Measuring the mortality reductions produced by organized cancer screening: a principled approach

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Biostatistics Branch Seminar Series
Division of Cancer Epidemiology & Genetics
US-NCI

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Dedication

HARVARDgazette

HSPH's Marvin Zelen dies at 87

Was considered a 'tremendous force' in biostatistics

November 19, 2014 | Editor's Pick

Photo by Shaina Andelman

Harvard Professor Marvin Zelen was noted for developing the statistical methods and study designs that are used in clinical cancer trials, in which experimental drugs are tested for toxicity, effectiveness, and proper dosage.

HSPH Communications

Professor Marvin Zelen of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health (HSPH) died on Nov. 15 after a battle with cancer. He was 87.

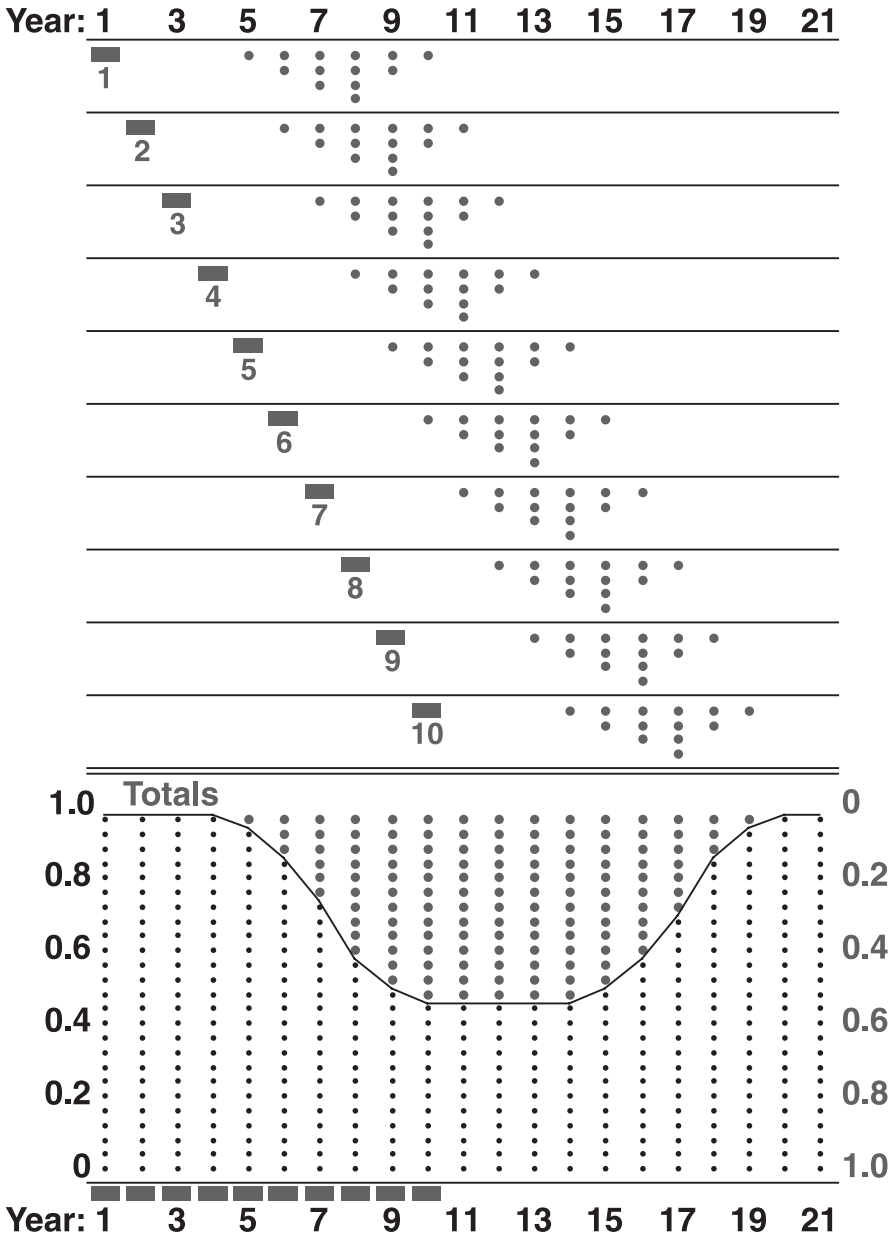
Outline

- Screening is different from prevention/treatment
- Bathtub-shaped Hazard Ratio function
- Trial (experimental) data: prostate (PSA) and colon (FOBT)
- Breast Cancer Screening with Mammography:
  21st century (non-experimental) population-based studies
- **It's all about TIMING – and the Lexis diagram helps !!**
- **Technical details on our model**

