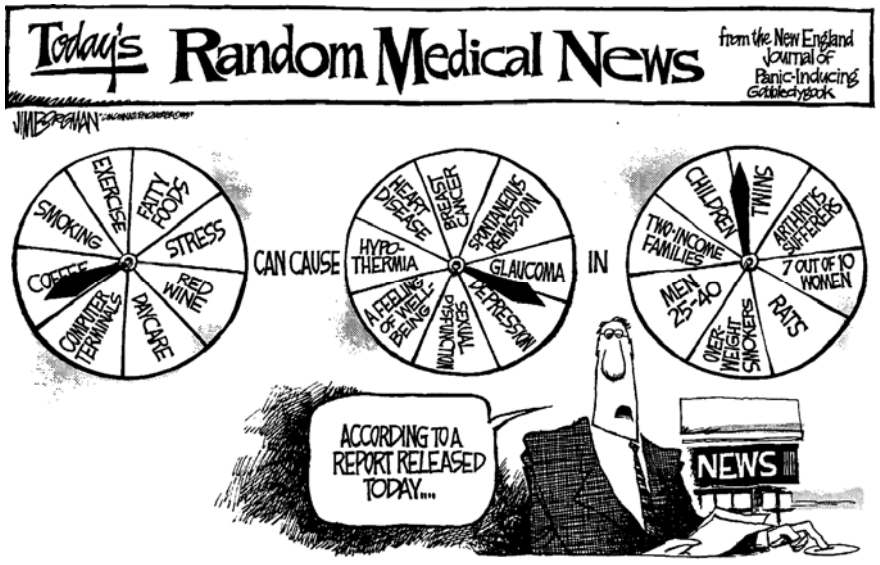
Confounding

opzet & interpretatie van mensgebonden onderzoek

b.siegerink@lumc.nl
Klinische epidemiologie



expositie veroorzaakt **uitkomst** in **domein**

Onderzoeksvraag

Expositie → Uitkomst

in Domein

Onderzoeksvraag

Expositie → Uitkomst

Stollingsfactor XI **Herseninfarct**

in Domein

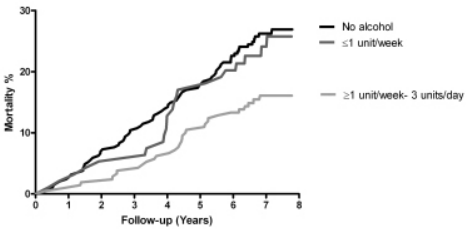
Vrouwen < 50 jaar

Glas bier na niertransplantatie is gezond

Uitgegeven: 19 november 2010 16:30
Laatst gewijzigd: 19 november 2010 16:30

GRONINGEN - Matig alcoholgebruik vermindert het risico op diabetes en vroegtijdige sterfte na een niertransplantatie. Dat blijkt uit een studie verricht door Dorien Zelle van het Universitair Medisch Centrum Groningen (UMCG).

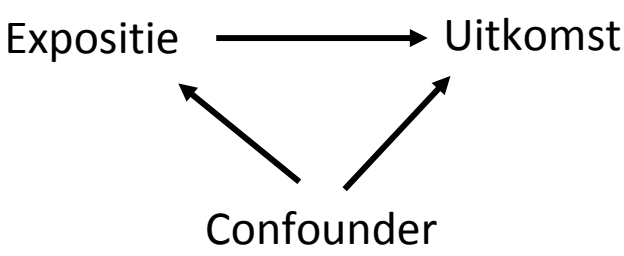
Figure1:Kaplan-Meier curve of mortality according to alcohol consumption



Uit eerder onderzoek is gebleken dat volwassenen die één of twee glazen alcohol per dag drinken, een kleinere kans hebben op diabetes en voortijdige sterfte dan mensen die helemaal niet drinken.

Tot nu toe was onbekend of dit ook geldt voor mensen die een niertransplantatie hebben ondergaan.

