Why is observational better than experimental epidemiology?

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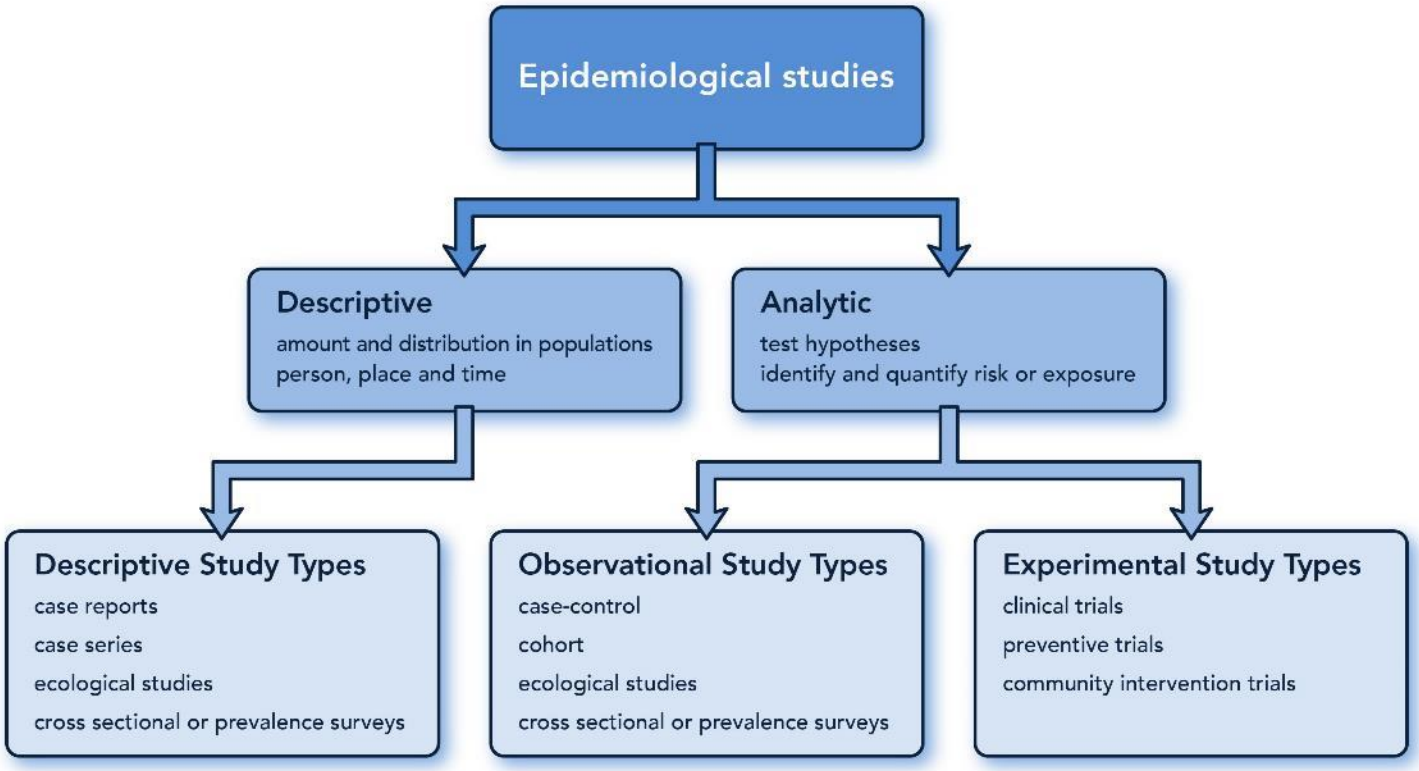
Outline

- Study designs
- Observational vs. experimental studies
- Causal inference
- New approaches
- Causal information from health registry data
- Concluding remarks

Study designs



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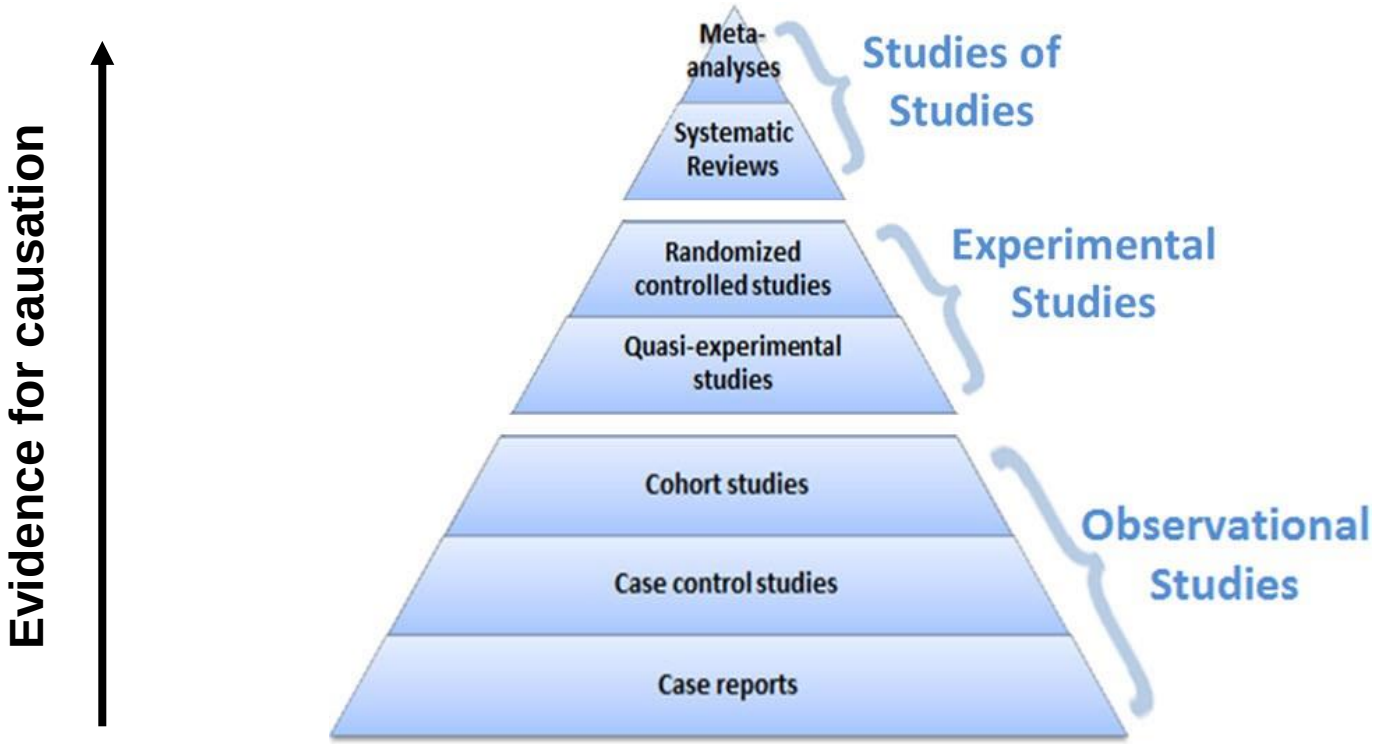
Hierarchy of study designs



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Observational vs. experimental studies: What is the evidence for a hierarchy?

- Often, a single RCT is considered to provide “truth” whereas results from any observational study are viewed with suspicion
- We have a rigid hierarchy of research design that underestimates the limitations of randomized controlled trials, and overstates the limitations of observational studies
- A more balanced and scientific justified approach is to evaluate the strengths and limitations of well done experimental and observational studies, recognizing the attributes of each type of design

Concato J. NeuroRx 2004; 1: 341-7

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[13]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[13]	418,343	0.77 (0.75–0.80)

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.

†CI denotes confidence interval.

Conclusions

The results of well-designed observational studies (with either a cohort or a case–control design) **do not systematically overestimate** the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic

Concato J, et al. NEJM 2000; 342: 1887-92

Understanding the divergent data on postmenopausal hormone therapy

Table 2. Results from Observational Studies of Combined Hormone Therapy and from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study.*

Disease	Women's Health Initiative	Heart and Estrogen/ Progestin Replacement Study	Observational Studies of Estrogen with Progestin
		relative risk (95% confidence interval)	
Breast cancer	1.26 (1.00–1.59)	1.30 (0.77–2.19)	
<5 yr			1.15[7]
≥5 yr			1.53[7]
Colorectal cancer	0.63 (0.43–0.92)	NA	0.66 (0.59–0.74)[8]†
Hip fracture	0.66 (0.45–0.98)	1.10 (0.49–2.50)	0.75 (0.68–0.84)[9]†
Stroke	1.41 (1.07–1.85)	1.2 (1.0–1.4)‡	1.45 (1.10–1.92)[10]
Pulmonary embolism	2.13 (1.39–3.25)	2.8 (0.9–8.7)	2.1 (1.2–3.8)[11]†
Coronary heart disease	1.29 (1.02–1.63)	0.99 (0.80–1.22)	0.61 (0.45–0.82)[12]

* Relative risks are for the women receiving hormone-replacement therapy as compared with those not receiving hormone-replacement therapy. Confidence intervals are nominal. NA denotes not available.
† Estimates are for any hormone use, since there were insufficient data for estrogen plus progestin.
‡ Relative risk is for the combined risk of fatal and nonfatal stroke.

Observational studies suggested a protective effect of hormones on coronary heart disease, whereas randomised controlled trials pointed to no benefit, or even harm

Grodstein F, et al. NEJM 2003; 348: 645-50

Understanding the divergent data on postmenopausal hormone therapy

Table 1. Potential Explanations for Discordant Findings from Randomized Trials and Observational Studies Regarding Postmenopausal Hormone Therapy and Coronary Heart Disease.

