Causal inference in registry research

Øystein Ariansen Haaland

Copenhagen, January 2020

Health Registries for Research
Norway

NordForsk

Outline

Causality vs. Association

Natural experiments

Sensitivity analysis

Bonus (if time)

Causality vs. association

Causality vs. association

E → O

child in kitchen

milk spilled

CAUSALITY

Causality vs. association

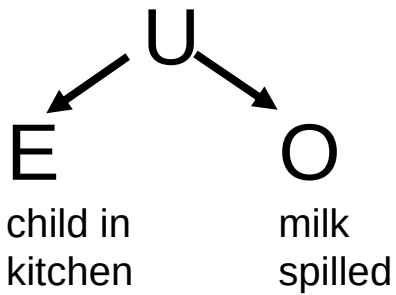
E ← O

child in kitchen

milk spilled

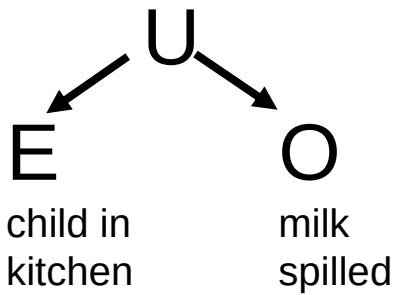
REVERSE CAUSALITY

Causality vs. association



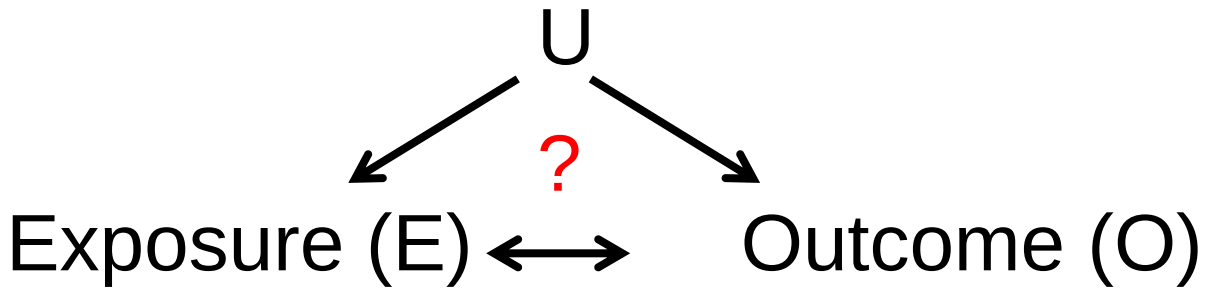
CONFOUNDING

Causality vs. association

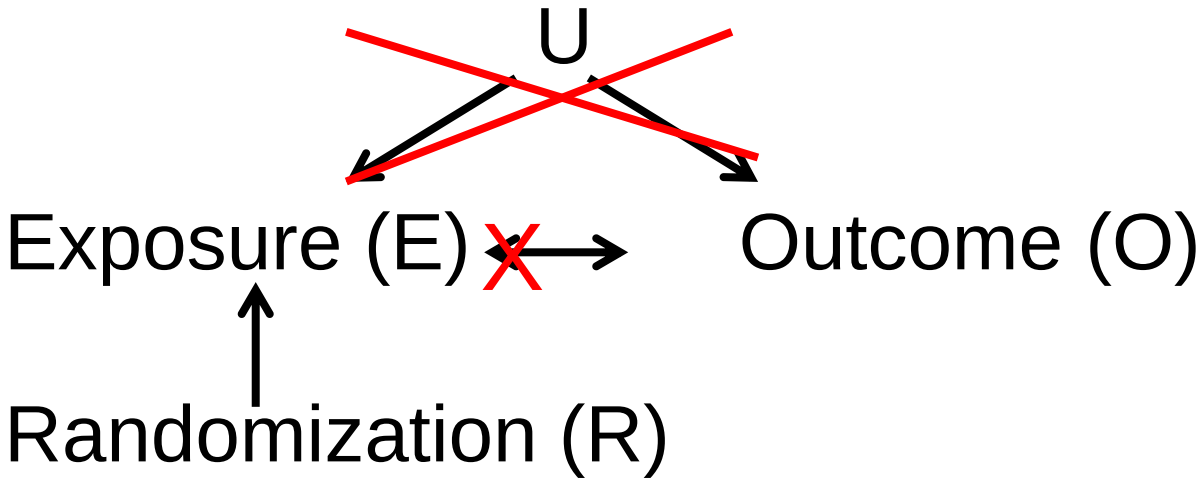


CONFOUNDING

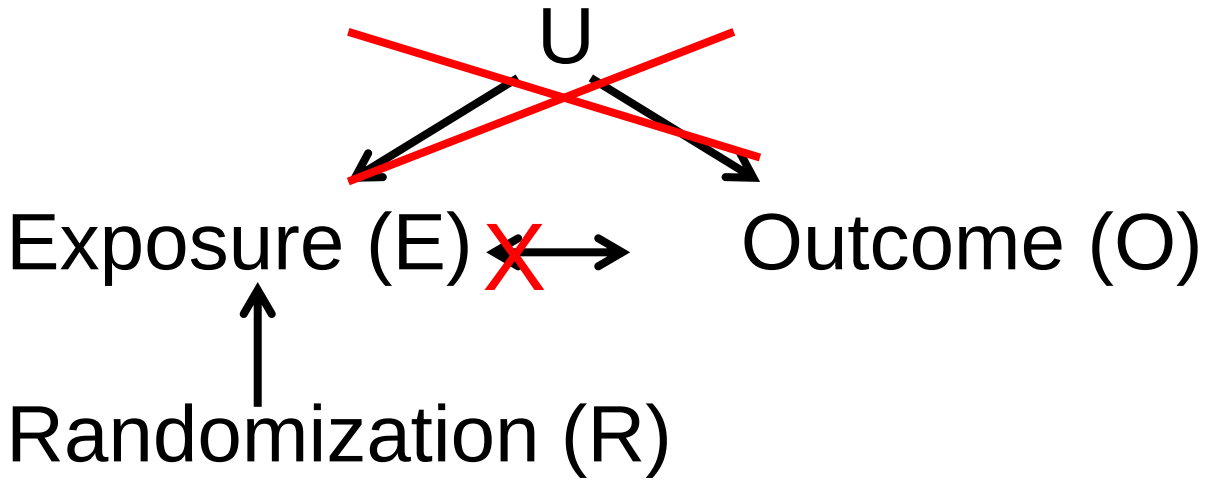
Causality vs. association



Randomized trial



Randomized trial



Often impractical or unethical!

Natural experiments

Antidepressants vs. self-harm and suicide

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

- Consider all patients given TCAs or SSRIs
- Compare rates or selft-harm and suicide

Antidepressants vs. self-harm and suicide

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

- Consider all patients given TCAs or SSRIs
- Compare rates or selft-harm and suicide

Risk difference: 0.11 per 100 in favor of TCAs (95% CI: 0.08 - 0.14)

Antidepressants vs. self-harm and suicide

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

- Consider all patients given TCAs or SSRIs
- Compare rates or selft-harm and suicide

Risk difference: 0.11 per 100 in favor of TCAs (95% CI: 0.08 - 0.14)

OK? Take 1-2 minutes and discuss possible sources of bias with your neighbor.

Antidepressants vs. self-harm and suicide

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

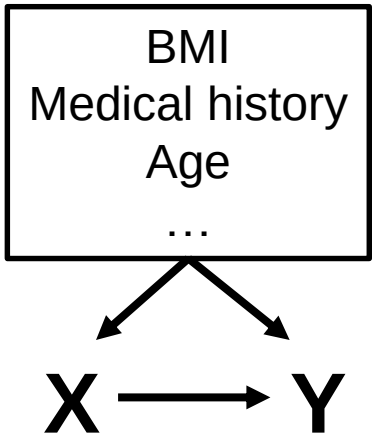
- Consider all patients given TCAs or SSRIs
- Compare rates or selft-harm and suicide

Risk difference: 0.11 per 100 in favor of TCAs (95% CI: 0.08 - 0.14)

Perhaps healthier patients tend to get TCAs?

Antidepressants vs. self-harm and suicide

Let **X** be drug status (TCA vs SSRI) and **Y** be outcome (self-harm or suicide).



Instrumental variable analysis

Consider instrument, **I**, as the exposure in addition to **X**.

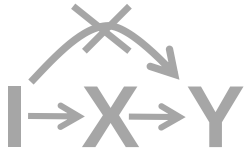
$$\mathbf{I} \rightarrow \mathbf{X} \rightarrow \mathbf{Y}$$

Instrumental variable analysis

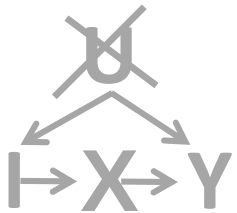
Need assumptions:

1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**



Instrumental variable analysis

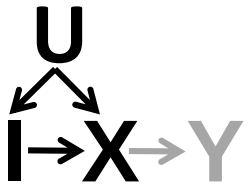
Need assumptions:

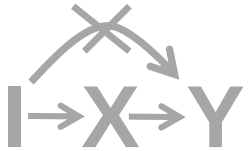
1- Causal relationship between **I** and **X**

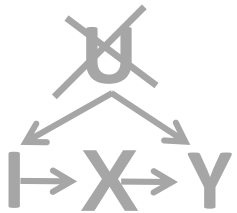
1- OK

2- The effect of **I** on **Y** is only through **X**

3- No common causes of **I** and **Y**



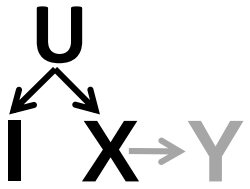




Instrumental variable analysis

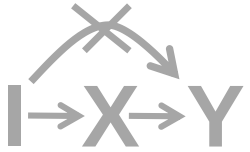
Need assumptions:

1- Causal relationship between **I** and **X**

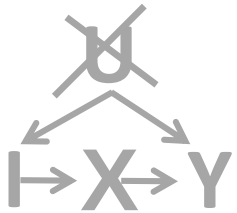


1- Also OK

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**

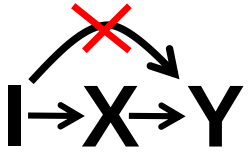


Instrumental variable analysis

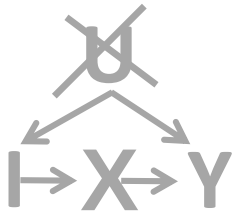
Need assumptions:

1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**

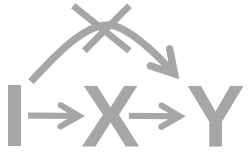


Instrumental variable analysis

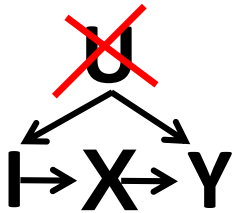
Need assumptions:

1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**



Instrumental variable analysis

ELSEVIER

Journal of Clinical Epidemiology 66 (2013) 1386–1396

Journal of Clinical Epidemiology

Physicians' prescribing preferences were a potential instrument for patients' actual prescriptions of antidepressants

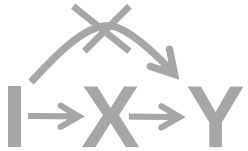
Neil M. Davies[a,b,*], David Gunnell[a], Kyla H. Thomas[a], Chris Metcalfe[a], Frank Windmeijer[c], Richard M. Martin[a,b]

Instrumental variable analysis

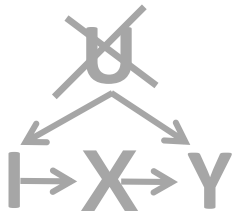
Need assumptions:

1- Causal relationship between **I** and **X**
OK: PP affects choice of TCA vs. SSRI.