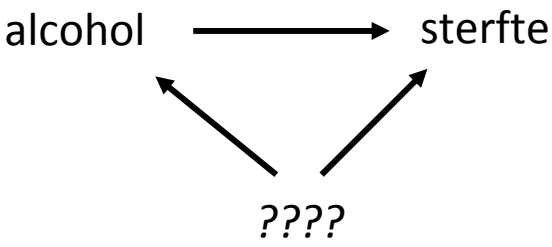
Antwoord op onderzoeksvraag?



In domein

confounding : het verwarren van twee effecten

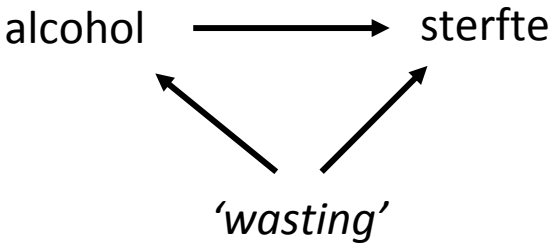
Antwoord op onderzoeksvraag?



In nier Tx patienten

confounding : het verwarren van twee effecten

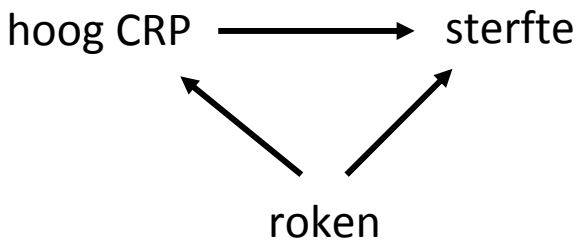
Antwoord op onderzoeksvraag?



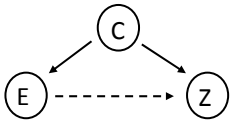
In nier Tx patienten

confounding : het verwarren van twee effecten

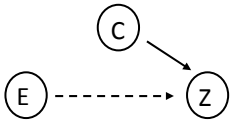
Antwoord op onderzoeksvraag?



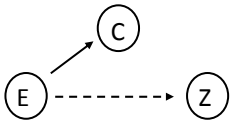
1. Confounder is oorzaak van uitkomst
2. Confounder hangt samen met expositie
3. Niet in het causale pad



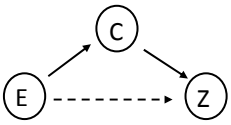
confounding



geen confounding
Andere risicofactor: FVL (e) gips (c) en trombose (z)



geen confounding
Geen oorzaak; roken (e) aansteker (c) en longkanker (z)



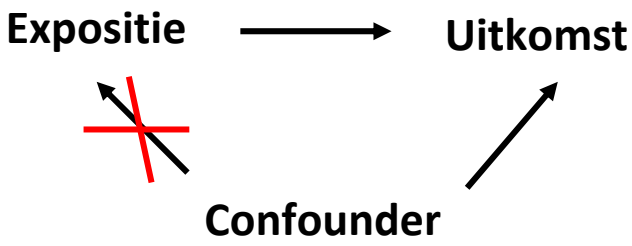
geen confounding
Causale pad; dieet (e) LDL (c) en MI (z)

Confounding is het verwarren van twee effecten

Omgaan met confounding

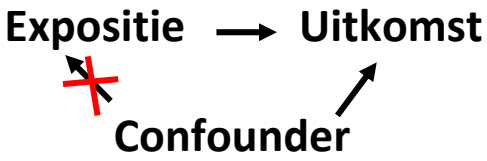
ontkoppelen confounders en expositie of uitkomst

Welke pijl kan weg?



