Causal inference in registry research

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Øystein Ariansen Haaland
Copenhagen, January 2019

Health Registries for Research
Norway

NordForsk

Outline

Causality vs. Association

Natural experiments

Causality vs. association

Causality vs. association

E → O

child in kitchen

milk spilled

CAUSALITY

Causality vs. association

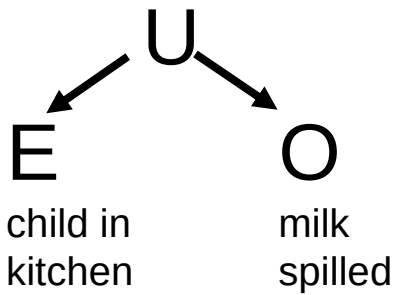
E ← O

child in kitchen

milk spilled

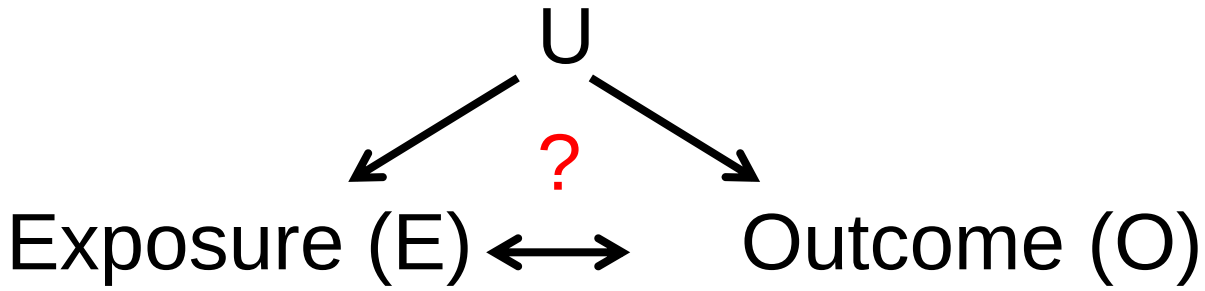
REVERSE CAUSALITY

Causality vs. association

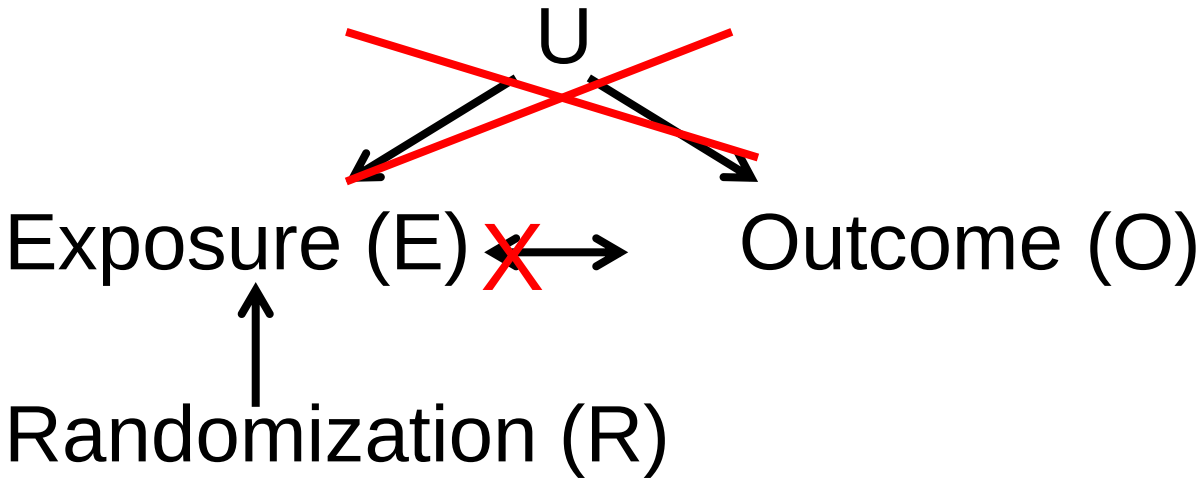


CONFOUNDING

Causality vs. association



Randomized trial



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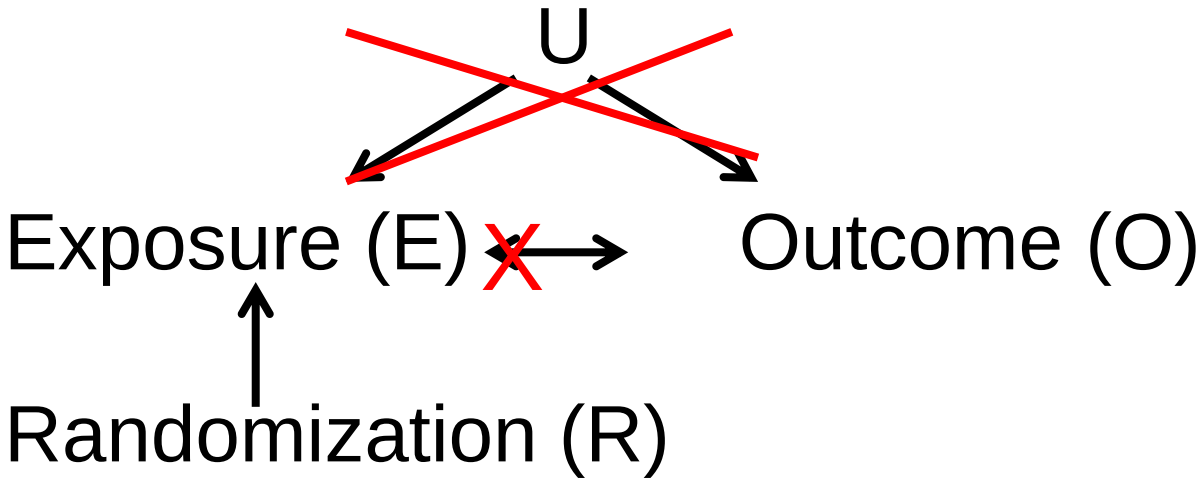

Often impractical or unethical!

