Publication bias Causality

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Epidemiologie E0350

Publication bias

High-impact journals prefer clear, positive results!

Bias in systematic reviews

Form of selection bias arising if null studies are not published

If not included the overall estimate is biased upwards

Minimised by searching grey literature, trial registers and conference proceedings to include null/negative results

e.g. the ‘drug effectiveness cycle’ (ß-blocker-mortality example in session 7), selective serotonin reuptake inhibitors in treating depression

Publication bias

Failure to publish

- a negative or inconclusive trial result
- a small trial may be abandoned

Duplicate publication

- a large treatment effect
- need for research output

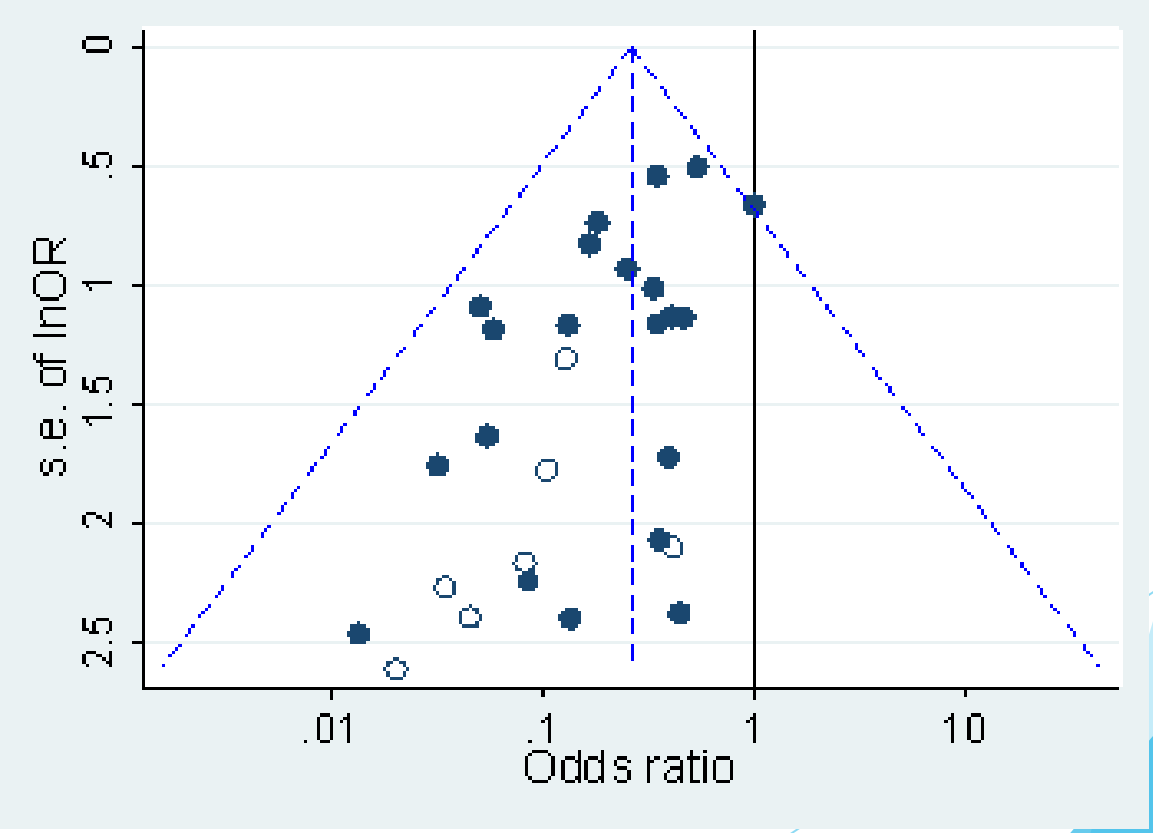
Eg. nine trials of ondansetron (antiemetic) in 23 publications (Tramer et al BMJ 1997)

