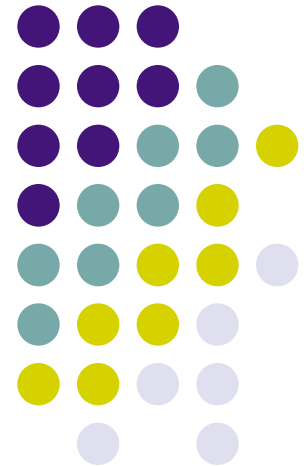


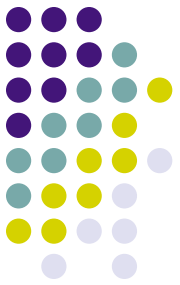
Manipulatie en bias in onderzoek

Luc Bonneux
Arts, epidemioloog en publicist





Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*



Bescherming grieprik

Als u de jaarlijkse grieprik heeft gehad, is de kans dat u griep krijgt veel kleiner.

Krijgt u toch griep, dan verloopt de ziekte meestal minder ernstig.

Bovendien is de kans op complicaties zoals longontsteking kleiner.

Verder verkleint de grieprik de kans dat uw 'eigen' ziekte erger wordt door griep.

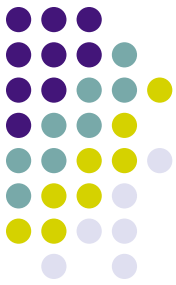
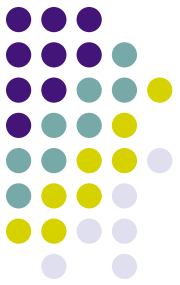


Table 3. Influenza Vaccine Effectiveness (VE) in Reducing Morbidity and Mortality During the 1999-2000 Influenza A Epidemic

Subgroup	GP Visit for ARD or CVD	Hospitalization for ARD or CVD	Death From Any Cause
High-risk children aged <18 y			
Vaccinated cases, No. (%)	69/160 (43)	3/3 (100)	1/1 (100)
Vaccinated controls, No. (%)	240/411 (59)	240/411 (59)	240/411 (59)
Unadjusted VE (95% CI)	48 (24 to 62)	NA	NA
Adjusted VE (95% CI)	43 (10 to 64)	NA	NA
Adjusted P value	.02	NA	NA
High-risk adults aged 18-64 y			
Vaccinated cases, No. (%)	255/363 (70)	14/23 (61)	22/47 (47)
Vaccinated controls, No. (%)	1246/1778 (70)	1246/1778 (70)	1246/1778 (70)
Unadjusted VE (95% CI)	1 (-27 to 23)	59 (-8 to 84)	71 (41 to 86)
Adjusted VE (95% CI)	26 (7 to 47)	87 (39 to 97)	78 (39 to 92)
Adjusted P value	.04	.009	.005
Elderly aged ≥65 y			
Vaccinated cases, No. (%)	879/1060 (83)	130/166 (78)	203/272 (75)
Vaccinated controls, No. (%)	5197/6404 (81)	5197/6404 (81)	5197/6404 (81)
Unadjusted VE (95% CI)	0 (-20 to 16)	40 (10 to 49)	43 (23 to 57)
Adjusted VE (95% CI)	7 (-11 to 23)	48 (7 to 71)	50 (23 to 68)
Adjusted P value	.42	.03	.002
All adults aged ≥18 y			
Vaccinated cases, No. (%)	1134/1423 (80)	144/189 (76)	225/319 (71)
Vaccinated controls, No. (%)	6443/8182 (79)	6443/8182 (79)	6443/8182 (79)
Unadjusted VE (95% CI)	0 (-16 to 13)	35 (7 to 54)	44 (27 to 56)
Adjusted VE (95% CI)	14 (0 to 26)	55 (24 to 63)	55 (34 to 70)
Adjusted P value	.04	.003	<.001

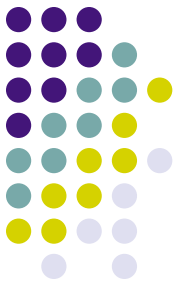
Abbreviations: ARD, acute respiratory disease including acute bronchitis or exacerbations of chronic lung disease, influenza, pneumonia, and acute otitis media; CI, confidence interval; CVD, cerebrovascular disease including myocardial infarction, stroke, and heart failure; GP, general practitioner; NA, not applicable due to low numbers in the outcome category.

1. **Hak E**, Buskens E, van Essen GA, de Bakker DH, **Grobbee DE**, Tacken MA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Arch Intern Med* 2005;165(3):274-80.

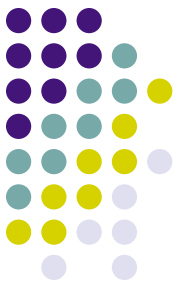


18-64	Vacc	Unvacc	Total	%
Died	22	25	47	47%
Lived	1246	532	1778	70%
Total	1268	557	1825	
		VE	Published	Adjusted
OR	(38%)	62%	71%	78%
RR	(67%)	33%		
65+	Vacc	Unvacc	Total	%
Died	203	69	272	75%
Lived	5197	1207	6404	81%
Total	5400	1276	6676	
		VE	Published	Adjusted
OR	(68%)	32%	43%	50%
RR	(92%)	8%		
NNV		55		

Framing



Het risico op dodelijke adderbeten in de Hoge Veluwe neemt sterk af door het dragen van onze hoge laarzen **Geefhengeenkans®**. Geef adders geen kans, draag **Geefhengeenkans®**. Voorkomen is beter dan genezen!



Numbers needed to vaccinate

- Klinische griep in een “goed” jaar: 40
- Klinische griep in een “slecht” jaar: 80
- Klinische griep in ongeselecteerde studie: 100
- Geen bewijs voor effect op longontsteking of totale sterfte (NNV mogelijk ∞)
- (Bewijs voor manipulatie, verdachte studies en systematische overschatting)

TABLE 2. Coronary Drug Project: Crude and adjusted 5-year mortality and adjusted relative risk (RR) of mortality in , according to compliance with treatment^a

Compliance	% Mortality			% Mortality		
	Crude	Adjusted ^b	RR ^c	Crude	Adjusted ^b	RR ^c
< 80%	24.6	22.5		28.2	25.8	
≥ 80%	15.0	15.7	0.70	15.1	16.4	0.64

^a Modified from Table 1 of Coronary Drug Project Research Group (7).

^b Adjusted for 40 baseline characteristics.

^c Adjusted RR of mortality in high-compliance group compared with low-compliance group.

TABLE 3. Beta-blocker Heart Attack Trial: 1-year mortality and crude and adjusted relative risk of mortality in men , according to compliance with treatment^a

Compliance	% Mortality	Relative risk		% Mortality	Relative risk	
		Crude	Adjusted ^{b,c}		Crude	Adjusted ^{b,c}
< 75%	4.6			7.0		
≥ 75%	1.4	0.32	0.34	3.0	0.40	0.37

^a Modified from Horwitz et al. (8).

^b Adjusted for clinical severity of coronary heart disease at baseline, smoking, marital status, education, race, and four psychosocial variables (stress, isolation, depression, type A personality).

^c Adjusted relative risk of mortality in high-compliance group compared with low-compliance group.

TABLE 4. Beta-blocker Heart Attack Trial: Mortality and crude relative risk of mortality in women , according to compliance with treatment^a

Compliance	% Mortality	Relative risk ^b	% Mortality	Relative risk ^b
< 75%	8.7		19.0	
≥ 75%	4.5	0.53	6.8	0.36

^a Modified from Table 1 of Gallagher et al. (9).

^b Relative risk of mortality in high-compliance group compared with low-compliance group.

TABLE 2. Coronary Drug Project: Crude and adjusted 5-year mortality and adjusted relative risk (RR) of mortality in patients assigned to receive clofibrate or placebo, according to compliance with treatment^a

Compliance	Clofibrate			Placebo		
	% Mortality		RR ^c	% Mortality		RR ^c
	Crude	Adjusted ^b		Crude	Adjusted ^b	
< 80%	24.6	22.5		28.2	25.8	
≥ 80%	15.0	15.7	0.70	15.1	16.4	0.64

^a Modified from Table 1 of Coronary Drug Project Research Group (7).

^b Adjusted for 40 baseline characteristics.

^c Adjusted RR of mortality in high-compliance group compared with low-compliance group.

TABLE 3. Beta-blocker Heart Attack Trial: 1-year mortality and crude and adjusted relative risk of mortality in men assigned to receive beta-blocker or placebo, according to compliance with treatment^a

Compliance	Beta-blocker			Placebo		
	% Mortality	Relative risk		% Mortality	Relative risk	
		Crude	Adjusted ^{b,c}		Crude	Adjusted ^{b,c}
< 75%	4.6			7.0		
≥ 75%	1.4	0.32	0.34	3.0	0.40	0.37

^a Modified from Horwitz et al. (8).

^b Adjusted for clinical severity of coronary heart disease at baseline, smoking, marital status, education, race, and four psychosocial variables (stress, isolation, depression, type A personality).

^c Adjusted relative risk of mortality in high-compliance group compared with low-compliance group.