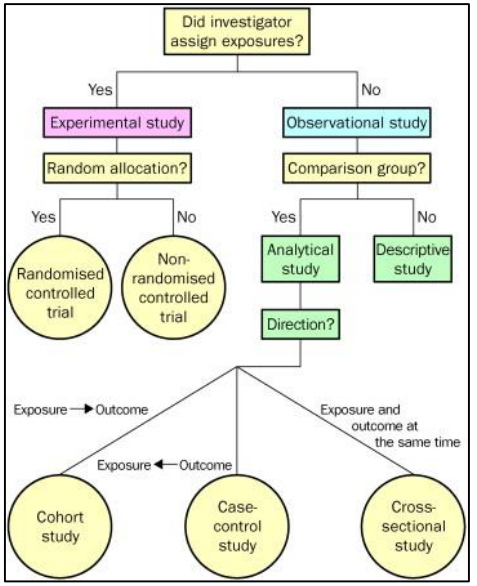
Methodologic differences
Confounding ("healthy user") bias
Compliance bias
Incomplete capture of early clinical events
Biologic differences
Hormone regimen (formulation and dose)
Characteristics of study population (endogenous estrogen level, time since menopause, and stage of atherosclerosis)

The observational studies and the randomized trials may be answering different questions

Grodstein F, et al. NEJM 2003; 348: 645-50

Study designs

- In **observational studies**, the researcher observes and systematically collects information, but does not try to change the people (or animals, or reagents) being observed
- In an **experiment**, by contrast, the researcher intervenes to change something (e.g., gives some patients a drug) and then observes what happens
- In an observational study there is **no intervention**



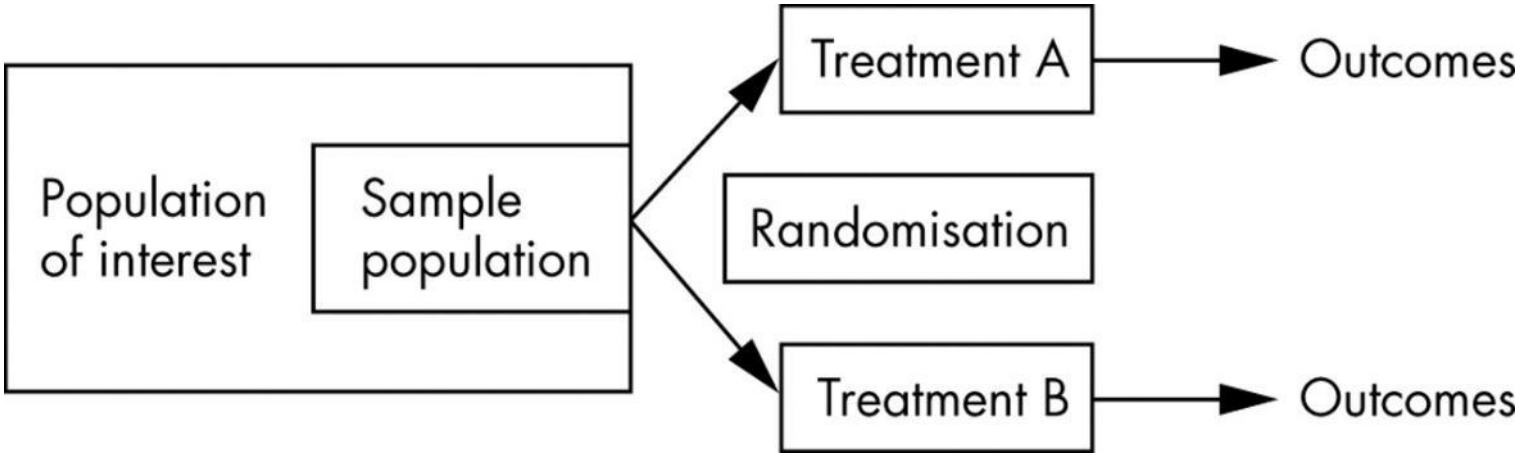
Grimes DA, et al.
Lancet 2002; 359: 57-61

Observational vs. experimental studies

- Experimental studies are ones where researchers introduce an intervention and study the effects
- Observational studies are ones where researchers observe the effect of a risk factor, diagnostic test, treatment or other intervention without trying to change who is or isn't exposed to it
- Observational studies make use of careful measurement of pattern of exposure and disease in populations to draw inferences about etiology
- In observational studies, the researcher is **an observer** rather than an agent who assigns interventions

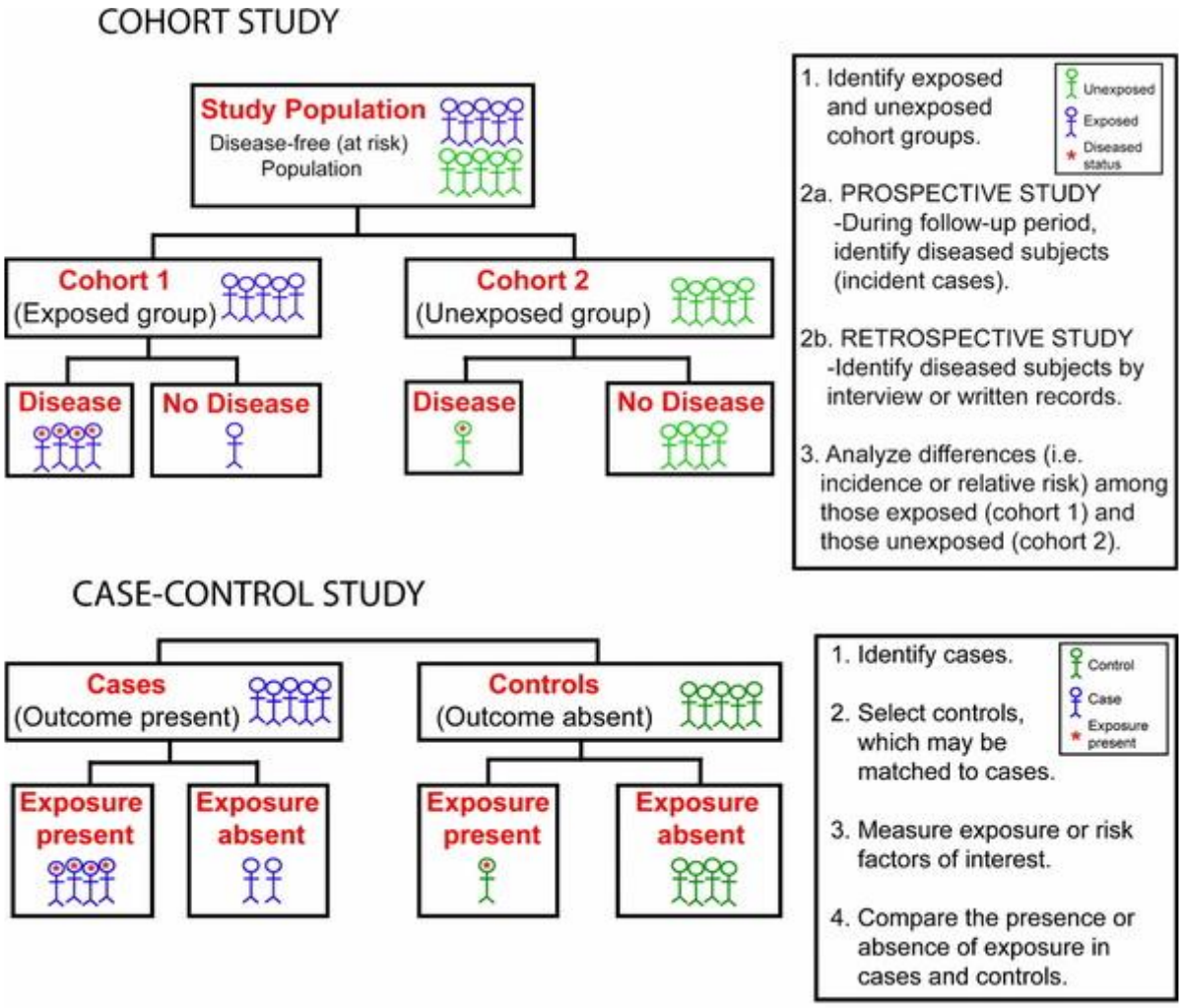
Rothman KJ, et al. Modern Epidemiology, 2008
Friis RH and Sellers TH, Epidemiology for Public Health Practice, 2009

