Introduction to confounding

Not everything that counts can be counted,
- and not everything that can be counted counts
Sign hanging in Albert Einstein's office at Princeton

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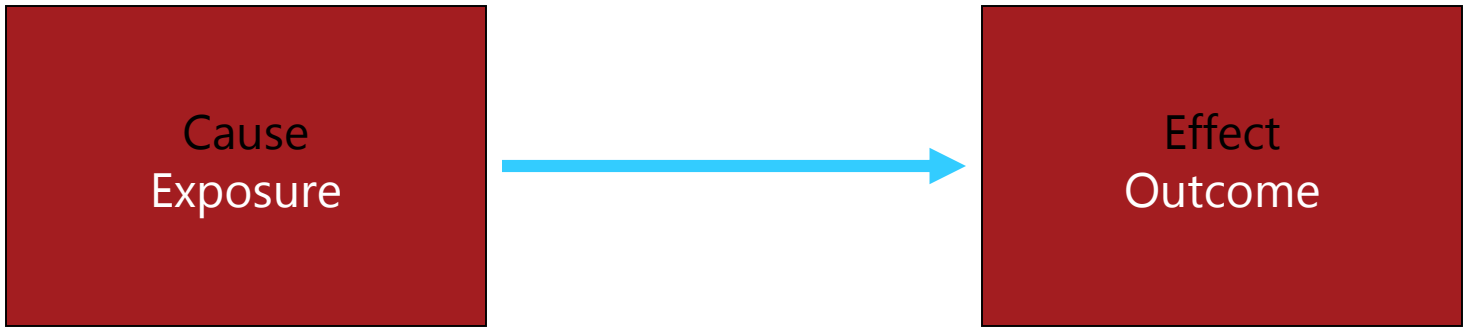
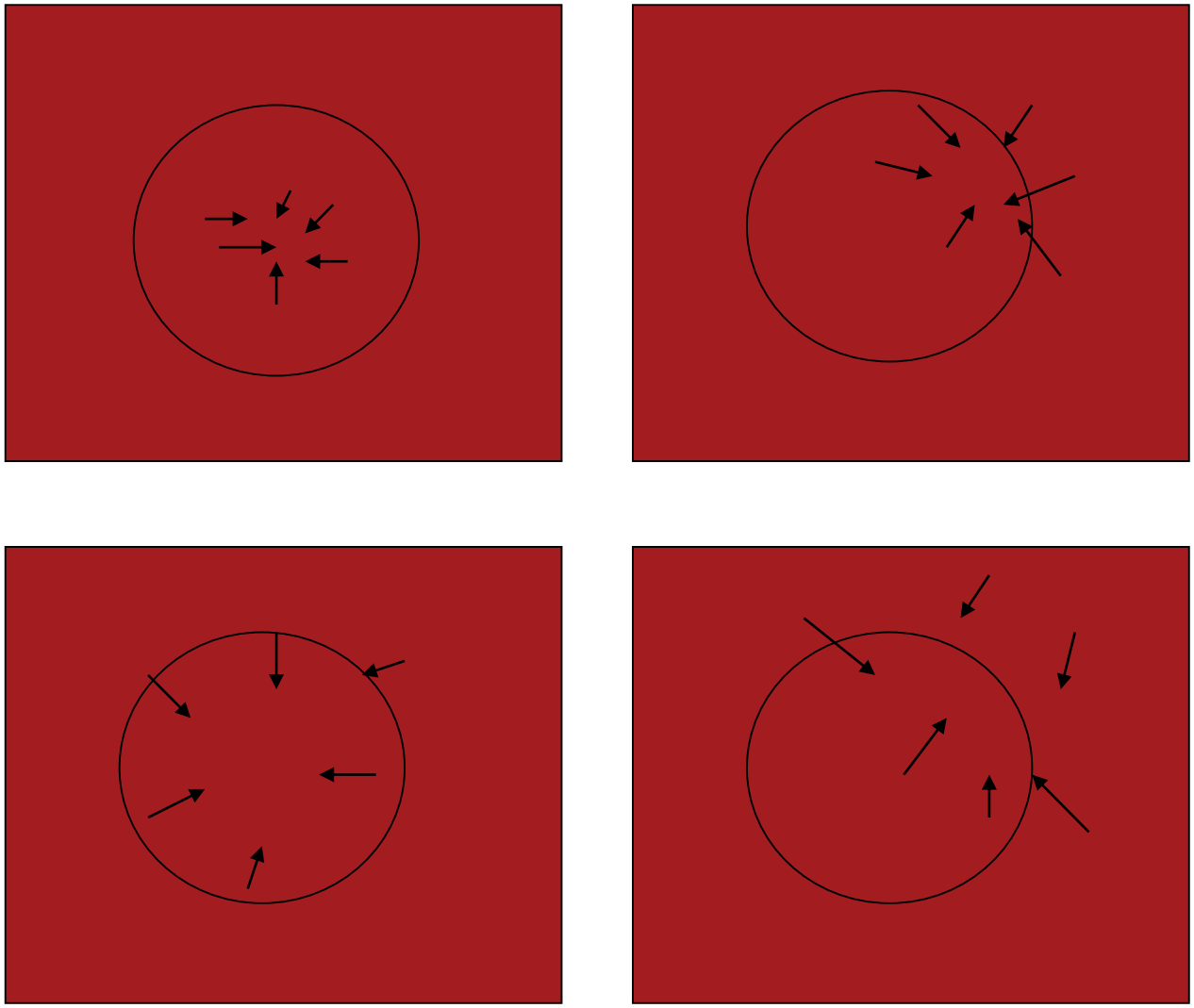
The simple universe from the perspective of an epidemiologist



The association between E og O is estimated

The association measure may describe a CAUSAL relation, however may also be
A chance finding: random variation
False: as a result of bias
True but non-causal: as a result of confounding
Dependent of other factors: interaction, effect measure modification
Non-generalizable: unique to the study population



Lack of precision

Bias

Precision

- Random error
- Precision increases with increasing sample size
- PRIOR to the study: Power calculations, where the α-level (level of significance) and the desired power are set, and the necessary sample size is determined

Type I error

An association is demonstrated, although no association exists

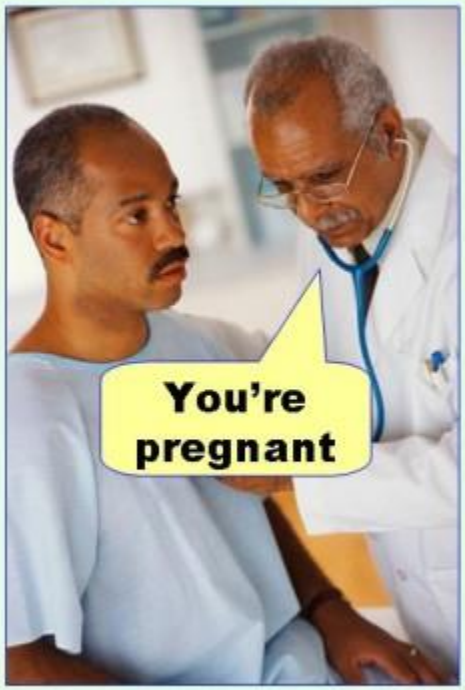
With an α-level of 5%, the risk of Type I error is 5%

If the α-level is diminished (eg. 1%), the risk of Type II error increases

Type II error

- No a … h actua
- The p … e. A powe … e of dem…

Type I error
(false positive)



Type II error
(false negative)

Bias

Systematic deviation of results or inferences from the truth or processes leading to such deviations Porta M: A Dictionary of Epidemiology. OUP, 2009

- Systematic errors in measurements
- Systematic errors of statistical associations resulting from measurement errors, design errors, or errors in analysis
- Errornous interpretations of statistical associations

Selection bias

Information bias

Selection bias

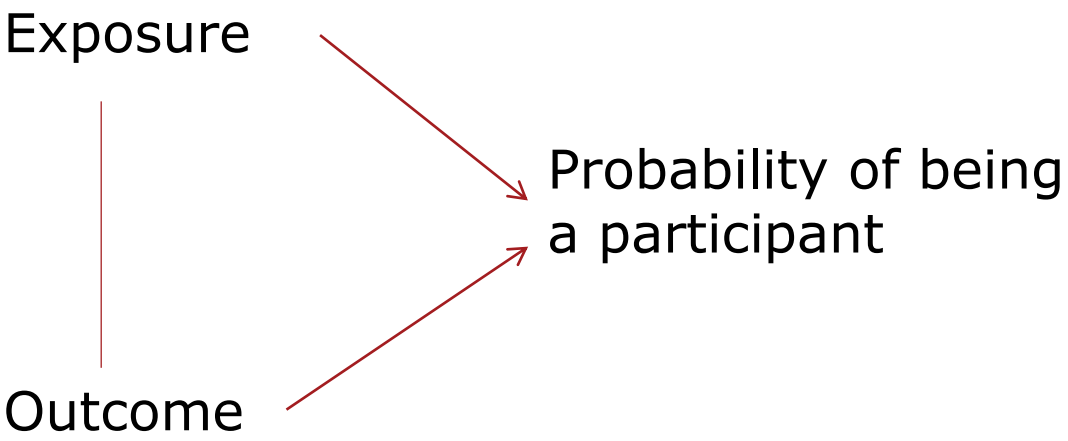
A situation where the selection or participation pattern in a study implies a systematic deviation of it's results

Occurs when participation is associeted with BOTH exposure status and outcome status

Case-control: OC and DVT : The hypothesis is known and exposure increases the probability of getting a diagnosis

Cohort: Eg. the Thule workers: All ill and exposed participated, non-participation in other groups

Selectionsbias



Will create an association between exposure and outcome that reflects the data collection procedures

Selectionsbias

Terms	
Self-selection bias eller volunteer bias	There are reasons ⋯⋯ semen quality studies
Self-selection bias eller motivation bias	In non-randomised studies → lack of exchangability
Healthy worker effect	E.g. Low back pain studies, fertility studies
Non-response bias	
Reverse causality	Selection to exposure due to outcome
Differential loss-to-follow-up	Dependent on disease status

Berkson's bias described by the American statistician Joseph Berkson (1899–1982)

(Berkson's paradox, ~ Simpson's paradox)

A form of selection bias that causes hospital cases and controls in a case control study to be systematically different from one another, because the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to the hospital.