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**



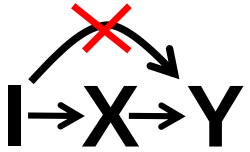
Instrumental variable analysis

Need assumptions:

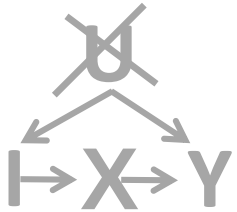
1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**

OK: PP does not cause self-harm or suicide



3- No common causes of **I** and **Y**

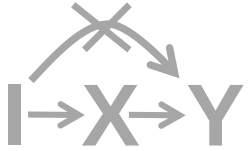


Instrumental variable analysis

Need assumptions:

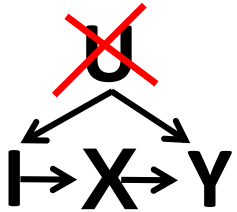
1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**

OK?: Any common causes of PP and self-harm or suicide?

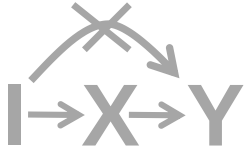


Instrumental variable analysis

Need assumptions:

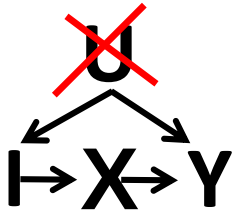
1- Causal relationship between **I** and **X**

2- The effect of **I** on **Y** is only through **X**



3- No common causes of **I** and **Y**

Any common causes of PP and self-harm or suicide? Discuss with neighbor (1-2 minutes).



Health Registries for Research
Norway

NordForsk

Instrumental variable analysis

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

Risk difference: 0.11 per 100 in favor of TCAs (95% CI: 0.08 - 0.14)

IVA-adjusted risk difference: 0.10 (-0.01 – 0.20)

Instrumental variable analysis

Are TCAs or SSRIs more likely to prevent self-harm and suicide?

Risk difference: 0.11 per 100 in favor of TCAs (95% CI: 0.08 - 0.14)

IVA-adjusted risk difference: 0.10 (-0.01 – 0.20)

WHICH DRUG WOULD YOU PREFER?

Geography

PERINATAL EPIDEMIOLOGY

Prenatal exposure to Chernobyl fallout in Norway: neurological and developmental outcomes in a 25-year follow-up

Rolv Terje Lie[1,2] · Dag Moster[1,3] · Per Strand[4,5] · Allen James Wilcox[6]

Geography

Birth Registry
-Mothers' municipality of residence at birth
-Gestational age
-Birth date

National Insurance Scheme
-Medical diagnoses

Central Bureau of Statistics
-Education
-Income

Norwegian Radiation Protection Agency
-Radiation at municipality level for 36 months after disaster (April 1986)

Geography

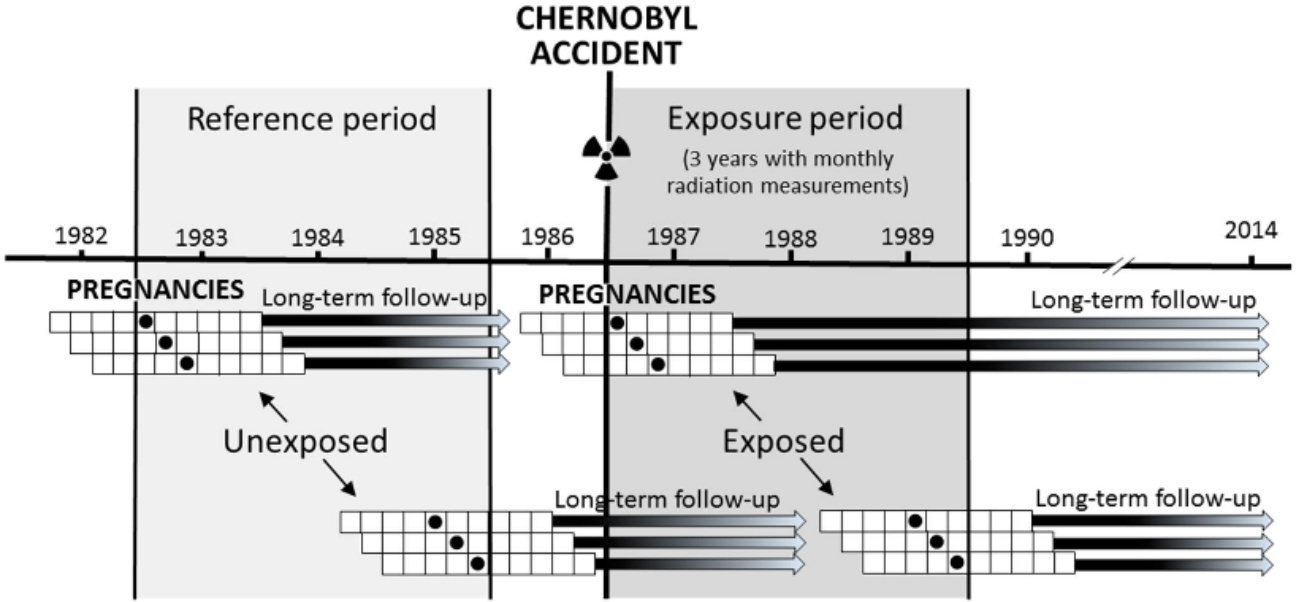


Fig. 1 Identification of persons from the exposure period for each calendar month and corresponding persons from the reference period for a particular municipality. Persons are included if calendar month 5 of pregnancy (counting month of LMP as month 1, and marked here by a dot) fell within the exposure or the reference period

Geography

Condition	Dose (mSv)*	Reference period May 1982–April 1985		Exposure period May 1986–April 1989		aRRR†	(95% CI)
		Cases	Per 1000	Cases	Per 1000		
Cerebral palsy	< 0.010	198	2.6	216	2.5	1.0	Ref.
	0.010–0.015	106	2.2	112	2.1	0.9	0.7–1.3
	0.016–0.023	40	2.4	53	2.9	1.0	0.6–1.7
	≥ 0.024	24	3.1	17	2.1	0.6	0.3–1.2

Geography

Condition	Dose (mSv)*	Reference period May 1982–April 1985		Exposure period May 1986–April 1989		aRRR†	(95% CI)
		Cases	Per 1000	Cases	Per 1000		
Cerebral palsy	< 0.010	198	2.6	216	2.5	1.0	Ref.
	0.010–0.015	106	2.2	112	2.1	0.9	0.7–1.3
	0.016–0.023	40	2.4	53	2.9	1.0	0.6–1.7
	≥ 0.024	24	3.1	17	2.1	0.6	0.3–1.2

Condition	RRR or ROR (95% CI)
Cerebral palsy	0.6 (0.3 – 1.2)
Mental retardation	1.1 (0.7 – 1.7)
Schizophrenia	1.7 (0.6 – 4.5)
Epilepsy	1.0 (0.6 – 1.7)
Hearing or vision problems	2.2 (1.0 – 5.0)
Not completed high school	1.07 (0.95 – 1.20)
Low income (<20%)	0.94 (0.80 – 1.11)
Low grade in mathematics	1.17 (0.92 – 1.48)
Low grade in Norwegian	1.16 (0.83 – 1.62)

Condition	RRR or ROR (95% CI)
Cerebral palsy	0.6 (0.3 – 1.2)
Mental retardation	1.1 (0.7 – 1.7)
Schizophrenia	1.7 (0.6 – 4.5)
Epilepsy	1.0 (0.6 – 1.7)
Hearing or vision problems	2.2 (1.0 – 5.0)
Not completed high school	1.07 (0.95 – 1.20)
Low income (<20%)	0.94 (0.80 – 1.11)
Low grade in mathematics	1.17 (0.92 – 1.48)
Low grade in Norwegian	1.16 (0.83 – 1.62)

LIMITATIONS?

Discuss with your neighbor for 1-2 minutes

Family

Children born after in-vitro fertilisation (IVF) have…

-…lower birth weight [25g (14g – 35g)]

-…shorter duration of gestation [2.0d (1.6d – 2.3d)]

-…increased risk of being small for gestational age [OR 1.26 (1.10 – 1.44)]

-…increased risk of perinatal death [OR 1.31 (1.05 – 1.65)]

Family

Children born after in-vitro fertilisation (IVF) have…

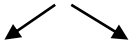
-…lower birth weight [25g (14g – 35g)]

-…shorter duration of gestation [2.0d (1.6d – 2.3d)]

-…increased risk of being small for gestational age [OR 1.26 (1.10 – 1.44)]

-…increased risk of perinatal death [OR 1.31 (1.05 – 1.65)]

Any confounders?



IVF status → Outcome

Family

Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study

Liv Bente Romundstad, Pål R Romundstad, Arne Sunde, Vidar von Düring, Rolv Skjærven, David Gunnell, Lars J Vatten

Conisdered children of women who had conceived

- at least once using IVF
- at least once using other approaches

Family

Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study

Liv Bente Romundstad, Pål R Romundstad, Arne Sunde, Vidar von Düring, Rolv Skjærven, David Gunnell, Lars J Vatten

Compared with non-IVF siblings, children born after IVF have…

- …similar birth weight [9g (-18g – 36g)]
- …similar duration of gestation [0.6d (-0.5d – 1.7d)]
- …similar risk of being small for gestational age [OR 0.99 (0.62 – 1.57)]
- …lower(!) risk of perinatal death [OR 0.36 (0.20 – 0.67)]

Family

Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study

Liv Bente Romundstad, Pål R Romundstad, Arne Sunde, Vidar von Düring, Rolv Skjærven, David Gunnell, Lars J Vatten

Compared with non-IVF siblings, children born after IVF have…

-…similar birth weight [9g (-18g – 36g)]

-…similar duration of gestation [0.6d (-0.5d – 1.7d)]

-…similar risk of being small for gestational age [OR 0.99 (0.62 – 1.57)]

-…lower(!) risk of perinatal death [OR 0.36 (0.20 – 0.67)]

LIMITATIONS?