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

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OK?

Antidepressants vs. self-harm and suicide

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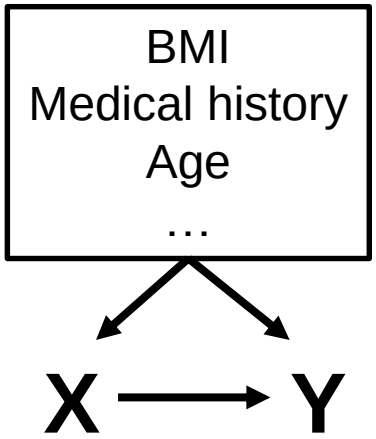
- Compare rates or selft-harm and suicide

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**.

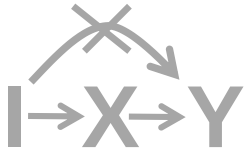
$$\mathbf{I} \rightarrow \mathbf{X} \rightarrow \mathbf{Y}$$

Instrumental variable analysis

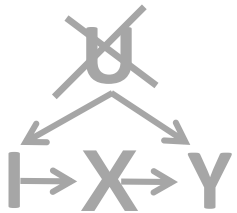
Need assumptions:

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:

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1- OK

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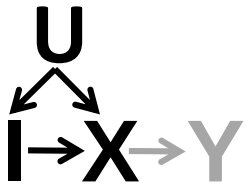
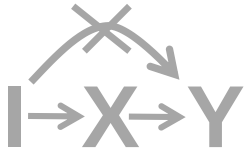
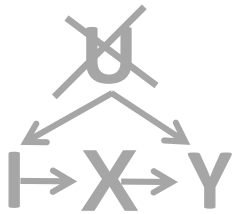


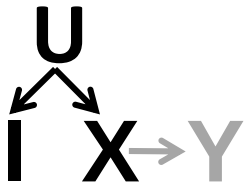




Instrumental variable analysis

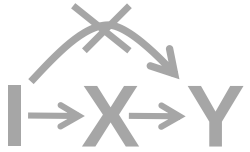
Need assumptions:

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

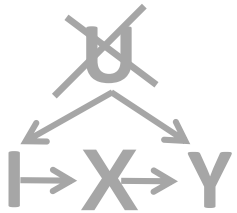


1- Also OK

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



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



Instrumental variable analysis

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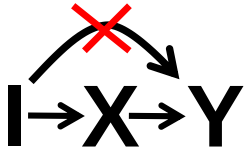

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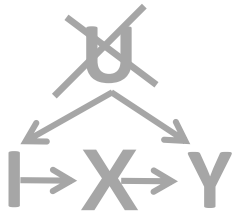

Instrumental variable analysis

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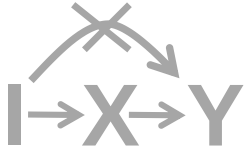

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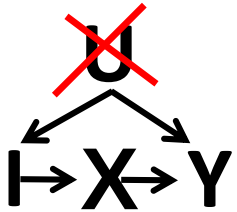


Instrumental variable analysis

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

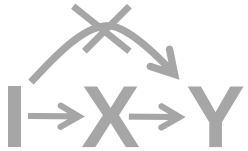
Neil M. Davies[a,b,*], David Gunnell[a], Kyla H. Thomas[a], Chris Metcalfe[a], Frank Windmeijer[c], Richard M. Martin[a,b]

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**



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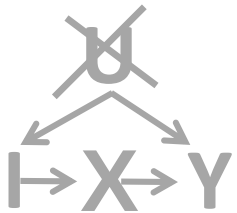


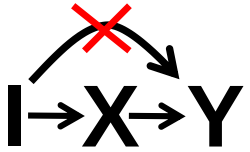
Instrumental variable analysis

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



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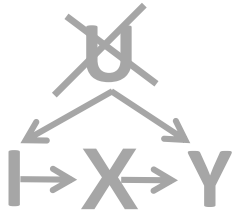

Instrumental variable analysis

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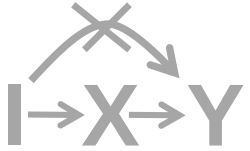
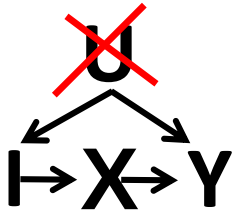


3- No common causes of **I** and **Y**

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



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)

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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?

Instrumental variable analysis

Other instruments:

- Genes (Mendelian randomization)
- Distance from hospital
- Month of birth
- Timing of admission (weekend vs. week day)