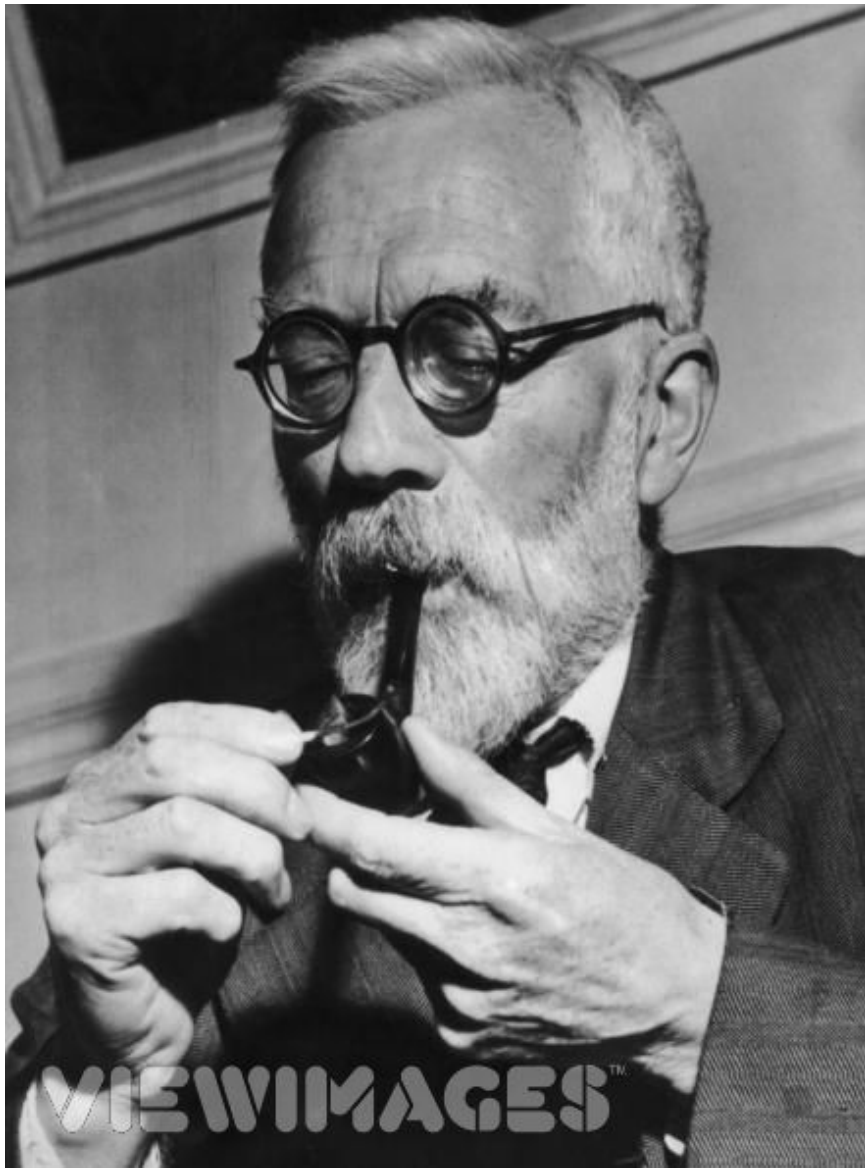
TABLE 4. Beta-blocker Heart Attack Trial: Mortality and crude relative risk of mortality in women assigned to receive beta-blocker or placebo, according to compliance with treatment^a

Compliance	Beta-blocker		Placebo	
	% Mortality	Relative risk ^b	% Mortality	Relative risk ^b
< 75%	8.7		19.0	
≥ 75%	4.5	0.53	6.8	0.36

^a Modified from Table 1 of Gallagher et al. (9).

^b Relative risk of mortality in high-compliance group compared with low-compliance group.

Petitti DB. Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? Ann Epidemiol 1994;4(2):115-8.



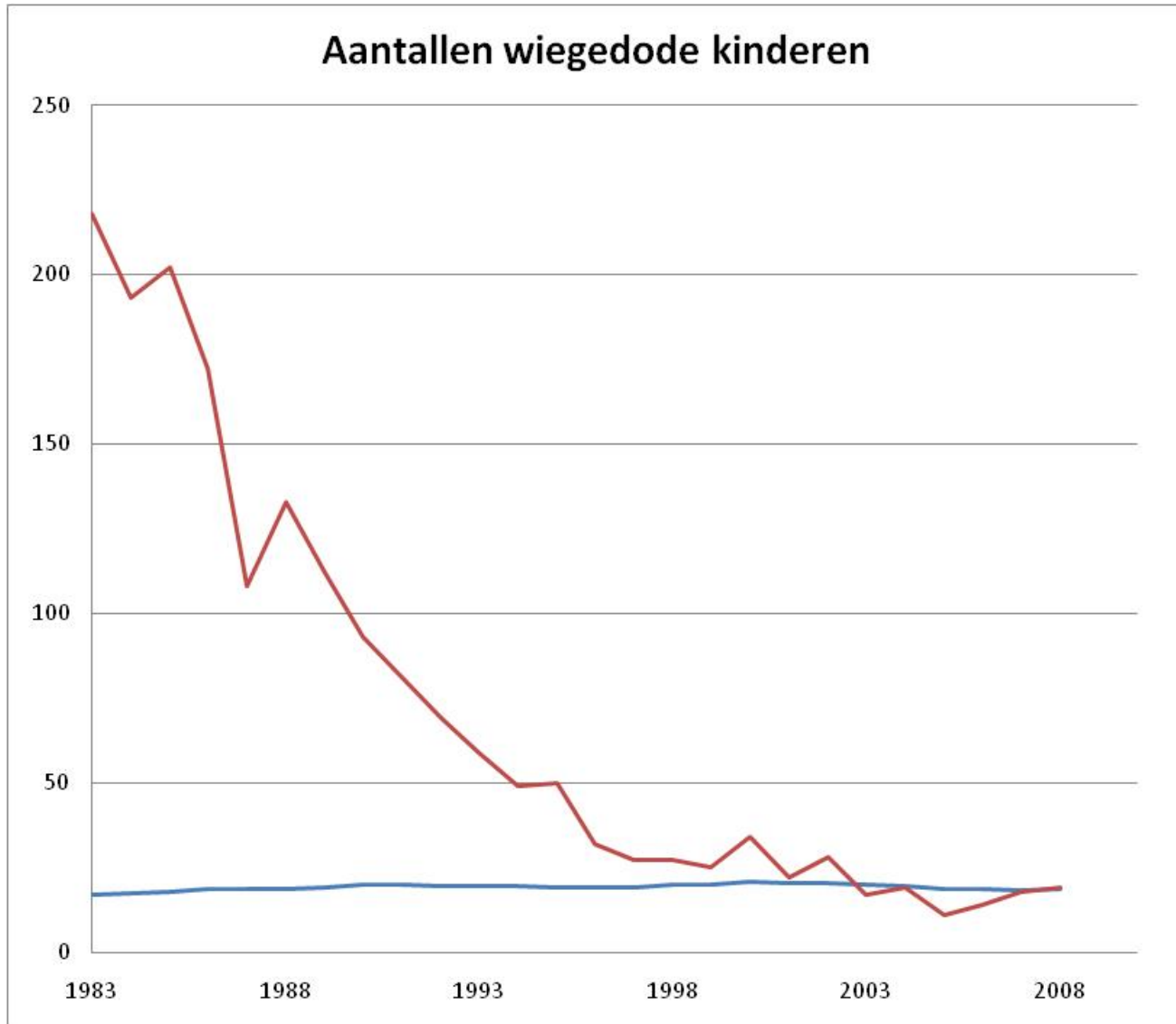
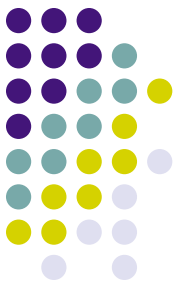
Sir Ronald Fisher

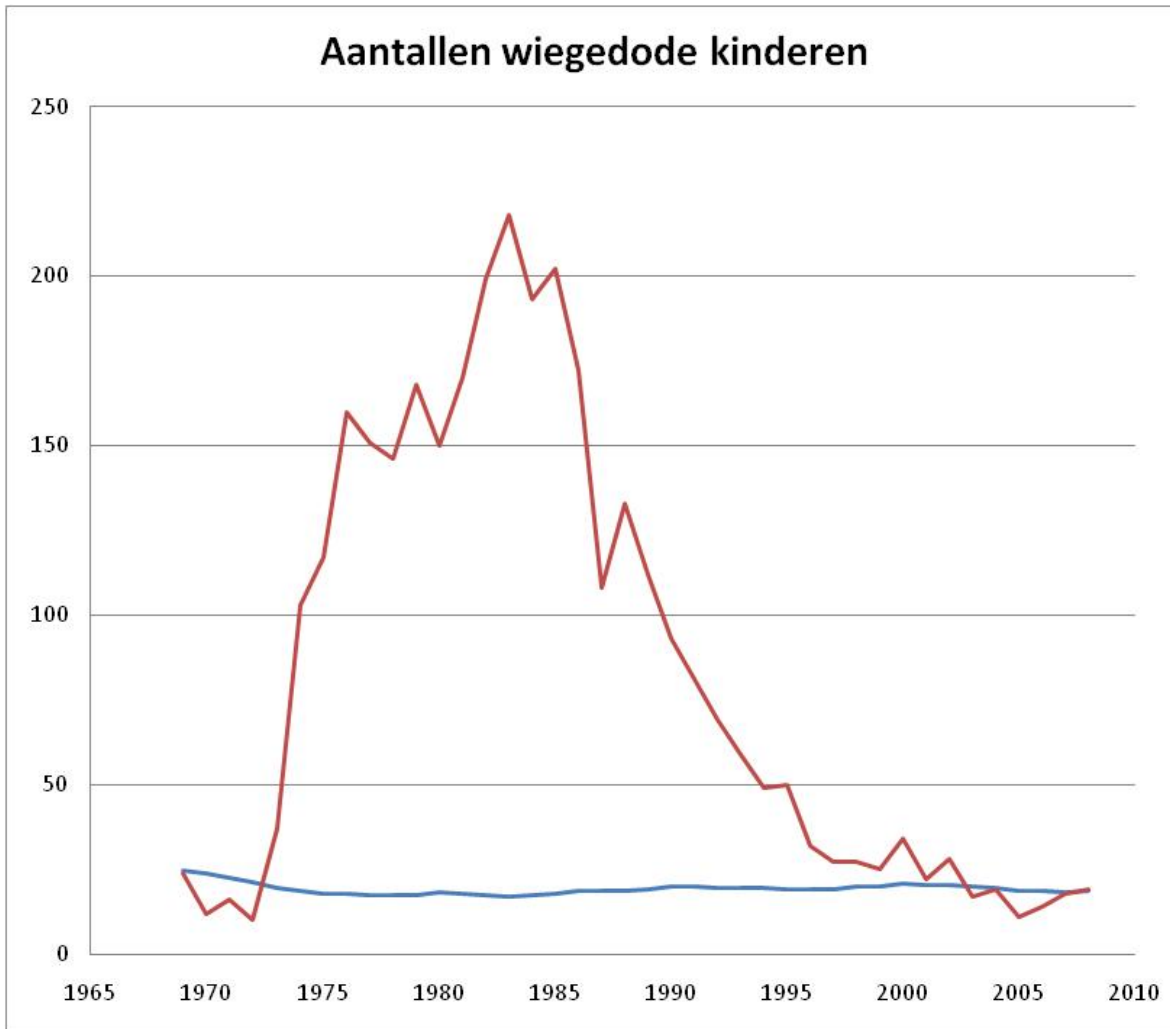


Sir Austin Bradford Hill

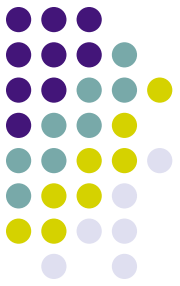


Een succes van preventie

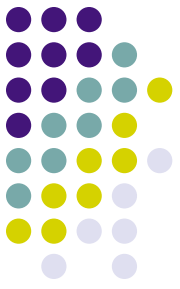




Bias door deelname (compliance)



- Hormoonvervangende therapie
 - NNH 200 (ernstige cardiovasculaire incidenten), te vermenigvuldigen met miljoenen gebruikers.
- Op de buik leggen van kinderen
 - NNK 1000, te vermenigvuldigen met honderdduizenden nieuwgeborenen
- (Griepvaccinatie, borstkankerscreening, ...)