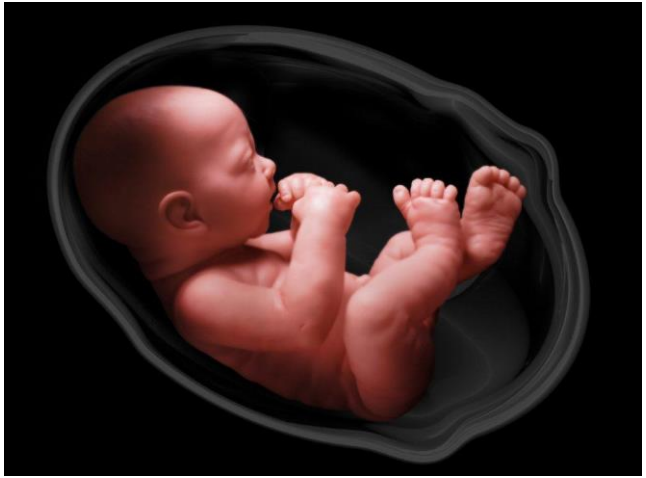
Family

Daughters of mothers who had an episode of preeclampsia are themselves at increased risk

Family

Daughters of mothers who had an episode of preeclampsia are themselves at increased risk

Risky womb (mother to daughter)?

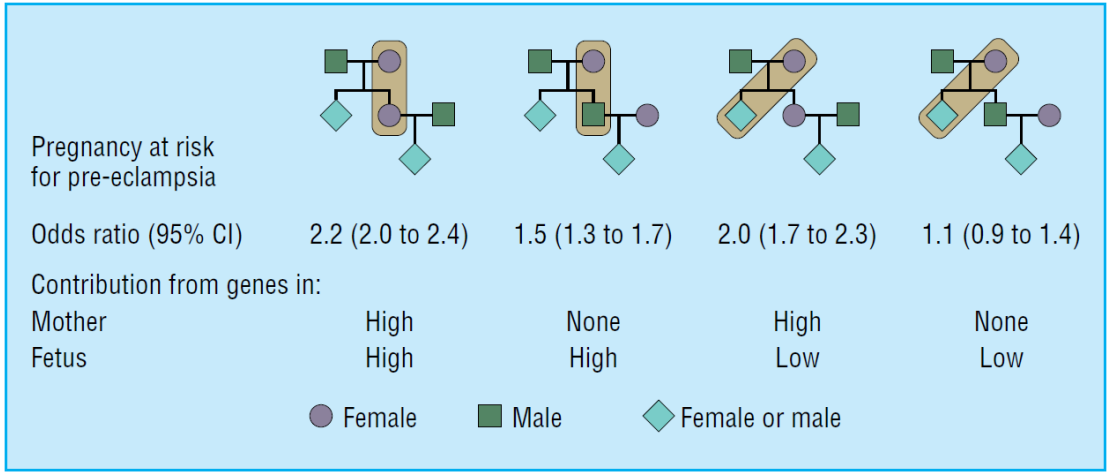


Bad child (daugher to child)?

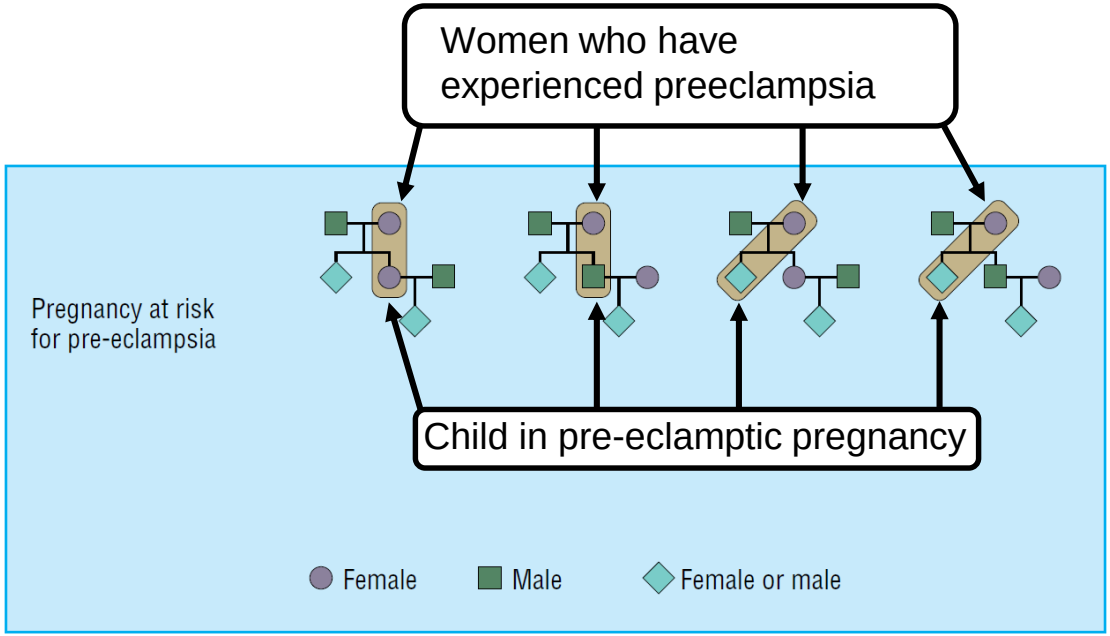
Family

Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort

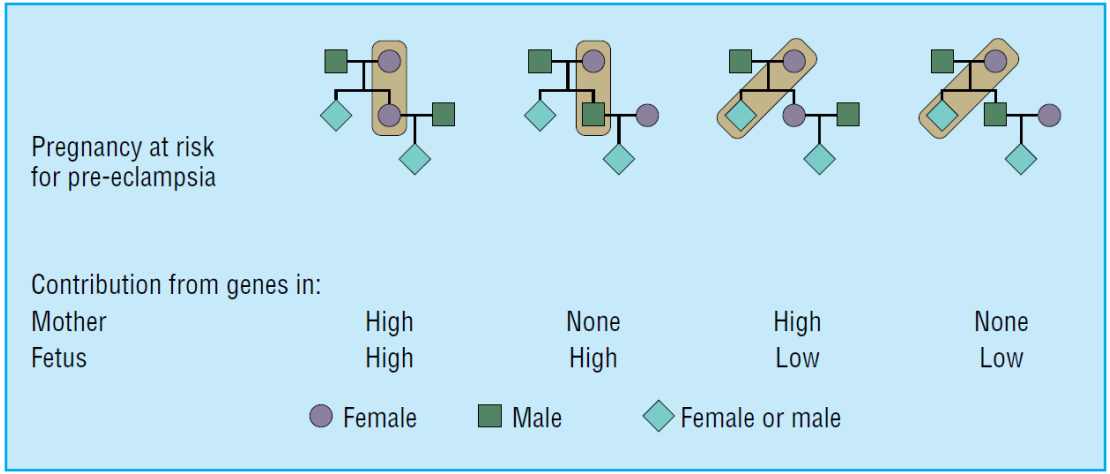
Rolv Skjærven, Lars J Vatten, Allen J Wilcox, Thorbjørn Rønning, Lorentz M Irgens, Rolv Terje Lie



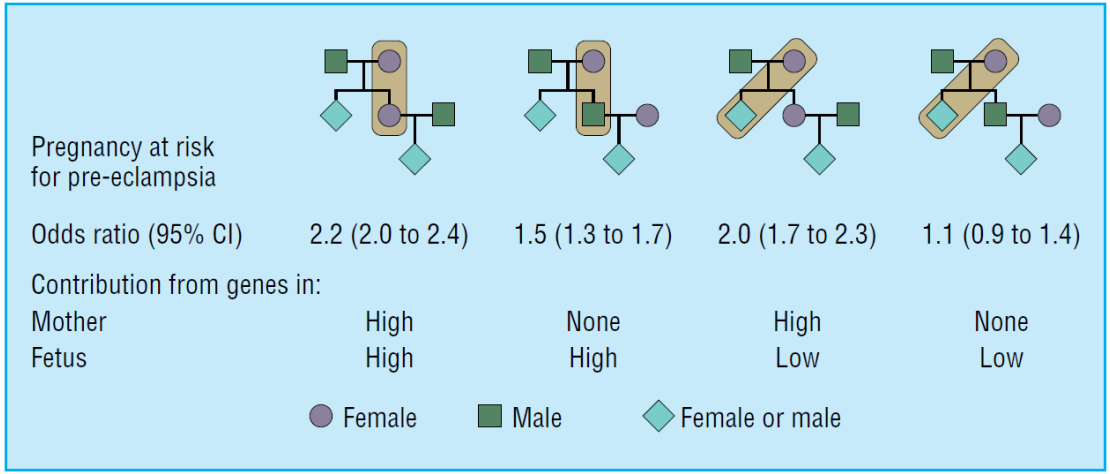
Family


Women who have experienced preeclampsia
Pregnancy at risk for pre-eclampsia
Child in pre-eclamptic pregnancy
Female
Male
Female or male

Family

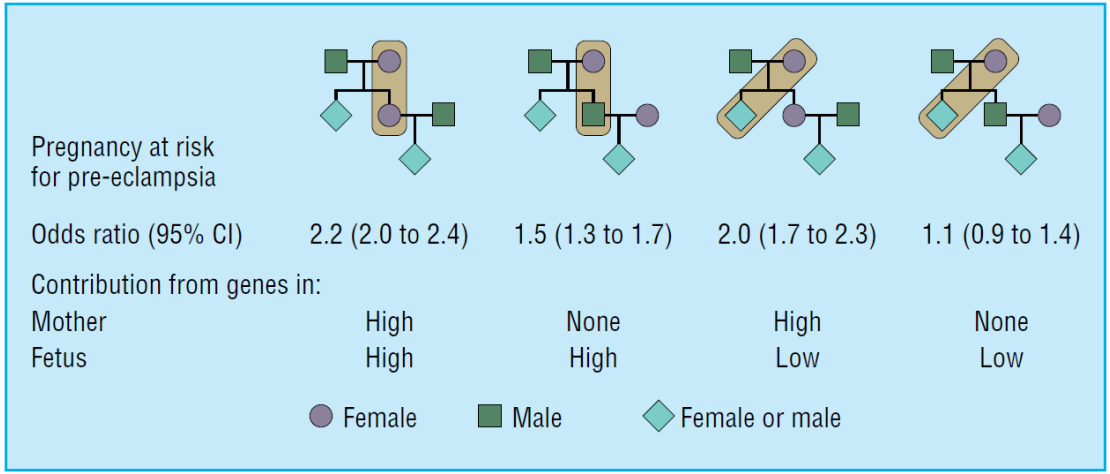

Pregnancy at risk
for pre-eclampsia
Contribution from genes in:
Mother
Fetus
High
High
None
High
High
Low
None
Low
Female
Male
Female or male