This produces a systematically higher exposure risk among hospital patients, so it distorts the odds ratio

Examples:

Oral contraceptives and DVT

Disease-disease associations in hospital data
individuals with two or more diseases have a higher probability of being hospitalized than persons with only one disease—even if these reasons are independent

What to do ……..

Data collection:

Avoid loss to follow-up or non-participation

Data analysis:

Drop-out analyses: Are participants equal to non-participants?

Intention-to-treat analyses: keep the random allocation to intervention and reference group despite *compliance* problems.

Information bias

Imprecise measurement of exposure: time, intensity, proxy measure

outcome: diagnostic imprecision, incomplete registration

Eg: recall bias, interviewer bias, respondent bias, instrument problems, uneven collection of data

Misclassification

Some study subjects are categorized in the wrong category

Non-differential misclassification:

The same magnitude of outcome misclassification among exposed and unexposed

or

The same magnitude of exposure misclassification among cases and non-cases

Leads to an underestimation of the association

Differential misclassification:

Validity of outcome status is dependent on exposure status

Estimate unpredictable

Bias and Misclassification

An example: Asbestos and mesothelioma

TRUE	+ mesotheliom	- mesotheliom
+ asbest	50	10
- asbest	50	90

OR = (ad) / (bc) = 9

Loss-to-follow-up: 50% in all categories

	+ mesotheliom	- mesotheliom
+ asbest	25	5
- asbest	25	45

OR = (ad) / (bc) = 9

Loss-to-follow-up: 50% among cases

	+ mesotheliom	- mesotheliom
+ asbest	25	10
- asbest	25	90

OR = (ad) / (bc) = 9

Bias and Misclassification

An example: Asbestos and mesothelioma

TRUE	+ mesotheliom	- mesotheliom
+ asbest	50	10
- asbest	50	90

OR = (ad) / (bc) = 9

50% under reporting of exposure: NON-DIFFERENTIAL MISCLASSIFICATION

	+ mesotheliom	- mesotheliom
+ asbest	25	5
- asbest	75	95

OR = (ad) / (bc) = 6.3

50% under reporting among healthy subjects: DIFFERENTIAL MISCLASSIFICATION

	+ mesotheliom	- mesotheliom
+ asbest	50	5
- asbest	50	95

OR = (ad) / (bc) = 19

Non-Differerential misclassification leads to underestimation of estimate
Differential misclassification leads to unpredictable bias

Warning: Not always true ….

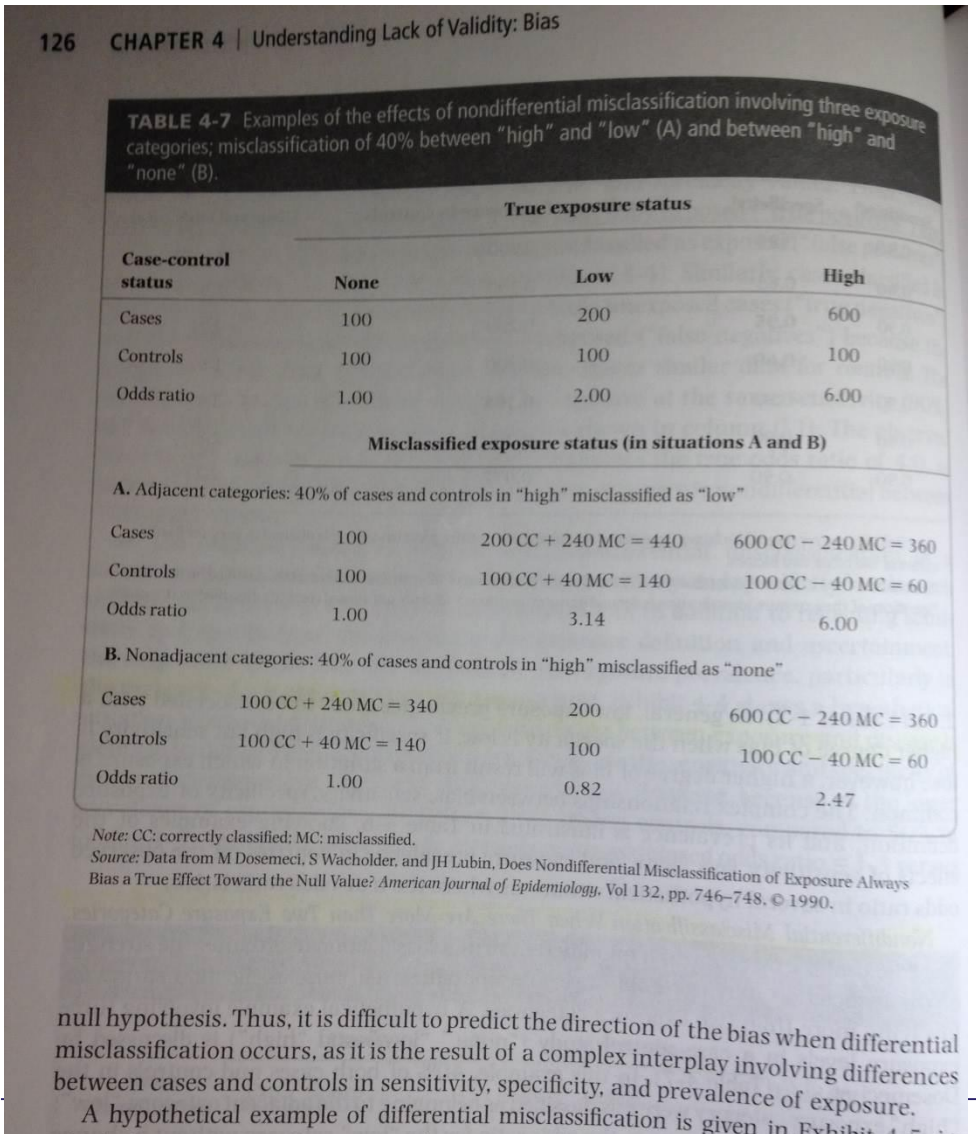


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TABLE 4-7 Examples of the effects of nondifferential misclassification involving three exposure categories; misclassification of 40% between "high" and "low" (A) and between "high" and "none" (B).

Case-control status	True exposure status: None	Low	High
Cases	100	200	600
Controls	100	100	100
Odds ratio	1.00	2.00	6.00
Misclassified exposure status (in situations A and B)			
A. Adjacent categories: 40% of cases and controls in "high" misclassified as "low"			
Cases	100	200 CC + 240 MC = 440	600 CC − 240 MC = 360
Controls	100	100 CC + 40 MC = 140	100 CC − 40 MC = 60
Odds ratio	1.00	3.14	6.00
B. Nonadjacent categories: 40% of cases and controls in "high" misclassified as "none"			
Cases	100 CC + 240 MC = 340	200	600 CC − 240 MC = 360
Controls	100 CC + 40 MC = 140	100	100 CC − 40 MC = 60
Odds ratio	1.00	0.82	2.47

Note: CC: correctly classified; MC: misclassified.
Source: Data from M Dosemeci, S Wacholder, and JH Lubin, Does Nondifferential Misclassification of Exposure Always Bias a True Effect Toward the Null Value? *American Journal of Epidemiology*, Vol 132, pp. 746–748, © 1990.

null hypothesis. Thus, it is difficult to predict the direction of the bias when differential misclassification occurs, as it is the result of a complex interplay involving differences between cases and controls in sensitivity, specificity, and prevalence of exposure.

A hypothetical example of differential misclassification is given in Exhibit

- More than two exposure categories
- Exposure misclassified in a non-adjacent category
- Example: Alcoholics claiming to be non-drinkers

Examples of bias sources

Healthy worker bias: A selection bias (being at the labour marked requires good health) or the opposite

Interviewer bias: Interviewer may influence data

Recall bias: Imbalanced rememberance, imprecision

Reporting bias: misclassification, social values

Withdrawal bias: ….. and continue in a study

Ascertainment bias: Imbalance in types of persones in a sample

Design bias: e.g. Un-controlled studies, where the effect of two processes are mixed

Detection bias: e.g. a disease is more likely to be diagnosed in one setting than in another

Digit preference bias: may produce false threshold values

Publication bias: which results are published?

Etc…… Not the name, but the contents are important!

Types of bias in different study designs (1)

RCTs:

Selective inclusion (not neccesarily selection *bias*).

Selective participation.

Differential loss-to – follow-up.

Differential compliance.

Blinding decreases information bias.

Cohort studies:

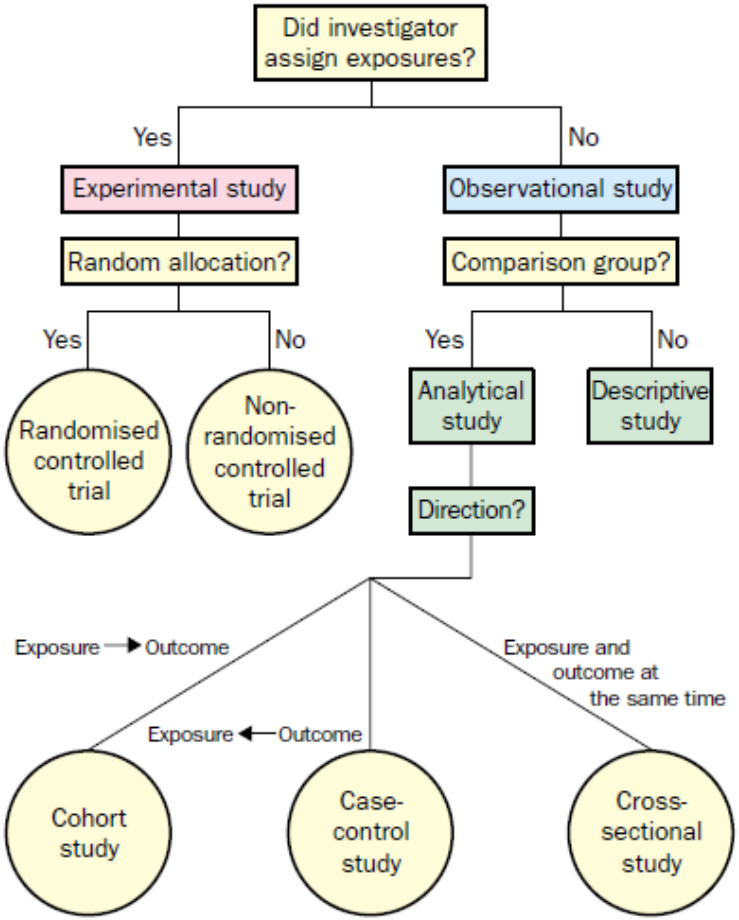
Selective inclusion (not neccesarily selection *bias*).