“... vaccinatie van risicogroepen, ook van ouderen, leidt tot een sterke afname in ziekenhuisopnames en sterfte (bij ouderen respectievelijk 48 en 50 procent).”

Dit is geknipt en geplakt uit het Gezondheidsraadadvies van 4 oktober 2007

De vragen “Wie gelooft dit” “Hoe kan dit” en “Wie baat dit” moeten eindelijk worden gesteld

You are here: [Home](#) ▶ [About ESWI](#) ▶ ESWI's partners

Mission statement

ESWI: A PARTNERSHIP

ESWI's partners

ESWI's scientific independence

ESWI's partners

Board of Directors (voting members)

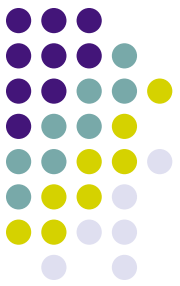
- [Dr. G.A. van Essen](#) - Nijmegen, The Netherlands (Executive Committee Member: Treasurer)
- [Dr. T. Heikkinen](#) - Turku, Finland
- [Dr. P. Openshaw](#) - London, UK (Executive Committee Member: Vice-President)
- [Dr. A.D.M.E. Osterhaus](#) - Rotterdam, The Netherlands (Executive Committee Member: Chairman)
- [Dr. R. Prymula](#) - Prague, Czech Republic
- [Dr. T. Szucs](#) - Basel, Switzerland
- [Dr. S. van der Werf](#) - Paris, France
- [Dr. A. Monto](#) - Ann Arbor, Michigan, U.S.A.
- [Dr. G. Gabriel](#) - Hamburg, Germany
- [Dr. B. Lina](#) - Lyon, France
- [Dr. M. Ciblak](#) - Istanbul, Turkey

Fourth ESWI Influenza Conference: highlights

Click on the conference logo below to watch our video impression



Borstkankerscreening



Jeder Mensch über **40** Jahre
sollte sich im Jahre einmal **gründlich**
untersuchen lassen.



Jedes Auto wird regelmäßig
durchgesehen, das findet jeder
selbstverständlich.

Bayes ijzeren wet: het is moeilijk gezonde mensen gezonder te maken

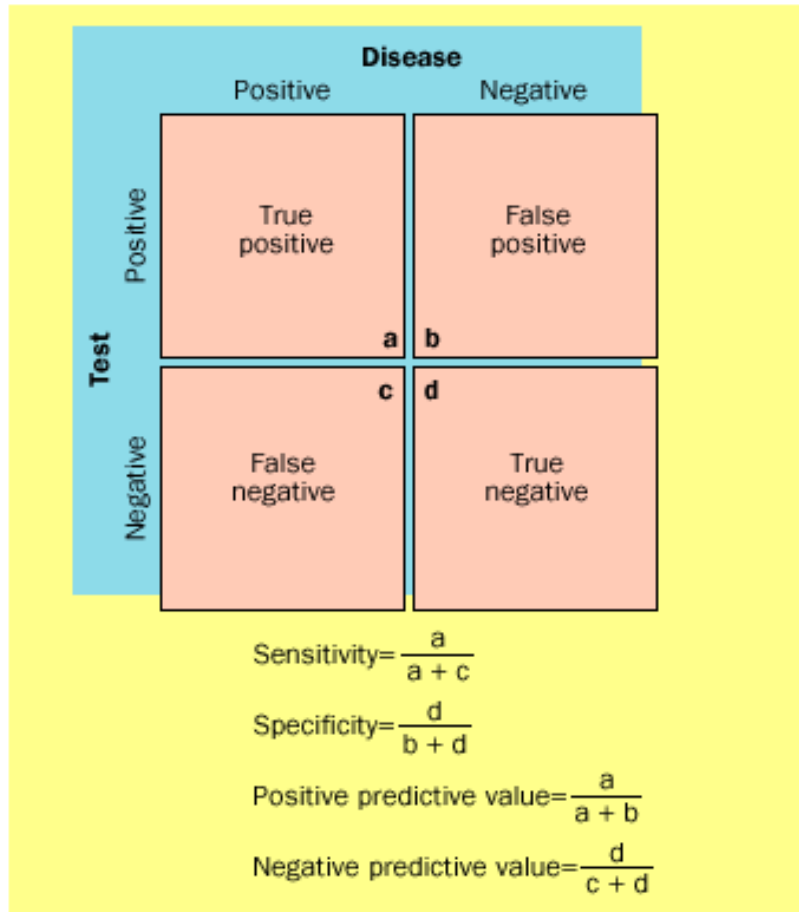
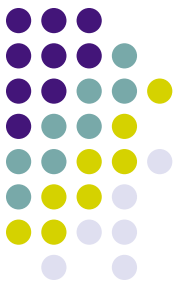
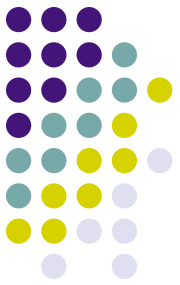


Figure 1: Template for calculation of test validity

In healthy population:

$a+b$ (disease) small

$b+d$ (healthy) large



	cancer	no cancer	
test pos	800	990	1790
test neg	200	98010	98210
	1000	99000	

Prevalence 1%

Specificity 99%

Sensitivity 80 %

55% of test positives false

Missed cases: 20% of present cancers



	cancer	no cancer	
test pos	950	4950	5900
test neg	50	94050	94100
	1000	99000	

Prevalence 1%

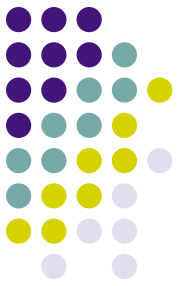
Specificity 95 %

Sensitivity 95 %

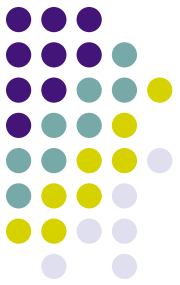
85% of test positives false

Missed: 5 %

Overleving in observationele studies van vroegtijdige diagnose



- Hoe beter de overleving, hoe verdachter!
- Door drie biases
 - Lead time
 - Length time
 - Pseudodiagnosis



Lead time

- Van Den Haag naar Leiden: 12 minuten
- Van Rotterdam naar Leiden: 35 minuten
- De overleving in de trein is geweldig toegenomen door vroeger in te stappen!
- (Trein rijdt op hetzelfde moment station binnen)

Length time

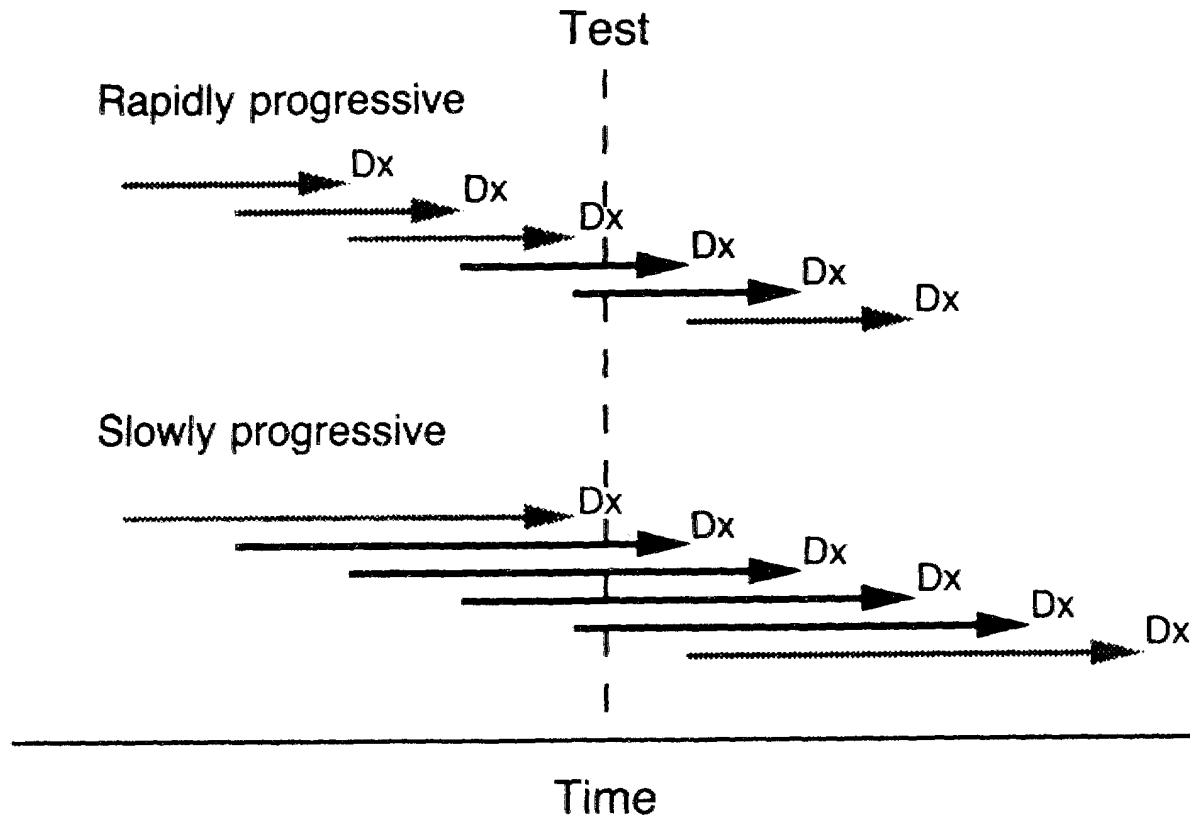
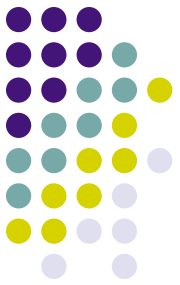
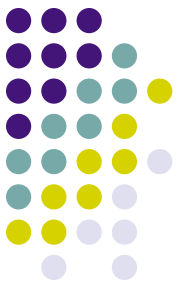


Figure 3. Influence of the Rate of Disease Progression on the Probability of Detection.