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

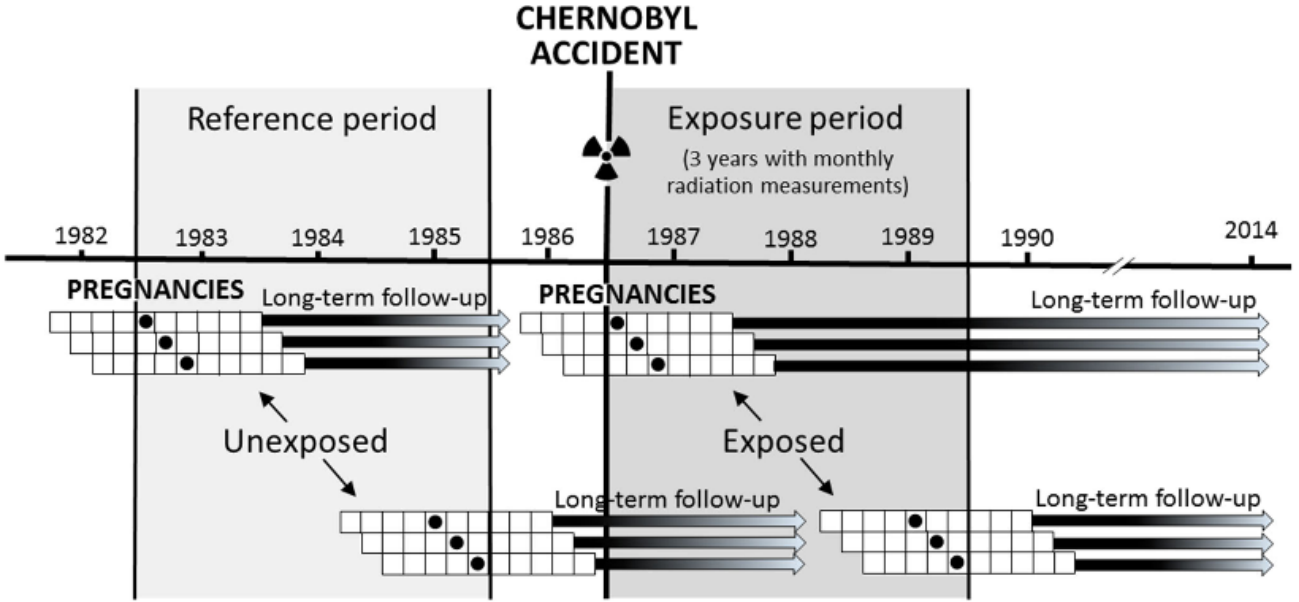

Fig. 1 Identification of persons from the exposure period for each calendar month and corresponding persons from the reference period for a particular municipality. Persons are included if calendar month 5 of pregnancy (counting month of LMP as month 1, and marked here by a dot) fell within the exposure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

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)

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LIMITATIONS?

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)]

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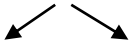
Any confounders?



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

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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

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LIMITATIONS?

Family

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

Family

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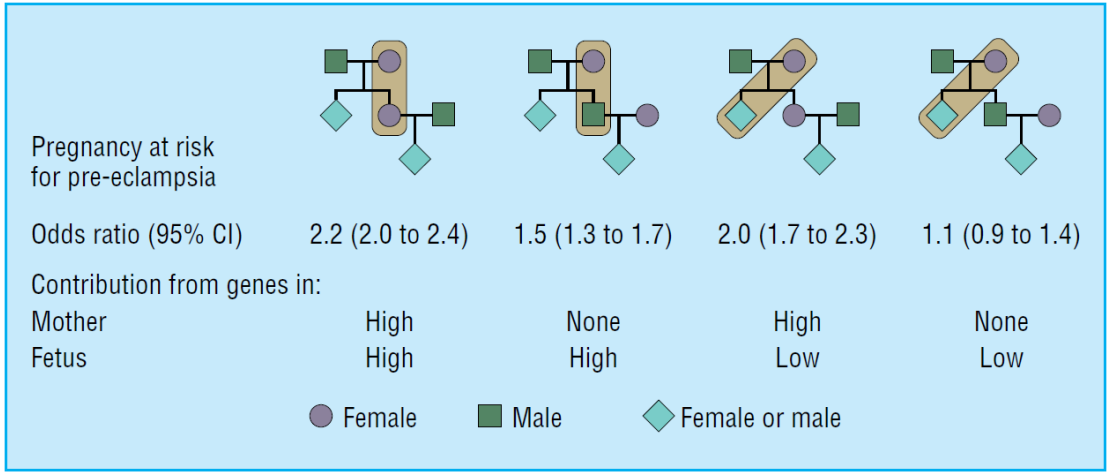
Risky womb (mother to daughter)?

Bad child (daugher to child)?