How to avoid publication bias

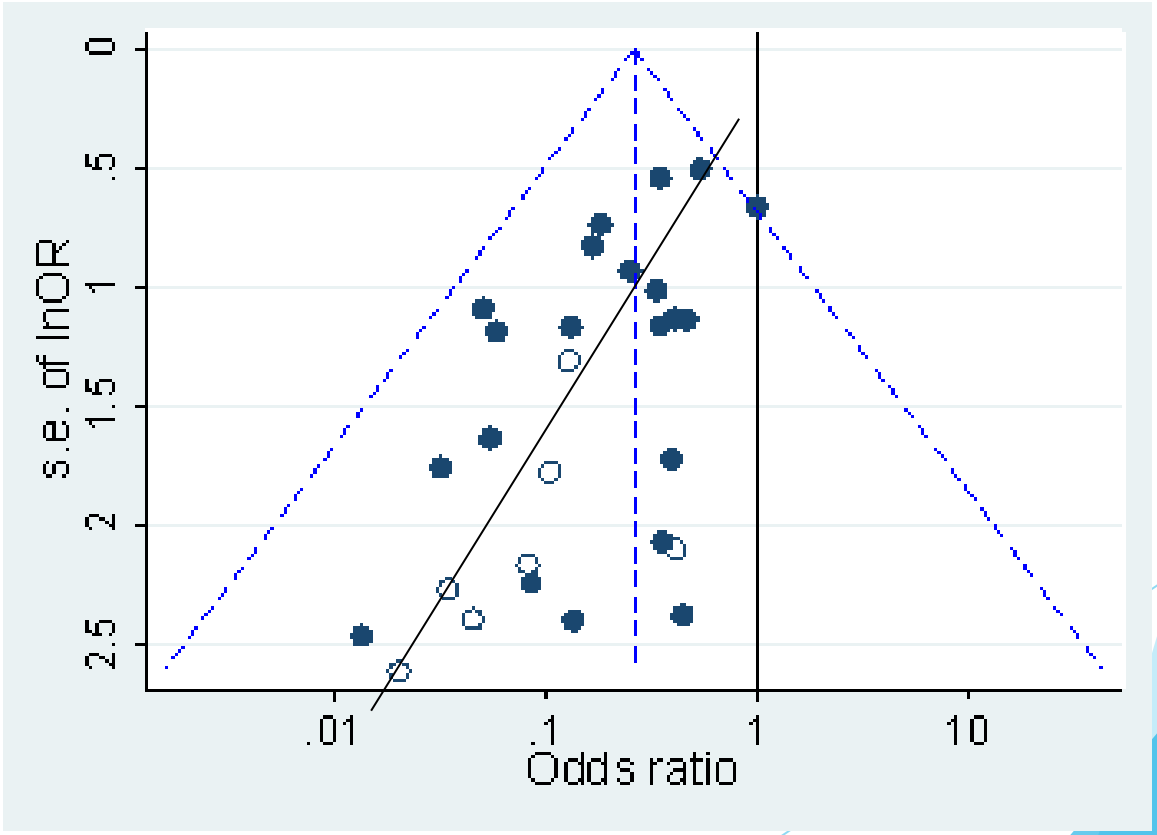
- To make sure studies are not double counted.
- To search for unpublished studies (e.g. contact researchers directly).
- To use non-English language publications.
- Statistical checking (funnel plots: smaller studies report more extreme results).
- Registration of studies and to make sure all results are in public domain (not yet fully achieved).
- Trial registration: assigns unique trial identification numbers, and to record other basic information about the trial so that essential details are made publicly available.
- From 2004 International Committee of Medical Journal Editors (ICMJE) would consider trials for publication only if they had been registered before the enrolment of the first participant.

Funnel plot:

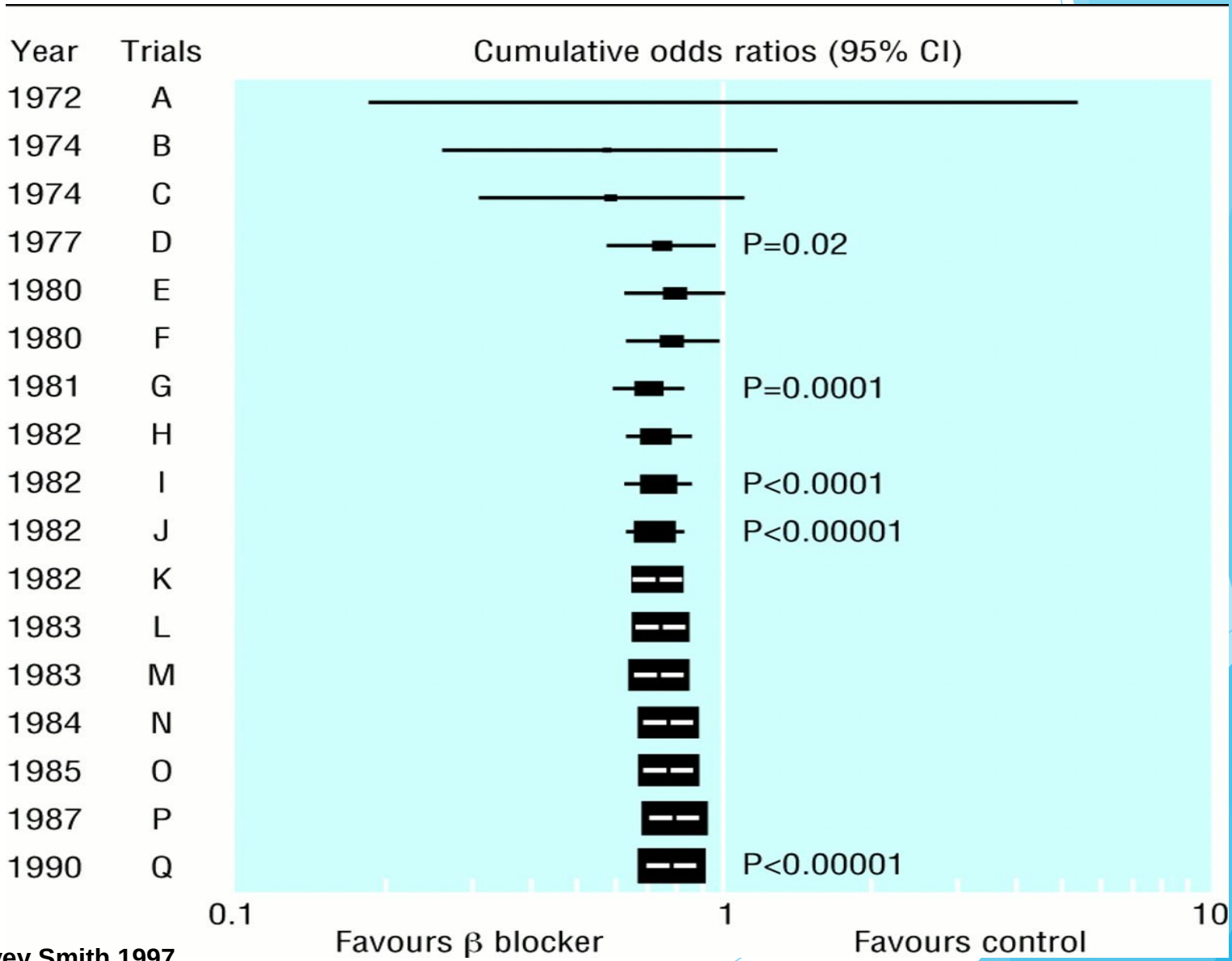
Asymmetrical plot in the presence of bias: some smaller studies (open circles) are of lower methodological quality and therefore produce exaggerated effect estimates



Funnel plot:



Beta-blockers and total mortality after MI: meta-analysis



Egger & Davey Smith 1997

Causality

1. We find an association between exposure and outcome

2. We need to ask whether the association is causal = **does the exposure cause the outcome?**

What is a cause?

Rothman (1986): Modern epidemiology:

An event, condition, or characteristic that plays an essential role in producing an occurrence of the disease.

- Something that has an effect
- Alters disease frequency or health status

Association versus Causation

- Epidemiological research aims to discover aetiology of disease.
- Epidemiology is the study of the association between a potential cause (risk factor/determinant) and a specific disease (outcome).
- Presence of a valid statistical association does not imply causality.
- Association is not the same as causation!
- Causation goes beyond association.
- When is there evidence in support of a causal association?