The VOMIT(*) syndrome

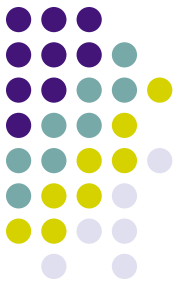
Table 1. Effect of Using Clinical and Microscopical Detection Thresholds in Three Canc

SITE	POPULATION AND AGE (YR)	PROBABILITY OF EVENTUALLY DYING FROM CANCER*	PREVALENCE*		UPPE OF I
			CLINICAL	MICROSCOPICAL	CLINI
			<i>percent (study)</i>		
Breast	Women (40–50)	3 (Seidman et al. ³¹)	1 (Feldman et al. ¹)	39 (Nielsen et al. ¹⁶)	10
Prostate	Men (60–70)	3 (Seidman et al. ³¹)	1 (Feldman et al. ¹)	46 (Montic et al. ²)	10
Thyroid	Adults (50–70)	0.1 (Vital statistics ³²)	0.1 (Feldman et al. ¹)	100 (Harach et al. ¹¹)	8

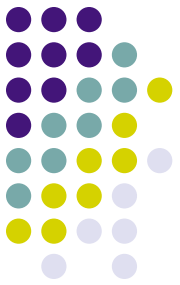
*References are in parentheses.

(*) “Victim of medical investigative technology”

Observational studies of screening

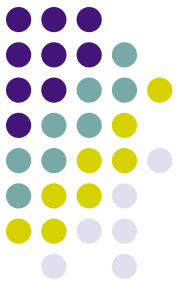


- Compliance bias (those who don't participate often have good reasons)
- Severe biases increasing survival:
 - Lead time and length time
- Severe overestimation of cure rates
 - Through VOMIT's

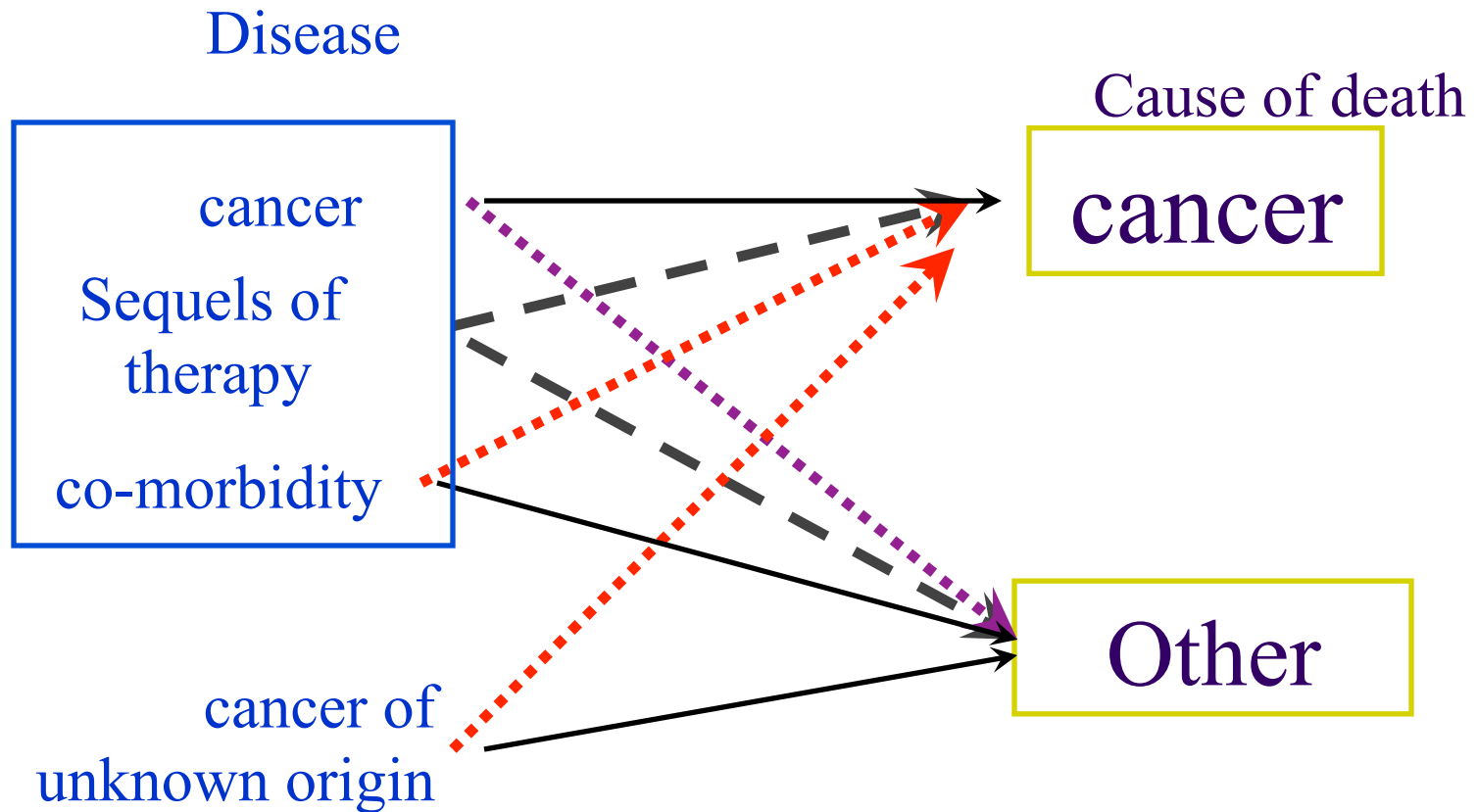


Dus RCT

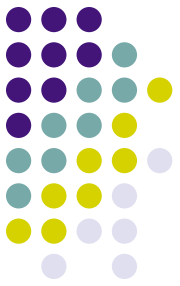
- Maar...
 - Kleine baten vergen enorme trials om deze aan te tonen
- Ziektespecifieke sterfte als eindpunt maar
 - De snelste manier om die te doen dalen, is andere ziektespecifieke sterfte te doen toenemen



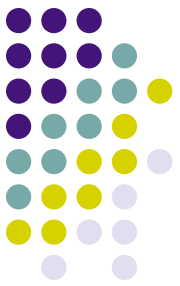
The mysterious ways to death



Screening trials

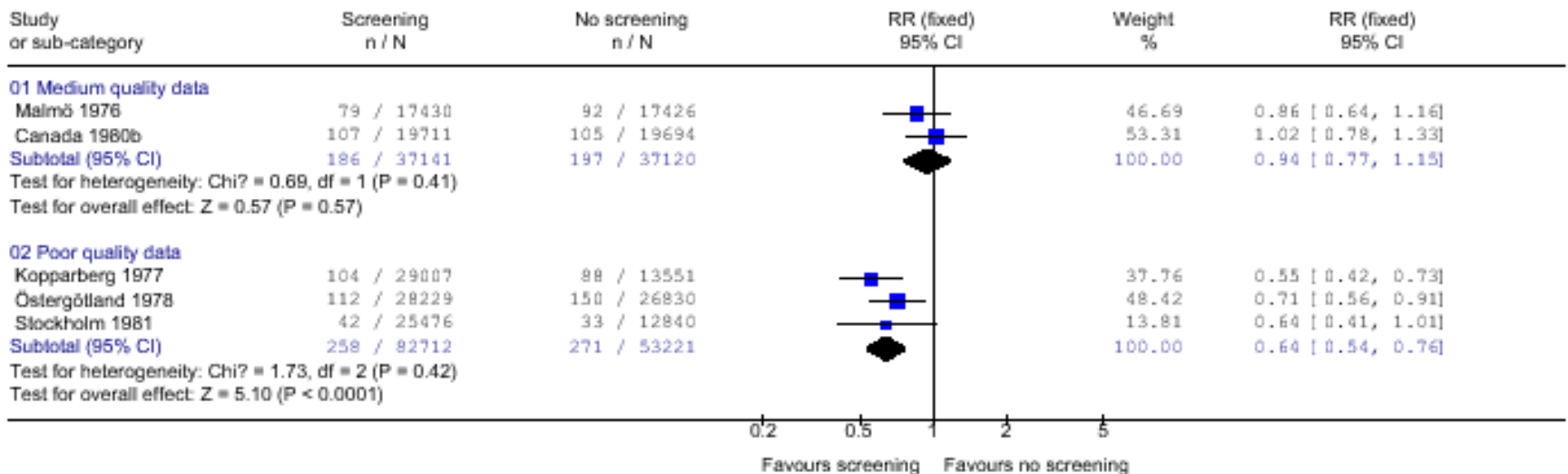


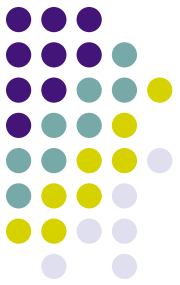
- Unblinded arms with great imbalance
 - Diagnosis and treatment in screen arm
- Very large populations