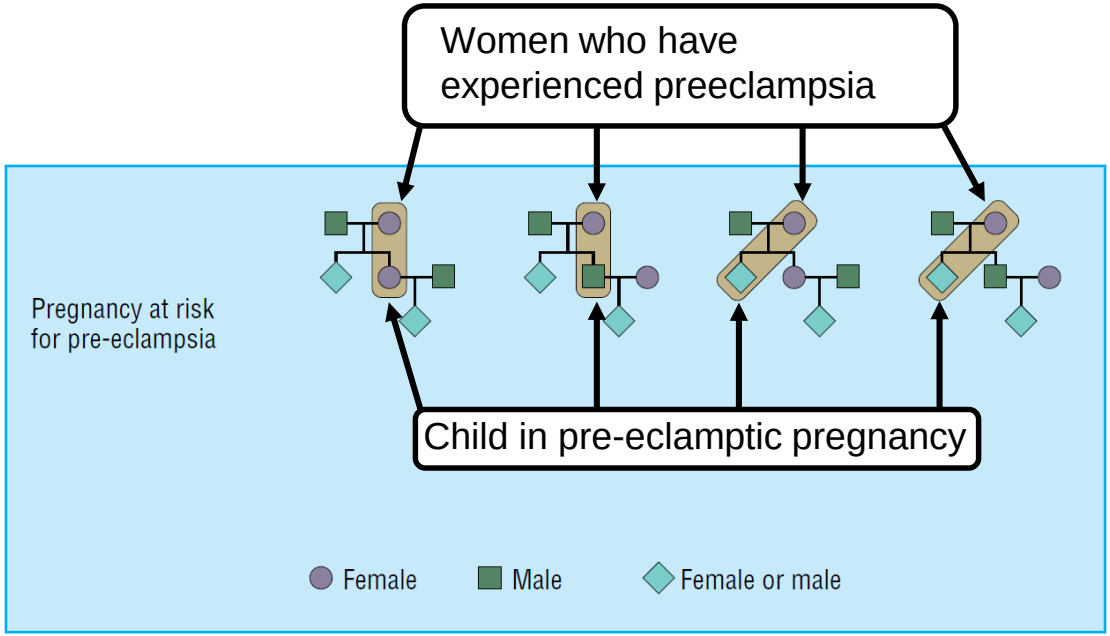
Family

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

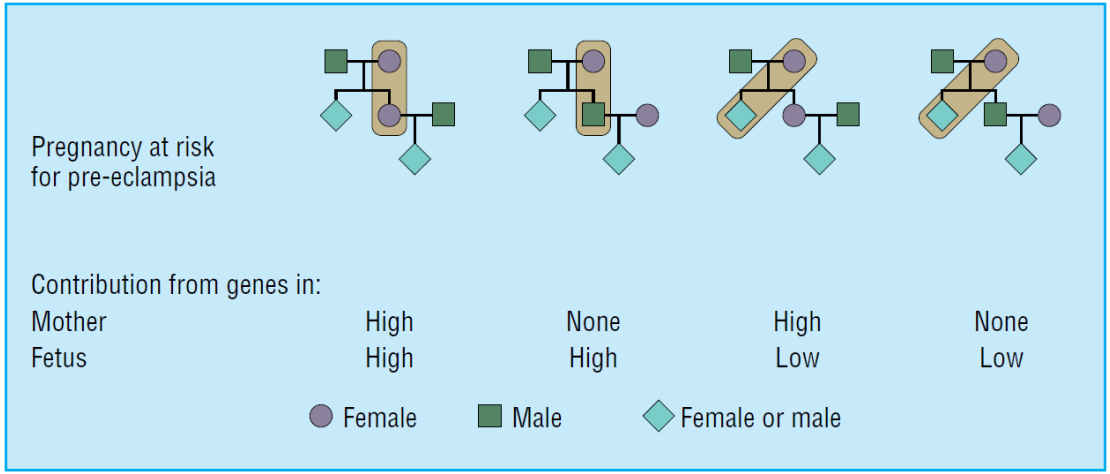
Rolv Skjærven, Lars J Vatten, Allen J Wilcox, Thorbjørn Rønning, Lorentz M Irgens, Rolv Terje Lie



