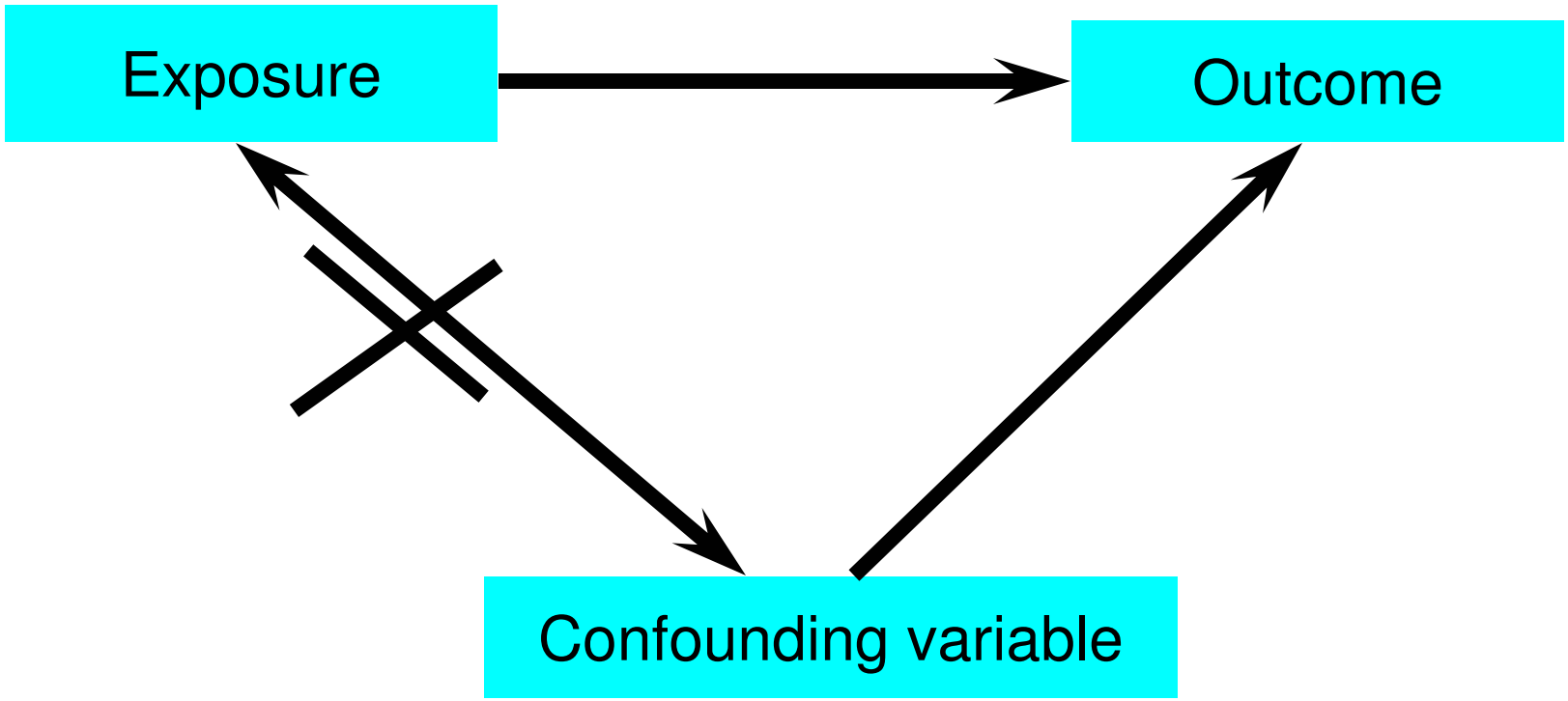
Mathematical modelling

- Logistic regression (conditional / unconditional)
- Cox proportional hazards
- Propensity scores

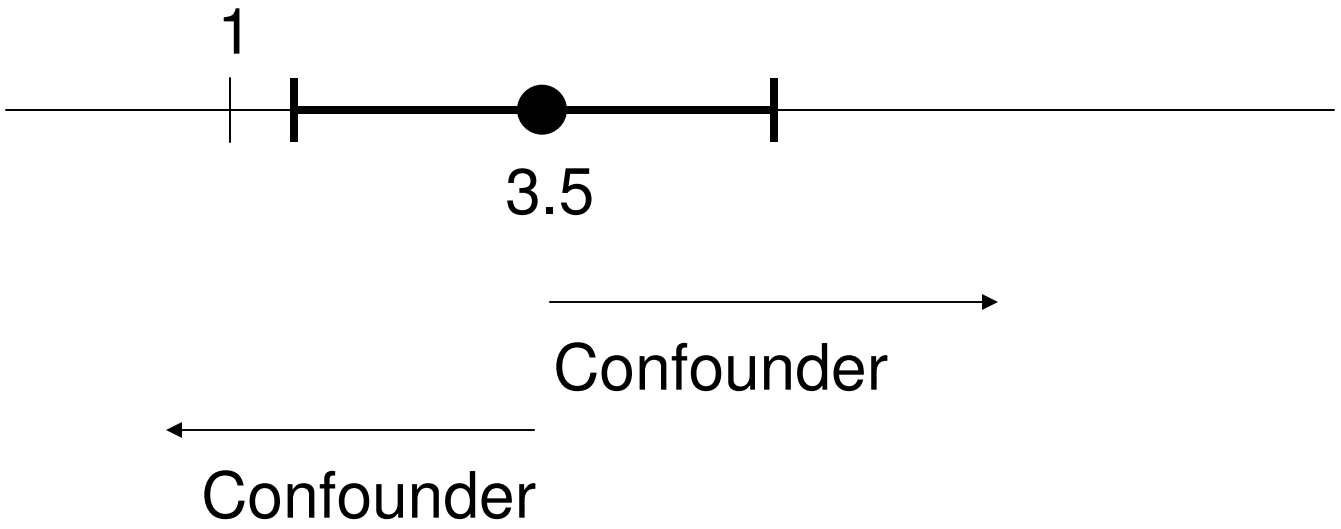


"I THINK YOU SHOULD BE
MORE EXPLICIT HERE IN STEP TWO"

Confounding



In which direction does the confounder « pull » the risk ratio?



- Magnitude ?

Conclusions

- Unmeasured confounding is the most serious limitation to observational studies
- In cohort studies, select an unexposed group as similar to the exposed as possible
- A variety of methods are available to account for measured confounders
  - Choice of method depends on context

Finally,

- The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge

Stephen Hawking

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- The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge

  Stephen Hawking

- Confounding by indication is the Achilles' heel of pharmacoepidemiology
- Every non-experimental study should be accompanied (preceded) by a drug utilisation study

Thank you!

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