Omgaan met confounding

- Door design
  - Restrictie
  - Matching
  - RCT
- Door analyse
  - Stratificatie
  - Standardisatie (direct / indirect)
  - Poolen d.m.v. Mantel Haenszel methode
  - Multivariate analyse
  - IPW / propensity score models



‘Nieuwe’ technieken

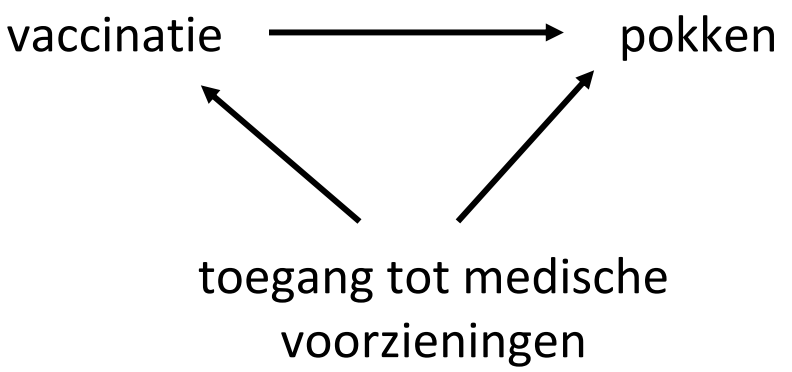
- Directed acyclic graphs (DAGs); formaliseert de visualisatie van confounding
- Inverse propability weighting (IPW)
  - Creeert een situatie waarin iedereen zowel exposed en nonexposed is
  - Alles is daarmee hetzelfde behalve de expositie
  - aanpak is niet nieuw: ceteris paribus

Ceteris paribus

variola

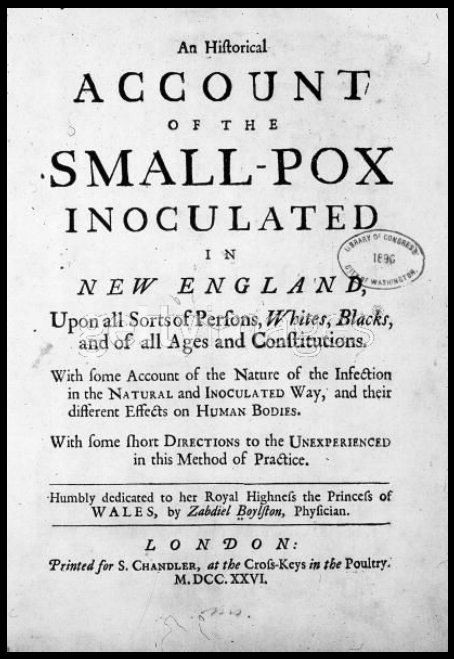
Boston, 1721

Vaccineren voor pokken?



Overheid vs. geestelijken

"Smallpox is 'a judgment of God on the sins of the people,' and that 'to avert it is but to provoke him more'. Thus 'inoculation is an encroachment on the prerogatives of Jehovah, whose right it is to wound and smite."



An Hiſtorical

ACCOUNT

OF THE

SMALL-POX

INOCULATED

IN

NEW ENGLAND,

Upon all Sorts of Perſons, *Whites*, *Blacks*, and of all Ages and Conſtitutions.

With ſome Account of the Nature of the Infection in the NATURAL and INOCULATED Way, and their different Effects on HUMAN BODIES.

With ſome ſhort DIRECTIONS to the UNEXPERIENCED in this Method of Practice.

Humbly dedicated to her Royal Highneſs the Princeſs of WALES, by *Zabdiel Boylſton*, Phyſician.

LONDON:

Printed for S. CHANDLER, *at the* Croſs-Keys *in the* Poultry. M.DCC.XXVI.

Geloofs-gemeenschap → Vaccinatie → Pokken

SES

	Totaal	†	Mortaliteit
Geloofsgemeenschap 1	**274**	**6**	**2%**
Geloofsgemeenschap 2	**6000**	**840**	**14%**

RR:0.15 95%CI 0.07 – 0.35

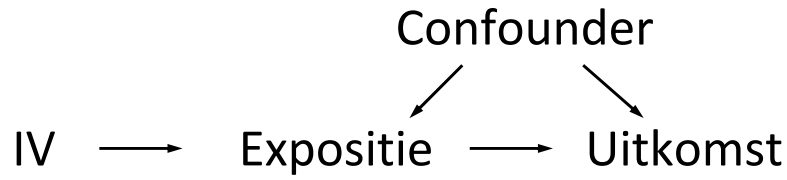
Pseudo-randomisatie / natuurlijk experiment