Family

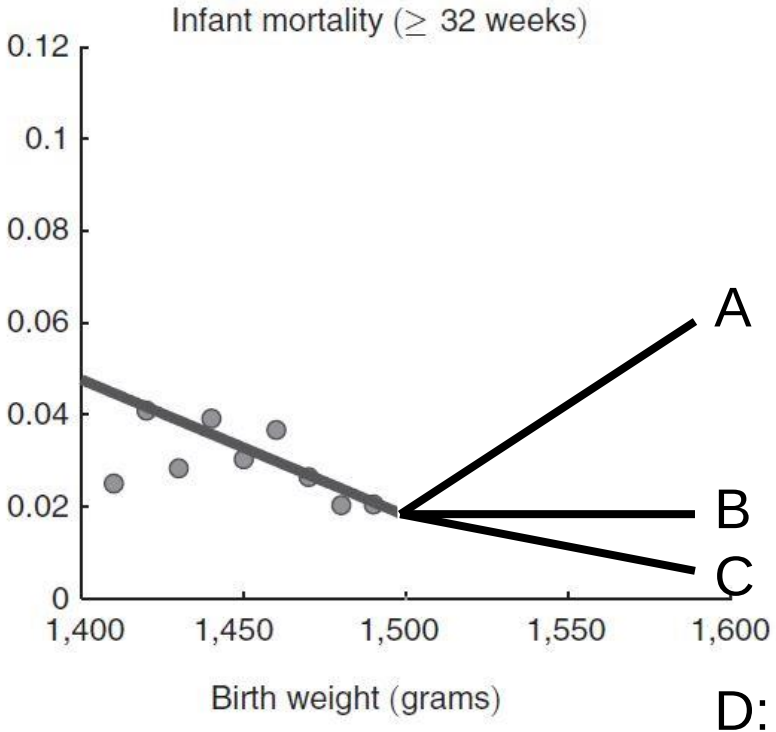

Pregnancy at risk for pre-eclampsia
Odds ratio (95% CI)
2.2 (2.0 to 2.4)
1.5 (1.3 to 1.7)
2.0 (1.7 to 2.3)
1.1 (0.9 to 1.4)
Contribution from genes in:
Mother
High
None
High
None
Fetus
High
High
Low
Low
Female
Male
Female or male

Family

LIMITATIONS?

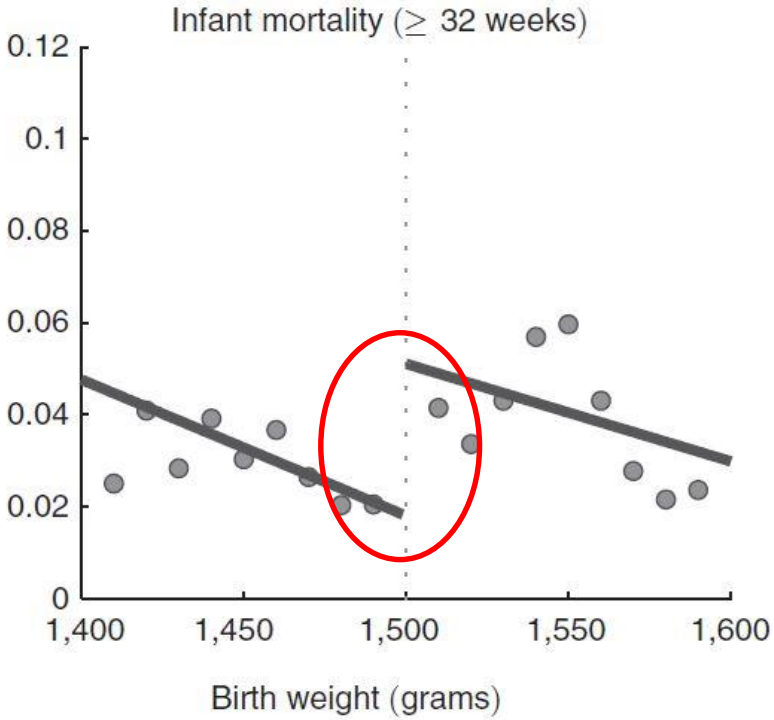


What happens (vote by raising hand)?



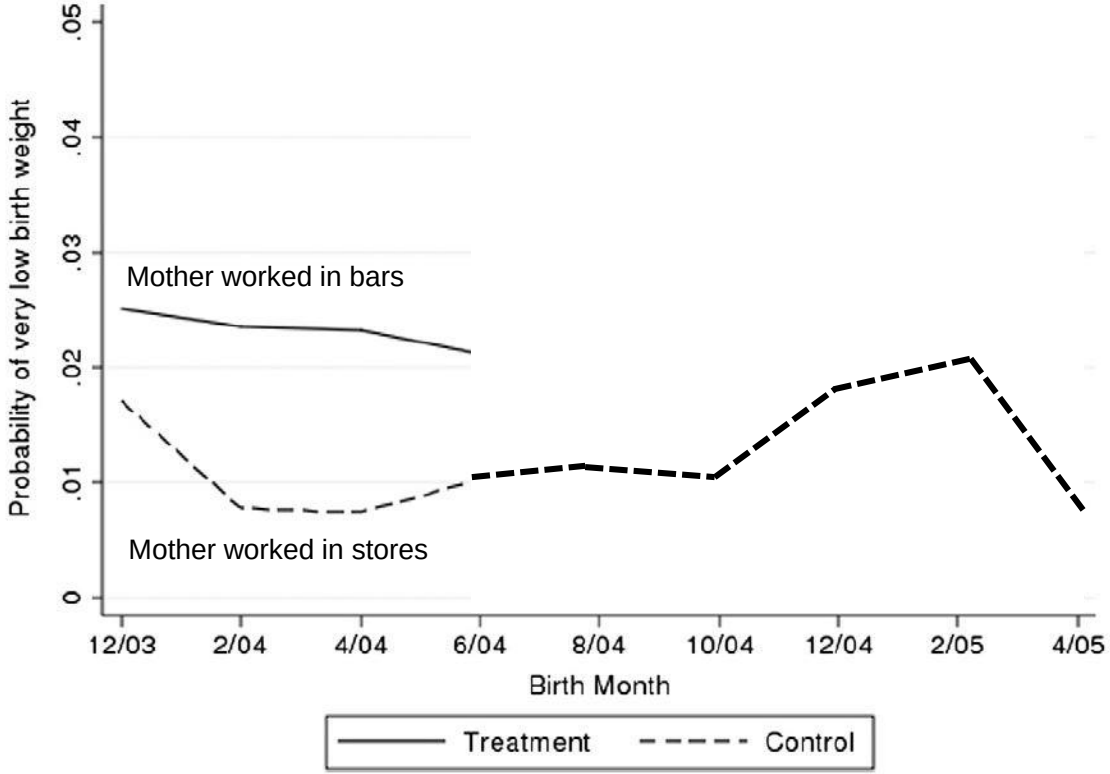
D: Neither

Regression discontinuity

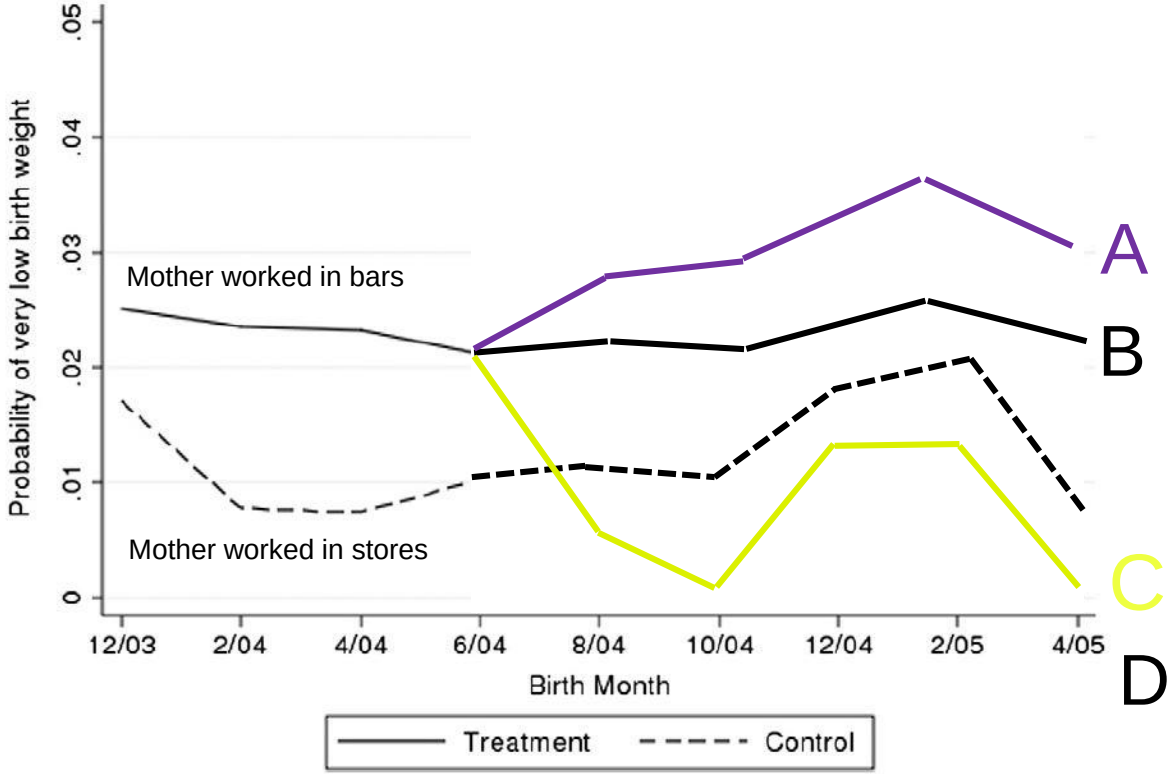


Prashant Bharadwaj et al. (2013). American Economic Review 2013, 103(5): 1862–1891

What happens?



What happens (vote by raising hand)?