Criteria for causal inference (inferring causality)

Koch's postulates (1890)

1. The agent must be found in every case of disease, but should not be found in healthy organisms
2. The agent must be isolated from diseased host and grown in culture
3. The cultured agent should cause same disease when introduced into healthy host
4. The agent must be recovered from the new host and shown to be the same as the original agent

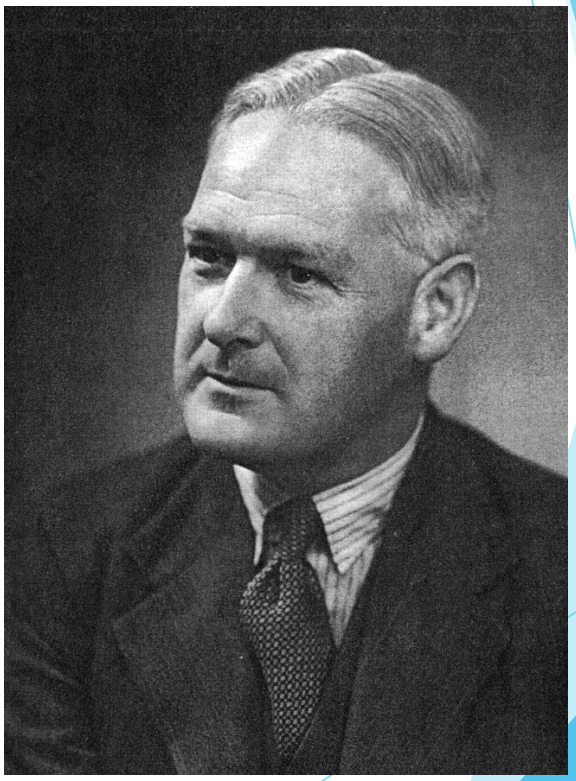
Potential issues:- (1) asymptomatic hosts, (2) not all grown in culture.

Satisfying Koch's postulates is sufficient, but not necessary to establish causation.

Sir Austin Bradford Hill (1897-1991)

Exposure and Disease: Association or Causation?

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Dose-response
6. Biological plausibility
7. Coherence
8. Reversibility



The Bradford-Hill criteria of causation (J Royal Soc Med 1965; 58: 295-300)

1. Bradford Hill Criteria Strength

- The stronger the association between exposure and outcome, the more likely it is to be a causal relationship (less likely to be due entirely to bias and confounding)
- A weak association does not rule out the possibility of causality

For example

- Effect measure for heavy smoking & lung cancer supported by p-value and narrow 95% CI

2. Bradford Hill Criteria Consistency

- Observing a relationship repeatedly improves the case for causation.
- Less likely that same biases present in all of them.
- A lack of consistency in one study does not rule out causality.
- Evidence of causation by replication of results
  - different samples, circumstances, study designs

For example

- Smoking and lung cancer – shown
- Oral contraceptives and breast cancer – not shown
- Meta-analysis - supportive

3. Bradford Hill Criteria Specificity

- Outcome is best predicted by one primary factor.
- One factor predicts one primary outcome.
- If demonstrated, adds evidence of causality.
- Lack of specificity does not negate causal association.

For example

- asbestos and mesothelioma – shown
- HIV and AIDS – shown
- Low lead exposure and IQ – not clear. IQ is not a definable brain condition so there is the potential for confounding e.g. SES

4. Bradford Hill Criteria Temporality

- Exposure must precede outcome. This is essential

What study design is appropriate to meet this criteria?

- **Optimal study design** = randomised intervention study or prospective cohort study
- **Weak design for temporality** = cross-sectional, case-control study

- Diseases with long latent periods can make it difficult to establish temporality

5. Bradford Hill Criteria
Biological gradient (dose-response)

- Gradient or dose-response relationship between exposure & outcome.
- Lack of a biological gradient does not rule out causality.
- Beware of threshold dose – outcome associations
- J or U shaped associations

Example - Persons who have increasingly higher exposure levels have increasingly higher risks of disease.