Doel:

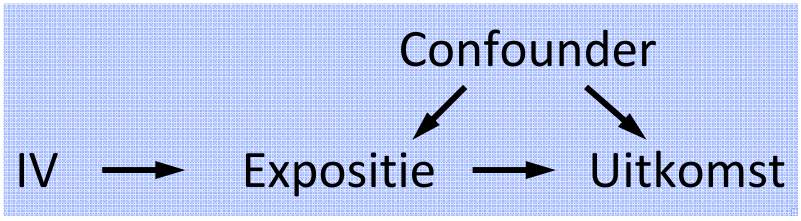
Ontkoppelen van de expositie van mogelijke confounders

Middel:

Expositie hangt samen met een derde 'random' variabele (instrumental variable), i.e. die niet samen hangt met confounders



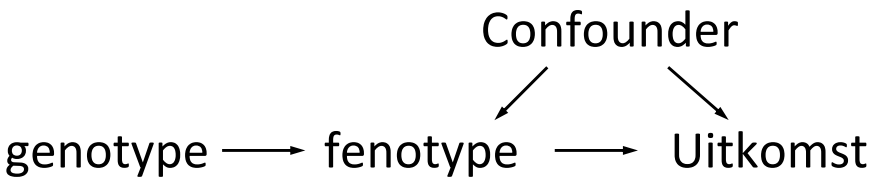
Assumpties IV



1. IV voorspelt expositie (niet perse causaal)
2. IV kent geen confounders
3. IV heeft geen andere paden dan via expositie (i.e. geen pleiotropy)

Mendelian Randomisation

- *Mendels Law of Independent Assortment :*
  - Genen zijn random verdeeld tijdens de meiose
- IV: Genetische variatie gebruiken als marker voor levenslange blootstelling aan fenotype



M. Katan

THE LANCET, MARCH 1, 1986

APOLIPOPROTEIN E ISOFORMS, SERUM CHOLESTEROL, AND CANCER

SIR,—It is unclear whether the relation between low serum cholesterol levels and cancer[1] is causal. In many studies occult tumour may have depressed cholesterol levels though in others the relation was found when serum cholesterol had been measured many years before the cancer was diagnosed. The relation is probably not explained by diet, because in the Seven Countries Study cohorts with widely different diets and corresponding differences in mean cholesterol levels experienced similar mean cancer rates.[2,3] On the other hand, within each region cancer incidence was higher in men with a serum cholesterol in the lowest part of the cholesterol distribution for that country.[3] Thus, naturally low cholesterol levels are sometimes associated with increased cancer risk.[1,3]

Differences in the aminoacid sequence of apolipoprotein E (apo E) are major determinants of differences in plasma cholesterol levels