Selective participation.

Differential loss-to – follow-up.

Known risk factors may increase probability of being diagnosed.

Known risk factors may influence exposure profile



Types of bias in different study designs (2)

X-sectional studies:

Selective participation

Reverse causality

Healthy worker effect

Information bias, incl. recall bias

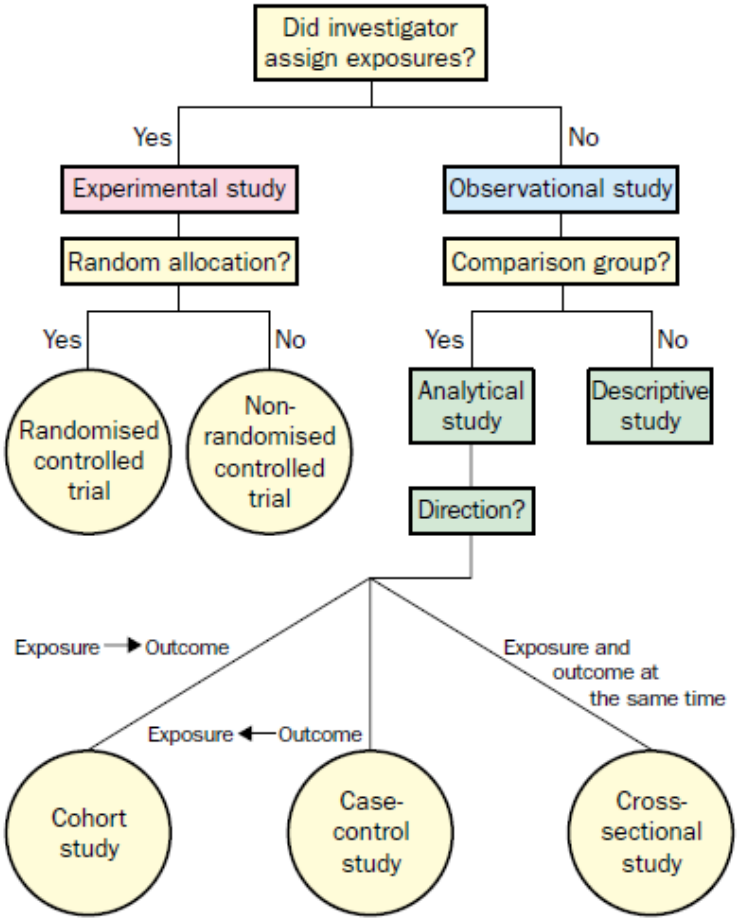
Length-sample-bias

Case-control undersøgelser

Selective participation

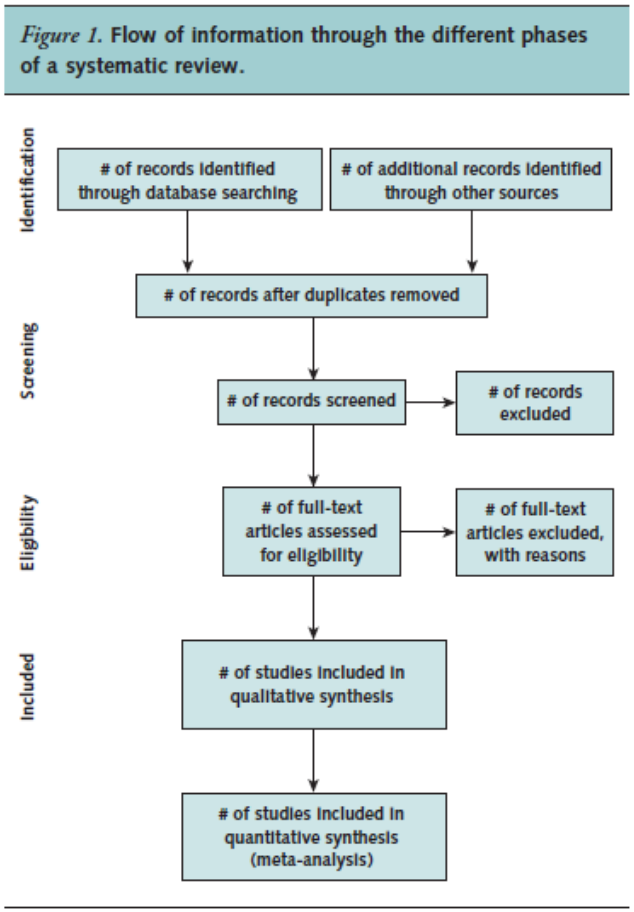
Recall bias – case status is known and may influence exposure information

Selection of controls dependent of exposure



Bias in systematic reviews and meta analyses

- Selection of included studies
- Publication bias
- Other bias types
- … systematic reviews may be biased, despite being in the top of the evidence hierarchy



Small study effects

Publication bias is one type of *small study effect*, where small studies can create bias, e.g.

- *Publication bias*: small studies are more likely to get published if they have statistically significant results
- *Outcome reporting bias:* Small studies select outcomes that are significant to increase publication chances
- *Clinical heterogeneity:* Small studies will often have more selected populations than larger studies. This is well known from RCTs
- *Chance* has a bigger influence on small studies than larger ones.

Funnel plot for detection of publication bias

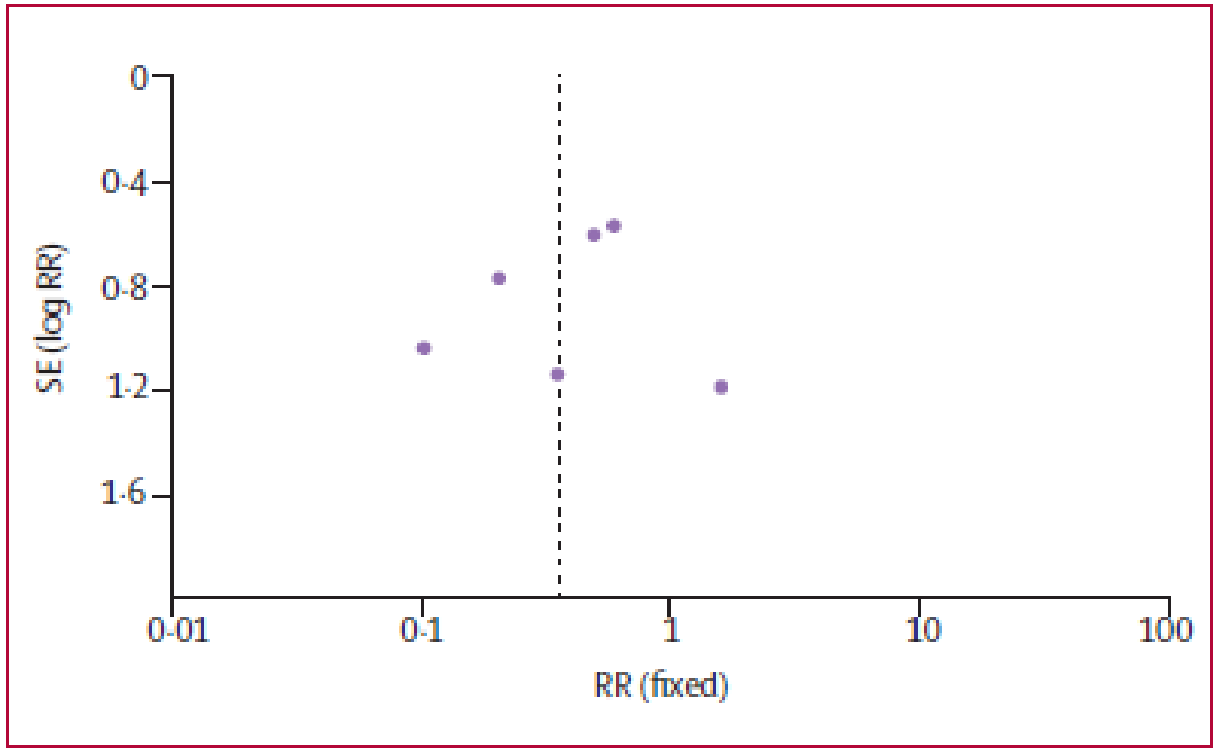
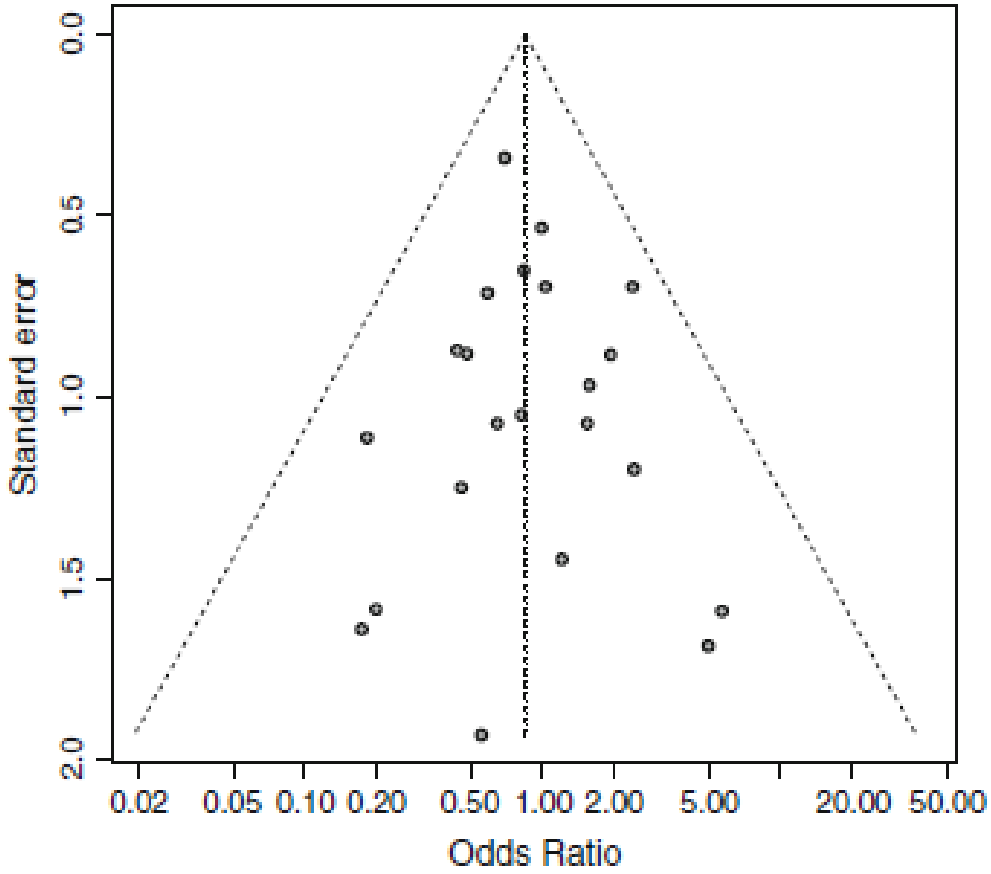