Randomised controlled trial (RCT) – basic structure

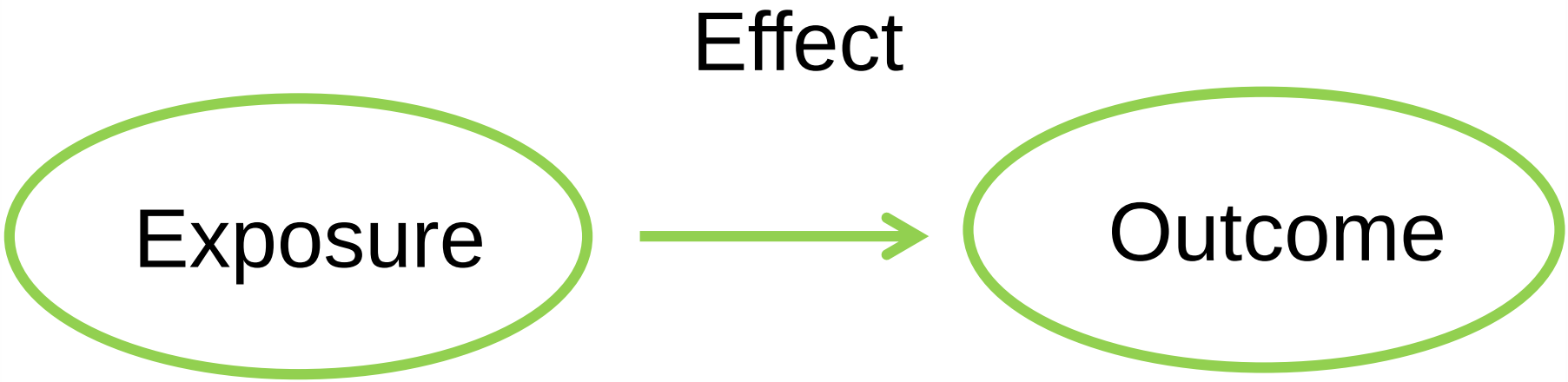


Akobeng AK. Arch Dis Child 2005; 90:840-4

Observational studies

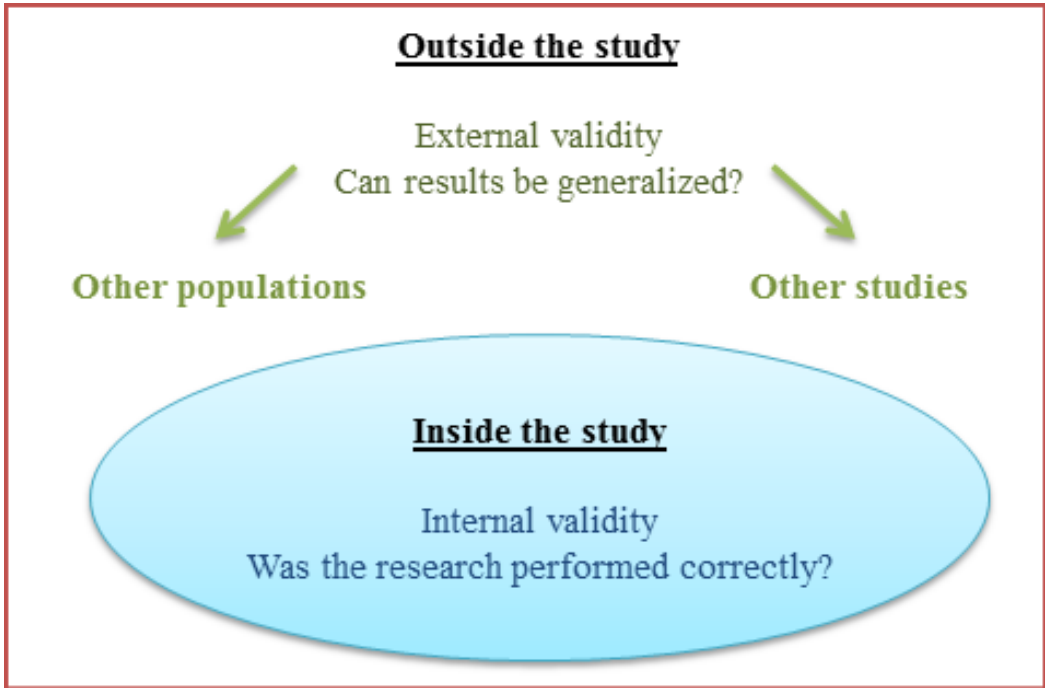


Song JW, et al. Plast Reconstr Surg 2010; 126: 2234-42



Bias / counfounding

Validity



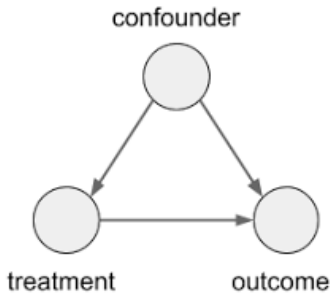
Internal validity implies that there is no bias in the way the data is collected, analysed and interpreted

External validity is the generalizability of the study results to subjects out of the study sample

Limitations of observational studies

«All observational studies have one crucial deficiency: The design is not an experimental one.»

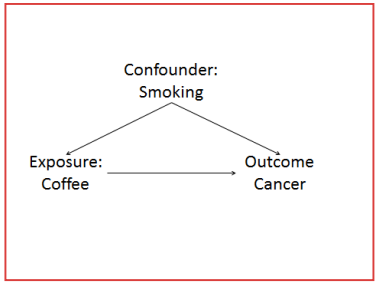
Pocock SJ et el. NEJM 2000; 342: 1907-9



https://www.inference.vc/

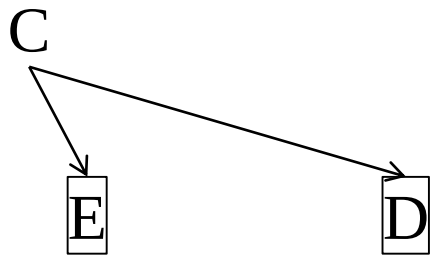
Confounding («traditional thinking»)

- Confounding is a term used to describe distortion of the estimate of the effect of an exposure of interest because it is mixed with the effect of an extraneous factor
- To be a confounder, the extraneous factor must satisfy the following three criteria
  1. Be a risk factor for the disease
  2. Be associated with the exposure under study in the population from which the cases derive
  3. Not be an intermediate step in the causal path between exposure and disease



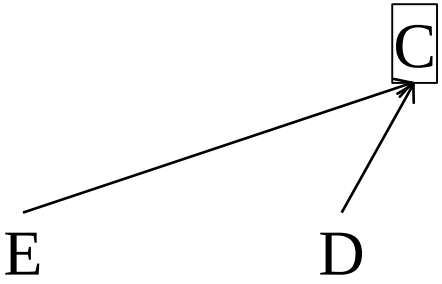
Friis RH and Sellers TH, Epidemiology for Public Health Practice, 2009

Confounder and collider (DAGs)



C is a common cause of E and D

Confounder



C is a common effect of E and D

Collider bias / selection bias

Bias

- **Selection bias** arises when the relation between exposure and disease is different for those who participate and those who would be theoretically eligible for study but do not participate
- **Information bias** is a kind of bias introduced as a result of measurement error in assessment of both exposure and disease

Friis RH and Sellers TH, Epidemiology for Public Health Practice, 2009

Observational studies

Table 2. Advantages and Disadvantages of the Cohort Study

Advantages
Gather data regarding sequence of events; can assess causality
Examine multiple outcomes for a given exposure
Good for investigating rare exposures
Can calculate rates of disease in exposed and unexposed individuals over time (e.g., incidence, relative risk)
Disadvantages
Large numbers of subjects are required to study rare exposures
Susceptible to selection bias
Prospective cohort study
May be expensive to conduct
May require long durations for follow-up
Maintaining follow-up may be difficult
Susceptible to loss to follow-up or withdrawals
Retrospective cohort study
Susceptible to recall bias or information bias
Less control over variables

Table 4. Advantages and Disadvantages of the Case-Control Study

Advantages
Good for examining rare outcomes or outcomes with long latency
Relatively quick to conduct
Relatively inexpensive
Requires comparatively few subjects
Existing records can be used
Multiple exposures or risk factors can be examined
Disadvantages
Susceptible to recall bias or information bias
Difficult to validate information
Control of extraneous variables may be incomplete
Selection of an appropriate comparison group may be difficult
Rates of disease in exposed and unexposed individuals cannot be determined

Song JW, et al. Plast Reconstr Surg 2010; 126: 2234-42

When to perform observational studies?

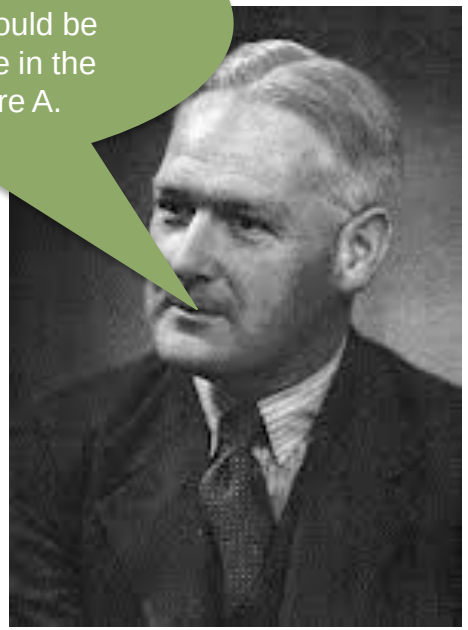
- When an experiment would be **impractical, unethical or infeasible.**
- Randomised treatment assigns has important conceptual strengths, especially for reducing bias, but it **is resource intensive** and often applied to **highly selected populations**, making generalizations difficult.
- The central tasks of observational epidemiology are to build **theoretical understanding of causal mechanisms**, identify opportunities to test and revise theories, and provide reliable evidence that can **serve as a basis** for making decisions about clinical or population-health interventions.
- To achieve relevance, we need **better alignment between observational studies and potential next steps**, which might include RCTs, development of clinical guidelines, informing individual behavioral decisions, or institutional or governmental policy changes.

Glymour MM, et al. . Am J Epidemiol 2019; 188: 836-9
Harper S. Am J Epidemiol 2019; 188: 840-5

Bradford Hill criteria for evidence of causation

1) Strength of association
2) Consistency
3) Specificity
4) Temporality
5) Biologic gradient
6) Plausibility
7) Coherence
8) Experiment
9) Analogy

The decisive question is whether the frequency of the undesirable event B would be influenced by a change in the environmental feature A.



Sir Austin Bradford-Hill (1897-1991)

Causal inference in epidemiology

- The analysis of data from epidemiologcal and clinical studies is undergoing fundamental changes
- More studies include extensive data collected over time than has previously been the case
- Causal modeling has become a major topic in epidemiology, with emphasis on graphical models, Bayesian networks and counterfactual models

→ **A systematic approach to evalute causality**

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Causal inference – new methods

- Counterfactual thinking (Robins JS)
- Seeing vs. doing (Pearl J)
- The importance of time (Aalen O)
- Direct and indirect effects (Cole SR, Hernan MA)

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

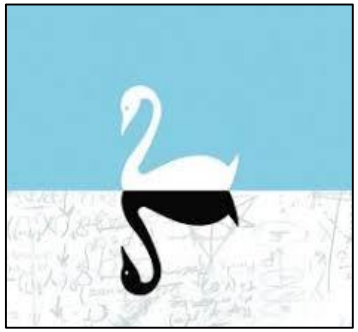
RCTs, observational studies and causal inference

- The RCT has long been seen as **the gold standard** for causal inference in medical research. In RCTs, the patients are randomly assigned to different groups (treatment and control group). The resulting effect estimate is the difference between the mean response in the two groups.
- **The ideal set-up can be violated for many reasons;** perfect control over patients is hard to achieve, randomization into placebo groups is not always ethical, and the presence of the randomization itself might influence the participation in the study. In other words, it is not always feasible to create a RCT.
- Observational studies have the same goal as the RCTs, but differ in that the investigator **cannot control treatment assignment**.
- Observational studies are often the only alternative for causal inference, and **methods** exist that permit the estimation of causal treatment effects from observational data, under certain assumptions.

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Contrafactual thinking

- The view on causality that is most natural in medicine is the contrafactual one.
- What would have happened if the intervention had not been made (or a different intervention had been made)?
- One compares the actual situation (with intervention) with the counterfactual one (without intervention) to see the causal effect of the intervention.
- The counterfactual factual world is carefully chosen under the assumption that all else should be equal except the condition under study.



Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

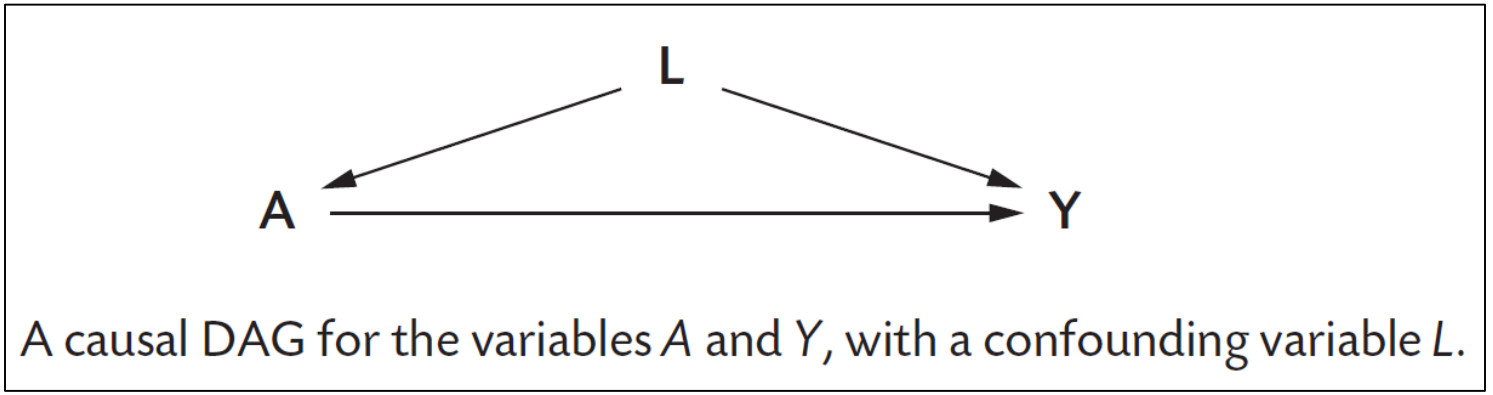
Directed acyclic graphs (DAGs)

- are often used to provide a graphical representation of the conditional independencies or causal relations between random variables
- serve as a powerful tool when looking at causal systems and come with strategies for how to estimate effects between them
- are helpful for understanding of key concepts such as confounding and selection bias, and in the process of selecting the variables to include in statistical models

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Directed acyclic graphs (DAGs)

- A DAG displays assumptions about the relationship between variables (often called nodes in the context of graphs). The assumptions we make take the form of lines (or edges) going from one node to another. These edges are *directed*, which means to say that they have a single arrowhead indicating their effect.
- A DAG is also *acyclic*, which means that there are no feedback loops.



A causal DAG for the variables *A* and *Y*, with a confounding variable *L*.

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Four types of causal structures

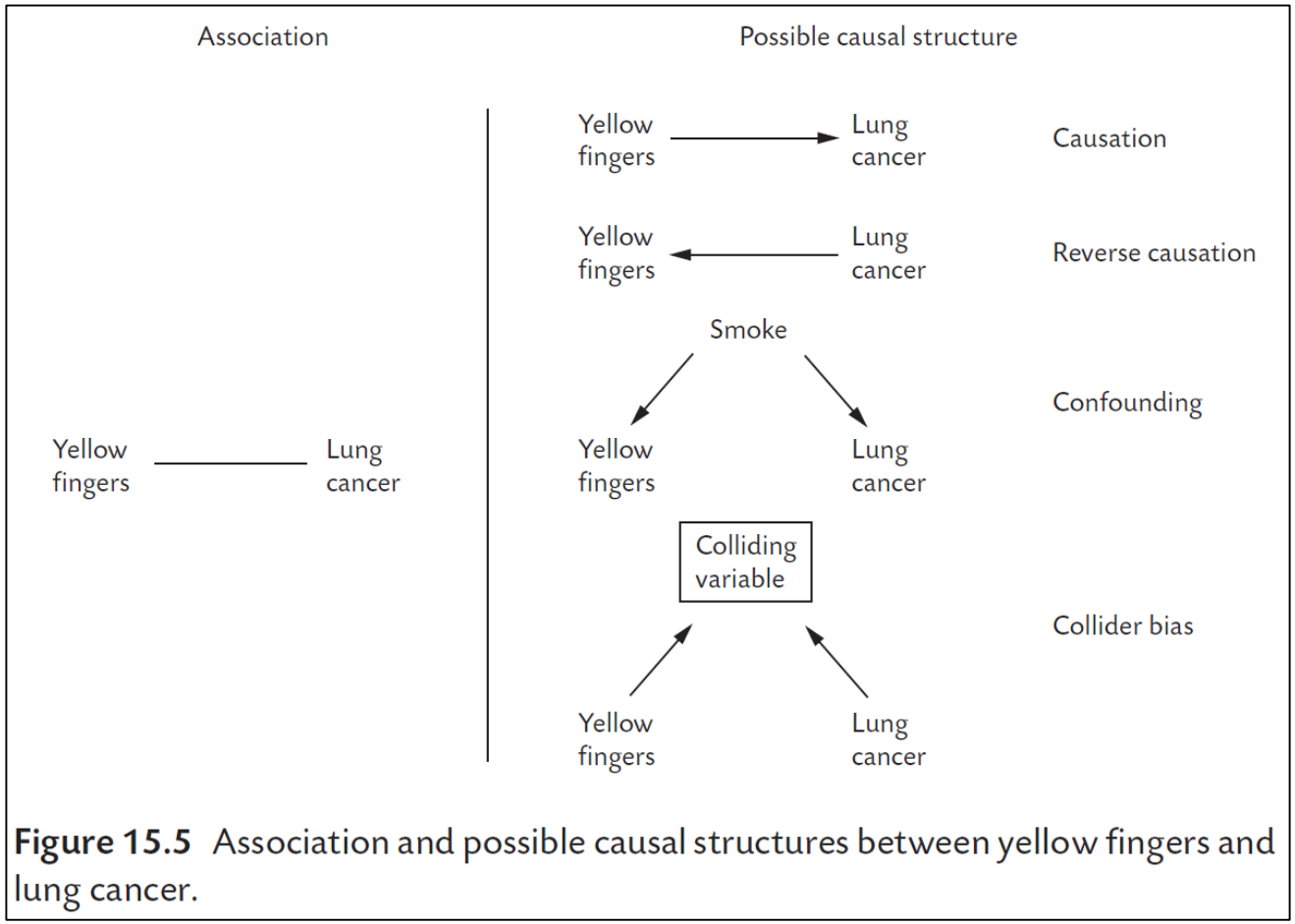


Figure 15.5 Association and possible causal structures between yellow fingers and lung cancer.

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Directed acyclic graphs (DAGs)

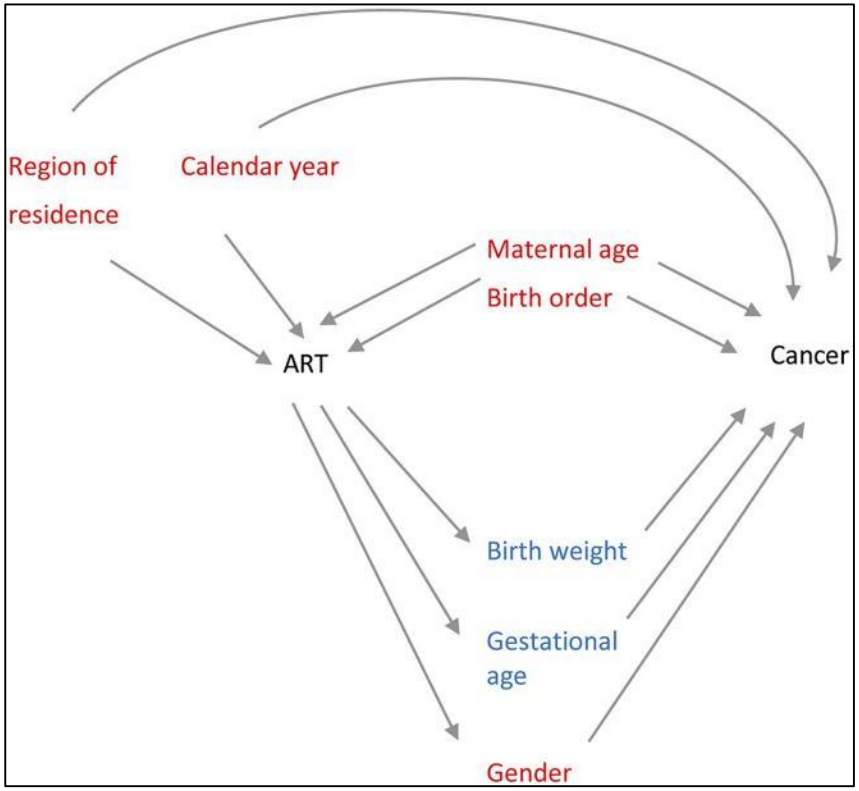


FIGURE 1
A directed acyclic graph showing confounding and mediating factors in the current study associated with ART and childhood cancer. Covariates in red indicate that they have been classified as confounding factors; covariates in blue have been classified as intermediate factors.

Reigstad MM, et al. Pediatrics 2016; 137: e20152061

Approaches to causal inference

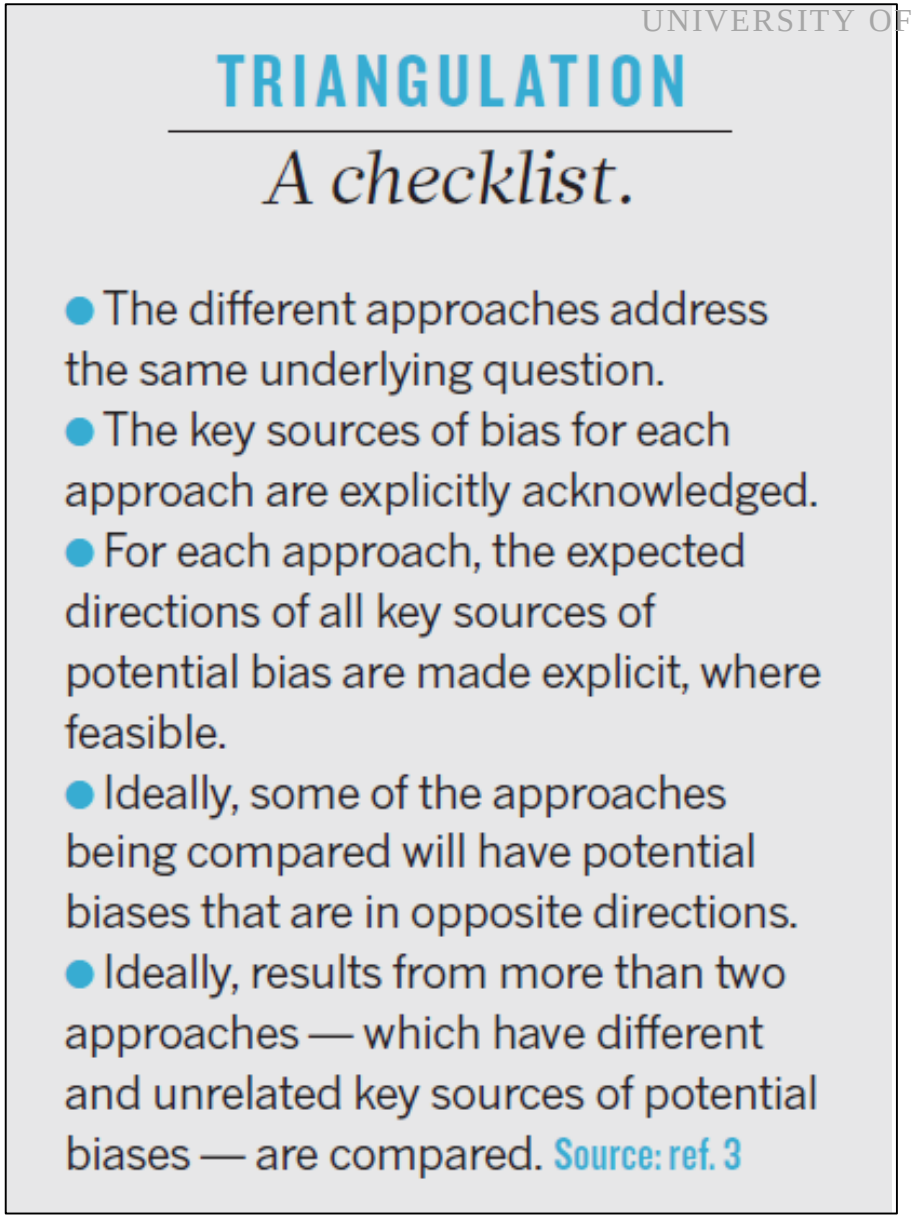
- **Triangulation** is the practice of obtaining more reliable answers to research questions through **integrating results from several different approaches**, where each approach has different key sources of potential bias that are unrelated to each other.
- With respect to causal questions in aetiological epidemiology, if the results of different approaches all point to the same conclusion, this strengthens confidence in the finding.
- This is particularly the case when the key sources of bias of some of the approaches would predict that findings would point in opposite directions if they were due to such biases.
- Where there are inconsistencies, understanding the key sources of bias of each approach can help to identify what further research is required to address the causal question.