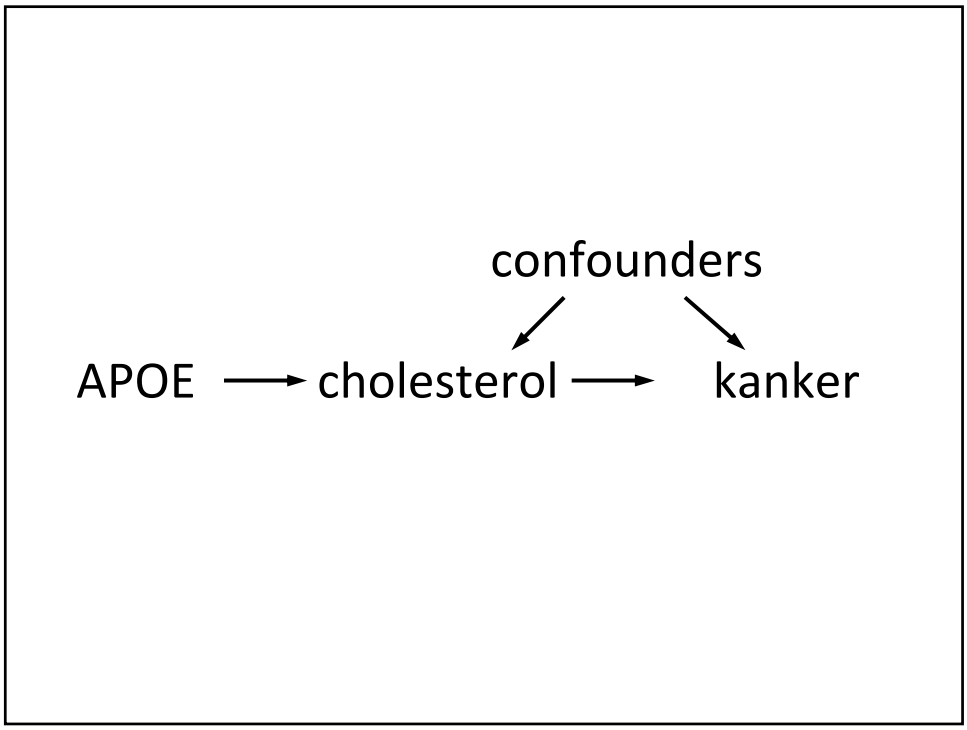
IV -> E

No confounding

Pleiotropy?

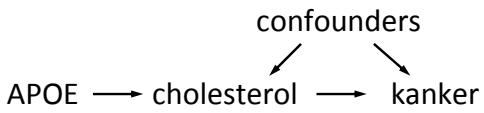
residue is replaced. As a result the avidity of apo E containing lipoproteins for lipoprotein receptors increases from apo E-2 to apo E-3 to apo E-4. In several populations,[6-8] including the Finns and the Japanese (Dr G. Utermann, personal communication), the gradient in serum cholesterol levels in the population is associated with a gradient in apo E phenotype, E-2 being associated with lower serum low-density lipoprotein and total cholesterol levels than E-3 and E-4. Thus, if a naturally low cholesterol favours tumour growth, then subjects with the E-2/E-2 or E-2/E-3 phenotype should have an increased risk of cancer.

Unlike most other indices of lipid metabolism, apolipoprotein aminoacid sequences are not disturbed by disease, and the apo E phenotype found in a patient will have been present since birth. A comparison of apo E phenotypes in cancer patients with those in matched controls might thus shed light on the relation between low cholesterol and cancer. If it is causal then the E-2 allele should be more common among patients and E-3 and E-4 more common among controls. On the other hand, equal distribution of apo E phenotypes among cases and controls would suggest that the association between low cholesterol and cancer is spurious. Measurement of apo E phenotype by isoelectric focusing of plasma is a routine determination in lipid laboratories; epidemiologists interested in cholesterol and cancer should include it in their



Geassocieerd, maar causaal?

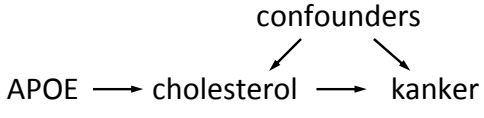
	Plasma Cholesterol Level[a]					
	Low vs. Intermediate[b]			Low vs. High[b]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Crude model						
Cancer incidence	1.45	1.05, 2.01	0.02	1.90	1.34, 2.70	<0.01
Cancer mortality	2.10	1.27, 3.50	<0.01	2.03	1.23, 3.34	0.01
Adjusted model[c]						
Cancer incidence	1.35	0.97, 1.89	0.08	1.70	1.16, 2.50	0.01
Cancer mortality	2.16	1.28, 3.64	<0.01	1.93	1.12, 3.34	0.02



Trompet et al, AJE nov 2009

Geassocieerd, maar causaal?