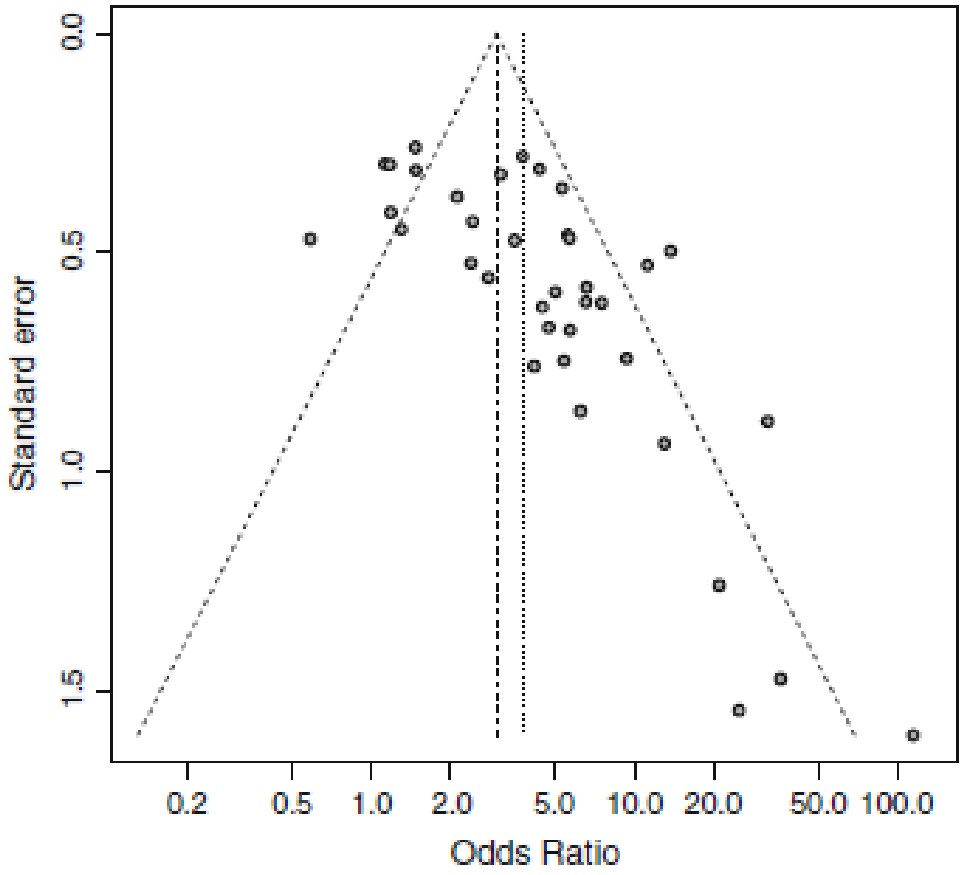
Figure 6: Funnel plot to assess publication bias

Funnel plot: Expected



Simulated ORs and SEs

Funnel plot: Observed



ORs and SEs from a metananlysis on NSAID and acute pain

Publication bias in a literature review:? Maternal toxoplasmosis and schizophrenia

Table 2: Population based studies of maternal IgG directed against Toxoplasma gondii and the risk of schizophrenia.

Study	Design and	Case ascertainment	Exposure measured	Adjustment for confounding	Main findings
Buka et al. 2001, USA	Nested case-control, Underlying cohort: 3.804 liveborn between 1959 and 1966 Cases: 27 Controls: 54	PD by DSM-IV 2-stage diagnostic assessment procedure *(i)*Identified through interviews and/or record linkage with psychiatric treatment facilities *(ii)* Diagnostic interviews.	Maternal blood samples at the delivery. Albumin-IgG-ratio. Solid phase enzyme immunoassay.	Sex, ethnicity, date of birth, social class, maternal mental illness, weight gain and smoking.	Mean difference=0,02 t-test=0,51, p=0,61
Brown et al. 2005, USA	Nested case-control Underlying cohort: 12.094 liveborn between 1959 and 1967 Cases: 63 Controls: 123	SSD by DSM-IV 3-stage diagnostic assessment procedure *(i)* Identified through pharmacy- and patient registers *(ii)* chart review *(iii)* Diagnostic interviews.	Maternal sera obtained during pregnancy. Absolut concentration of IgG titers, maternal serum, positive TG-titer >90th percentile. Sabin-Feldman dye test.	Maternal age.	OR=2,61 95% CI:1.00-6,82
Blomström et al. 2012, Sweden	Population based case-control. Participants born between 1975 and 1985 and followed up until 2004 Cases: 198 Controls: 524	SC by ICD-10 and 9 2-stage diagnostic assessment procedure, *(i)* Identified through the psychiatric healthcare registration system. *(ii)* Review of diagnoses to verify concordance between clinical and research diagnose	Neonatal dried blood samples, 3-14 days old. Absolut concentration of IgG titers, positive TG-titer >90th percentile. Immunoassay.	Maternal age, sex, migration, place and date of birth.	OR=3,2 95%CI:1.0-9,8
Mortensen et al. 2007, Denmark	Population based case-control Participants born 1981 or later and followed up through 1999 Cases: 71 Controls: 648	SC by ICD-10, 1-stage diagnostic assessment procedure, *(i)* Identified through the Danish National Psychiatric Register.	Neonatal dried blood samples, 5-7 days old. Absolut concentration of IgG titers, positive TG-titer >75th percentile. Immunoassay.	Place and year of birth, gender, family history of mental illness.	OR=1,79 95% CI:1,01-3,15

Note: PD, Psychotic disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; SSD, Schizophrenia Spectrum Disorders; OSSD, Other Schizophrenia Spectrum Disorders; ICD, International Classification of Diseases; AD, Affective Disorders.

Another example ……

Maternal Use of Selective Serotonin Reuptake Inhibitors and Risk of Miscarriage – Assessing Potential Biases

Rie Laurine Rosenthal Johansen, Laust Hvas Mortensen, Anne-Marie Nybo Andersen, Anne Vinkel Hansen, Katrine Strandberg-Larsen

Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Paediatric and Perinatal Epidemiology, 2015, **29**, 72–81

Abstract

Background: The use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has been associated with miscarriage, but the association may be biased by maternal mental illness, lifestyle and exposure misclassification.
Methods: A register study on all pregnancies in Denmark between 1996 and 2009 was conducted using individualised data from the Danish National Patient Register, the Medical Birth Register, the Danish Psychiatric Central Register, the Danish National Prescription database and the Danish National Birth Cohort (DNBC).
Results: A total of 1 191 164 pregnancies were included in the study, of which 98 275 also participated in the DNBC. Pregnancies exposed to SSRIs during or before pregnancy were more likely than unexposed pregnancies to result in first trimester miscarriage, hazard rate (HR) = 1.08 [95% confidence interval (CI) 1.04, 1.13] and HR = 1.26 [95% CI 1.16, 1.37], respectively. No difference was observed for second trimester miscarriage. SSRI-exposed pregnancies without a maternal depression/anxiety diagnosis from a psychiatric department were less likely to result in first trimester miscarriage than unexposed pregnancies with a diagnosis, HR = 0.85 [95% CI 0.76, 0.95]. SSRI-exposed pregnancies were characterised by an unhealthier maternal lifestyle and mental health profile than unexposed pregnancies, whereas no convincing differences were observed between pregnancies exposed to SSRIs during versus before pregnancy. Substantial disagreement was found between prescriptions and self-reported use of SSRIs, but it did not affect the estimated hazard ratios.
Conclusion: Confounding by indication and lifestyle in pregnancy may explain the association between SSRI use and miscarriage.

Every result should be critical evaluated with respect to bias

- Bias can not be (easily) adjusted for in the analyses
- Direction and magnitude of bias should be considered
- Quanitative bias analyses are warranted
- Every study has it's own bias risks

WORK

Which sources of bias may affect your study and how can you address these potential biases?

Work 10 minutes with each project

Quick Overview

Probability of:	Ecological	Cross-sectional	Case–control	Cohort	Randomized trial
Selection bias					
Selection of subjects	N/A	medium	high	low	low
Loss to follow-up	N/A	N/A	low	high	medium
Recall bias	N/A	high	high	low	low
Confounding	high	medium	medium	low	very low

[a] Modified from Beaglehole *et al.* (1993)
N/A = Not applicable.

Confounding

Learning objectives:

What is confounding?