Lawlor DA, et al. Int J Epidemiol 2016; 45: 1866-86

Repeating experiments is not enough

Verifying results requires disparate lines of evidence — a technique called triangulation. **Marcus R. Munafò** and **George Davey Smith** explain.

Nature 2018; 553: 399



"We believe that an essential protection against flawed ideas is triangulation.

- This is the strategic use of multiple approaches to address one question.
- Each approach has its own unrelated assumptions, strengths and weaknesses.
- Results that agree across different methodologies are less likely to be artefacts."

Nature 2018; 553: 399

Triangulation – different approaches

- Conventional approaches
  - RCTs, multiple regression in observational data
- Refinements using general populations
  - Cross-context comparisons, different control groups, natural experiments
- Refinements using specific populations
  - Within sibling comparisons
- Refinements of exposure
  - Instrument variable (IV) analysis, IVs to test intermediates in RCTs, genetic IVs in observational data, non-genetic IVs in observational data, exposure negative control studies
- Refinements of outcome
  - Outcome negative control studies

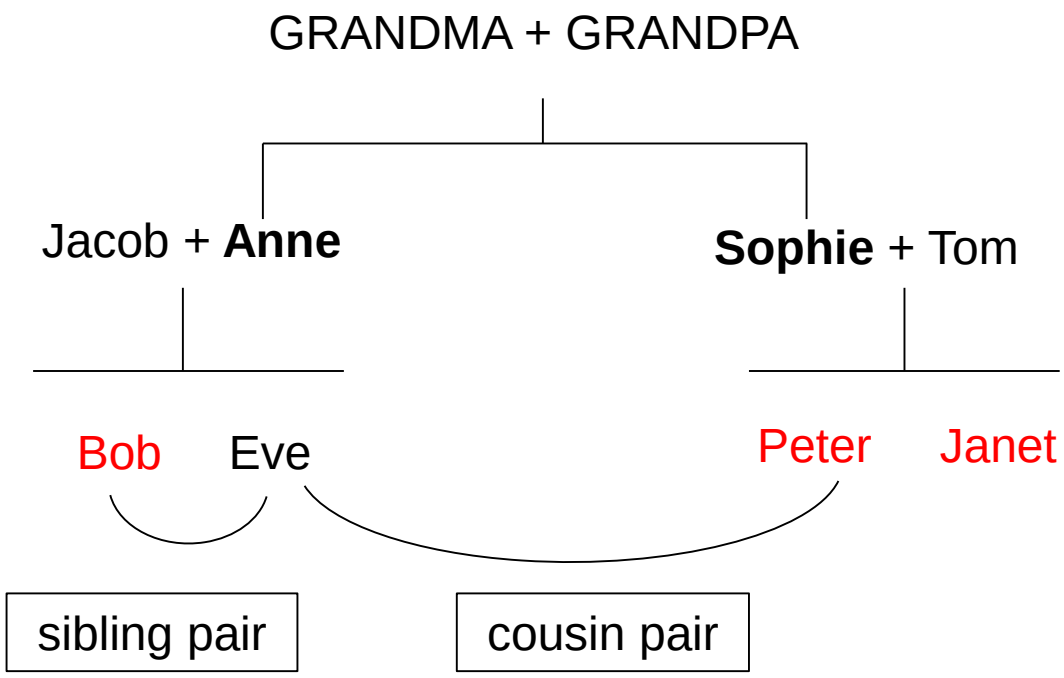
Lawlor DA, et al. Int J Epidemiol 2016; 45: 1866-86

Family-based design

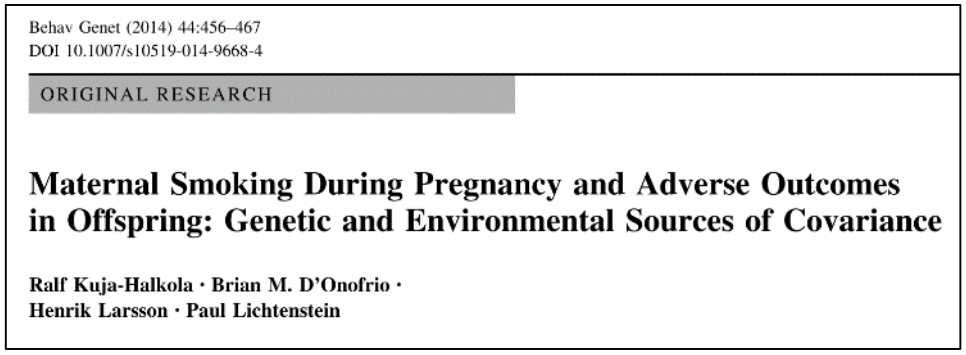
- Sibling comparison designs
  - Twins, full siblings, and half-siblings are increasingly used as comparison groups in matched cohort an matched case-control studies
  - The «within-pair» estimates acquired through these comparisons are **free from confounding from all factors that are shared by the siblings**

Frisell T, et al. Epidemiology 2012; 23: 713-20

Family-based design



Red indicates that mother smoked in this pregnancy



Behav Genet (2014) 44:456–467
DOI 10.1007/s10519-014-9668-4

ORIGINAL RESEARCH

Maternal Smoking During Pregnancy and Adverse Outcomes in Offspring: Genetic and Environmental Sources of Covariance

Ralf Kuja-Halkola · Brian M. D'Onofrio · Henrik Larsson · Paul Lichtenstein

Effects of maternal smoking during pregnancy on birth weight (95% CI)

	Effect measure	Cohort	Within-family	
		All children	Full-cousins	Full-siblings
Birth weight (g)	Regression coefficients	-181 (-184 to -179)	-185 (-192 to -177)	-92 (-97 to -86)

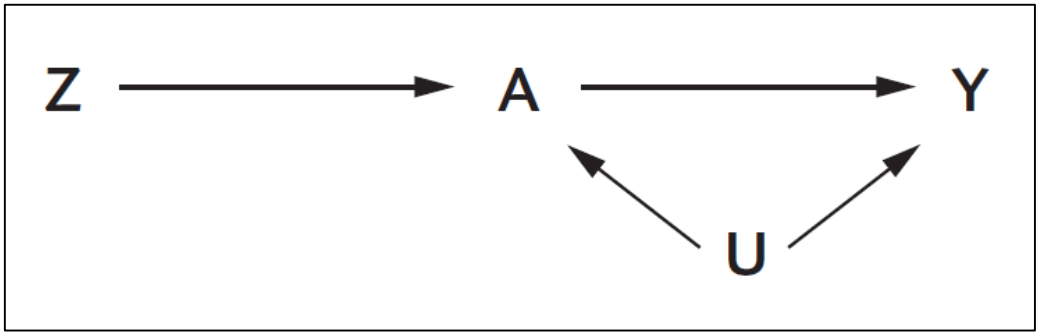
All models were adjusted for gender, birth year, and maternal age.

Association within family analyses:
full siblings, half-siblings, **full cousins** and half-cousins

Instrument variable analysis

- A method to control for unmeasured confounding in observational studies

- If an instrument Z for A exists, one can test for a causal effect of A on Y
- Z is a valid instrument for A if
  - Z affects A
  - Z affects A only through A, and
  - Z and Y share no common causes



A causal DAG for the variables A and Y, with an unmeasured confounding variable U and an instrument Z

Veierød MB, et al. Medical statistics in clinical and epidemiological research, Gyldendal Norsk Forlag 2012

Mendelian randomization (MR) analysis

- Mendelian randomisation is a research method that provides evidence about putative causal relations between modifiable risk factors and disease, using genetic variants as natural experiments
- Mendelian randomisation is less likely to be affected by confounding or reverse causation than conventional observational studies
- Like all analytical approaches, however, Mendelian randomisation depends on assumptions, and the plausibility of these assumptions must be assessed
- Moreover, the relevance of the results for clinical decisions should be interpreted in light of other sources of evidence