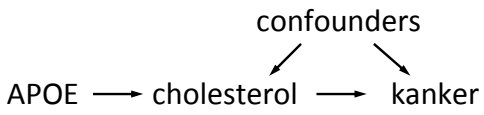
	Apolipoprotein E Genotype					
	E2+ vs. *E3/E3*[b]			*E2*+ vs. *E4*+[b]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Crude model						
Cancer incidence						
Cancer mortality						
Adjusted model[c]						
Cancer incidence						
Cancer mortality						



Trompet et al, AJE nov 2009

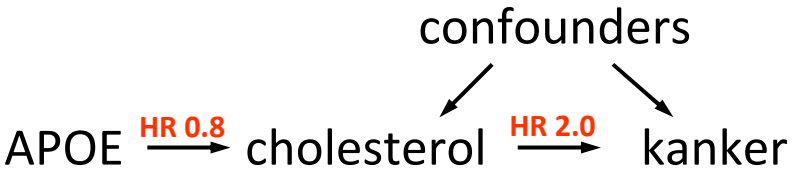
Geassocieerd, maar causaal?

	Apolipoprotein E Genotype					
	E2+ vs. *E3/E3*[b]			*E2*+ vs. *E4*+[b]		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Crude model						
Cancer incidence	0.90	0.41, 1.81	0.67	0.91	0.53, 1.54	0.72
Cancer mortality	0.86	0.56, 1.45	0.69	0.74	0.33, 1.68	0.47
Adjusted model[c]						
Cancer incidence	0.88	0.55, 1.41	0.59	0.86	0.50, 1.47	0.59
Cancer mortality	0.85	0.40, 1.79	0.67	0.70	0.30, 1.60	0.39



Trompet et al, AJE nov 2009

Cholesterol en kanker: niet causaal!



De assumpties van een IV zitten verborgen in pijlen die *niet* getekend kunnen worden

JUPITER trial

toepassing MR op CRP

JUPITER trial

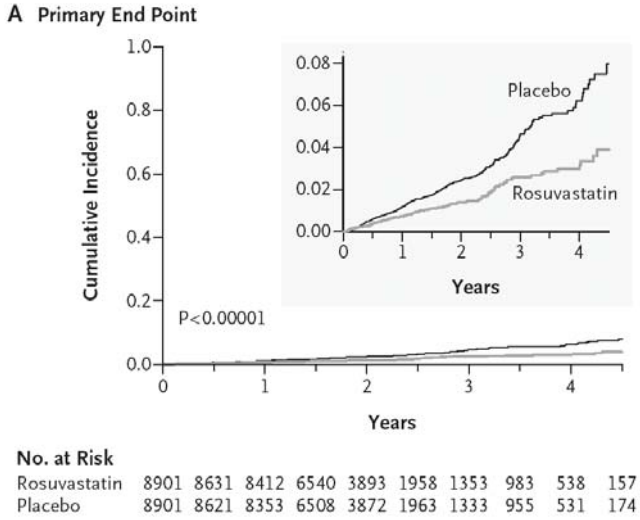
Rosuvastatine
vs
placebo

Hart- &
vaatziekten

In patiënten met ↓Cholesterol & ↑ CRP

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.*

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age — yr		
Median	66.0	66.0
Interquartile range	60.0–71.0	60.0–71.0
Female sex — no. (%)	3426 (38.5)	3375 (37.9)
Race or ethnic group — no. (%)†		
White	6358 (71.4)	6325 (71.1)
Black	1100 (12.4)	1124 (12.6)
Hispanic	1121 (12.6)	1140 (12.8)
Other or unknown	322 (3.6)	312 (3.5)
Body-mass index‡		
Median	28.3	28.4
Interquartile range	25.3–32.0	25.3–32.0
Blood pressure — mm Hg		
Systolic		
Median	134	134
Interquartile range	124–145	124–145
Diastolic		
Median	80	80
Interquartile range	75–87	75–87
Current smoker — no. (%)	1400 (15.7)	1420 (16.0)
Family history of premature CHD — no. (%)§	997 (11.2)	1048 (11.8)
Metabolic syndrome — no. (%)¶	3652 (41.0)	3723 (41.8)
Aspirin use — no. (%)	1481 (16.6)	1477 (16.6)
High-sensitivity C-reactive protein — mg/liter‖		
Median	4.2	4.3



No. at Risk

Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

HR: 0.56 (95% CI 0.46–0.69)

CRP causaal?