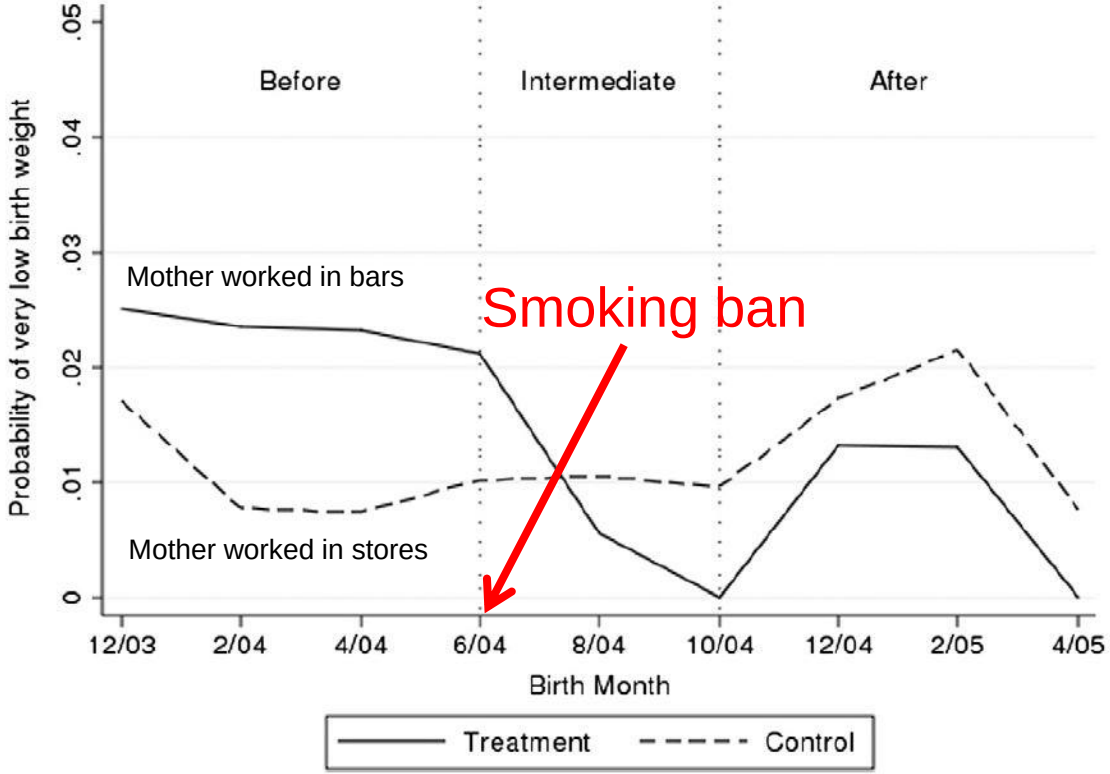


D: Neither

Health Registries for Research
Norway

NordForsk

Differences in differences



Prashant Bharadwaj et al. (2014). Journal of Public Economics 115 (2014) 72–93

Ignorance

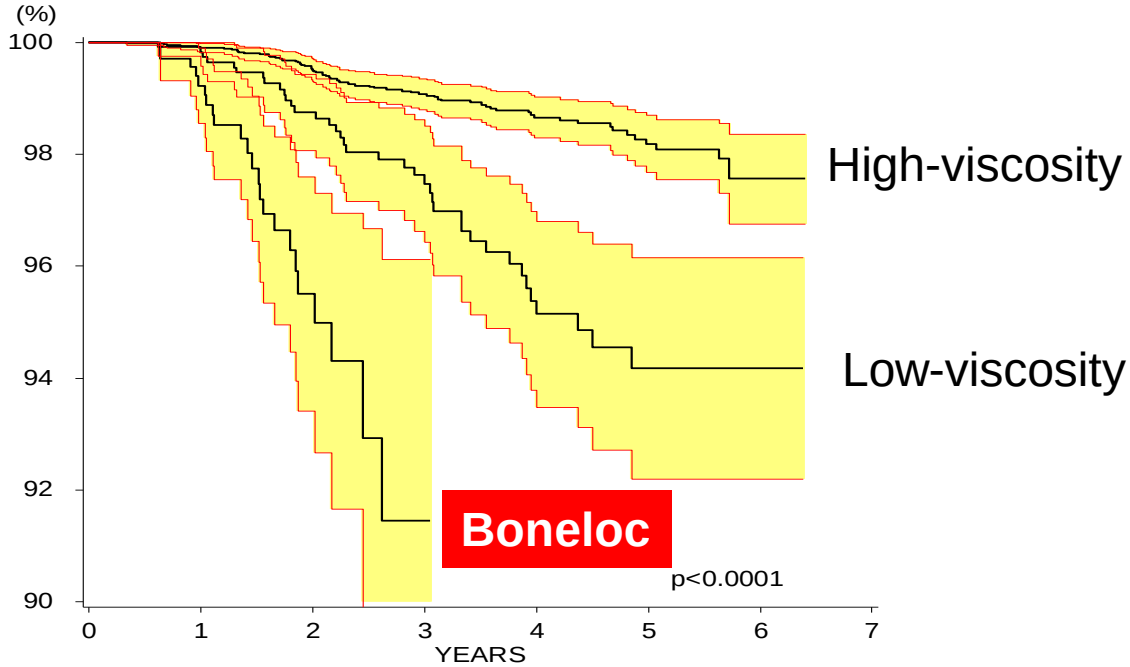
The Effect of the Type of Cement on Early Revision of Charnley Total Hip Prostheses

A Review of Eight Thousand Five Hundred and Seventy-nine Primary Arthroplasties from the Norwegian Arthroplasty Register*

By Leif Ivar Havelin, M.D.†, Birgitte Espehaug, M.Sc.†, Stein Emil Vollset, M.D., M.P.H., Dr.P.H.†, and Lars Birger Engesæter, M.D., Ph.D.†, Bergen, Norway

Which kind of cement yields the longest survival for hip protheses?

Ignorance

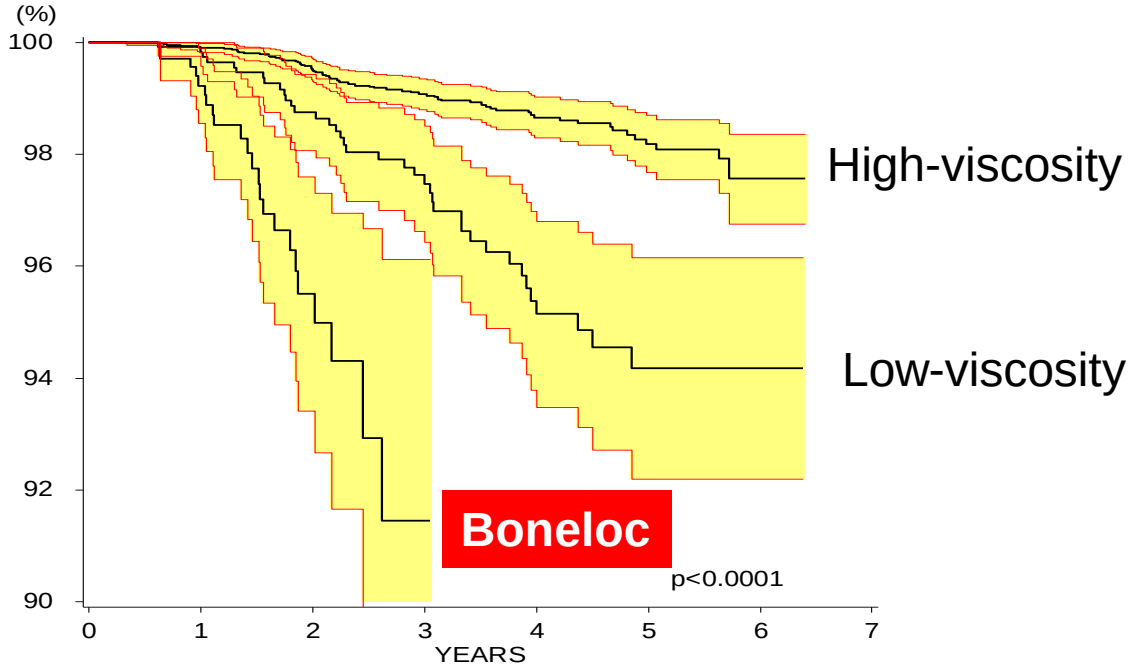


Health Registries for Research
Norway

NordForsk

Ignorance

LIMITATIONS?

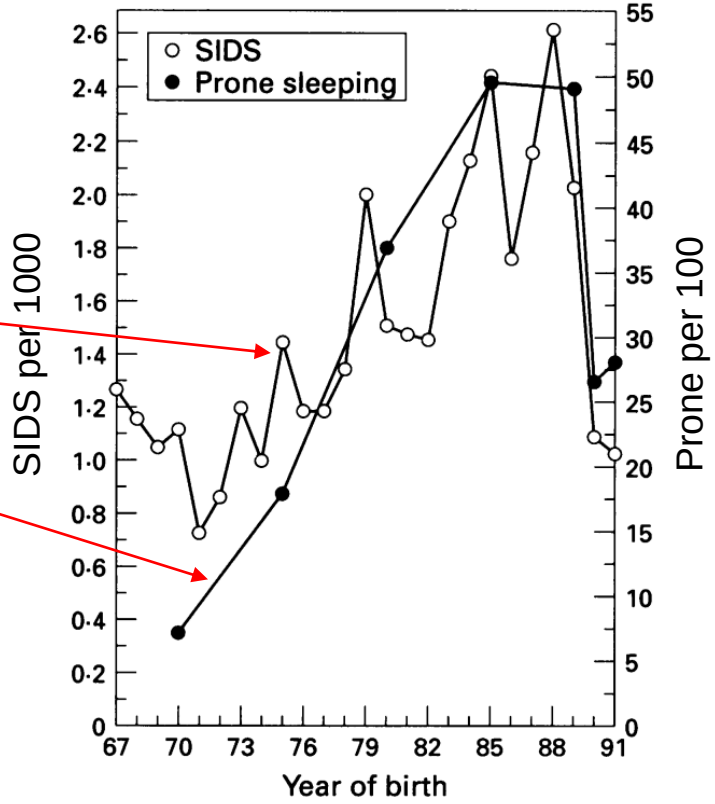


Interrupted time-series

Sudden infant death syndrome (SIDS)

Risk of SIDS in Norway

Prone sleeping (on the belly)