Ways in which cancer screening differs from prevention/treatment

- Prevention aims to stop cancer from ever developing
- Treatment combats it once it becomes apparent
- Screening: pursuit of earlier diagnosis
  - disease not necessarily present at 1st screen.. must repeat
  - benefits not immediate, but delayed, & time-limited
  - in screening: no screening comparisons, if screening works as intended, mortality hazard rates are non-proportional

Bathtub-shaped Hazard Ratio function



<— deaths averted by screen 1

<— deaths averted by screen 2

...

<— deaths averted by screen 10

Figure (after Miettinen et al. 2002.) is from Hanley JA. Analysis of Mortality Data From Cancer Screening Studies: Looking in the Right Window. *Epidemiology, Vol 16, 2005*, pp 786-790.

See also. Liu Z at al. J Med Screening. 2013.

'*% Reduction function*' (bathtub shape)

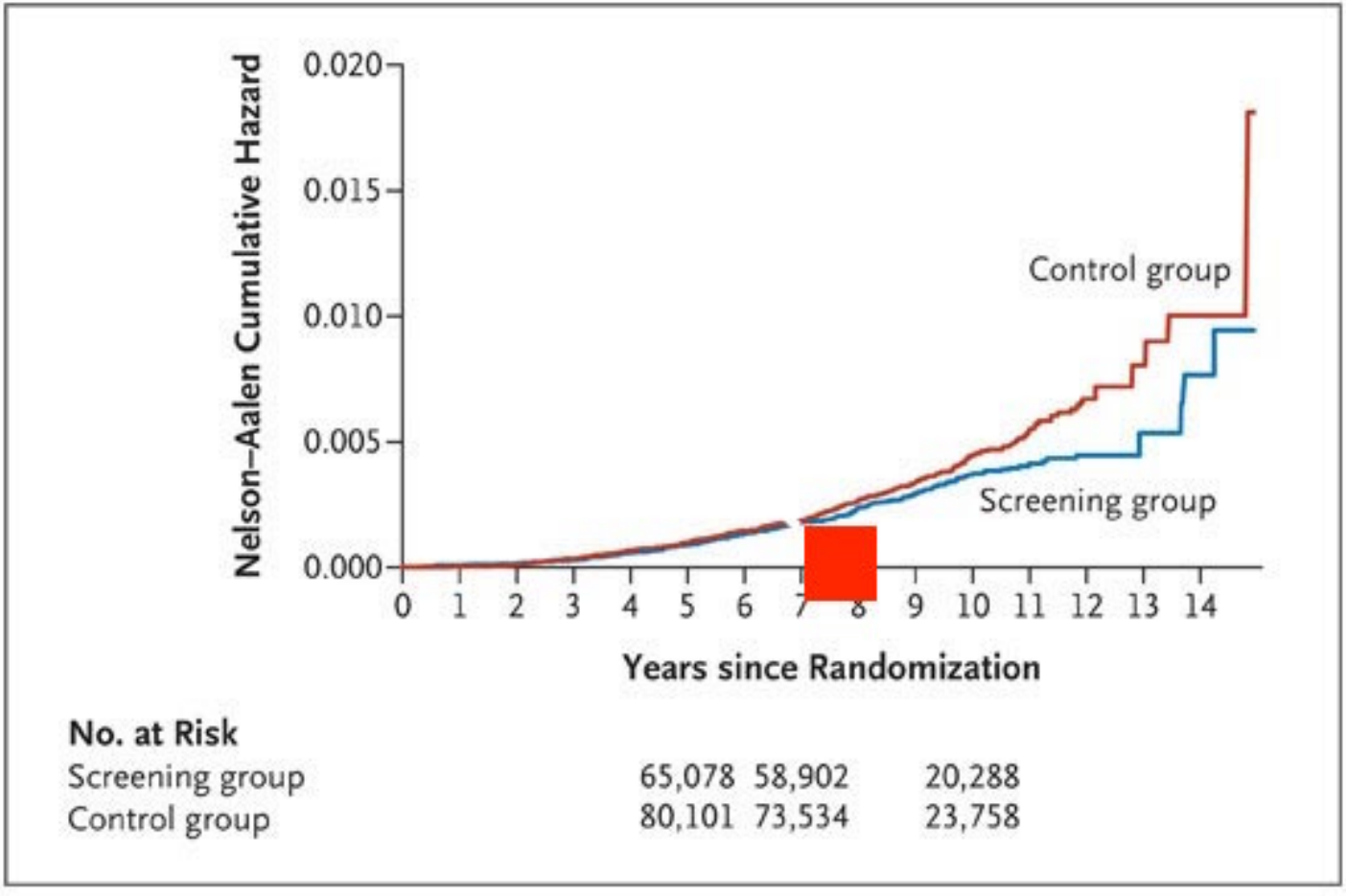
- The asymptote is the ultimate estimand
- It is determined by ...
  - number and spacing of rounds, and
  - the contribution of each round of screening
- From published trials, can one ..
  - estimate the '% Reduction function' ?
  - estimate contribution of each round ?
    (?? function shape if different schedule or if a program)