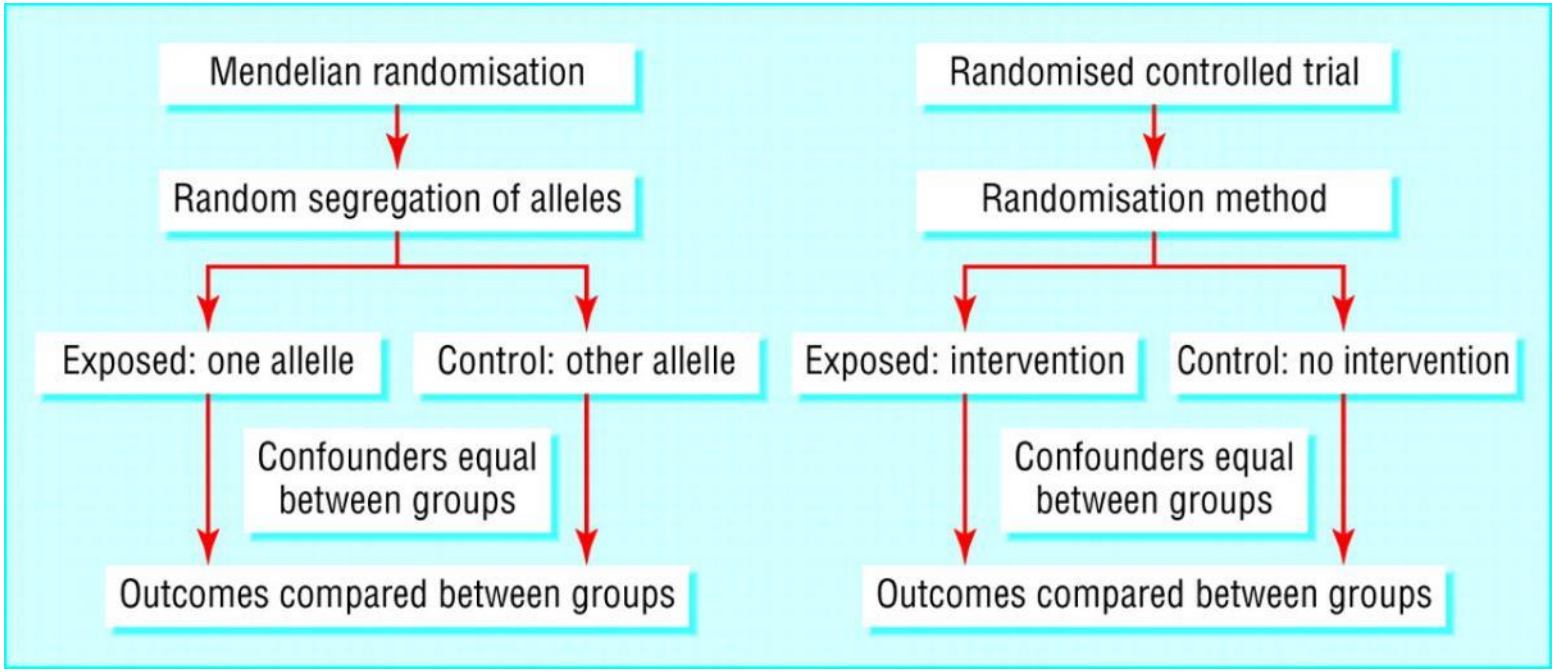
Davies NM, et al. BMJ 2018; 362: k601

Mendelian randomization

- Mendelian randomisation is a recent development in genetic epidemiology based on Mendel's second law that inheritance of one trait is independent of inheritance of other traits
- It uses common genetic polymorphisms that are known to influence exposure patterns (such as propensity to drink alcohol) or have effects equivalent to those produced by modifiable exposures (such as raised blood cholesterol concentration)
- Associations between genetic variants and outcome are not generally confounded by behavioural or environmental exposures
- This means that observational studies of genetic variants have similar properties to intention to treat analyses in randomised controlled trials

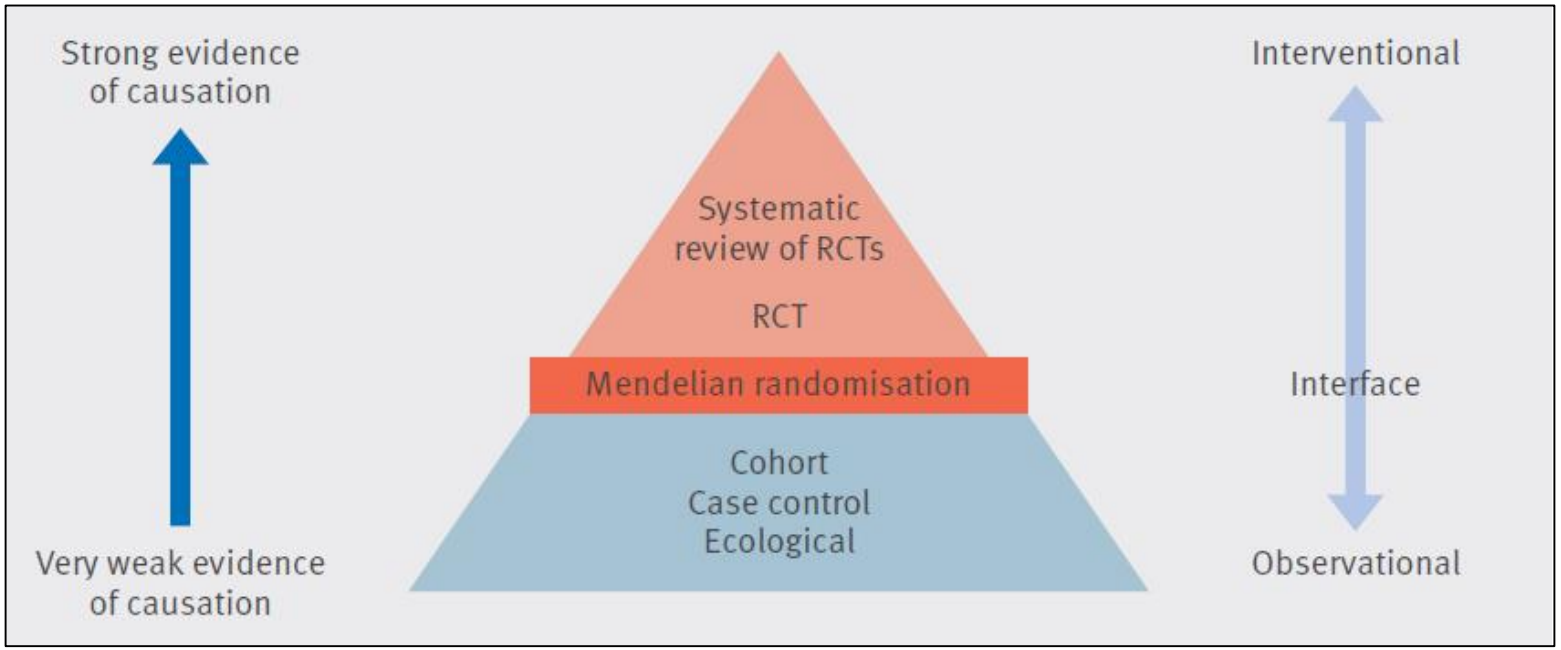
Smith GD, Ebrahim S. BMJ 2005; 330: 1076-9.

Comparison of design



Davey Smith, G. et al. BMJ 2005;330:1076-1079

A hierarchy of observational and experimental data

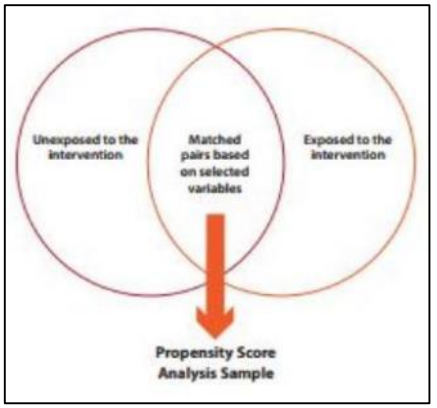


Mendelian randomisation studies sit at the interface of experimental and observational studies. Their findings can be used to provide more reliable evidence to guide interventional research and provide information about potential public health interventions when a randomised controlled trial may not be feasible.

Davies NM, et al. BMJ 2018; 362: k601

Propensity score (PS) analysis

- Propensity score (PS) analysis of observational studies is an alternative method of estimating causal treatment effects for clinically important questions in observational studies
- PS analysis is a causal inference technique for treatment effect estimation in observational studies by accounting for the conditional probability of treatment selection, thus allowing for reduction of bias when comparing interventions between treatment arms



Yao XI, et al. JNCI 2017; 109: djw323

Propensity score (PS) analysis

- In 1983, alternative methods for control of confounding in observational studies based on the propensity score were proposed
- The propensity score is the probability that an individual would have been treated based on that individual's observed pretreatment variables
- Adjustments using the estimated propensity score tend to balance observed covariates that were used to construct the score
- Several adjustment methods incorporating the estimated propensity score have been proposed, including matching, regression adjustment, and weighting

Kurth T, et al. Am J Epidemiol 2006; 163:262-70

Propensity score

- The propensity score is the probability that an individual would have been treated based on that individual's observed pretreatment variables.
- The propensity score e(X) for an individual is defined as the conditional probability of being treated given his or her covariates
- X: $e(X) = \Pr(Z = 1 \mid X)$.

Kurth T, et al. Am J Epidemiol 2006; 163:262-70

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

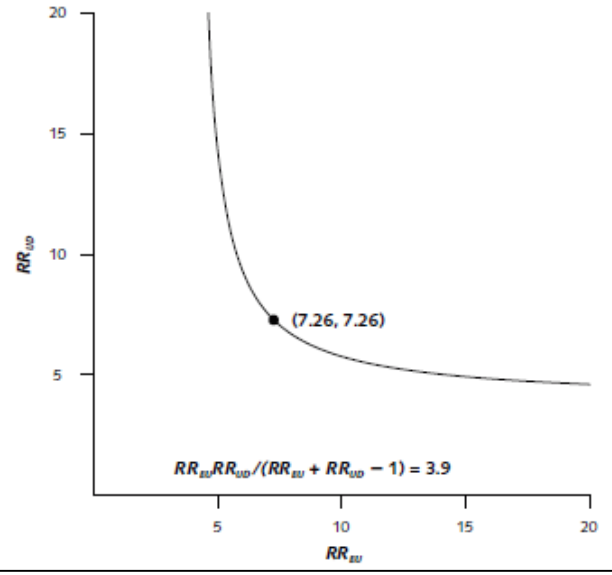
Sensitivity Analysis in Observational Research: Introducing the E-Value

Tyler J. VanderWeele, PhD, and Peng Ding, PhD

Sensitivity analysis is useful in assessing how robust an association is to potential unmeasured or uncontrolled confounding. This article introduces a new measure called the "E-value," which is related to the evidence for causality in observational studies that are potentially subject to confounding. The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates. A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate. A small E-value implies little unmeasured confounding would be needed to explain away an effect estimate.