Methods to prevent confounding

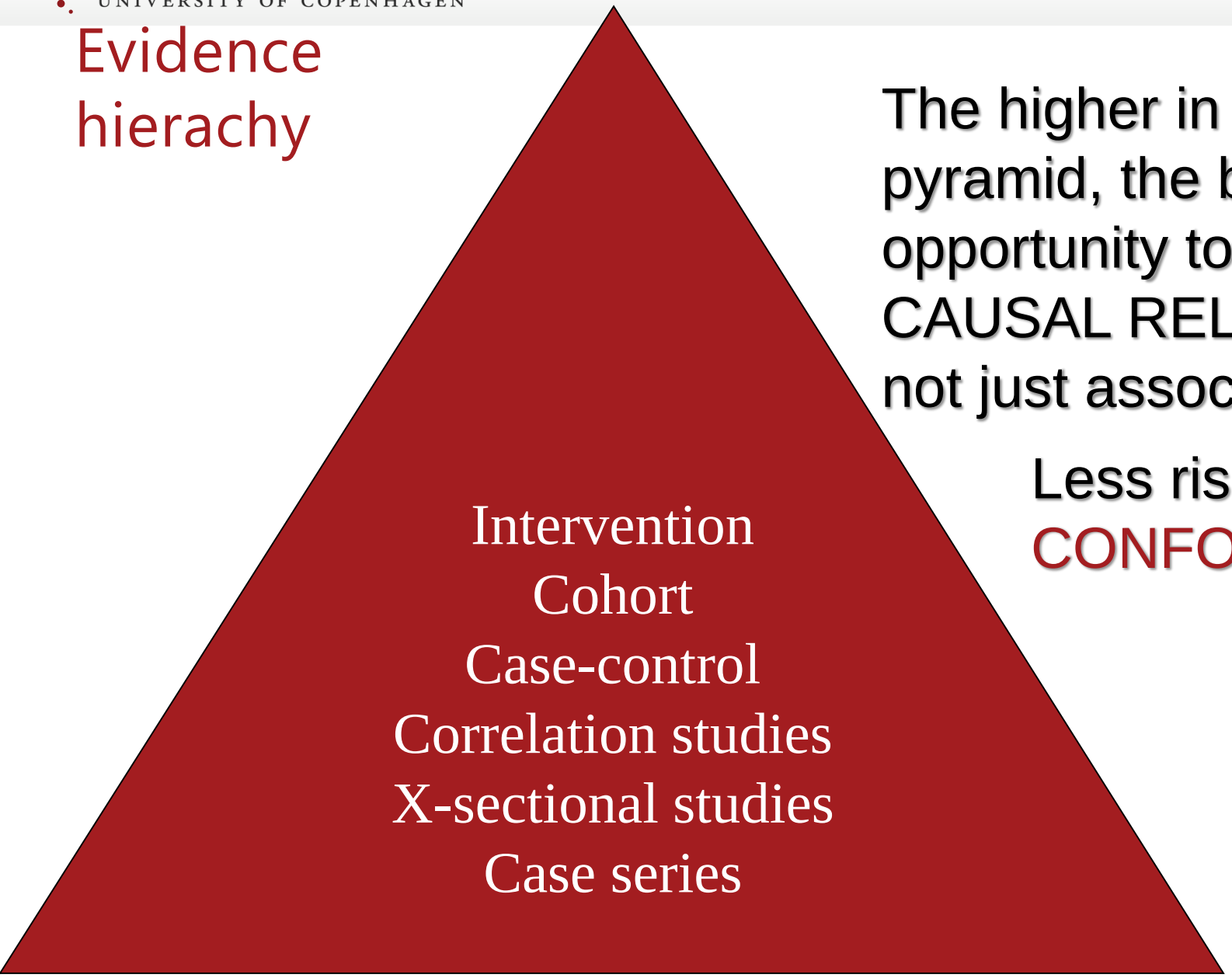
Methods to evaluate confounding

What is confounding ?

- *A situation in which effects of two risk factors for the disease under study are mixed*, or
- *An association between an exposure and an outcome is mixed up with the real effect of another exposure on the same outcome*

Dictionary of epidemiology

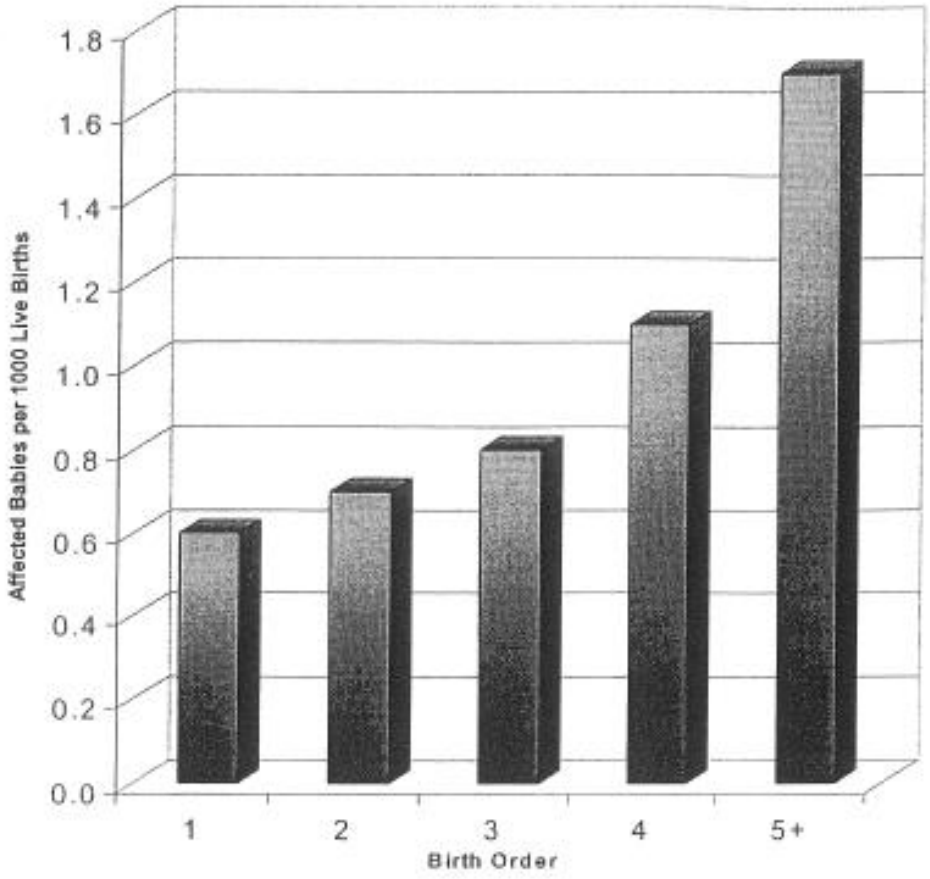
Evidence hierachy



The higher in the pyramid, the better opportunity to assess CAUSAL RELATIONS, not just assocations

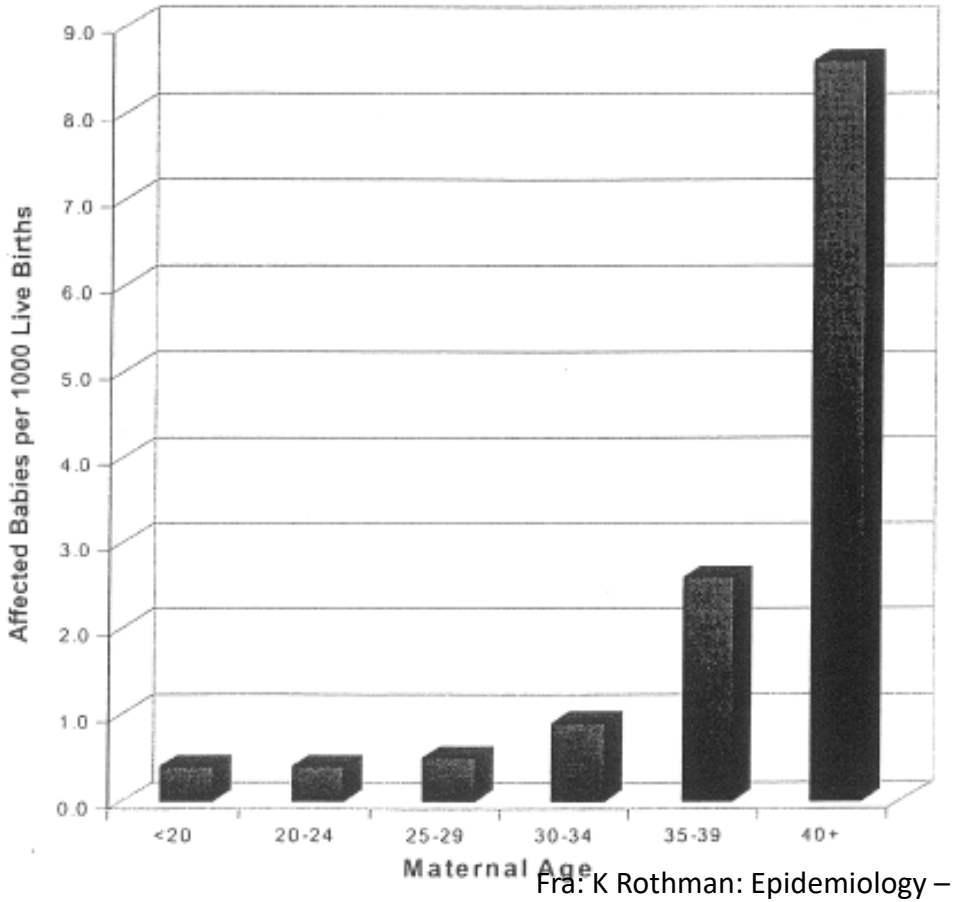
Less risk of CONFOUNDING

Prevalence of Down Syndrom according to birth order



Fra: K Rothman: Epidemiology – An Introduction 2002

Prevalence of Down Syndrom according to maternal age



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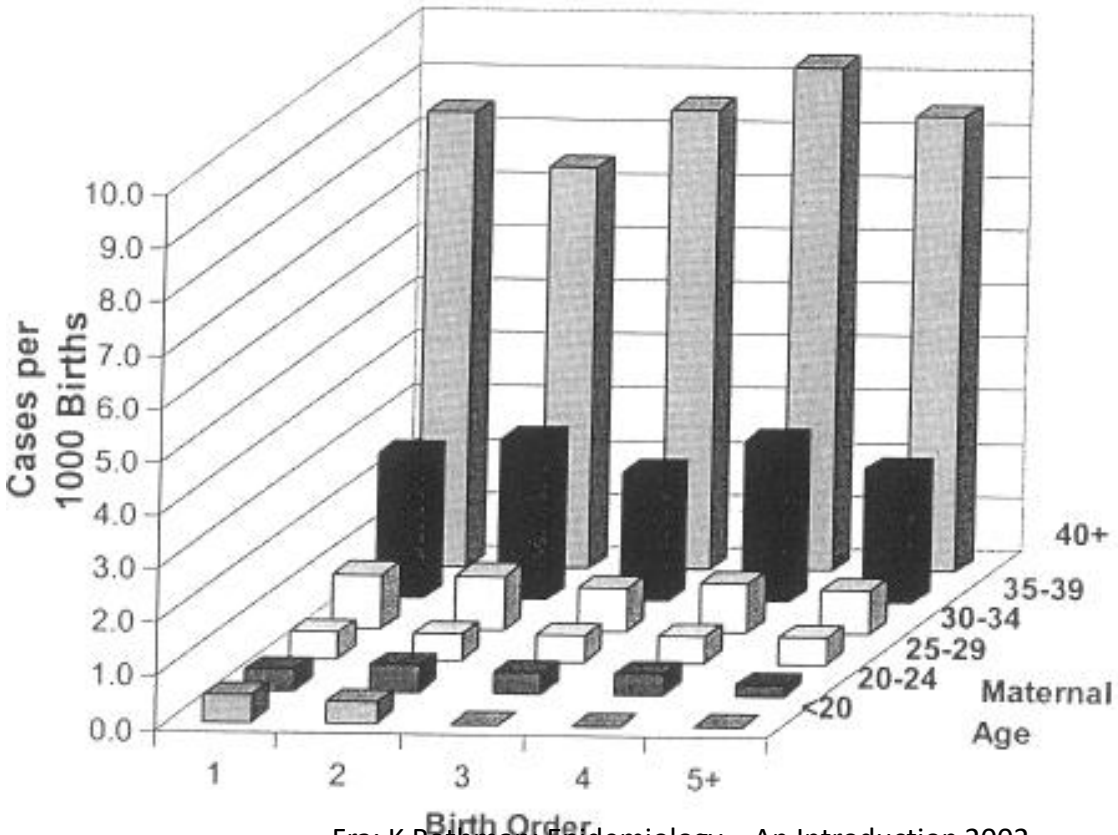
Prevalence af Down Syndrom according to birth order and maternal age