Smoking Status	Lung Cancer risk
None	1.0
Ex-smoker	1.1 (0.7-1.6)
1-20 per day	2.6 (1.7-4.0)
20-40 per day	4.4 (2.8-6.9)
40+ per day	6.8 (4.3-10.7)

6. Bradford Hill Criteria Biological Plausibility

- There is a rational biological basis for the observed association.
- The association supported by biological theory.
- No consensus on amount of evidence required.
- Not necessary, since the plausibility may yet to be discovered (depends on current knowledge).
- Weak criterion

For example

- Cigarettes & lung cancer. Carcinogenic substance.
- Low fibre diet & colon cancer. Dietary fibre increases intestinal motility and dilutes/absorbs fecal carcinogens.

7. Bradford Hill Criteria Coherence

- Reported association does not conflict with current knowledge.
- Can lead to publication bias.
- Can discourage search for alternative associations.
- Lack of coherence should not rule out causality.

Example of coherence

- Serum cholesterol lowering effect on heart attack, regardless of the means e.g. diet or drug

Note:- Coherence is subtly different to plausibility. Coherence – should not conflict, while plausibility – should be in line with knowledge.

8. Bradford Hill Criteria Reversibility (Experiment)

- Removing/reducing the potential causal factor reduces the risk of disease.
- Likelihood of the association being causal is strengthened by showing reversibility.
- Currently perceived as the strongest type of evidence.
- May be difficult to ascertain in diseases with long lag times between exposure and disease.

Examples

- Smoking cessation → lower risk of lung cancer?

Causal Inference

- Not just ticking boxes
- Weigh evidence of causal association against other explanations
- Understanding, judgement & interpretation
- Cannot prove a causal association
- Can only be inferred based on evidence
- May change in the light of new evidence

Reverse causality

- Refers to the possibility that the link between exposure and outcome is a result of the disease or disease process being studied, not the exposure.

- Reverse causality is a type of confounding in the sense that it is ‘real’ and not an artefact of study design.

Example of potential reverse causality

Researchers are interested in the link between blood levels of inflammatory markers and later CVD

There are 4 possible explanations:

1. Inflammation → atherosclerosis (causal association)
2. Atherosclerosis → inflammation (reverse causal association)
3. Inflammation ←→ atherosclerosis (association is bi-directional)
4. Other processes lead both to atherosclerosis and inflammation (confounding) e.g. diet

Causation and Public health policy

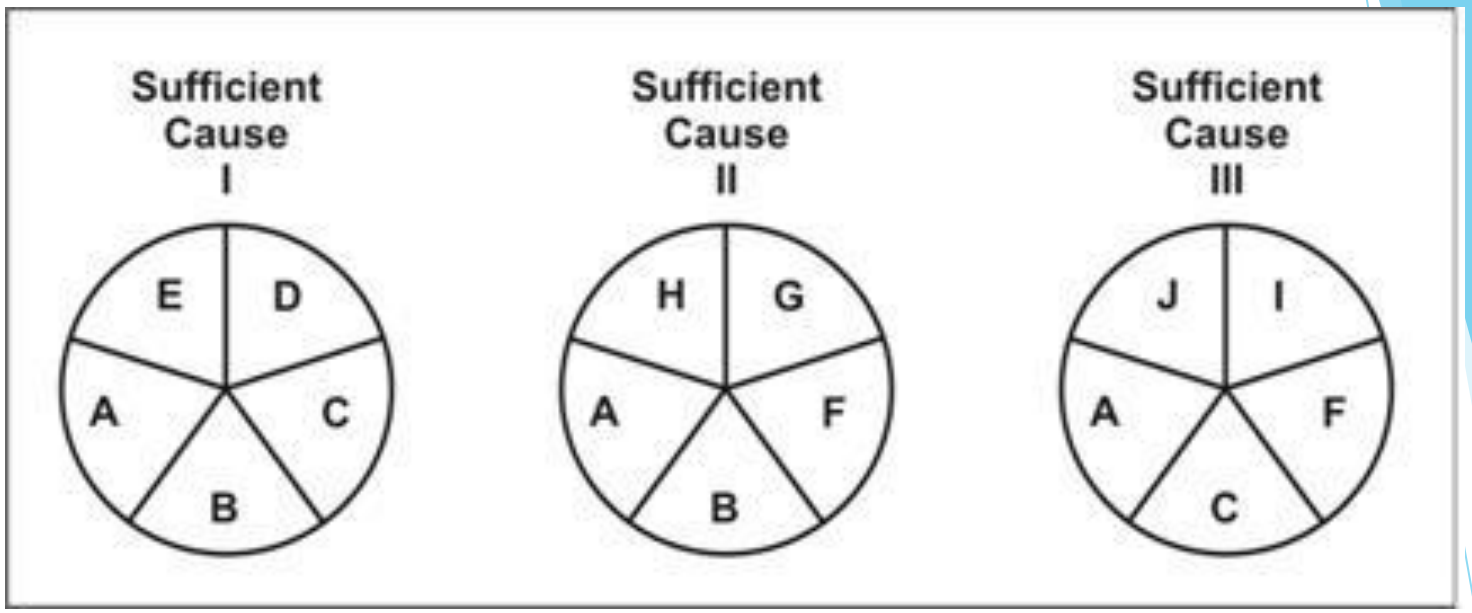
- Ideally based on ‘evidence’ - meta-analyses and systematic reviews
- Eradication of poverty for improving health?
- Reduction in social inequality for reducing health inequality?
- Removing endocrine disruptor chemical from environment reduces immunological disorders?