PROSTATE CANCER

Screening & Prostate-Ca Mortality in Randomized European Study '92-'08 ("ERSPC" nejm2009.04)

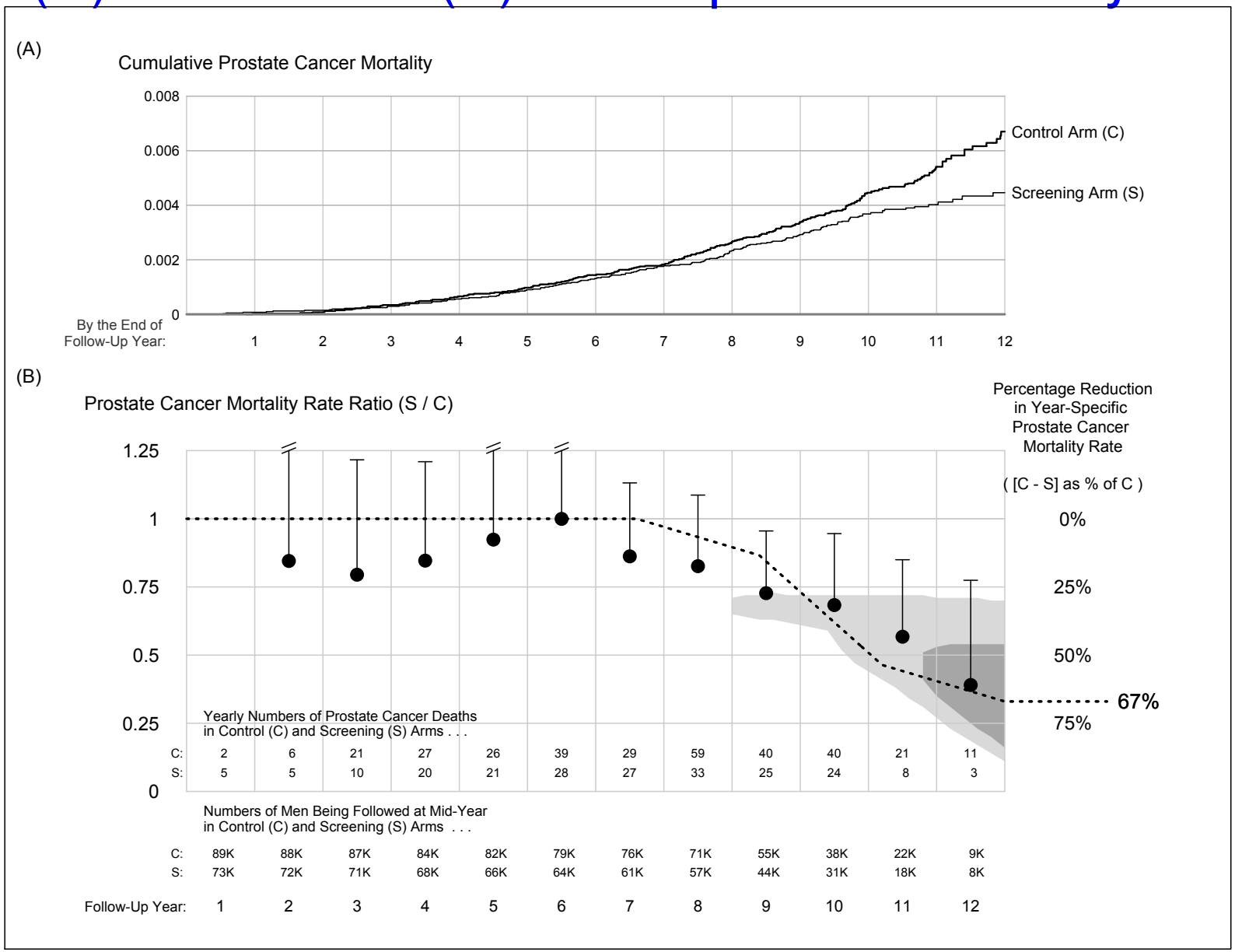
As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. (...) The adjusted **rate ratio** for death from prostate cancer in the screening group was **0.80** (95% CI, 0.65 to 0.98; P=0.04).