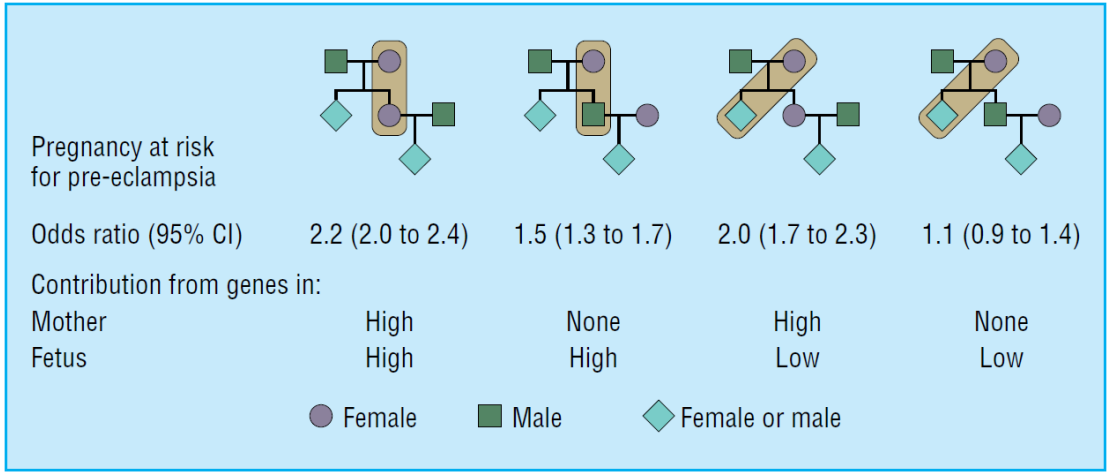
Family


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)
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2.0 (1.7 to 2.3)
1.1 (0.9 to 1.4)
Contribution from genes in:
Mother
High
None
High
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High
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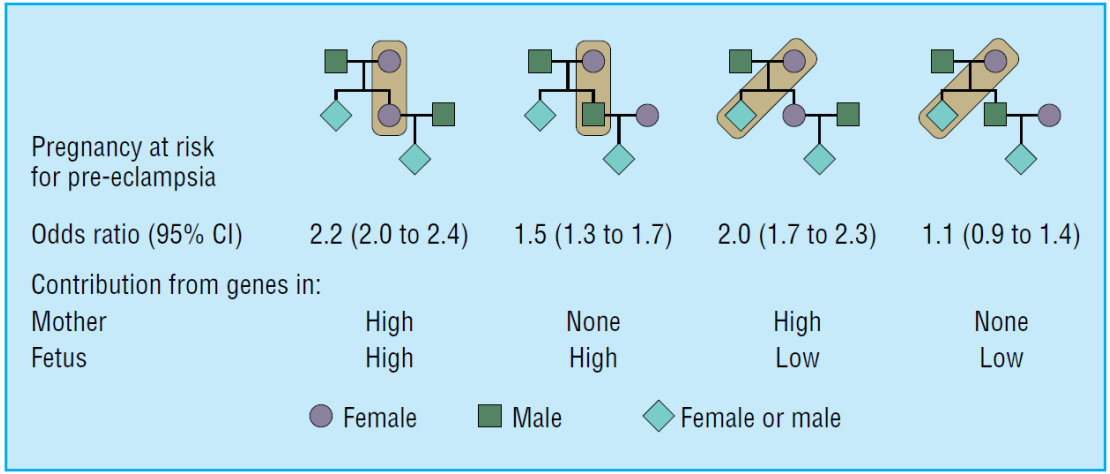
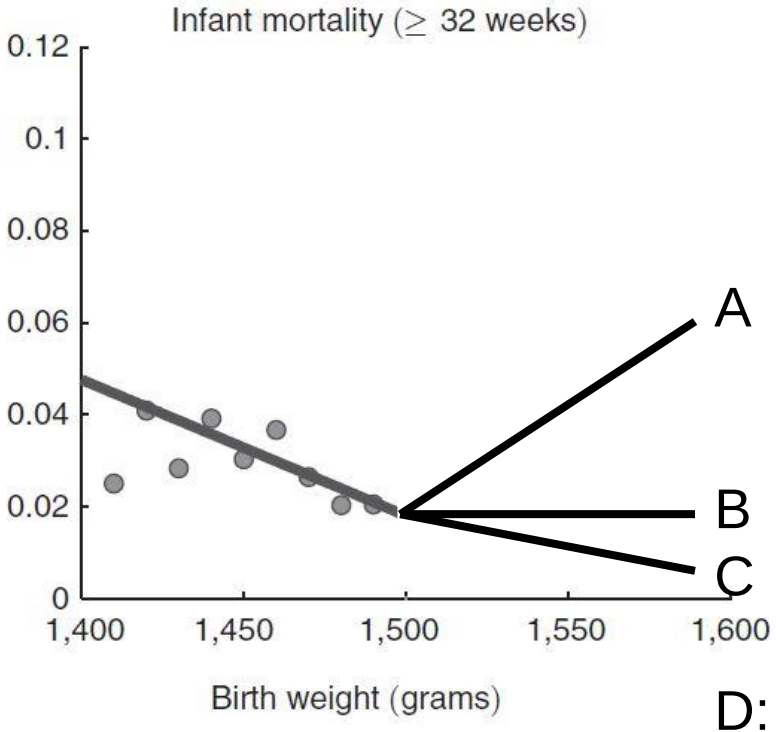
Male
Female or male

Family

LIMITATIONS?

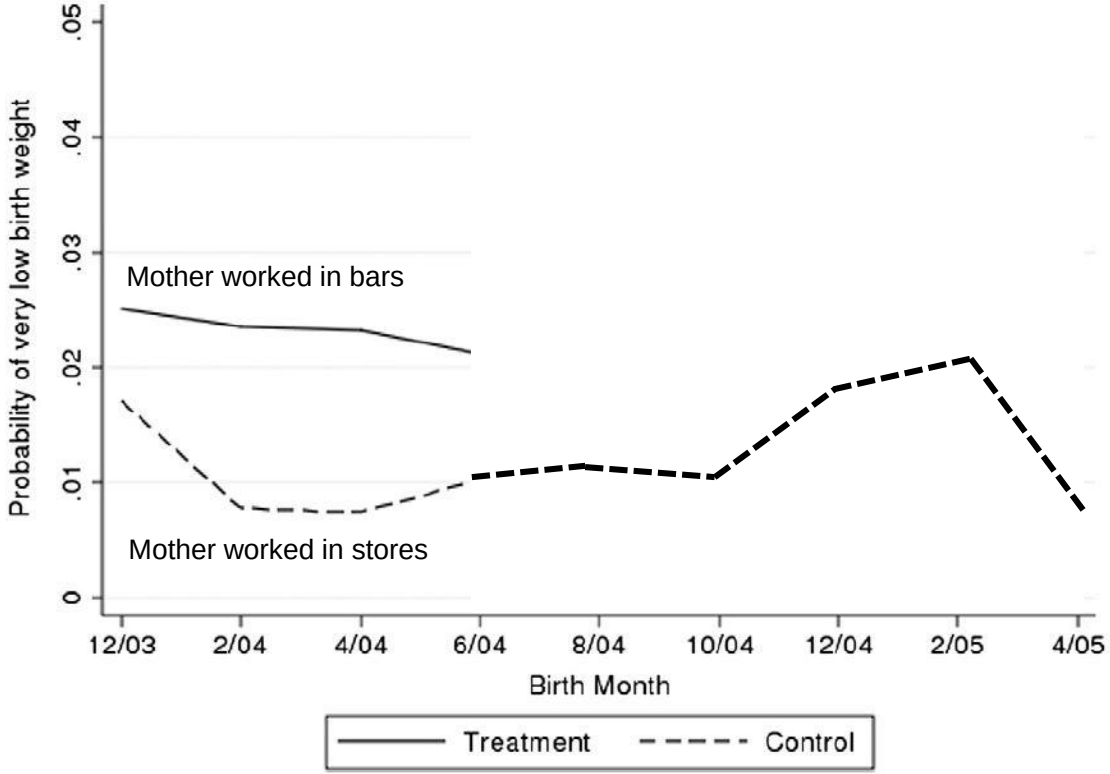


What happens (vote by raising hand)?



D: Neither

What happens?