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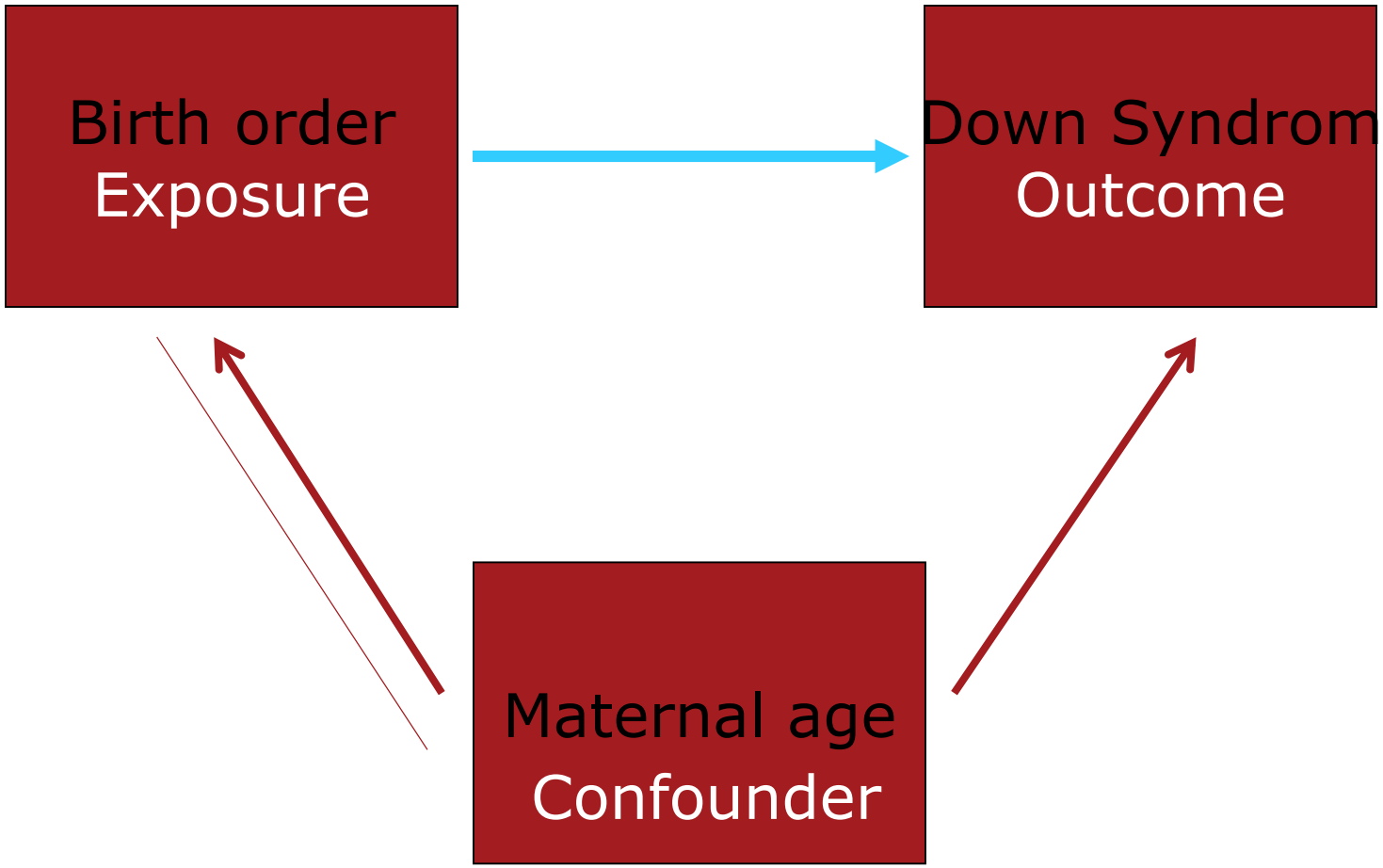
Stratification

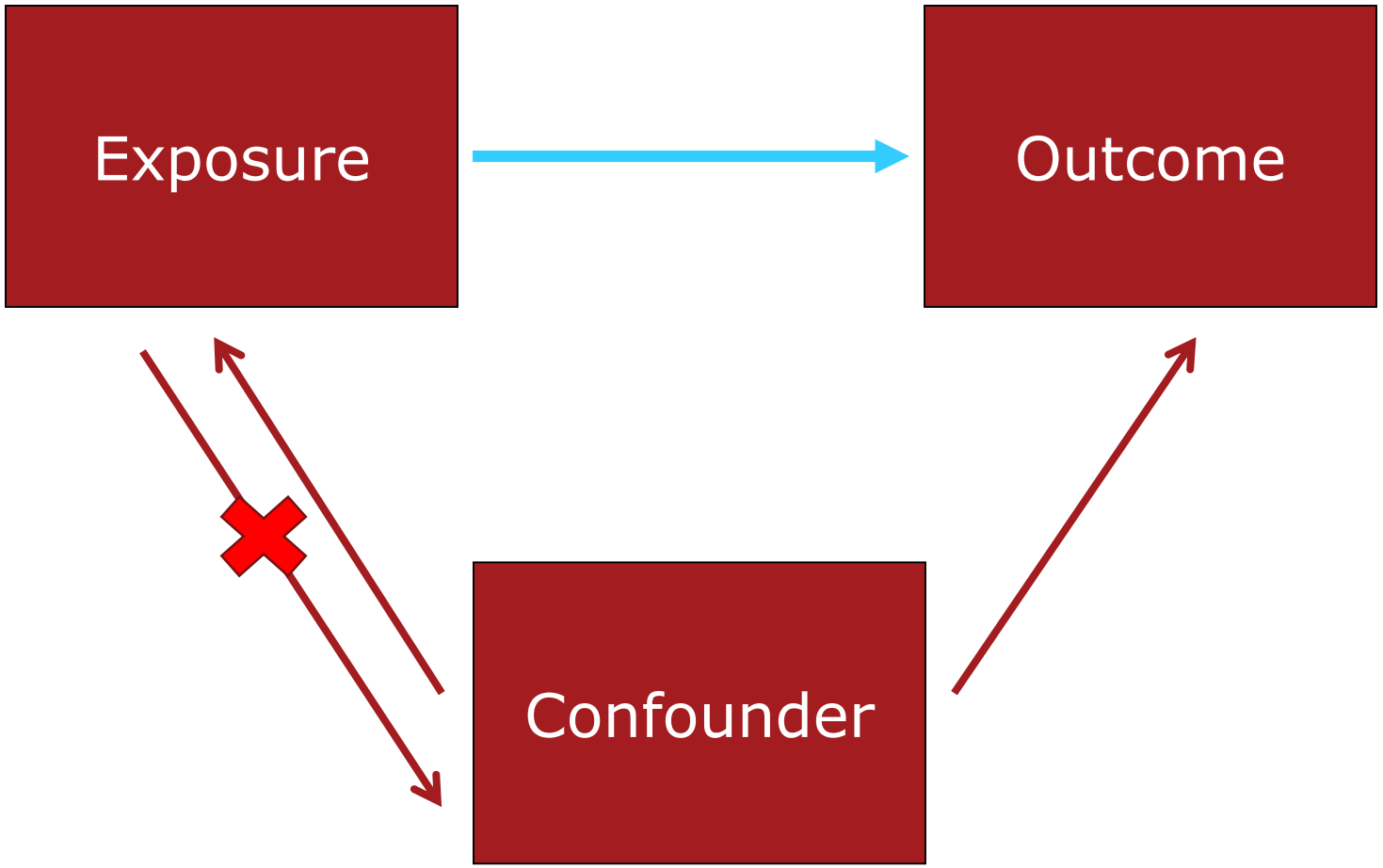
In the epidemiologic universe



Characteristics of a confounder

1. An independent risk factor for outcome (i.e. among non-exposed)
2. Statistical associated with exposure
3. Not an intermediate between exposure and outcome

In the epidemiologic universe



Confounding example:
Paternal age and spontaneous abortion

Hypothesis:

Old fathers are a risk factor for abortion

Data:

Cohort of 100.000 children and information about parental age

What is the obvious confounding factor?