Breast cancer in menopausal women

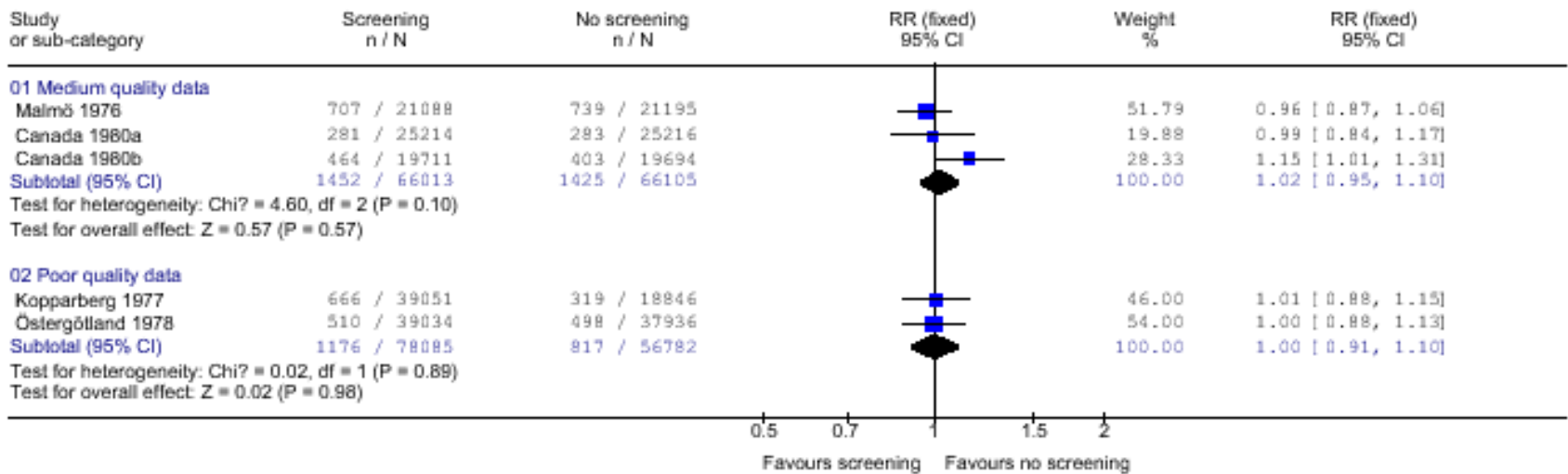
Review: Screening for breast cancer with mammography (Lancet, Sept 2001)
 Comparison: 01 Screening with mammography versus no screening
 Outcome: 13 Deaths ascribed to breast cancer, 13 years follow-up, elderly women (at least 50 years of age)

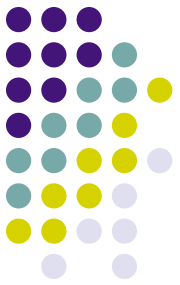




All cancer

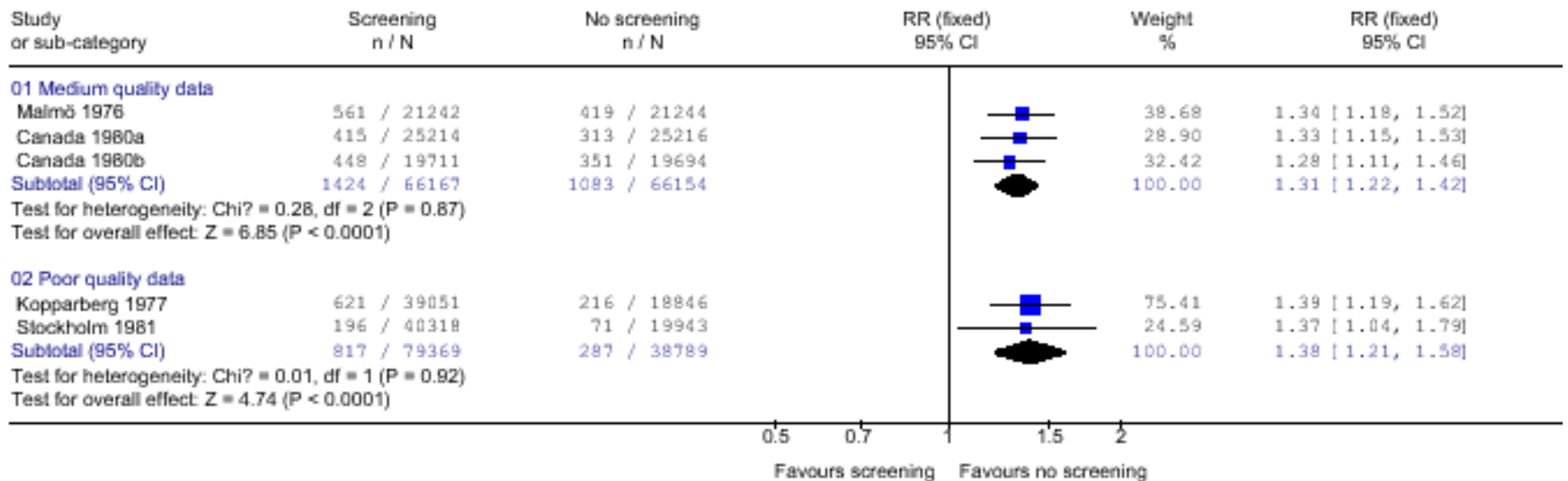
Review: Screening for breast cancer with mammography (Lancet, Sept 2001)
 Comparison: 01 Screening with mammography versus no screening
 Outcome: 14 Deaths ascribed to any cancer, all women

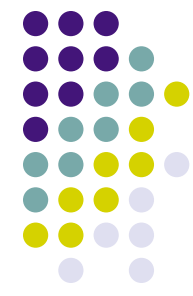




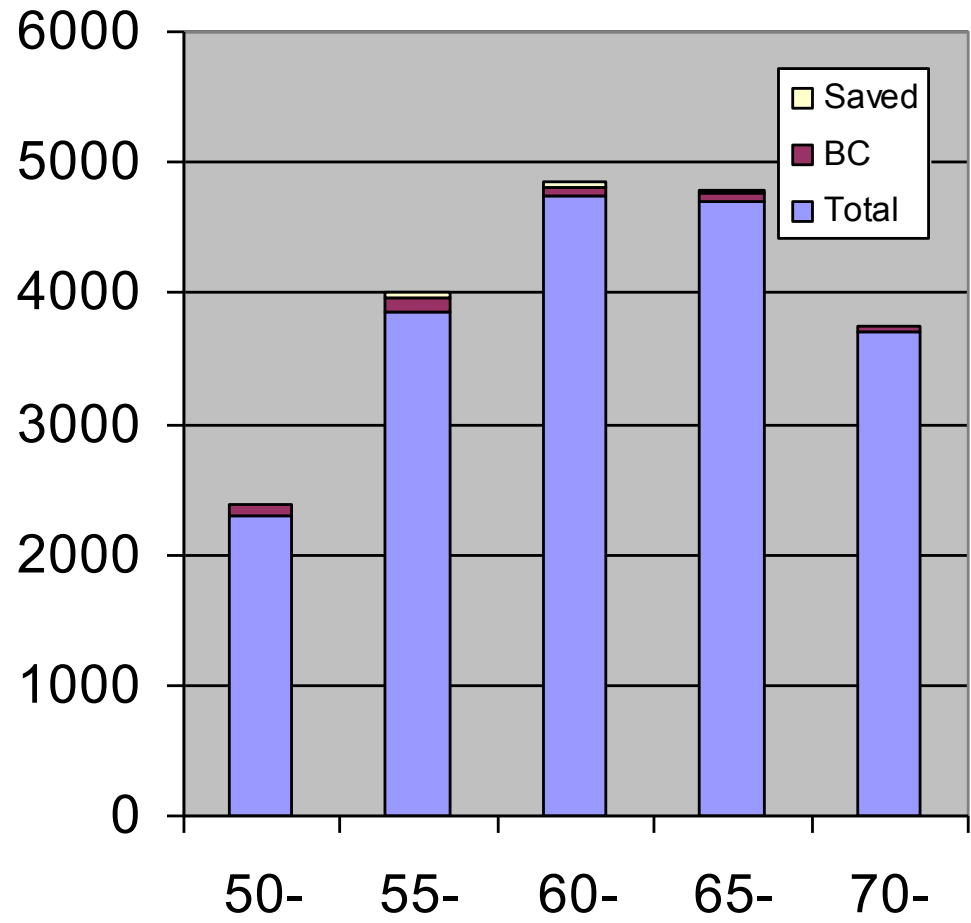
The price of early tumors

Review: Screening for breast cancer with mammography (Lancet, Sept 2001)
 Comparison: 01 Screening with mammography versus no screening
 Outcome: 15 Number of mastectomies and tumourectomies





“Modest reduction of mortality (Swedish meta-analysis)”