Irgens et al., 1995

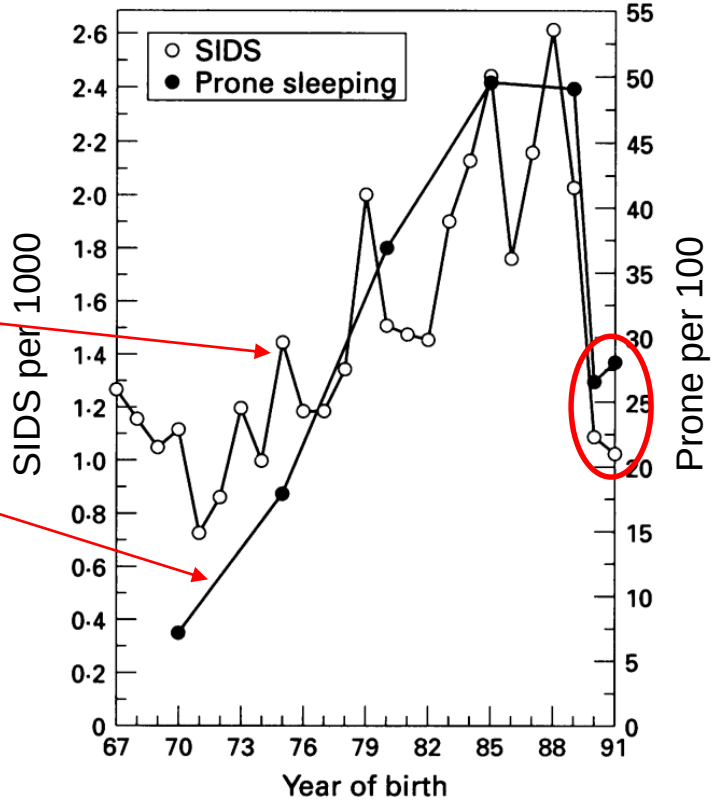
Interrupted time-series

Sudden infant death syndrome (SIDS)

Risk of SIDS in Norway

Prone sleeping (on the belly)

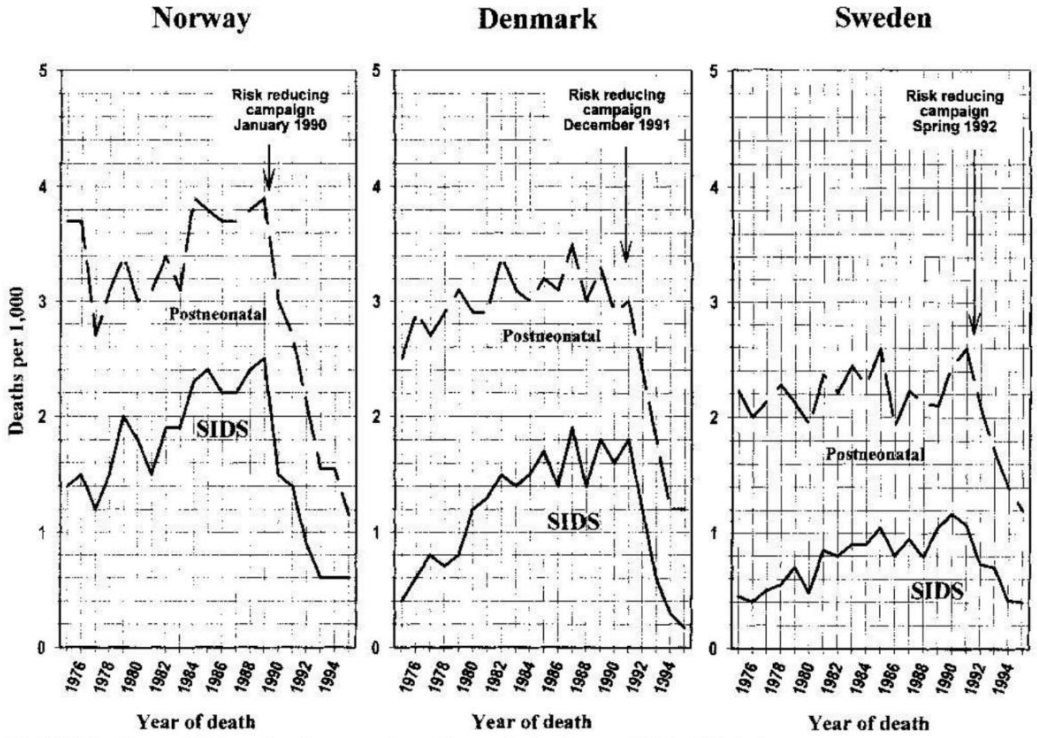
From January 1990 mothers were advised to avoid prone sleeping



Irgens et al., 1995

Interrupted time-series

Similar campaigns in Denmark and Sweden as well.

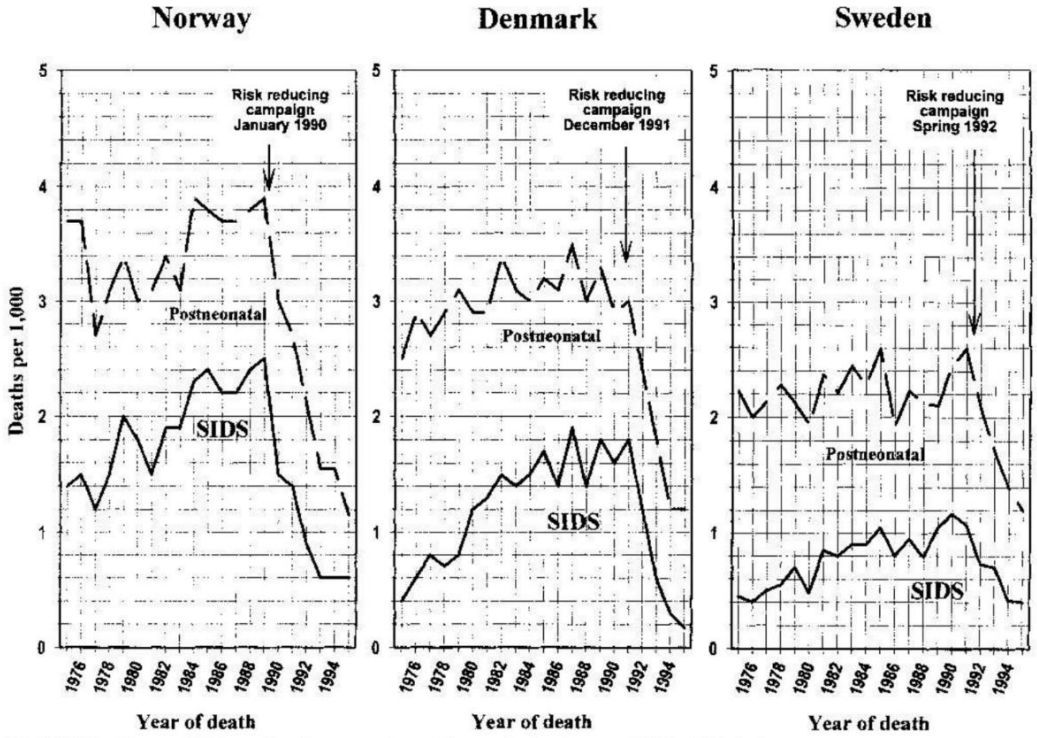


Wennergren et al., 1997

Interrupted time-series

Similar campaigns in Denmark and Sweden as well.

Are findings causal?



Wennergren et al., 1997

Exercise

Get together in groups

Discuss

- Pick one design that you thought was the strongest
- Pick one design that you though was the weakest

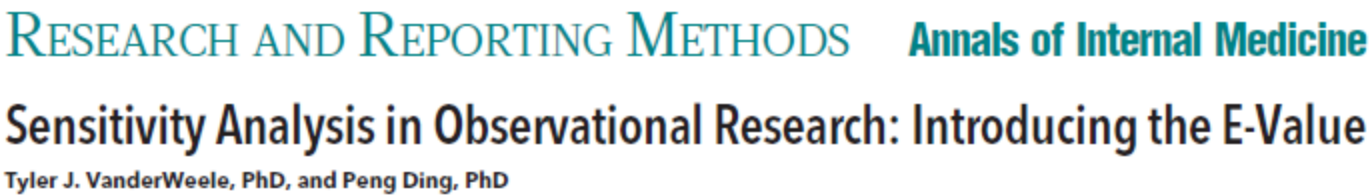
Return after the break + 15 minutes

- Present and defend your choices

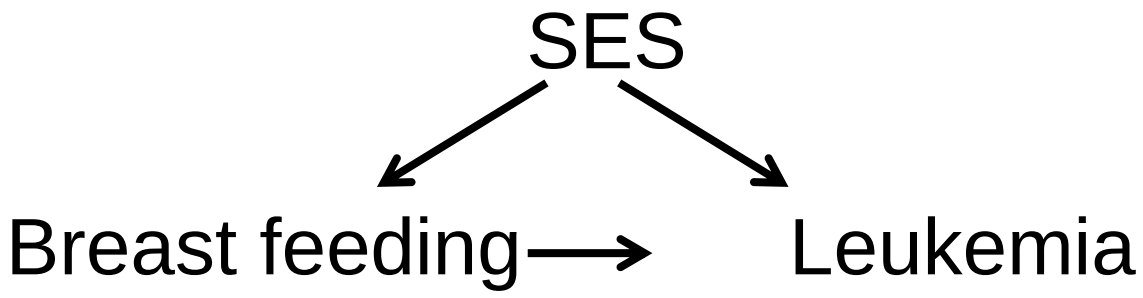
Wennergren et al., 1997

Sensitivity analysis

Sensitivity analysis

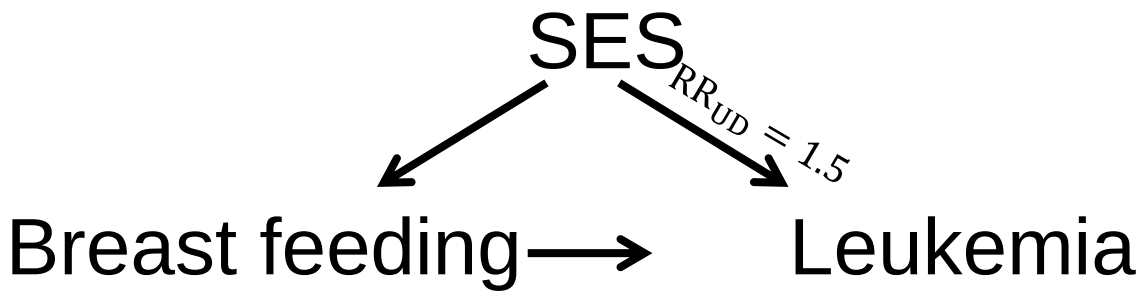


Sensitivity analysis



RR = 1.23 (1.10 – 1.41), p<0.001

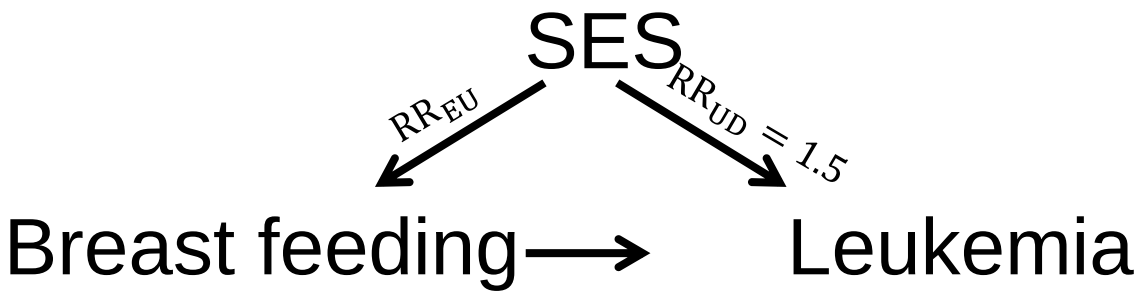
Sensitivity analysis



RR = 1.23 (1.10 – 1.41), p<0.001

RR_{UD}: Effect of SES on outcome

Sensitivity analysis

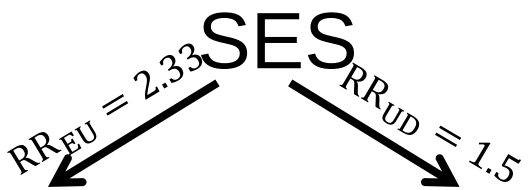


RR = 1.23 (1.10 – 1.41), p<0.001

RR_{UD}: Effect of SES on outcome

RR_{EU}: Imbalance in treatment group regarding SES

Sensitivity analysis



Breast feeding ⟶ Leukemia

RR = 1.23 (1.10 – 1.41), p<0.001

Low SES:

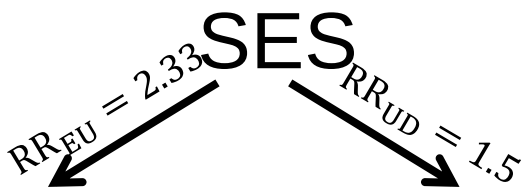
-Increases risk by 1.5 (RR_{UD})

-30% in the breast feeding group

-70% in the non-breast feeding group

-0.70/0.30=2.33 (RR_{EU})

Sensitivity analysis



Breast feeding ⟶ Leukemia

RR = 1.23 (1.10 – 1.41), p<0.001

Low SES:

-Increases risk by 1.5 (RR_{UD})

-30% in the breast feeding group

-70% in the non-breast feeding group

-0.70/0.30=2.33 (RR_{EU})

$$B = \frac{RR_{EU} \times RR_{UD}}{RR_{EU} + RR_{UD} - 1}$$

«bias factor»

Sensitivity analysis

Breast feeding ⟶ Leukemia

RR = 1.23 (1.10 – 1.41), p<0.001

Low SES:

-Increases risk by 1.5 (RR_{UD})

-30% in the breast feeding group

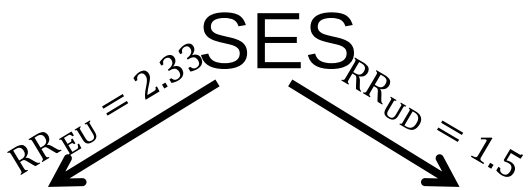
-70% in the non-breast feeding group

-0.70/0.30=2.33 (RR_{EU})

$$B = \frac{2.33 \times 1.5}{2.33 + 1.5 - 1} = 1.23$$

«bias factor»

Sensitivity analysis



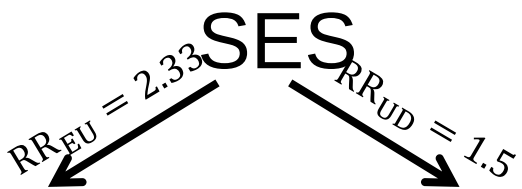
Breast feeding ⟶ Leukemia

RR = 1.23 (1.10 – 1.41), p<0.001

$$B = \frac{2.33 \times 1.5}{2.33 + 1.5 - 1} = 1.23$$

RR_{adj} = 1.23/B = 1.23/1.23 = 1.0

Sensitivity analysis



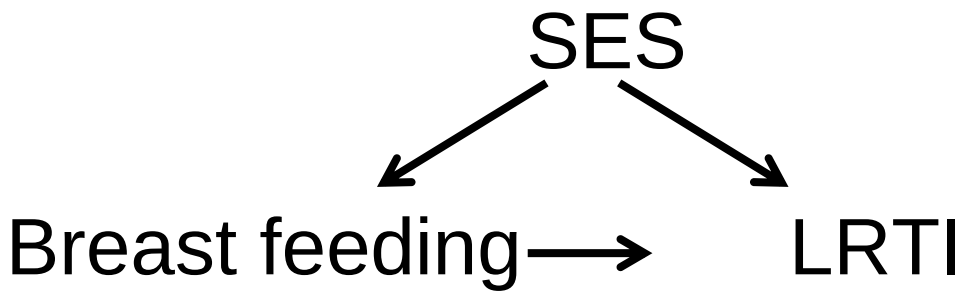
Breast feeding ⟶ Leukemia

RR = 1.23 (1.10 – 1.41), p<0.001

$$B = \frac{2.33 \times 1.5}{2.33 + 1.5 - 1} = 1.23$$

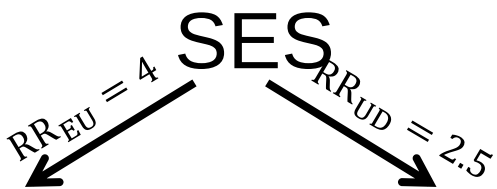
RR_{adj} (CI) = 1.0 (0.89 – 1.14)

Sensitivity analysis



RR = 3.6 (1.9 – 7.1), p<0.001

Sensitivity analysis



Breast feeding ⟶ LRTI

RR = 3.6 (1.9 – 7.1), p<0.001

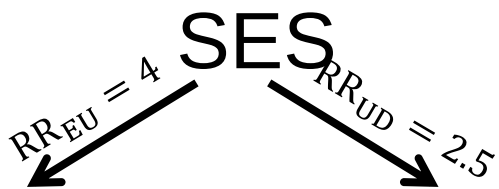
Low SES:

-Increases risk by 2.5

-20% in the breast feeding group

-80% in the non-breast feeding group

Sensitivity analysis



Breast feeding ⟶ LRTI

RR = 3.6 (1.9 – 7.1), p<0.001

Low SES:

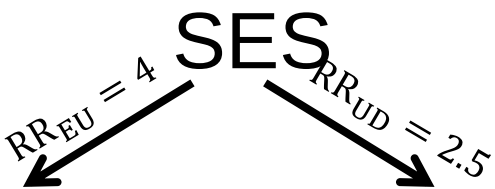
-Increases risk by 2.5

-20% in the breast feeding group

-80% in the non-breast feeding group

$$B = \frac{4 \times 2.5}{4 + 2.5 - 1} = 1.8$$

Sensitivity analysis



Breast feeding ⟶ LRTI

RR = 3.6 (1.9 – 7.1), p<0.001

Low SES:

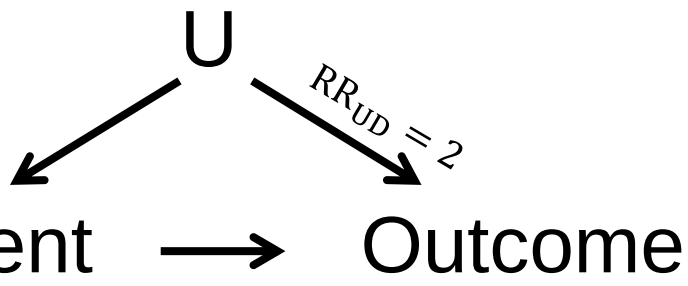
-Increases risk by 2.5

-20% in the breast feeding group

-80% in the non-breast feeding group

RR_{adj} (CI) = 2.0 (1.0 – 3.9)

Find B and adjust OR (CI) – I



RR = 2.5 (2.0 – 3.3)

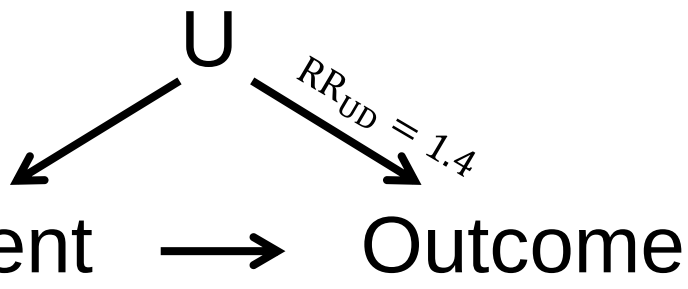
U:

-60% among unexposed

-80% among exposed

$$B = \frac{RR_{EU} \times RR_{UD}}{RR_{EU} + RR_{UD} - 1}$$

Find B and adjust OR (CI) – II



RR = 0.90 (0.89 – 0.91)

U:

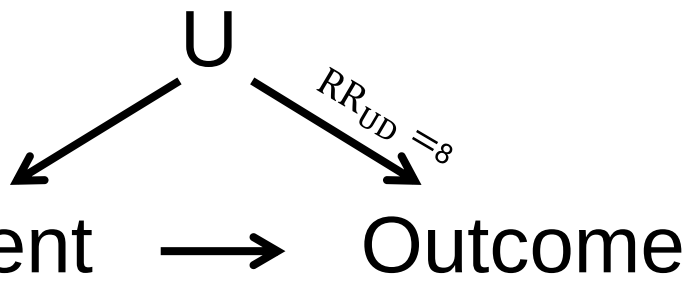
-10% among unexposed

-20% among exposed

$$B = \frac{RR_{EU} \times RR_{UD}}{RR_{EU} + RR_{UD} - 1}$$

Use 1/RR instead of RR!