The authors propose that in all observational studies intended to produce evidence for causality, the E-value be reported or some other sensitivity analysis be used. They suggest calculating the E-va… men… deno… prac… deno… and …

Figure 2. Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away an observed treatment–outcome risk ratio of *RR* = 3.9, as in the study by Victora and colleagues (23).



$$\text{E-value} = \text{RR} + \sqrt{\text{RR} \times (\text{RR} - 1)}$$

The E-value

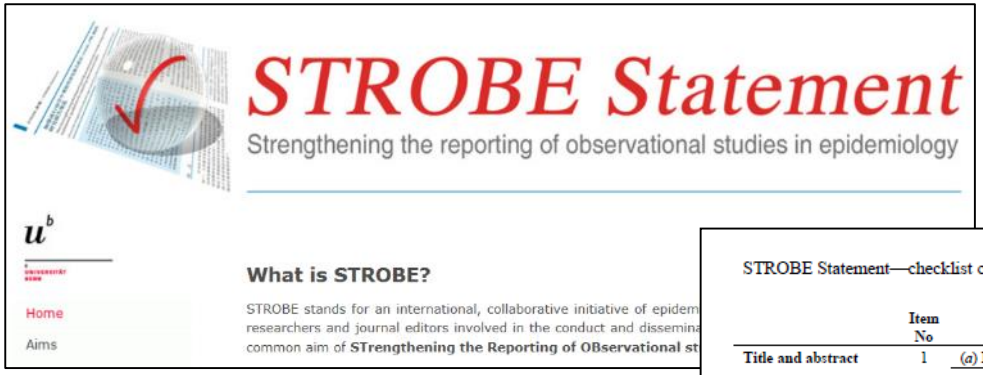
- The E-value is an alternative approach to sensitivity analyses for unmeasured confounding in observational studies that avoids making assumptions.
- An E-value analysis asks the question: How strong would the unmeasured confounding have to be to negate the observed results?
- The E-value itself answers this question by quantifying the minimum strength of association on the risk ratio scale that an unmeasured confounder must have with both the treatment and outcome, while simultaneously considering the measured covariates, to negate the observed treatment–outcome association.
- If the strength of unmeasured confounding is weaker than indicated by the E-value, then the main study result could not be overturned to one of “no association” (ie, moving the estimated risk ratio to 1.0) by the unmeasured confounder.
- E-values can therefore help assess the robustness of the main study result by considering whether unmeasured confounding of this magnitude is plausible.
- The E-value provides a measure related to the *evidence* for causality, hence the name “E-value.”

Haneuse S, et al. JAMA 2019; 321: 602-3

The E-value: Advantages

- It requires no assumptions
- It is intuitive because the lowest possibe number is 1
  - The higher the E-value is, the stronger the unmeasured counfounding must be to explain the observed association
- The calculation is also readily applied to the bounds of a 95%CI
  - Investigators can assess the extent of unmeasured counfounding that would be required to to shift the CI so that it includes a risk ratio of 1.0 (ie. no association)
- The E-value is simple to calculate for a range of effect measures and study designs

Haneuse S, et al. JAMA 2019; 321: 602-3



strobe-statement.org

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Evidence-Based Medicine in Surgery

The Importance of Both Experimental and Observational Study Designs

Ryan P. Merkow, MD
Clifford Y. Ko, MD, MS, MSHS

section and radiation therapy did not lead to worse outcomes compared with total mastectomy.[4] More recently, the NSABP B-32 trial[5] demonstrated the efficacy of sentinel lymph

Merkow RP, et el. JAMA 2011; 306: 436-7

The importance of both experimental and observational study designs

- Results from RCTs have changed breast cancer care, saving countless of women from undergoing radical surgery
- The significance of occult micrometastasis in sentinel lymph nodes and bone marrow in women with early stage disease was addressed observationally with a prospective cohort study design
- Occult bone marrow metastases was no longer associated with decreased survival after adjustment

Merkow RP, et el. JAMA 2011; 306: 436-7

The importance of both experimental and observational study designs

- The observational study
  - offers a clear example of how well-designed observational studies can address relevant clinical questions
  - provides significant insight that will help guide daily treatment decisions

Merkow RP, et el. JAMA 2011; 306: 436-7

The importance of both experimental and observational study designs

- To account for the potential limitations of observational studies, investigators can use **several statistical and methodological techniques**
- In a retrospective cohort study, designed to investigate long-term outcomes after bariatric surgery among high-risk veterans, the authors compared survival after bariatric surgery with outcomes in high-risk controls, both in unmatched and propensity-matched cohorts
- The survival advantage observed in the unmatched cohort (adjusted HR 0.80; 95% CI, 0.63-0.995) disappeared in the propensity score–matched cohort (adjusted HR, 0.94; 95% CI, 0.64-1.39)

Maciejewski ML, et al. JAMA 2011; 305: 2419-26

From randomized controlled trials to observational studies

- Randomized controlled trials are considered **the gold standard** in the hierarchy of research designs for evaluating the efficacy and safety of a treatment intervention
- However, their results can have **limited applicability** to patients in clinical settings
- Observational studies using large health care databases can complement findings from randomized controlled trials by assessing treatment effectiveness in patients encountered in **day-to-day clinical practice**
- Results from these designs can expand upon outcomes of randomized controlled trials because of the use of larger and **more diverse patient populations with common comorbidities and longer follow-up periods**
- Furthermore, well-designed observational studies can identify clinically important differences among therapeutic options and provide data on long-term drug effectiveness and safety

Silverman SL. Am J Med 2009; 122: 114-20

Table 1 Randomized Controlled Trial Methodology

Strengths	Limitations
Well-defined study population	Excludes many patients requiring clinical treatment
Design maximizes internal validity	Outcomes are difficult to extrapolate to a more general patient population
Tightly controlled treatment conditions	Short duration and modest sample sizes limit ability to identify rare or long-term adverse events
Compliance maximized through strict protocols	

Silverman SL. Am J Med 2009; 122: 114-20

When an Entire Country Is a Cohort

Lone Frank

«It is a moral obligation to exploit data gathered at great expence.»

«Would it not be unethical not to use it to improve the populations's health and health care?»

National health registries

- The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness.
- Can we derive **causal information** from the nationwide health registries?

The Nordic countries

The Nordic countries have special preconditions for conducting large population-based studies

- the populations are relatively homogeneous (being genetically reasonably similar with quite similar lifestyles)
- the individuals have free access to public health services
- nation-wide registers have been running for decades
- every resident has a unique personal identification number (country-specific) that is used by the registries, making precise record linkages possible
- a strict confidentiality and data protection legislation allows the use of health registry data for research purposes

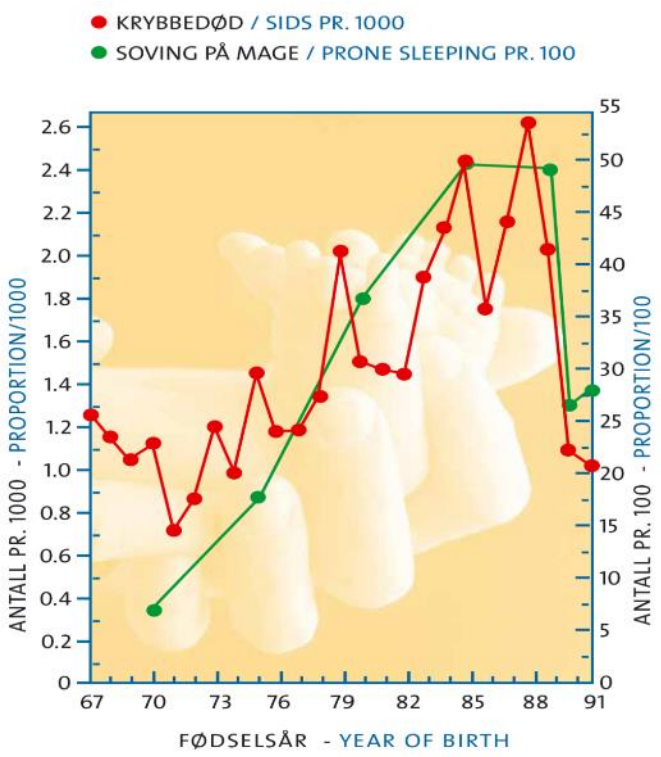
Sankila R. Maturitas 2010; 66; 180-1

National health registries

	National health registries	Responsible
1	Cause of Death Registry	Norwegian Institute of Public Health
2	Medical Birth Registry of Norway	Norwegian Institute of Public Health
3	Register of Pregnancy Termination	Norwegian Institute of Public Health
4	Norwegian Surveillance System for Communicable Diseases	Norwegian Institute of Public Health
5	Norwegian Surveillance System for Virus Resistance	Norwegian Institute of Public Health
6	Norwegian Immunisation Registry	Norwegian Institute of Public Health
7	Norwegian Surveillance System for Antimicrobial Drug Resistance	Norwegian Institute of Public Health
8	Norwegian Surveillance System for Antibiotic Use and Healthcare-Associated Infections	Norwegian Institute of Public Health
9	Norwegian Prescription Database	Norwegian Institute of Public Health
10	Cancer Registry of Norway	Cancer Registry of Norway/Oslo University Hospital
11	Norwegian Patient Registry	Norwegian Directorate of Health
12	Norwegian Information System for the Nursing and Care Sector	Norwegian Directorate of Health
13	ePrescription Database	Norwegian Directorate for eHealth
14	Registry of the Norwegian Armed Forces Medical Services	Armed Forces Medical
15	Norwegian Cardiovascular Disease Registry	Norwegian Institute of Public Health
16	Municipal Patient and User Registry	Norwegian Directorate of Health
17	Genetic Screening of Newborns	Oslo University Hospital
18	Medical Archives Registry	Directorate for Cultural Heritage

fhi.no

Sudden infant death syndrome (SIDS) and sleeping position



Data

- Time trend in SIDS from the Medical Birth Registry of Norway
- Exposure from ad hoc survey in 1992
- Time trend in retrospectively reported sleeping position i 1992 for the years 1970, 75, 80, 85, 89, 90, 91 by 24438 mothers (70% response rate) sampled from 20 largest maternity institutions
- For each year and institution 250 mothers were randomly selected 7x20x250=35,000
- One page questionnaire
- 92.5% stated they were certain about the babies sleeping position at 3 months of age

Irgens LM, et al. Arch Dis Child 1995;72:478-82.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