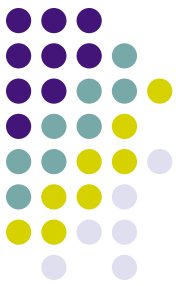


Follow-up yrs: 1.2 million

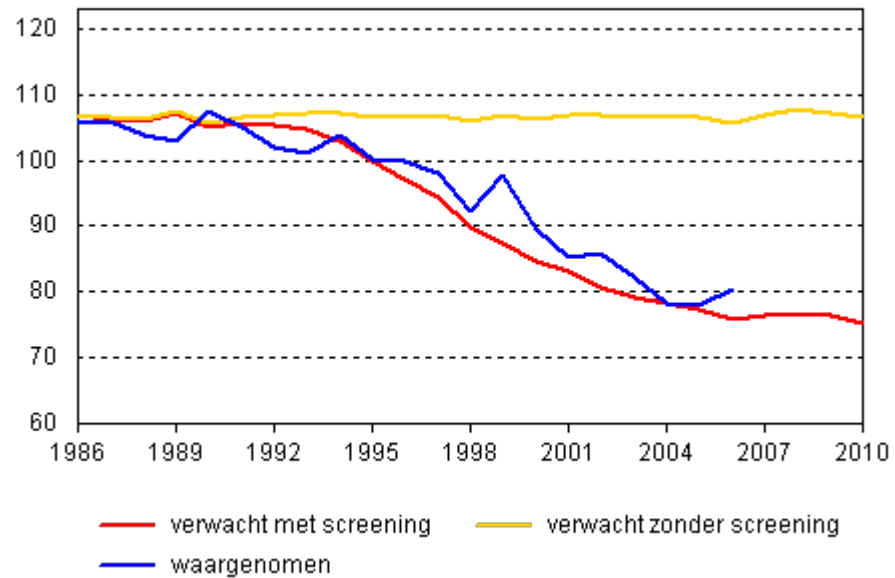
Deaths: 20.000

Breast ca deaths: 371

Saved BC deaths: 99



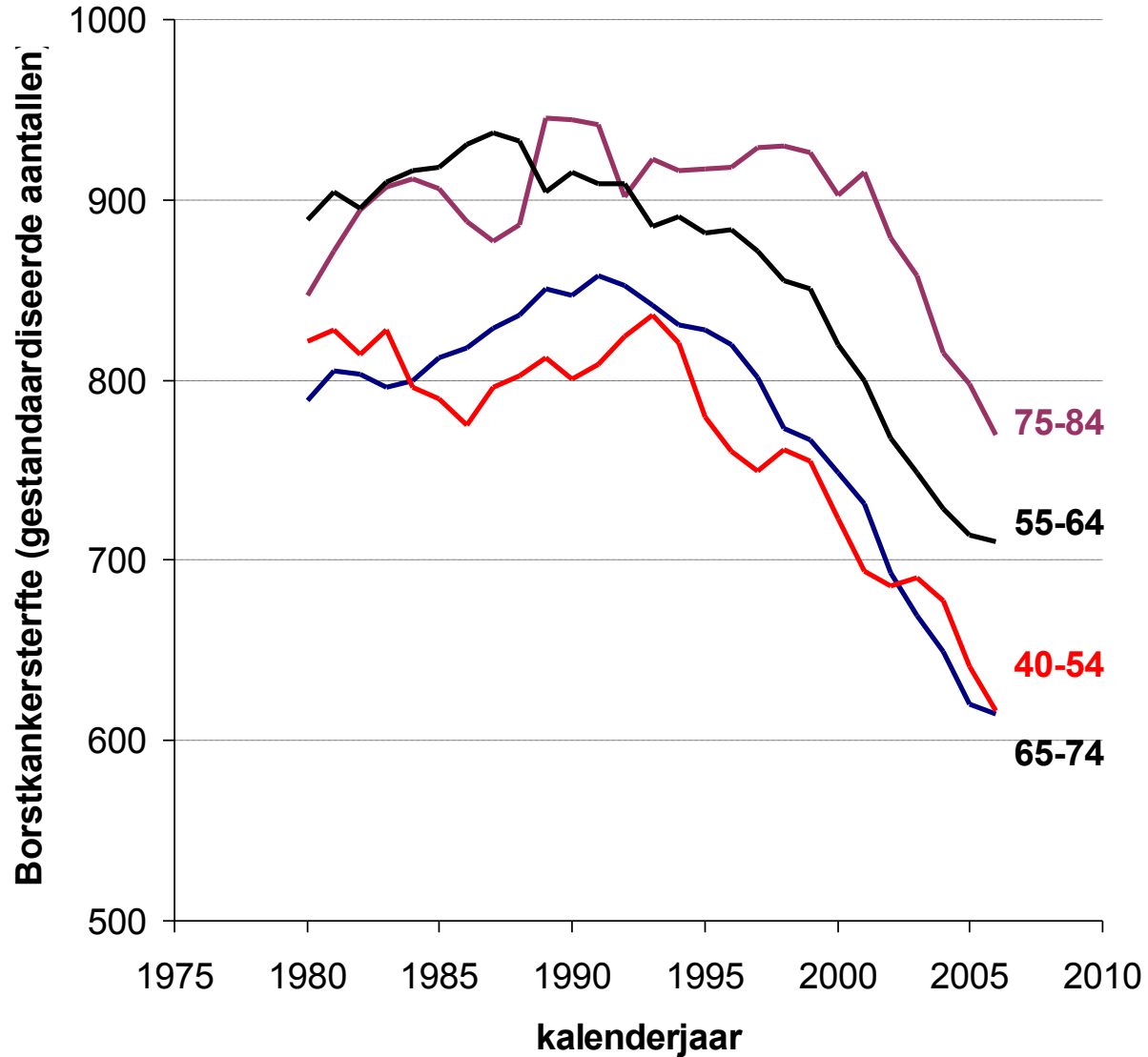
borstkankersterfte per 100.000 vrouwjaren



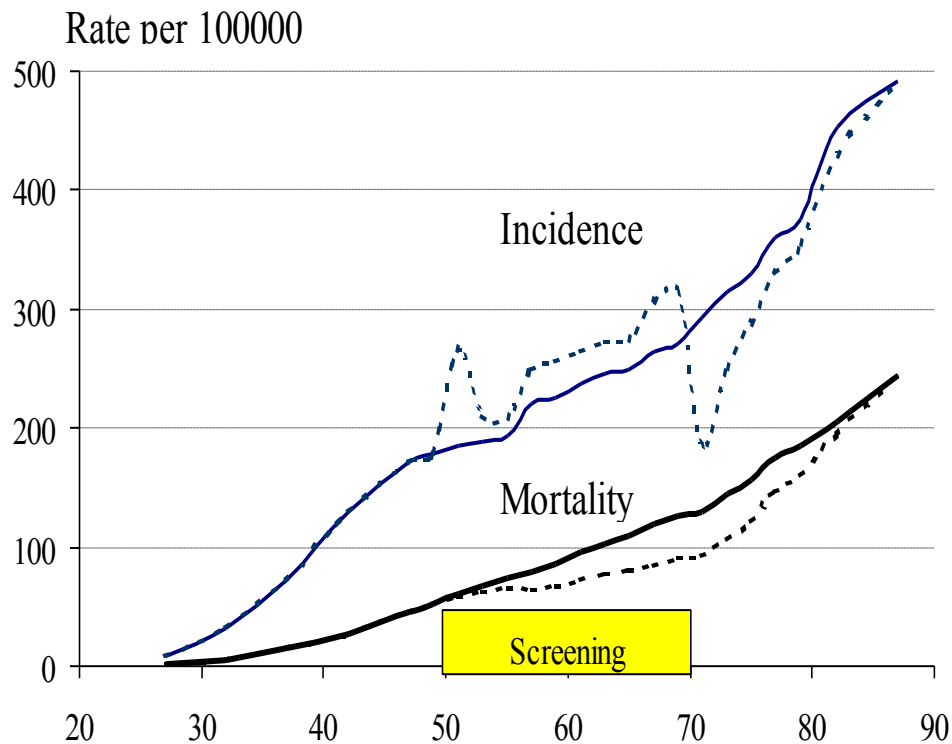
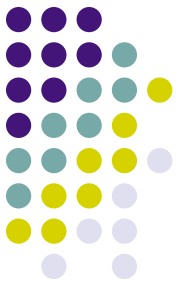
nationaalkompas.nl