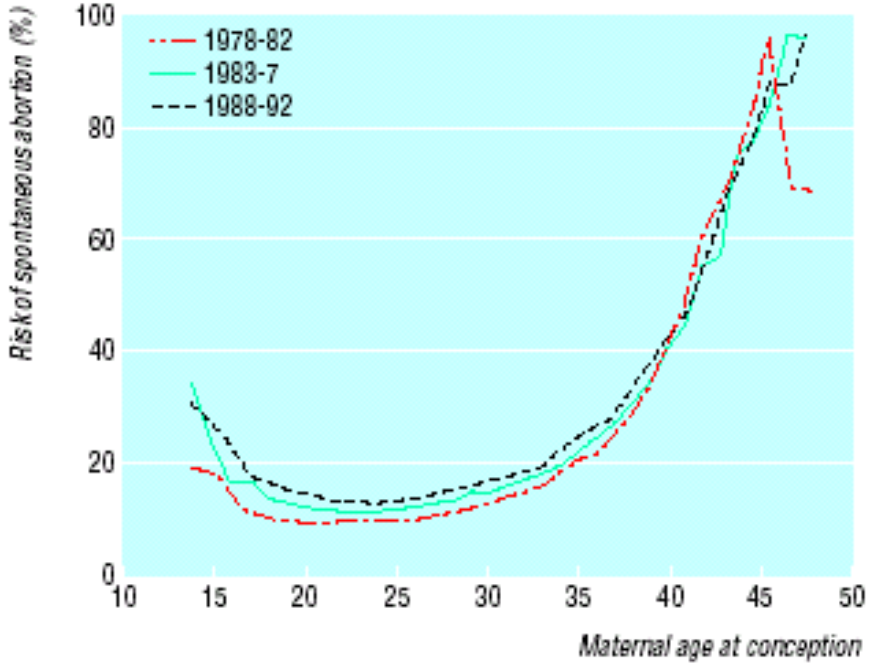


Fig 2 Risk of spontaneous abortion according to maternal age at conception, stratified according to calendar period

American Journal of Epidemiology

Advanced Paternal Age and Risk of Fetal Death: A Cohort Study

Anne-Marie Nybo Andersen[1], Kasper Daniel Hansen[2], Per Kragh Andersen[2], and George Davey Smith[3]

TABLE 4. Crude and adjusted hazard ratios of fetal death according to paternal age at conception among 23,821 pregnancies, Danish National Birth Cohort, 1997–1999*

Paternal age	No. of events	Risk of fetal death	
		Crude	
		Hazard ratio	95% confidence interval
≤24 years	60	1.01	0.76, 1.32
25–29 years	294	1	Referent
30–34 years	367	1.02	0.87, 1.20
35–39 years	213	1.38	1.15, 1.64
40–44 years	62	1.35	1.03, 1.77
45–49 years	18	1.54	0.96, 2.48
≥50 years	11	2.65	1.45, 4.84

* Three different types of adjustment for maternal age.
† Adjusted for maternal age, parity, number of previous abortions, alcohol and coffee consumption during pregnancy, maternal and paternal smoking, and maternal and paternal occupational status.

Correlation between maternal and paternal age

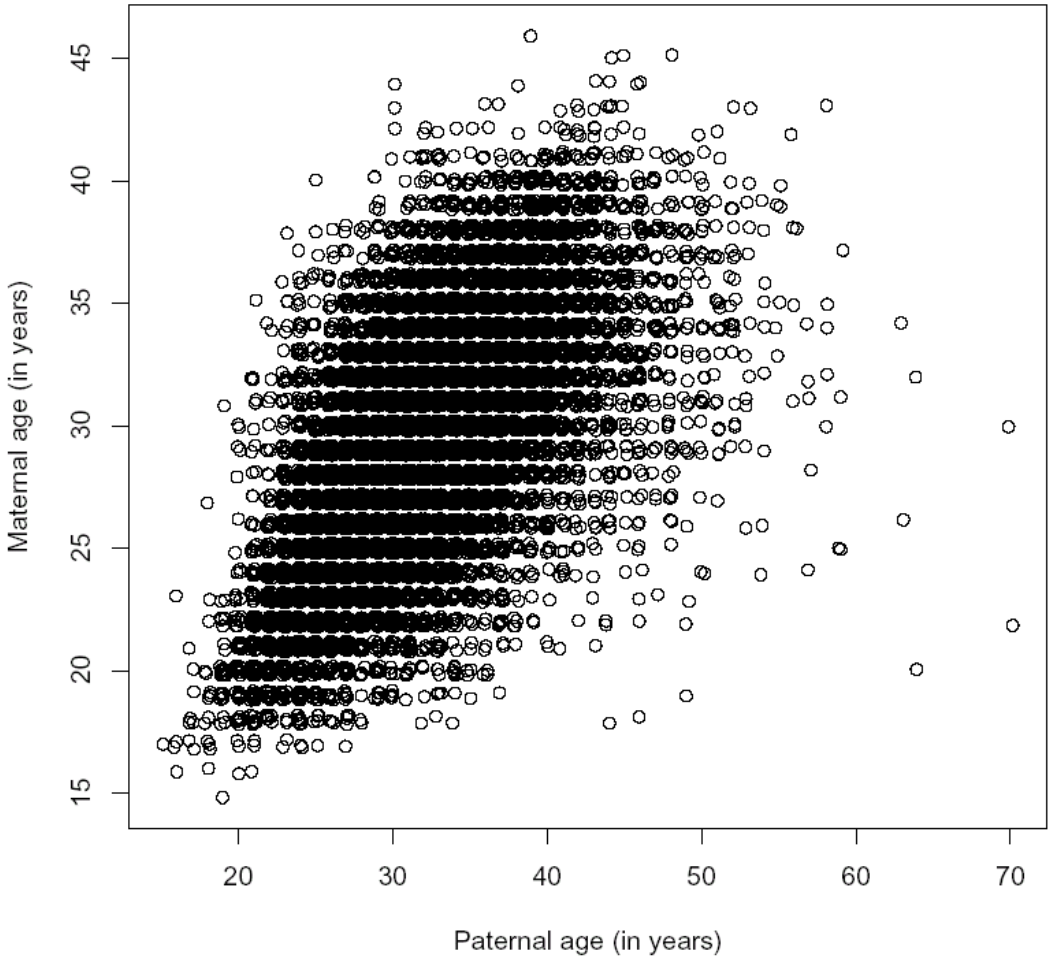


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TABLE 4. Crude and adjusted hazard ratios of fetal death according to paternal age at conception among 23,821 pregnancies, Danish National Birth Cohort, 1997–1999*

Paternal age	No. of events	Risk of fetal death							
		Crude		Adjusted†					
				Maternal age in 5-year groups		Maternal age in 1-year groups		Maternal age modeled using restricted cubic splines	
		Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
≤24 years	60	1.01	0.76, 1.32	1.09	0.81, 1.47	1.11	0.82, 1.51	1.09	0.80, 1.49
25–29 years	294	1	Referent	1	Referent	1	Referent	1	Referent
30–34 years	367	1.02	0.87, 1.20	0.87	0.74, 1.04	0.90	0.76, 1.07	0.89	0.75, 1.05
35–39 years	213	1.38	1.15, 1.64	0.98	0.80, 1.21	0.99	0.80, 1.23	0.97	0.79, 1.21
40–44 years	62	1.35	1.03, 1.77	0.82	0.60, 1.12	0.79	0.58, 1.09	0.79	0.57, 1.08
45–49 years	18	1.54	0.96, 2.48	1.03	0.63, 1.70	1.02	0.61, 1.68	1.00	0.60, 1.65
≥50 years	11	2.65	1.45, 4.84	1.69	0.91, 3.15	1.71	0.91, 3.21	1.62	0.86, 3.03

* Three different types of adjustment for maternal age.

† Adjusted for maternal age, parity, number of previous abortions, alcohol and coffee consumption during pregnancy, maternal and paternal smoking, and maternal and paternal occupational status.

New analyses

2014 study (in progress, confidential results)
Material and methods:
All registered pregnancy outcomes in Denmark, 1994-2010 (N=1,589,208), with full and valid information (N=1,153,049). Exclusions: Registered partner a woman (1046); No father assigned (371,065); Other exclusions: no or impossible maternal age (67), ectopic pregnancies (16,270), impossible GA (3078), no information on parental education (42,700). GA at event <5 weeks (1939).

Numbers	Live birth	Stillbirth	2nd trim. misc.	1st trim. misc.	Induced abortion	*All pregnancies
Total	906,801	4,748	22,487	105,229	112,908	1,154,988

Events	Stillbirth	late misc.	early misc.	All pregnancies	
Paternal age				N	%
<20 years	21	47	258	3,608	0.3
20-24 years	313	1,231	5,320	74,246	6.4
25-29 years	1,274	5,533	24,033	316,717	27.4
30-34 years	1,593	7,993	35,491	414,011	35.8
35-39 years	1,012	4,938	24,328	231,361	20.0
40-44 years	404	1,976	10,781	82,637	7.2
45-49 years	91	561	3,582	23,465	2.0
50+ years	40	208	1,436	8,943	0.8
Total	4,748	22,487	105,229	1,154,988	100

Assignment of **father**: Minimal differential misclassification, i.e. sole adult male living together with the mother or married to mother at time of conception.

Parental age at conception: Age at date of birth minus GA on event. If missing: single value imputation: 280 d. for live births, 252 d for stillbirths, 62 d. for miscarriage, 56 d for 1st trim. terminations, 108 d. for 2nd trimester terminations.

Work in progress: respect confidentiality, please

Residual confounding

Maternal age adjustments

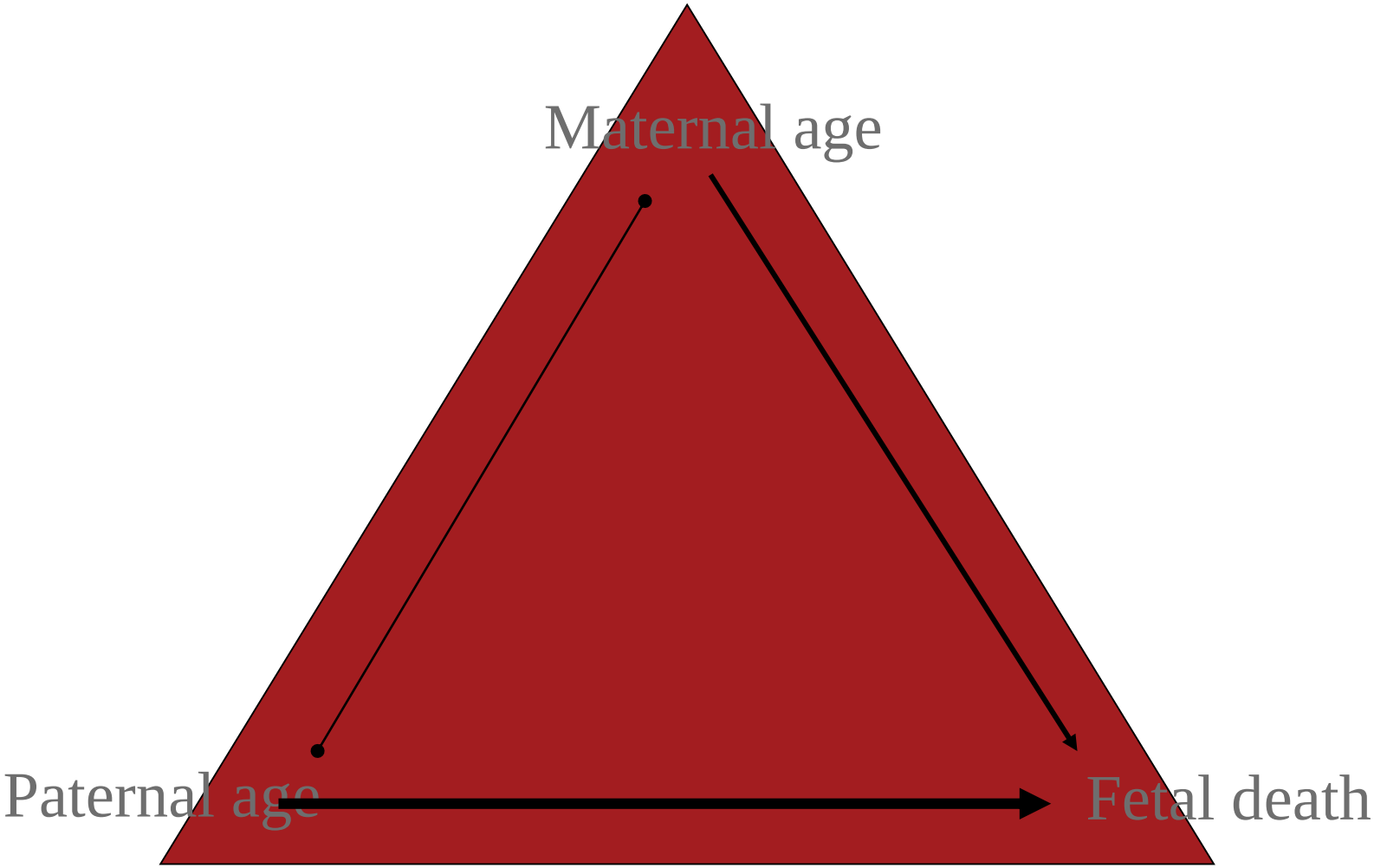
Relative risk of miscarriage according to paternal age at conception. (Hazard Ratios, HR [95% CI in brackets] . Pregnancies in Denmark, 1994-2010