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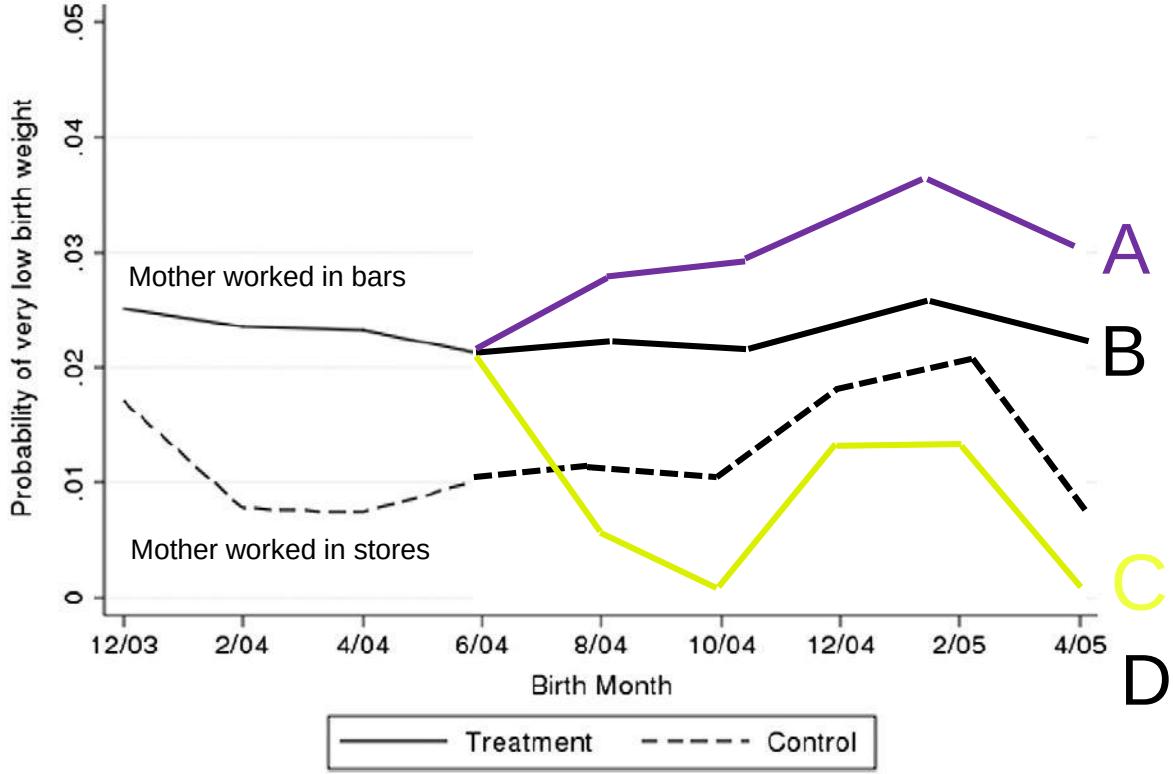


D: Neither

Health Registries for Research
Norway

NordForsk

Ignorance

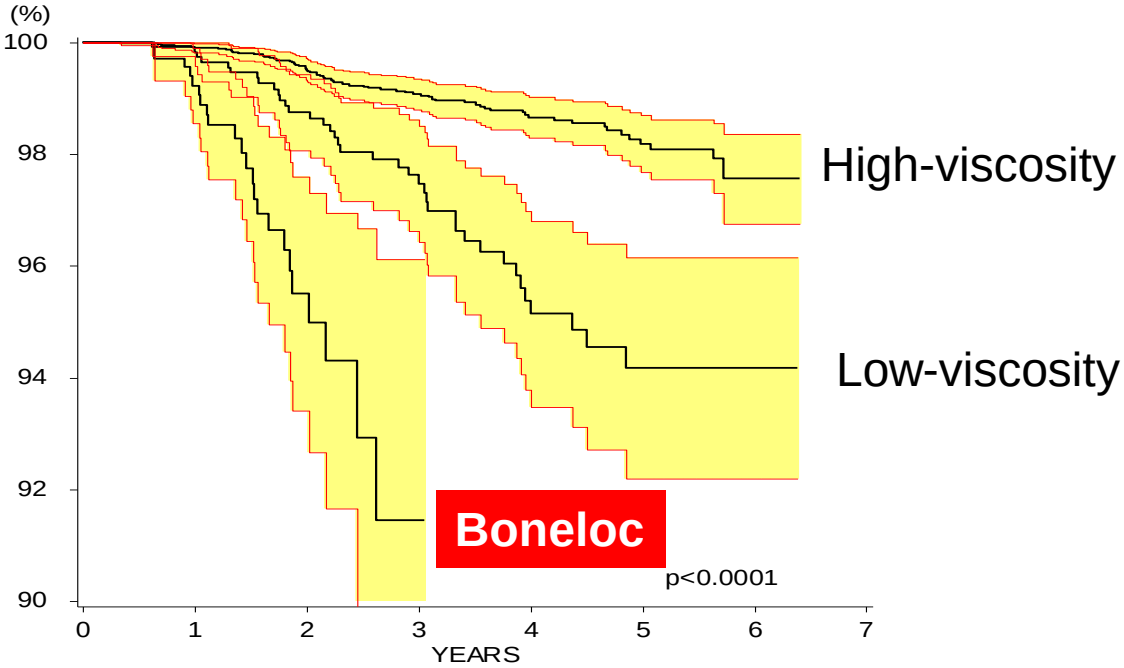
The Effect of the Type of Cement on Early Revision of Charnley Total Hip Prostheses