Borstkankersterfte in Nederland



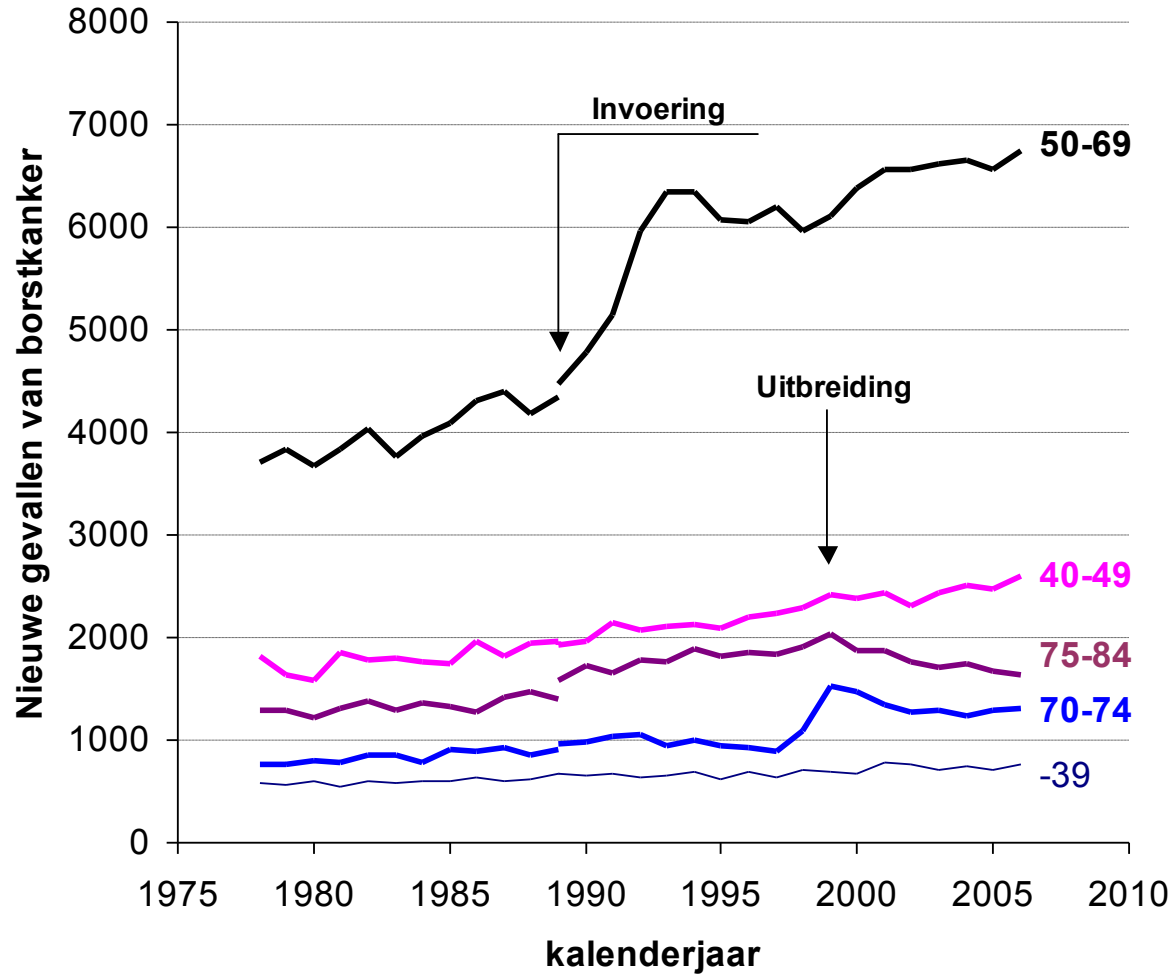
Leugens, smerige leugens, simulaties

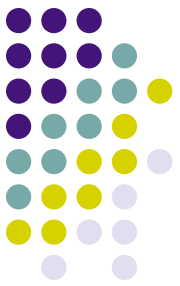


Het Nederlandse MISCAN model



Incidence of breast cancer after screening





Pseudo-experimenten

- “A natural experiment”: de plek waar de waterleiding het water ophaalt, bepaalt zeer sterk het risico op cholera
- John Snow verdient de titel “vader van de epidemiologie” door zeer zorgvuldig te argumenteren dat de kans om water van de ene of de andere waterleiding te krijgen wordt bepaald door toeval, en niets anders.

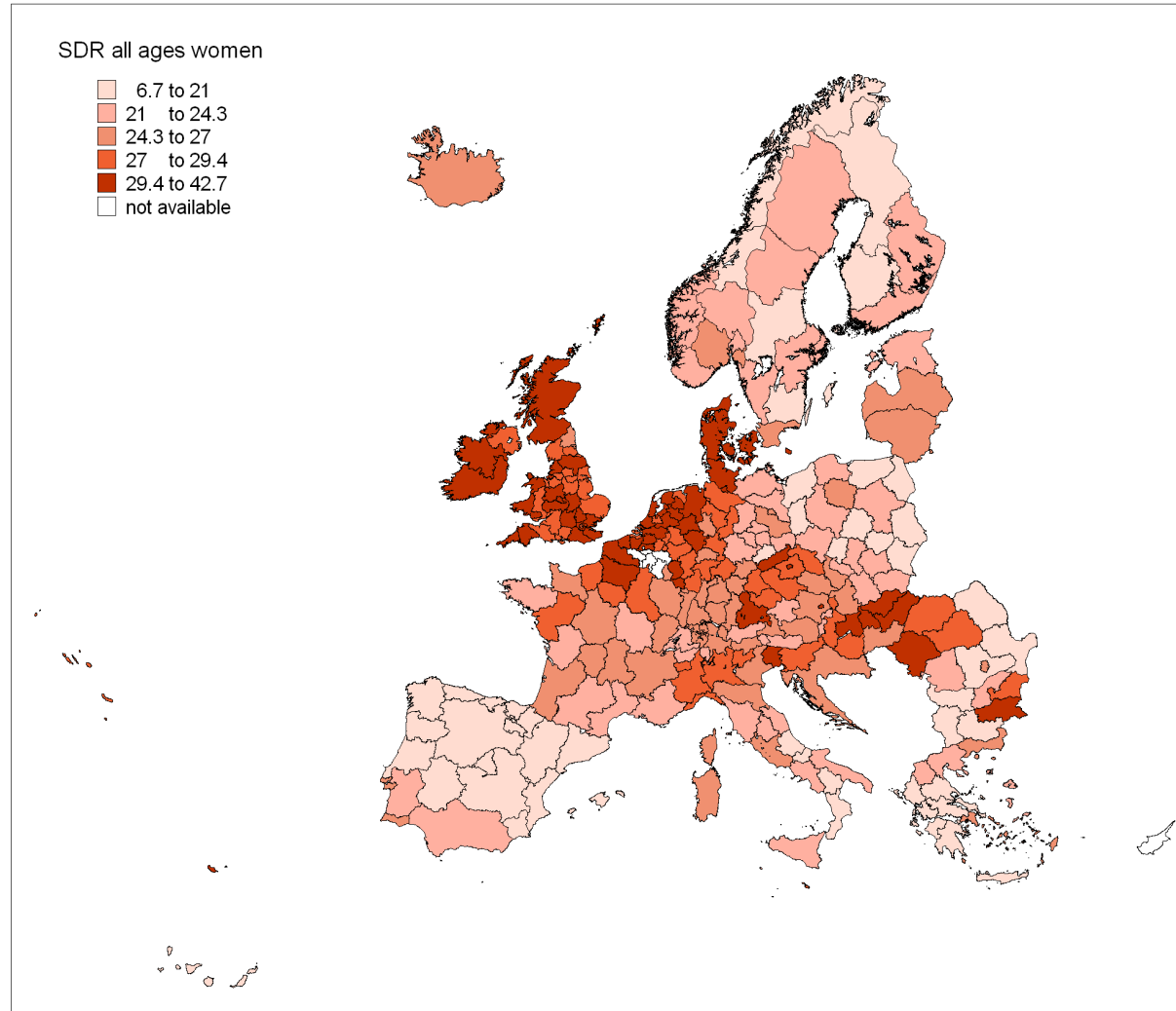
Verskil in kankersterftetrends tussen vroege en late invoerders