Level	12 Mo	
	Rosuvastatin	Placebo
High-sensitivity C-reactive protein (mg/liter)		
Median	2.2	3.5
Interquartile range	1.2–4.4	2.0–6.2
LDL cholesterol (mg/dl)		
Median	55	110
Interquartile range	44–72	94–125

Moeten we selective CRP remmers ontwikkelen?

ORIGINAL ARTICLE

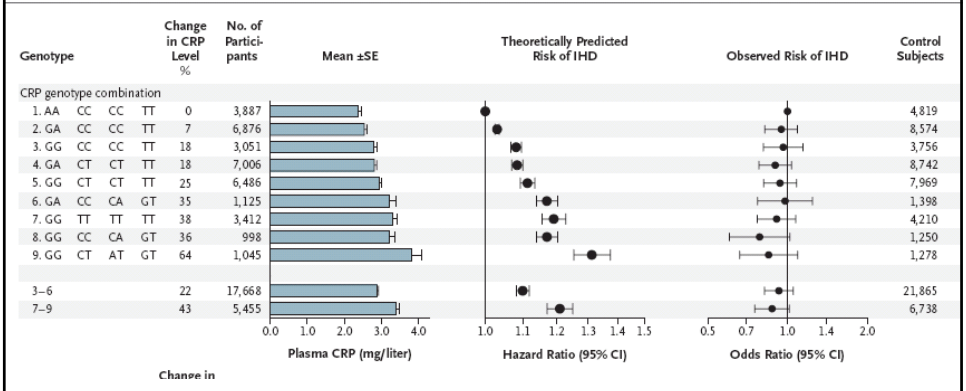
Genetically Elevated C-Reactive Protein and Ischemic Vascular Disease

Jeppe Zacho, M.D., Anne Tybjærg-Hansen, M.D., D.M.Sc.,
Jan Skov Jensen, M.D., D.M.Sc., Peer Grande, M.D., D.M.Sc.,
Henrik Sillesen, M.D., D.M.Sc., and Børge G. Nordestgaard, M.D., D.M.Sc.

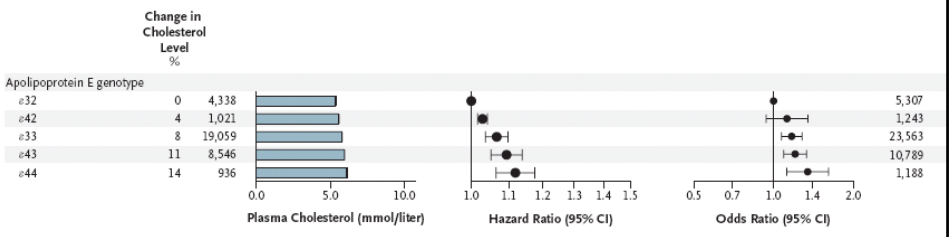
Copenhagen general population study

- General population (31.992), crosssectional
- CRP, CRP polymorphisms
- Ischaemic heart disease

CRP ⟶ ischeamic heart disease



Cholesterol → ischeamic heart disease



Proof of concept ApoE
Geen relatie CRP haplotypes en risico IHD

CRP niet causaal

Confounding

- Verwarring van twee mogelijke *oorzaken* van ziekte
- Beoordelen van confounder op basis van '*subject knowledge*'
- Tegen te gaan in study design en analyse
- Denk '*ceteris paribus',* maar RCT is niet de enige mogelijkheid om dat te bereiken!
  - Instrumental variables (MR)

VIEWPOINT

When are observational studies as credible as randomised trials?