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

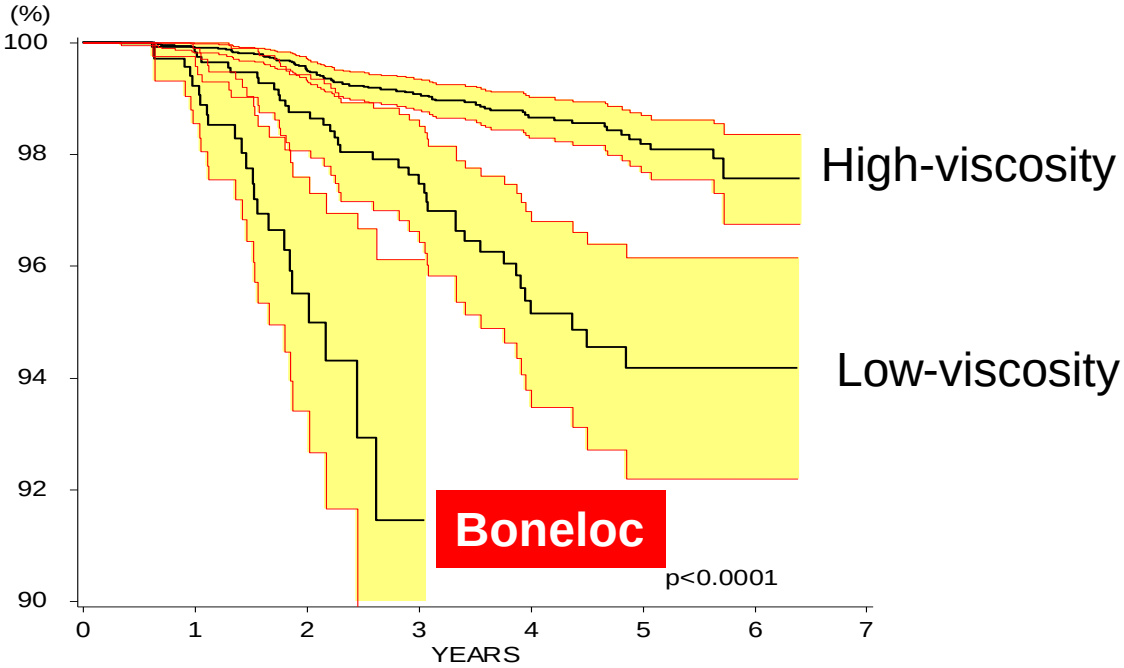
BY LEIF IVAR HAVELIN, M.D.†, BIRGITTE ESPEHAUG, M.SC.†, STEIN EMIL VOLLSET, M.D., M.P.H., DR.P.H.†, AND LARS BIRGER ENGESÆTER, M.D., PH.D.†, BERGEN, NORWAY

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

Ignorance


(%)
100
98
96
94
92
90
0
1
2
3
4
5
6
7
YEARS
High-viscosity
Low-viscosity
Boneloc
p<0.0001

Ignorance



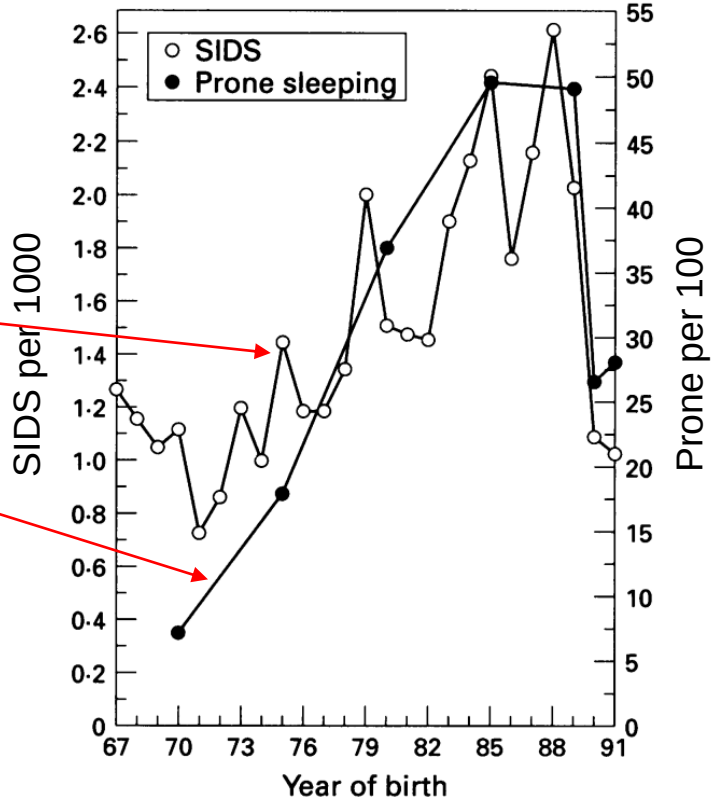
LIMITATIONS?

Interrupted time-series

Sudden infant death syndrome (SIDS)

Risk of SIDS in Norway

Prone sleeping (on the belly)



Irgens et al., 1995

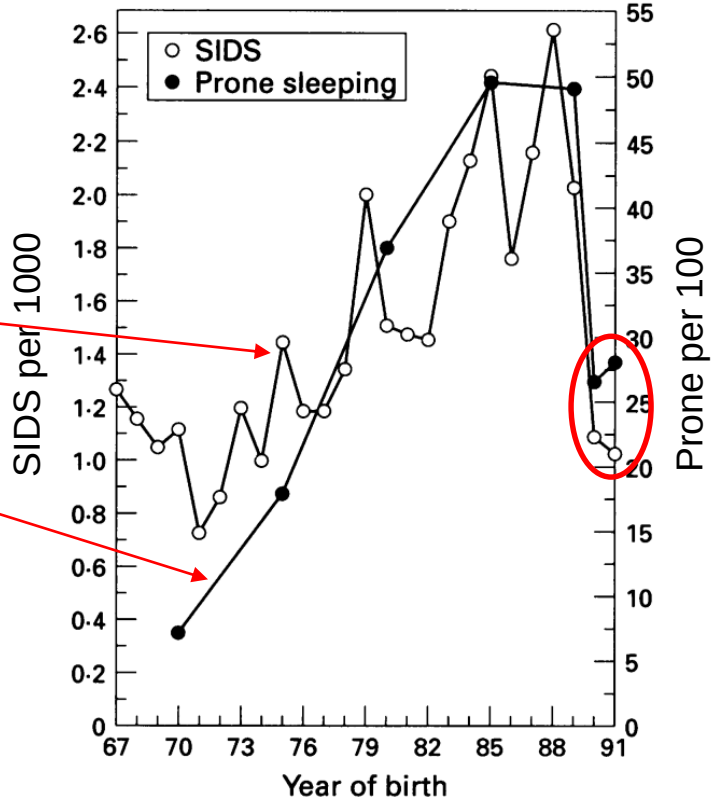
Interrupted time-series

Sudden infant death syndrome (SIDS)