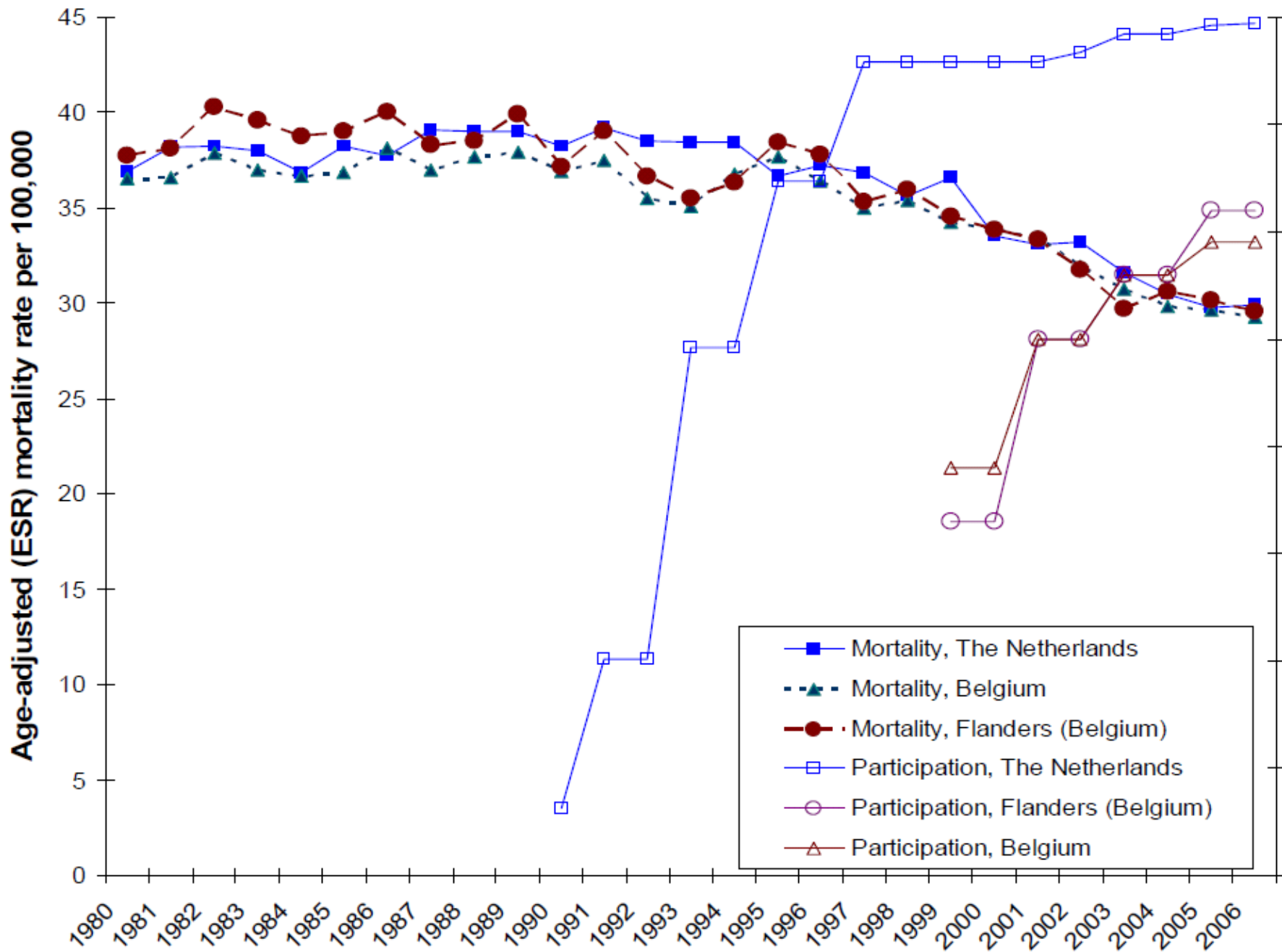


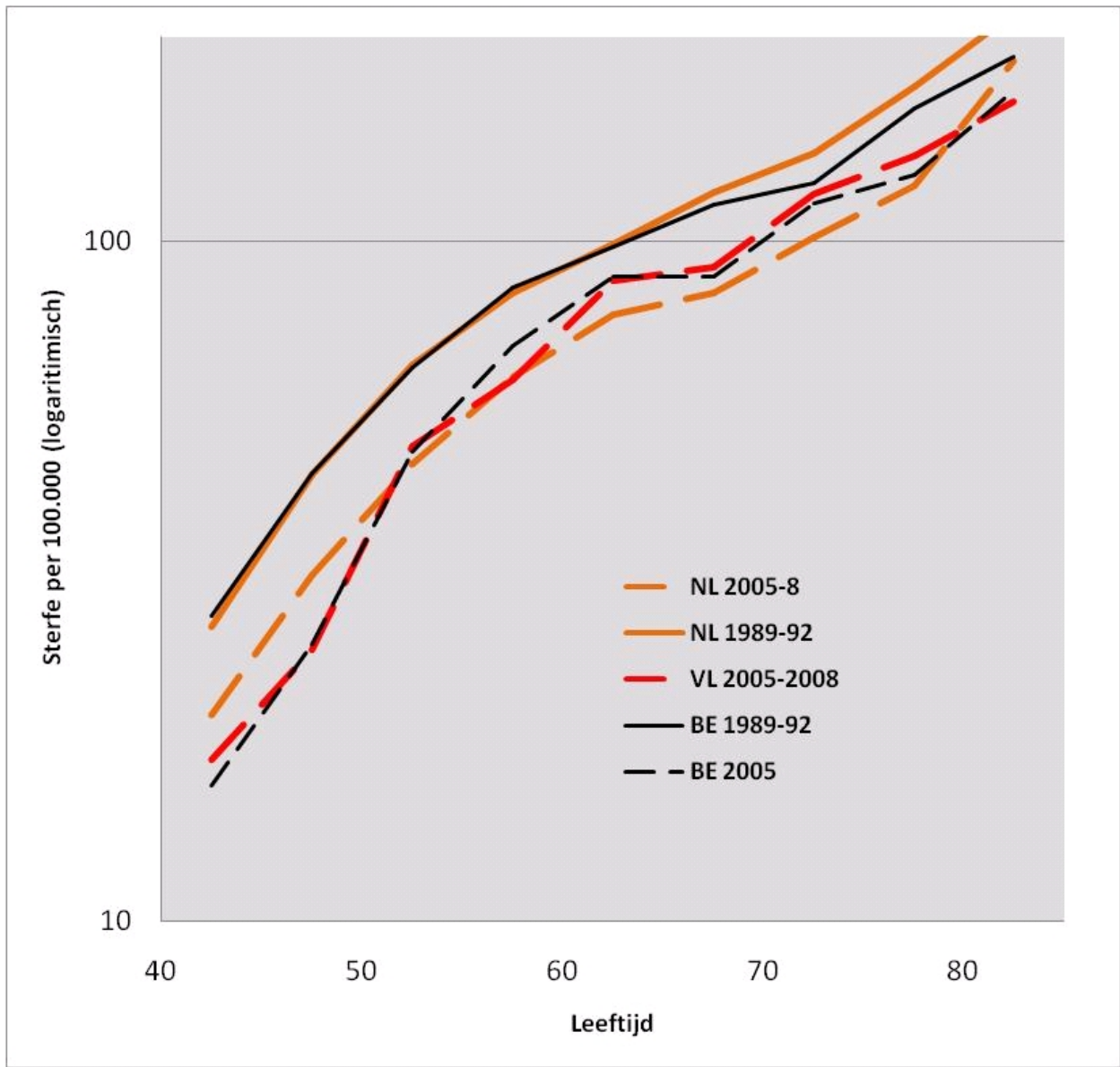
- Enige maar meest overtuigende argument van de effectiviteit van baarmoederhalskanker screening
 - Sterfte in NL 50% lager (met efficient programma) dan in B (programma “met de Frans-Belgische slag”)



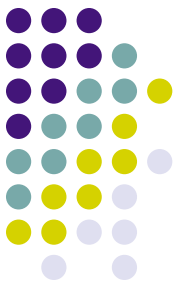
Mortality of breast cancer in Europe







Geen Verschil In borstkankertrends tussen vroege en late invoerders



- Minstens tien jaar verschil tussen invoering:
 - VL/B en NL
 - Noorwegen en Zweden
 - Ierland en Noord Ierland (UK)



Public Knowledge of Benefits of Breast and Prostate Cancer Screening in Europe

J Natl Cancer Inst 2009;101:1216-1220

Table 1. Estimated reduction of breast cancer mortality through regular participation in mammography screening (women only)*

Reduction out of 1000	Percentage of responders									
	Mean	Germany	France	Austria	The Netherlands	Italy	United Kingdom	Spain	Poland	Russia
None	6.4	1.4	0.8	2.4	0.7	5.3	2.0	3.9	4.2	16.1
1	1.5	0.8	1.3	2.9	1.4	1.3	1.9	2.7	0.8	1.7
10	11.7	12.8	15.7	11.0	10.7	10.6	10.3	6.9	9.7	12.4
50	18.9	21.3	21.7	22.1	22.6	17.4	13.9	11.7	20.5	20.1
100	15.0	16.8	21.5	20.8	22.5	13.9	17.0	11.3	14.8	10.8
200	15.2	13.7	23.7	11.0	20.1	15.2	26.9	15.7	17.1	6.8
Don't know	31.4	33.1	15.3	29.8	22.1	36.3	28.0	48.0	32.9	32.1

* Question: How many fewer women die from breast cancer in the group who participate in screening, compared to women who do not participate in screening? Mean across all nine countries is weighted by sample size.

Reduction out of 1000	Mean	The Netherlands
None	6.4	0.7
1	1.5	1.4
10	11.7	10.7
50	18.9	22.6
100	15.0	22.5
200	15.2	20.1
Don't know	31.4	22.1

Liegen dat het gedrukt staat

- Sterfteschatting drie maal hoger dan RCT, zesmaal hoger dan observationele vergelijking
- “Doet de kans op borstkankersterfte dalen.”
Geen NNS
- Valse zekerheid over effect
- Intervalkankers geminimaliseerd door framing
- Overbehandeling van VOMIT vele malen lagere evidence van RCT en observatie
- (Schaamteloze leugens over voorkomen amputaties)












Onderzoek naar borstkanker

2011

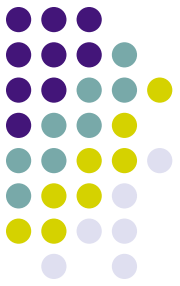




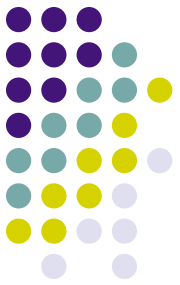
Voor en nadelen van borstkankerscreening grafisch voorgesteld (2500 mammografieën)

-  1 **Borstkanker, gered door screening**
-  2 Dood door borstkanker na screening
-  2 **Dood door intervalekanker na screening**
-  3 **Intervalekanker gemist, overlevend**
-  3 Overdiagnose door screening
-  4 Overdiagnose door screening of vroegtijdige opsporing
-  15 **Kanker, vroeger ontdekt zonder voordeel**
-  31 **Borstbiopsie wegens vals positieve diagnose**
-  2440 **Deelnemers zonder voordeel**

Scientia vincerit tenebras



- Een handjevol onbezoldigde sceptici heeft de miljardenindustrie van borstkankerscreening zware schade toegebracht
 - Consensus draait om
 - Meer en meer waarschuwingen tegen vroegtijdige diagnose
 - USA, UK herziet aanbevelingen
 - Groeiend inzicht dat advisering beter moet worden afgeschermd van industriële belangen

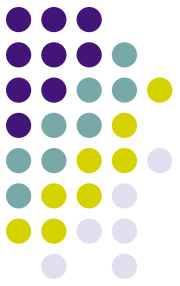


**Van der Linde ... schaadt daarmee ...
ongegrond en welbewust het vertrouwen
van de bevolking in de bescherming van de
volksgezondheid door het RIVM.**

(
[http://www.rivm.nl/Bibliotheek/Algemeen Actueel/
Nieuwsberichten/2011/
Uitspraken huisarts_aangevochten_bij_de_rechter](http://www.rivm.nl/Bibliotheek/Algemeen_Actueel/Nieuwsberichten/2011/Uitspraken_huisarts_aangevochten_bij_de_rechter) accessed 16
november 2011)

**Critici worden meer en meer
belaagd met zeer dure
smaadprocessen**

Samenvatting



Griepvaccinatie en compliance bias

- Framing: relatieve afnames van onbekende cijfers
- Eis “NNT (NNS, NNV, ...)”

Kankerscreening en misleiding door lead time, length time en pseudodiagnosis

Problemen van RCT over kankerscreening

“Pseudo-randomisatie” en het natuurlijke experiment

Liegen dat het gedrukt staat: de vreemde opvattingen van RIVM en Gezondheidsraad over publieksinformatie en advisering

Wetenschap (en evidence based medicine) overwint het duister



LUC BONNEUX



Het zal u misschien verbazen, maar wij verkeren allen in een onvoorstelbaar goede gezondheid. Evolutie en natuurlijke selectie hebben ons gezegend met een ijzersterk gestel, en de medische wetenschap is er in geslaagd de gevaarlijkste infectieziekten onder controle te krijgen.

Tot zover het goede nieuws. Want hoe gezond we ook mogen zijn, ons leven is nog altijd eindig. Al willen media, bedrijven, politici, milieubewegingen en 'gezondheidsdeskundigen' ons maar al te graag van het tegendeel overtuigen. Preventiecampagnes en gezondheidsadviezen volgen elkaar in ijtempo op. Massaal cholesterolverlagende margarines smeren, zon en fijn stof mijden en elke dag een glas rode wijn drinken. Dan wacht ons het eeuwig leven. Of toch niet?

*En ze leefden
nog lang
en gezond*

Hoe gezondheid een industrie werd

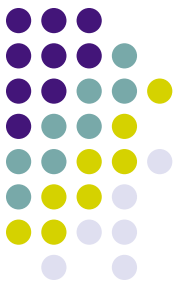
LANNOO



LUC BONNEUX

*En ze leefden nog
lang en gezond*





Gezondheidsraad heeft griepvaccinatie uitgebreid van 65+ tot de 60+.

Zou u het uitvoeren van een grote RCT over griepvaccinatie bij 55-64 jarigen ondersteunen?

Wat vindt u van griepvaccinatie bij hoogbejaarde en demente verpleeghuisbewoners?