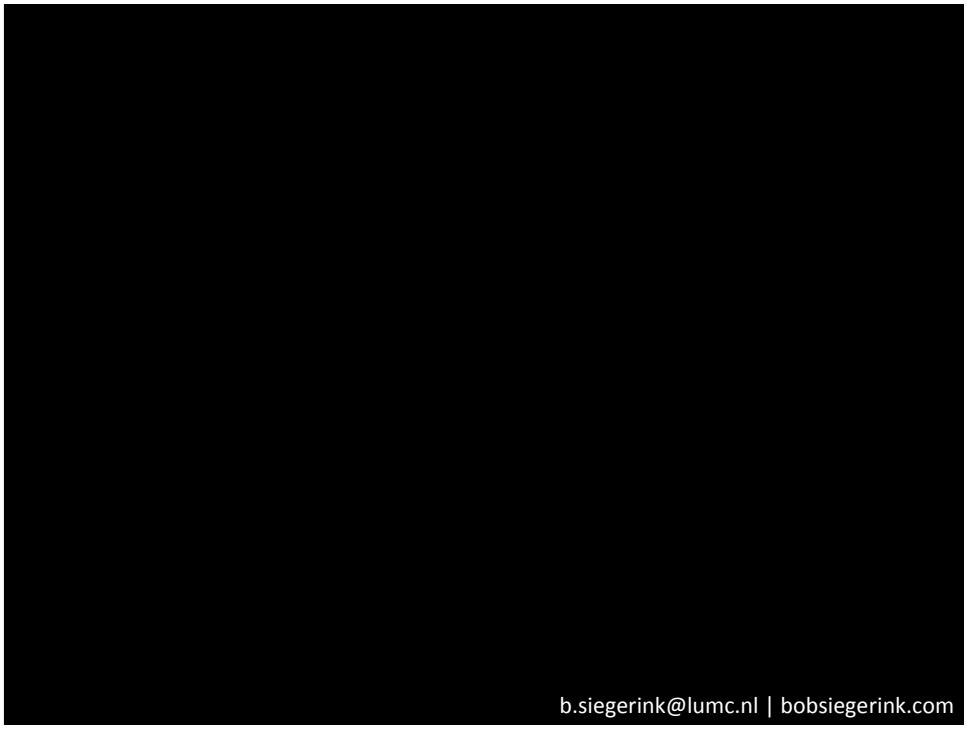
Jan P Vandenbroucke

Observational studies have a record of extremely successful contributions to medicine. They are essential for our knowledge about causes and pathogenesis—eg, genetic, environmental, or infectious causes of disease. Additionally, for medical practice we rely on observational studies of prognosis and diagnosis. Nevertheless, over the past years, we have seen recurrent debates about the merit of observational versus randomised research. The debates have been fuelled recently because of seeming total failures, in which the results of observational studies were completely overturned by randomised studies. Hormone replacement therapy showed protection from myocardial infarction in observational studies, but a small increase was seen in randomised trials; a similar reversal happened for β carotene and lung cancer. Such discrepancies raise the question: in what circumstances can observational comparisons be as convincing as randomised experiments? To answer that question: I will first recall what is expected from randomisation. I will then describe two specific issues, adverse effects of drugs and genetic causes

by clinicians, it does not guarantee that two groups will be equal in all relevant prognostic factors. Think about the human genome, with its 3 billion base pairs: even in a very large randomised trial, say of 20 000 people, thousands of genetic differences are sure to arise between the groups. Some of these differences—which we do not yet know—might be important for prognosis. Randomisation guarantees that such differences are indeed due to chance. It means that statistical theory based on random sampling can be used to calculate confidence intervals that express the potential magnitude of such chance events.[2]

Adverse drug reactions: breaking the link between prescription and prognosis

The average randomised drug trial is too small, and does not have sufficient follow-up to detect adverse effects that are fewer than about one per 200 per year, or that take longer than 1 year to develop. To investigate adverse drug reactions, either case-control studies or large-scale observational follow-up studies are needed.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