Find B and adjust OR (CI) – III



RR = 0.10 (0.04 – 0.17)

U:

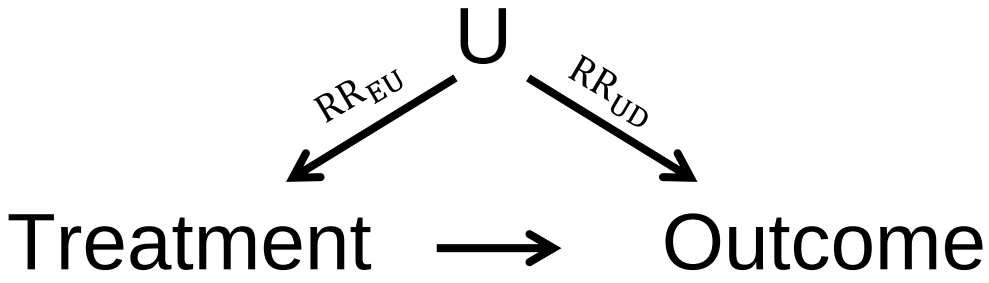
-10% among unexposed

-50% among exposed

$$B = \frac{RR_{EU} \times RR_{UD}}{RR_{EU} + RR_{UD} - 1}$$

Sensitivity analysis

The E-value

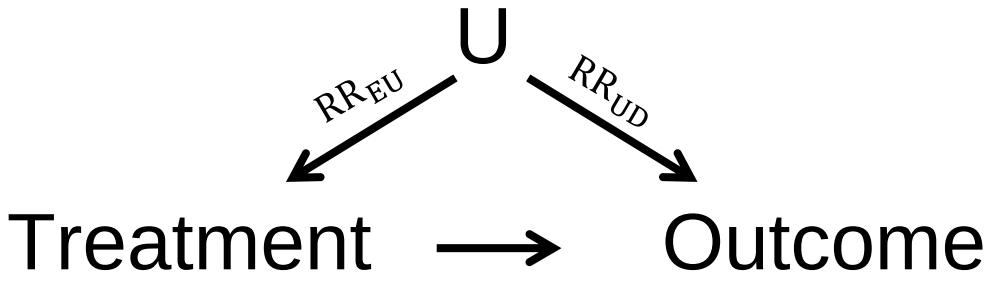


RR_{EU}: Imbalance in treatment group regarding U

RR_{UD}: Effect of U on outcome

Sensitivity analysis

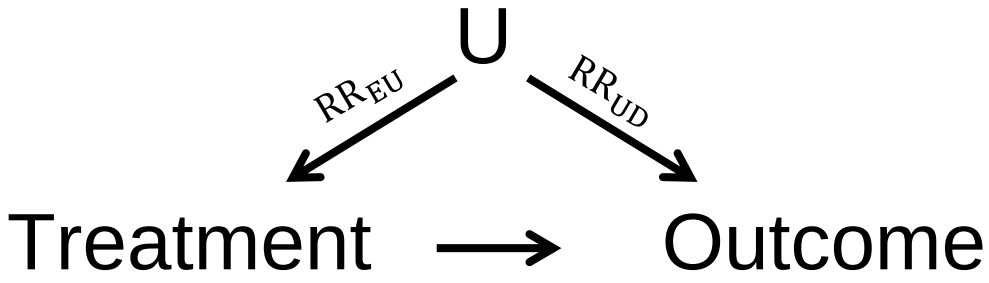
The E-value



E: Minimum value such that $RR_{EU} = RR_{UD}$, and $RR_{adj}=1$ (in other words, B=RR)

Sensitivity analysis

The E-value

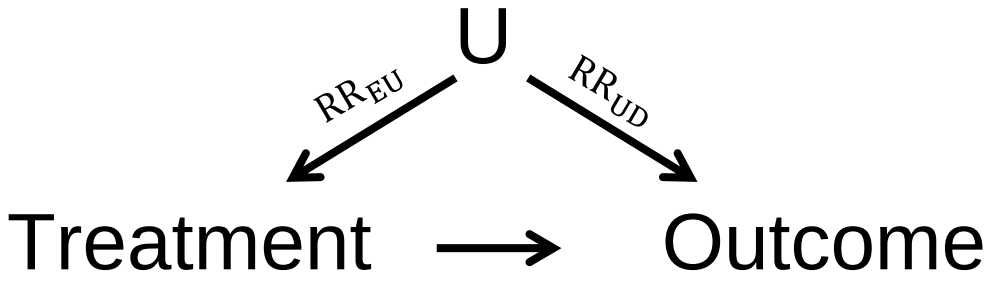


E: Minimum value such that $RR_{EU} = RR_{UD}$, and $RR_{adj}=1$ (in other words, B=RR)

«The observed risk ratio of RR could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of E each, above and beyond the measured confounders, but weaker confounding could not do so.»

Sensitivity analysis

The E-value

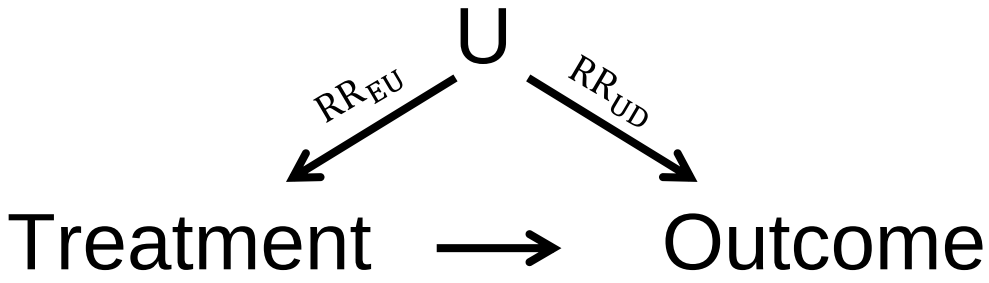


E: Minimum value such that $RR_{EU} = RR_{EU}$, and $RR_{adj}=1$ (in other words, B=RR)

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

Sensitivity analysis

The E-value



E: Minimum value such that $RR_{EU} = RR_{EU}$, and $RR_{adj}=1$ (in other words, B=RR)

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

Calculate both for RR and for part of CI that is closest to 1

Sensitivity analysis

Table 1. Calculating the E-Value for Risk Ratios

Estimate or CI, by Direction of Risk Ratio	Computation of the E-Value
***RR* >1**	
Estimate	E-value = $RR + \text{sqrt}\{RR \times (RR - 1)\}$
CI	If $LL \leq 1$, then E-value = 1 If $LL > 1$, then E-value = $LL + \text{sqrt}\{LL \times (LL - 1)\}$
***RR* <1**	
Estimate	Let $RR^* = 1/RR$ E-value = $RR^* + \text{sqrt}\{RR^* \times (RR^* - 1)\}$
CI	If $UL \geq 1$, then E-value = 1 If $UL < 1$, then let $UL^* = 1/UL$ and E-value = $UL^* + \text{sqrt}\{UL^* \times (UL^* - 1)\}$

LL = lower limit of the CI; *RR* = risk ratio; *RR** = inverse of *RR*; *UL* = upper limit of the CI; *UL** = inverse of *UL*.

Find E

RR = 0.40 (0.30 – 0.51) ⇒ E = 4.4 (3.3)

RR = 0.90 (0.89 – 0.91) ⇒ E = 1.5 (1.4)

RR = 0.10 (0.04 – 0.17) ⇒ E =

RR = 10.0 (6 – 25) ⇒ E =

RR = 3.1 (1.8 – 4.7) ⇒ E =

Sensitivity analysis

Table 2. E-Values for Other Effect Measures

Effect Measure	Computation of Approximate E-Value
OR or HR for rare outcomes	When the outcome is relatively rare (e.g., <15%) by the end of follow-up, the E-value formula in Table 1 may be used (37). In a case–control study, the outcome only needs to be rare in the underlying population, not in the case–control study.
Rate ratio for count and continuous outcomes	For ratio measures for count outcomes (or nonnegative continuous outcomes), the E-value may be found by replacing the risk ratio with the rate ratio (or the ratio of expected values) in the E-value formula in Table 1 (37).
OR for common outcomes	When the outcome is common (>15% at the end of follow-up), an approximate E-value may be obtained by replacing the risk ratio with the square root of the OR (45), i.e., $RR \approx \text{sqrt(OR)}$, in the E-value formula in Table 1.
HR for common outcomes	When the outcome is common (>15% at the end of follow-up), an approximate E-value may be obtained (45) by applying the approximation $RR \approx (1 - 0.5^{\text{sqrt(HR)}})/(1 - 0.5^{\text{sqrt(1/HR)}})$ in the E-value formula in Table 1.
Difference in continuous outcomes	With standardized effect sizes d (mean of the outcome variable divided by the SD of the outcome) and an SE for this standardized effect size s_d, an approximate E-value may be obtained (45–47) by applying the approximation $RR \approx \exp(0.91 \times d)$ in the E-value formula. An approximate CI for the risk ratio may be found by using the approximation $(\exp\{0.91 \times d - 1.78 \times s_d\}, \exp\{0.91 \times d + 1.78 \times s_d\})$. This approach relies on additional assumptions and approximations. Other sensitivity analysis techniques have been developed for this setting (27–29), but they generally require additional assumptions, and the variables do not necessarily have a corresponding E-value.
Risk difference	If the adjusted risks for the treated and untreated are p_1 and p_0, then the E-value may be obtained by replacing the risk ratio with p_1/p_0 in the E-value formula. The E-value for the CI on a risk difference scale is more complex, and software to obtain this is described in the Supplement (available at Annals.org). Alternatively, if the outcome probabilities p_1 and p_0 are not very small or very large (e.g., if they are between 0.2 and 0.8), then the approximate approach for differences in continuous outcomes given previously may be used. Other sensitivity analysis techniques have been developed for this setting (27–29) but generally require additional assumptions and do not provide a corresponding E-value.

HR = hazard ratio; OR = odds ratio; *RR* = risk ratio.

Triangulation

NATURE | COLUMN: WORLD VIEW

Publish houses of brick, not mansions of straw

Papers need to include fewer claims and more proof to make the scientific literature more reliable, warns William G. Kaelin Jr.

23 May 2017

Triangulation

COMMENT · 23 JANUARY 2018

Robust research needs many lines of evidence

Replication is not enough. Marcus R. Munafò and George Davey Smith state the case for triangulation.

Marcus R. Munafò ✉ & George Davey Smith

Triangulation

TRIANGULATION — A CHECKLIST

- The different approaches address the same underlying question.
- The key sources of bias for each approach are explicitly acknowledged.
- For each approach, the expected directions of all key sources of potential bias are made explicit, where feasible.
- Ideally, some of the approaches being compared will have potential biases that are in opposite directions.
- Ideally, results from more than two approaches — which have different and unrelated key sources of potential biases — are compared.

Bradford Hill criteria for causality

1. Strength (effect size). Stronger is better!
   E-value argues this as well.

2. Consistency (reproducibility). Consistent findings across methods and in different places.
   Triangulation approach.

3. Specificity. The more specific, the higher the likelihood of causality.
   Natural experiments.

4. Temporality. Effect after cause.

Bradford Hill criteria for causality

5. Biological gradient. Logical relationship between exposure and incidence.
   More exposure often yields higher incidence.

6. Plausibility. Can a plausible mechanism be proposed?
   Detailed biological mechanism are often not in the scope of register epidemiology.
   «Something genetic»

7. Coherence. Epidemiological and laboratory results should be similar.

8. Experiment. Experimental evidence can be useful when available.
   RCTs.

9. Analogy. «If this is bad, than that sould be bad as well.»

Thanks for listening!