Little *direct causal* evidence, but the *weight* of evidence

- Competing interests:
  - Public, Industry, Government, Scientific community
  - Considerations of efficiency, cost-effectiveness and harm

From single to multiple causes

Kenneth Rothman (1986)

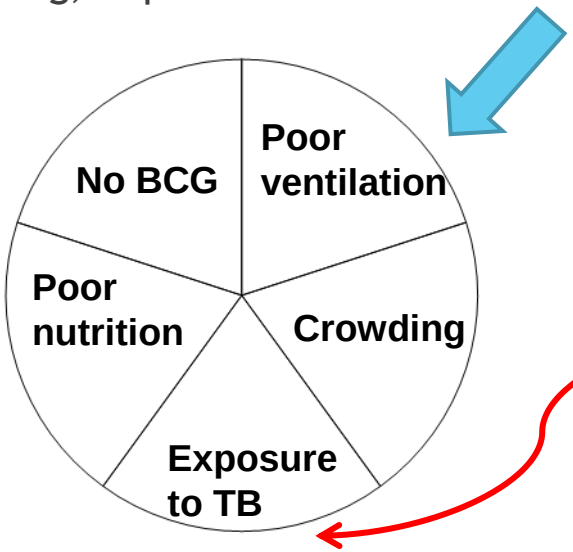


- The individual factors are called **component causes**.
- The complete pie, which might be considered a causal pathway, is called a **sufficient cause**.
- **A disease may have more than one sufficient cause**, with each sufficient cause being composed of several component causes that may or may not overlap.
- A component that appears in every pie or pathway is called a **necessary cause**, because without it, disease does not occur.
- In this figure, that **component cause A** is a necessary cause because it appears in every pie.

Sufficient cause

Sufficient cause – a minimum set of factors and circumstances which if present will produce disease

For example. In the 19th/20th century, no BCG, poor ventilation, poor nutrition, crowding, exposure to TB ➔ TB



What is absolutely necessary for disease to occur?

Necessary component = exposure to TB

Source – Modern Epidemiology. Rothman 1986

Necessary and Sufficient Components

- **Necessary and sufficient -** factor necessary for disease to occur, and no other factors required
- **Necessary but not sufficient** - factor necessary for disease to occur, but other factors also required
- **Sufficient but not necessary** - factor alone can cause disease, but so can other factors in its absence
- **Neither sufficient not necessary** – factor cannot cause disease on its own, nor is it a factor that is required for disease to occur

Multiple causes

- Rarely a single cause
- Disease results from a complex interaction of factors
- Web of causation / chain of causation
- Common in social epidemiology