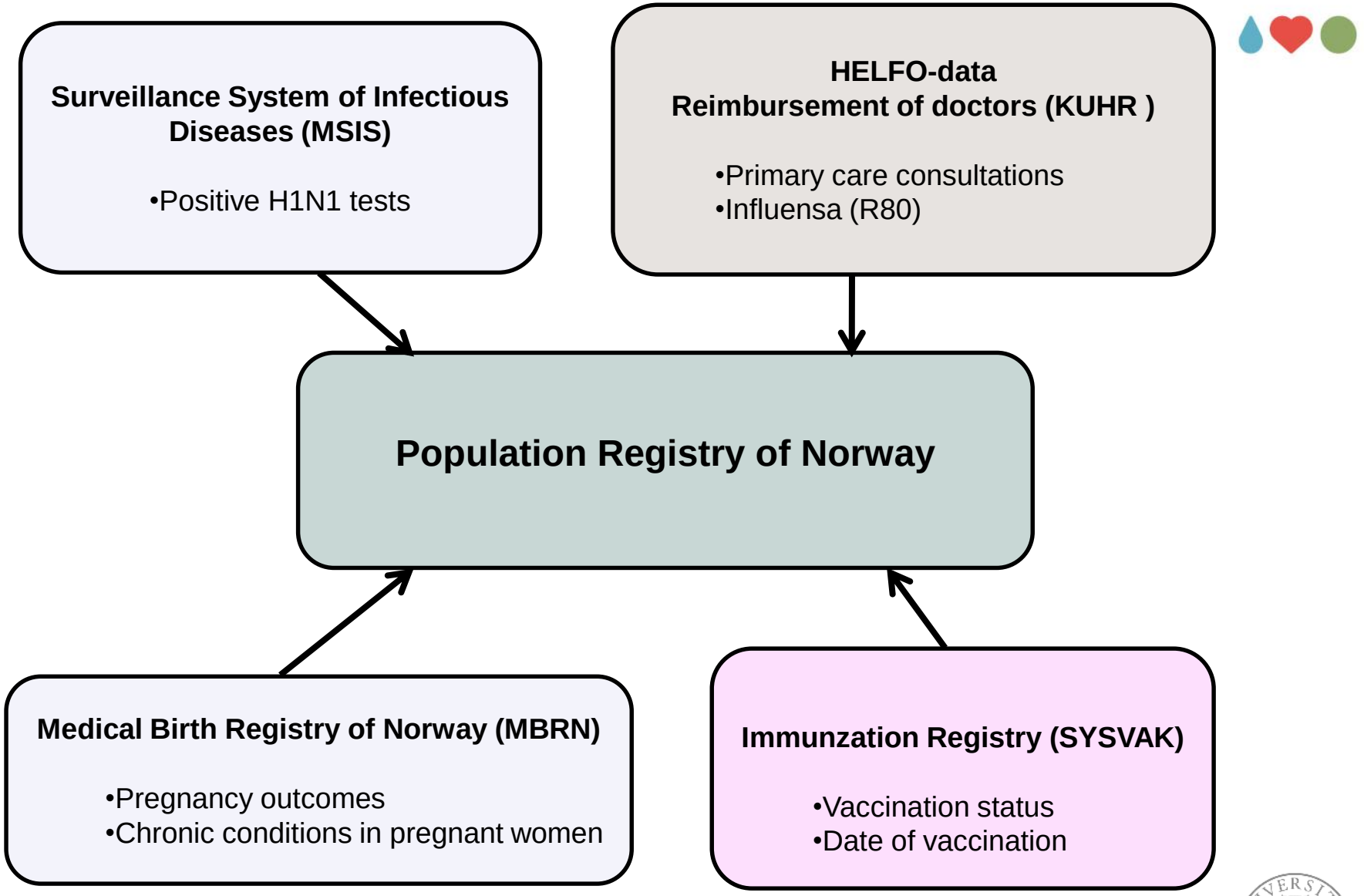
Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination

Siri E. Håberg, M.D., Ph.D., Lill Trogstad, M.D., Ph.D., Nina Gunnes, Ph.D., Allen J. Wilcox, M.D., Ph.D., Håkon K. Gjessing, Ph.D., Sven Ove Samuelsen, Ph.D., Anders Skrondal, Ph.D., Inger Cappelen, Ph.D., Anders Engeland, Ph.D., Preben Aavitsland, M.D., Steinar Madsen, M.D., Ingebjørg Buajordet, Ph.D., Kari Furu, Ph.D., Per Nafstad, M.D., Ph.D., Stein Emil Vollset, M.D., Dr.P.H., Berit Feiring, M.Sc.Pharm., Hanne Nøkleby, M.D., Per Magnus, M.D., Ph.D., and Camilla Stoltenberg, M.D., Ph.D.

BACKGROUND

During the 2009 influenza A (H1N1) pandemic, pregnant women were at risk for severe influenza illness. This concern was complicated by questions about vaccine safety in pregnant women that were raised by anecdotal reports of fetal deaths after vaccination.

Håberg SE, et al. NEJM 2013; 368: 333-40



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CONCLUSIONS

Pandemic influenza virus infection in pregnancy was associated with an increased risk of fetal death. Vaccination during pregnancy reduced the risk of an influenza diagnosis. Vaccination itself was not associated with increased fetal mortality and may have reduced the risk of influenza-related fetal death during the pandemic.

Håberg SE, et al. NEJM 2013; 368: 333-40

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 28, 2014 VOL. 371 NO. 9

Long-Term Colorectal-Cancer Mortality after Adenoma Removal

Magnus Løberg, M.D., Mette Kalager, M.D., Ph.D., Øyvind Holme, M.D., Geir Hoff, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Michael Bretthauer, M.D., Ph.D.

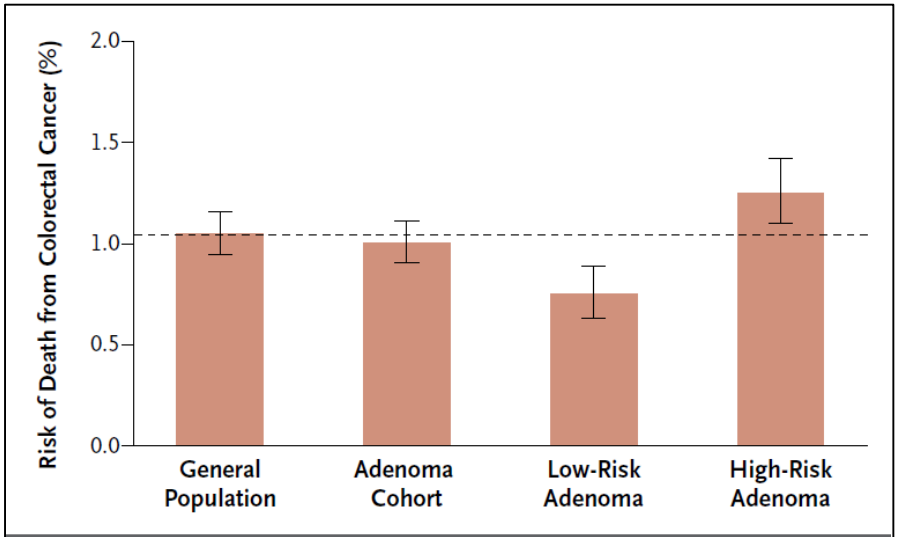

Figure 1. Colorectal-Cancer Mortality in a Cohort of Patients Who Underwent Removal of Adenomas and in the General Population.

CONCLUSIONS

After a median of 7.7 years of follow-up, colorectal-cancer mortality was lower among patients who had had low-risk adenomas removed and moderately higher among those who had had high-risk adenomas removed, as compared with the general population. (Funded by the Norwegian Cancer Society and others.)

Løberg M, et al. NEJM 2014; 371: 799-807

Annals of Internal Medicine

ORIGINAL RESEARCH

β-Blocker Use in Pregnancy and the Risk for Congenital Malformations

An International Cohort Study

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Background: β-Blockers are a class of antihypertensive medications that are commonly used in pregnancy.

Objective: To estimate the risks for major congenital malformations associated with first-trimester exposure to β-blockers.

Design: Cohort study.

Setting: Health registries in the 5 Nordic countries and the U.S. Medicaid database.

Patients: Pregnant women with a diagnosis of hypertension and their offspring.

Measurements: First-trimester exposure to β-blockers was assessed. Outcomes were any major congenital malformation, cardiac malformations, cleft lip or palate, and central nervous system (CNS) malformations. Propensity score stratification was used to control for potential confounders.

Results: Of 3577 women with hypertensive pregnancies in the Nordic cohort and 14 900 in the U.S. cohort, 682 (19.1%) and 1668 (11.2%), respectively, were exposed to β-blockers in the first trimester. The pooled adjusted relative risk (RR) and risk difference per 1000 persons exposed (RD_{1000}) associated with β-blockers were 1.07 (95% CI, 0.89 to 1.30) and 3.0 (CI, −6.6 to 12.6), respectively, for any major malformation; 1.12 (CI, 0.83 to 1.51) and 2.1 (CI, −4.3 to 8.4) for any cardiac malformation; and 1.97 (CI, 0.74 to 5.25) and 1.0 (CI, −0.9 to 3.0) for cleft lip or palate. For CNS malformations, the adjusted RR was 1.37 (CI, 0.58 to 3.25) and the RD_{1000} was 1.0 (CI, −2.0 to 4.0) (based on U.S. cohort data only).

Limitation: Analysis was restricted to live births, exposure was based on dispensed medication, and cleft lip or palate and CNS malformations had few outcomes.

Conclusion: The results suggest that maternal use of β-blockers in the first trimester is not associated with a large increase in the risk for overall malformations or cardiac malformations, independent of measured confounders.

Primary Funding Source: The Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Söderström König Foundation.

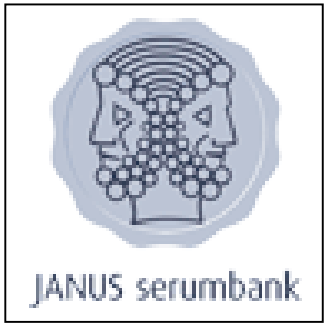
Ann Intern Med. doi:10.7326/M18-0338 **Annals.org**

For author affiliations, see end of text.

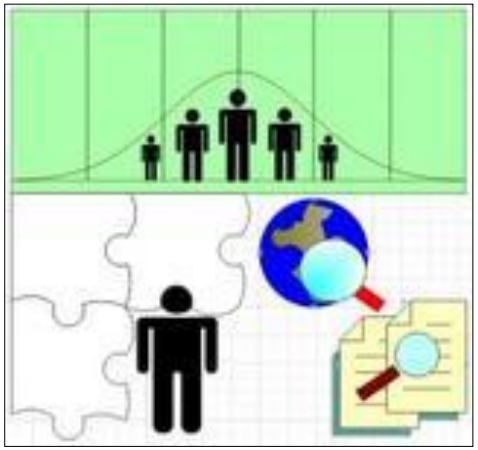
This article was published at Annals.org on 16 October 2018.

Other large data sources

Clinical quality registries, large cohorts, and biobanks (associated with cohorts) are designed to study causes of diseases and to identify best treatments



Why (or when) is observational better than experimental epidemiology?



Conclusions / key points

- when RCTs are impractical, unethical, infeasible or costly
- huge data sources (national registry data)
- use of advanced designs, methods and modelling
- real-life experiences and long follow-up

Thanks to my colleagues at EPISTAT, IGS, UiB

Thanks for your attention!

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