Risk of SIDS in Norway

Prone sleeping (on the belly)

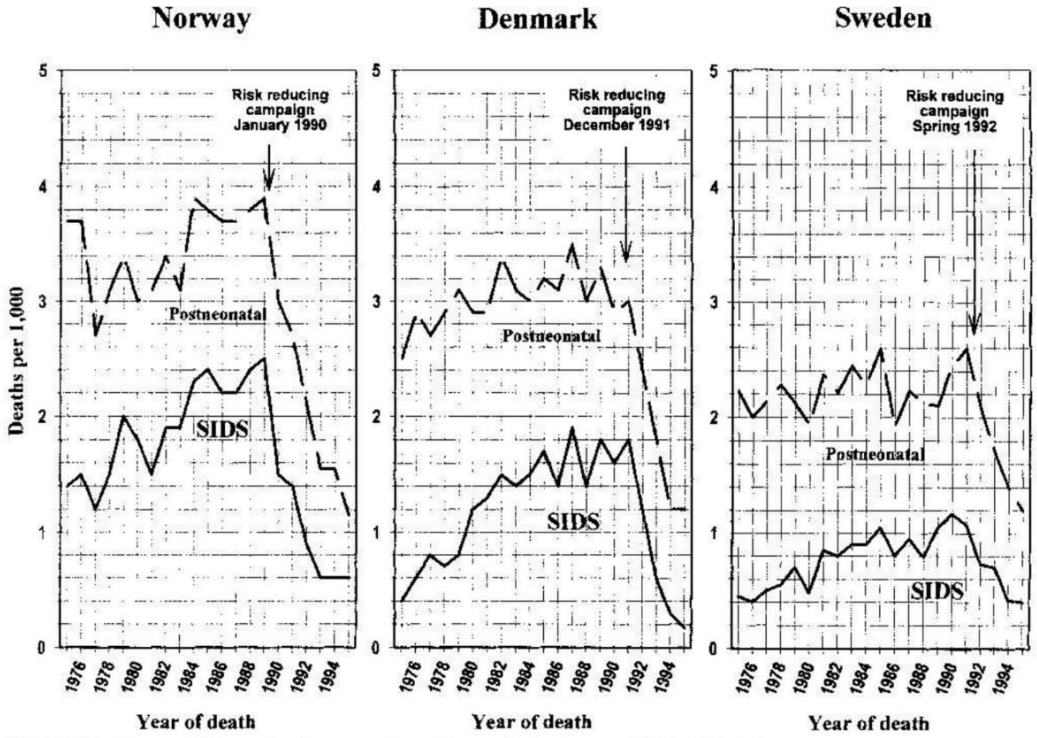
From January 1990 mothers were advised to avoid prone sleeping



Irgens et al., 1995

Interrupted time-series

Similar campaigns in Denmark and Sweden as well.

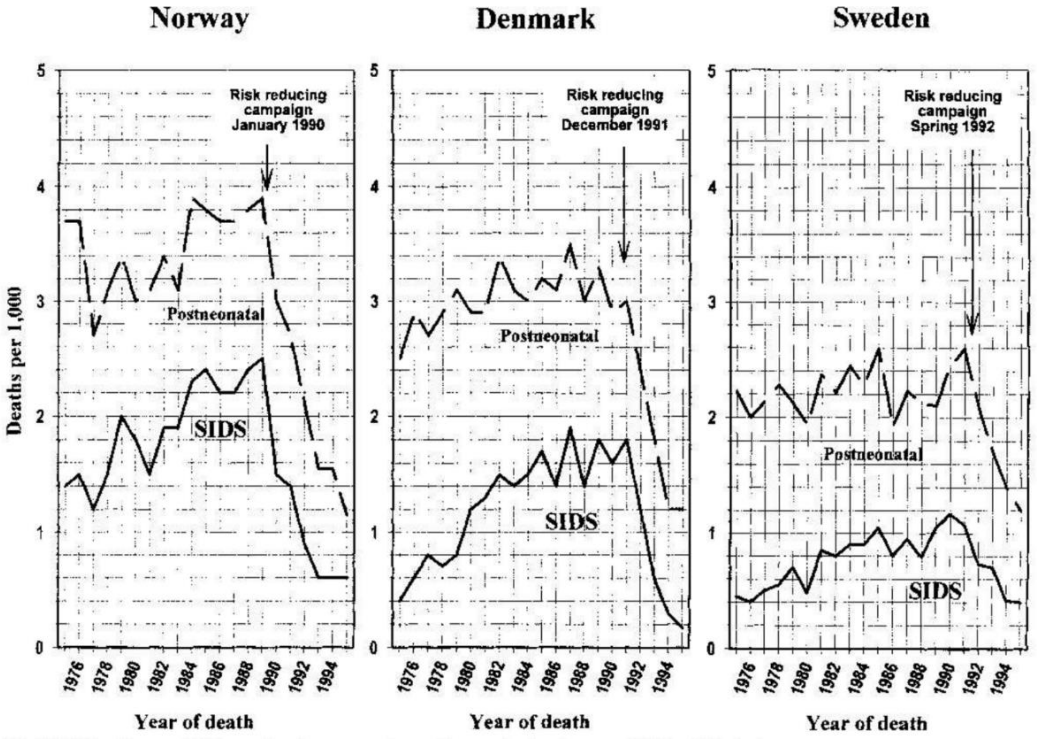


Wennergren et al., 1997

Interrupted time-series

Similar campaigns in Denmark and Sweden as well.

Are findings causal?



Wennergren et al., 1997

Thanks for listening!