Causal pathway model of the association between education and health conceptual

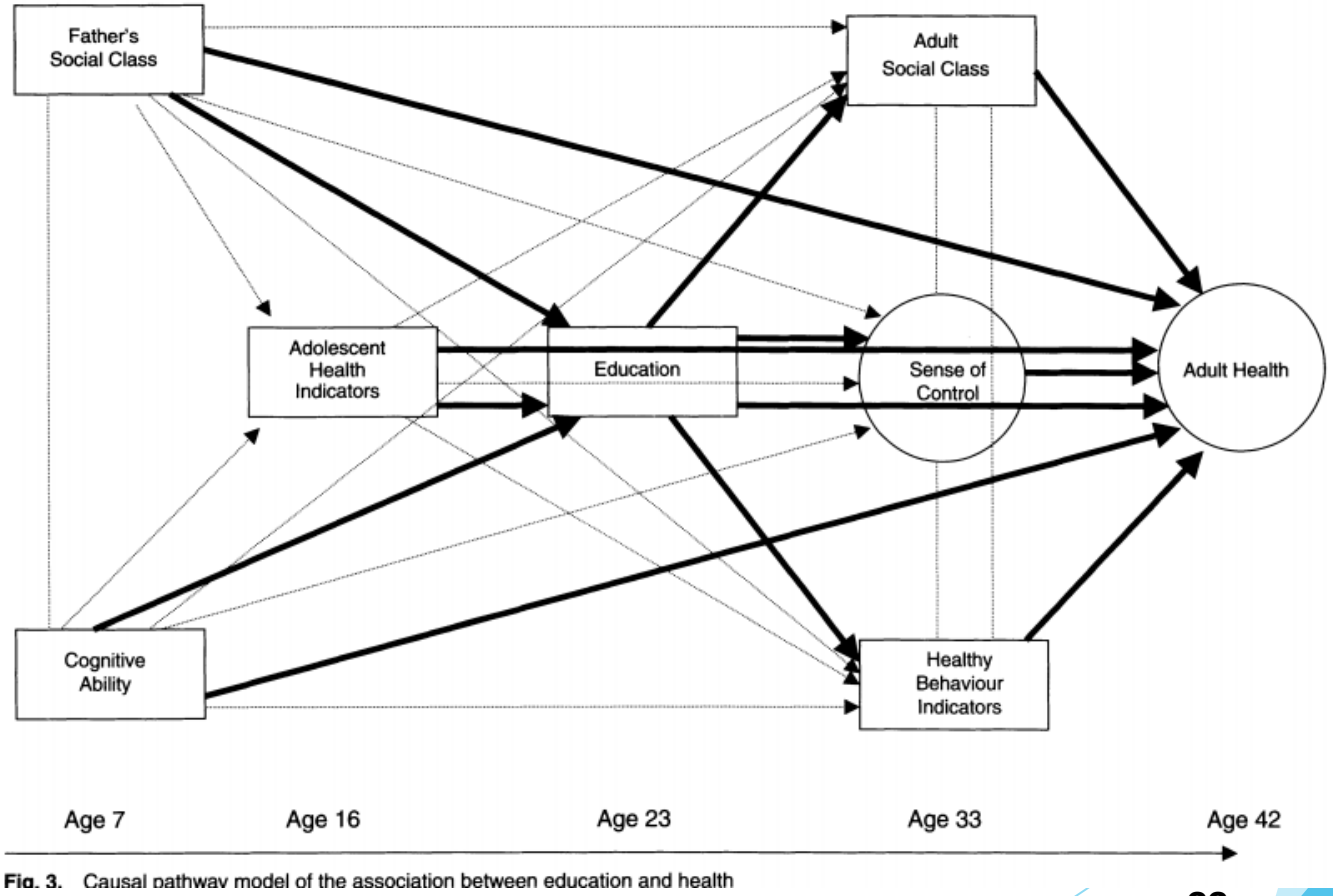


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Fig. 3. Causal pathway model of the association between education and health

Source: https://www.jstor.org/stable/pdf/3559677.pdf **Bold arrow = pathway supported by evidence**

Further reading on causality

- Bhopal 2002 or 2016, *Concepts of Epidemiology* chapter 5. Also available free online

http://oxfordmedicine.com/view/10.1093/med/9780198739685.001.0001/med-9780198739685