Paternal age	5-year groups	1-year groups	Continuous
<20 years	1.06 [0.94,1.18]	1.06 0.94,1.19]	1.67 [1.49,1.87]
20-24 years	1.03 [1.00,1.05]	1.02 [0.99,1.05]	1.28 [1.25,1.32]
25-29 years	1 [ref]	1 [ref]	1 [ref]
30-34 years	1.01 [1.00,1.03]	1.01 [0.99,1.03]	0.91 [0.89,0.92]
35-39 years	1.15 [1.13,1.17]	1.01 [0.99,1.03]	0.93 [0.91,0.95]
40-44 years	1.28 [1.25,1.31]	1.01 [0.98,1.03]	1.04 [1.02,1.07]
45-49 years	1.35 [1.30,1.39]	1.00 [0.96,1.04]	1.16 [1.12,1.20]
50+ years	1.39 [1.32,1.47]	1.02 [0.97,1.08]	1.21 [1.15,1.27]

Models only adjusted for maternal age

Work in progress: respect confidentiality, please

Confounding



What does confounding?

Over-estimation of causal associations

Under-estimering of causal associations

May flop the causal association around

But even a confounded estimate may inform about risk markers or risk groups

The special role of SES and e.g. ethnicity

Identification af confounding

Is a theoretical piece of work, not a empirical ,

i.e. potential confounders are selected a priori

Overadjustment is just as bad as confounding (underadjustment)

Causal diagrams are helpful! To be drawn…….

Directed Acyclic Graphs

Statistical analysis

The Directed Acyclic Graph (DAG) presented in Fig. 1 was constructed by having three epidemiologists construct the DAG independently. The epidemiologists were instructed to draw a DAG of maternal smoking, maternal prepregnant BMI and birthweight without consideration of the data available. The resulting DAGs were then reviewed and synthesized by the first and last author. The resulting DAG is a quantification of the authors' subjective beliefs and should not be considered as a 'true' model of the causal relationships, but rather as one model among other possible models. The DAG predicts that, conditional on confounders and education, BMI and smoking should be independent of each other (i.e. BMI and smoking should be d-separated by education and the confounders). To test this, we calculated Cochrane Mantel–Haenzel tests of conditional independence.

For the analyses of mediation, we decomposed the total effect (TE) into a direct effect and an indirect effect. Commonly, the strategy of decomposition is only used when there is no (unit-level) interaction between exposure and outcome (Robins and Greenland, 1992; Kaufman *et al*., 2004). Statistical interaction is a phenomenon that is dependent on the

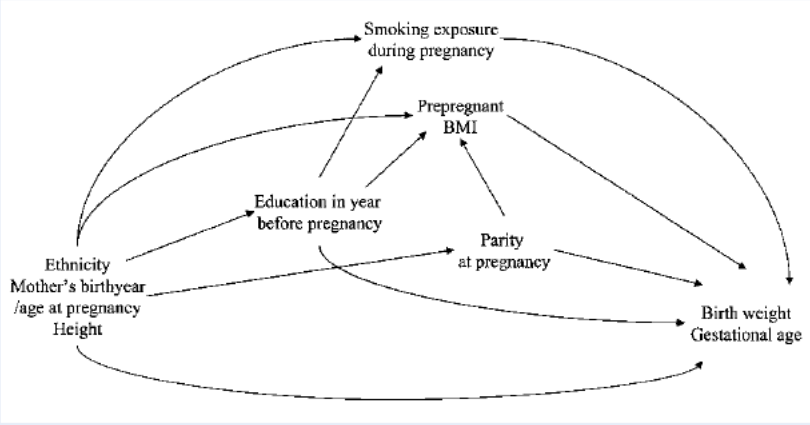


Figure 1 Causal Direct Acyclic Graph of the association between confounders, maternal education, smoking, BMI and birthweight at term.

Greenland et al, Epidemiology 1999;10:37 ff

How does your causal diagram look like?

Exposure

Outcome

Intermediates

Confounders

Which variables are available?

How are the arrows (according to you)

Control of confounding

DESIGN

Randomization

Restriction

- Balance, exchangeability

Matchning

- Matching variable cannot be assessed
- Twin- and sibling designs

Natural experiments

Replication in populations with different confounder structure

Compare plausible and implausible associations

ANALYSES

Standardisation

- Indirect
  - (one population is the standard)
- Direct
  - (external standard population)

Stratified analyses

- Few covariates

Multiple regression

- Many covariates

Paracetamol during pregnancy: Paracetamol Confounding by indication

- No adverse pregnancy outcomes, but preeclampsia Int J Epidemiol. 2009 Jun;38(3):706. J Matern Fetal Neonatal Med. 2010 May;23(5):371. Am J Obstet Gynecol. 2008;198(2):178
- Cryptorchidism Epidemiology. 2010 Nov;21(6):779-85
- ADHD like behaviour JAMA Pediatr. 2014 Apr;168(4):313-20
- Asthma Rebordosa C et al. Int J Epidemiol. 2008 Jun;37(3):583-90

Table 4 Relative risks (RR) for physician-diagnosed asthma/bronchitis and wheezing at 18 months according to pre-natal exposure to paracetamol and/or aspirin

		18-months-old population ($N = 66445$)		
			Doctor-diagnosed asthma	Wheezing ever up to 18-months-old
APAP[a]	AAS[a]	n (%)	RR[b] (95% CI)	RR[b] (95% CI)
1st trimester				
No	No	43 840 (66.0)	1 (ref)	1 (ref)
Yes	No	18 960 (28.5)	1.15 (1.10–1.19)	1.11 (1.08–1.14)
No	Yes	2617 (3.9)	0.94 (0.84–1.04)	1.04 (0.96–1.12)
Yes	Yes	1028 (1.6)	1.08 (0.94–1.25)	1.15 (1.04–1.28)
2nd trimester				
No	No	50 326 (75.7)	1 (ref)	1 (ref)
Yes	No	14 727 (22.2)	1.13 (1.08–1.18)	1.09 (1.05–1.12)
No	Yes	1085 (1.6)	0.99 (0.85–1.16)	1.02 (0.91–1.14)
Yes	Yes	307 (0.5)	1.24 (0.97–1.58)	1.17 (0.97–1.41)
3rd trimester				
No	No	46 154 (69.5)	1 (ref)	1 (ref)
Yes	No	19 109 (28.8)	1.17 (1.13–1.22)	1.10 (1.06–1.13)
No	Yes	783 (1.2)	0.92 (0.77–1.10)	1.05 (0.92–1.19)
Yes	Yes	399 (0.6)	1.10 (0.89–1.36)	1.21 (1.04–1.40)
Ever				
No	No	27 878 (42.0)	1 (ref)	1 (ref)
Yes	No	33 556 (50.5)	1.19 (1.14–1.24)	1.15 (1.11–1.18)
No	Yes	2251 (3.4)	1.00 (0.89–1.12)	1.10 (1.02–1.20)
Yes	Yes	2760 (4.2)	1.06 (0.96–1.17)	1.11 (1.03–1.19)

[a]APAP stands for paracetamol and AAS for acetylsalicylic acid (aspirin).
[b]Adjusted by parental asthma, gender of the child, social class, gestational age, breastfeeding, tobacco exposure during pregnancy and antibiotic use during pregnancy.

Are the observed association due to chance, error (bias), non-causal due to confonding or causal?

- Chance?

  Power of the study?

  P-values/ confidence intervals
- Biased
- Causal?

  Bradford Hill criteria, critical challenges

Bradford Hill criteria for causality

- Temporal relationship
- Biological plausibility (however, ….)
- Consistency (however, ….)
- Strength (however, ….)
- Exposure-response relationship (however, ….)
- Specificity (however, ….)
- (Reversibility)
- Coherence (however, ….)

Validity and generalizability

Validity: Credibility of results according to the aim of the study (= internal validity)

Generalizability: Credibility of results in other populations (=external validity)

General comments

Rare that one study alone provide enough "proof" that a certain exposure affects the risk of disease

- Re-analysis in other settings
- Meta-analysis

Remember that we live in a confounded world

Quick Overview

Probability of:	Ecological	Cross-sectional	Case–control	Cohort	Randomized trial
Selection bias					
Selection of subjects	N/A	medium	high	low	low
Loss to follow-up	N/A	N/A	low	high	medium
Recall bias	N/A	high	high	low	low
Confounding	high	medium	medium	low	very low

[a] Modified from Beaglehole *et al.* (1993)
N/A = Not applicable.