"PSA-based screening reduced the rate of death from prostate cancer by **20%**. "



RE-ANALYSIS OF ERSPC DATA
using
year-specific prostate cancer mortality ratios

(A) Overall vs. (B) Year-specific mortality ratios



Hanley, *J Medical Screening*, 2010.

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

*Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators**

Summary

Background The European Randomised study of Screening for Prostate Cancer (ERSPC) has shown significant reductions in prostate cancer mortality after 9 years and 11 years of follow-up, but screening is controversial because of adverse events such as overdiagnosis. We provide updated results of mortality from prostate cancer with follow-up to 2010, with analyses truncated at 9, 11, and 13 years.

Methods ERSPC is a multicentre, randomised trial with a predefined centralised database, analysis plan, and core age group (55–69 years), which assesses prostate-specific antigen (PSA) testing in eight European countries. Eligible men aged 50–74 years were identified from population registries and randomly assigned by computer generated random numbers to screening or no intervention (control). Investigators were masked to group allocation. The primary outcome was prostate cancer mortality in the core age group. Analysis was by intention to treat. We did a secondary analysis that corrected for selection bias due to non-participation. Only incidence and no mortality data at 9 years' follow-up are reported for the French centres. This study is registered with Current Controlled Trials, number ISRCTN49127736.

Findings With data truncated at 13 years of follow-up, 7408 prostate cancer cases were diagnosed in the intervention group and 6107 cases in the control group. The rate ratio of prostate cancer incidence between the intervention and control groups was 1·91 (95% CI 1·83–1·99) after 9 years (1·64 [1·58–1·69] including France), 1·66 (1·60–1·73) after 11 years, and 1·57 (1·51–1·62) after 13 years. The rate ratio of prostate cancer mortality was 0·85 (0·70–1·03) after 9 years, 0·78 (0·66–0·91) after 11 years, and 0·79 (0·69–0·91) at 13 years. The absolute risk reduction of death from prostate cancer at 13 years was 0·11 per 1000 person-years or 1·28 per 1000 men randomised, which is equivalent to one prostate cancer death averted per 781 (95% CI 490–1929) men invited for screening or one per 27 (17–66) additional prostate cancer detected. After adjustment for non-participation, the rate ratio of prostate cancer mortality in men screened was 0·73 (95% CI 0·61–0·88).

Interpretation In this update the ERSPC confirms a substantial reduction in prostate cancer mortality attributable to testing of PSA, with a substantially increased absolute effect at 13 years compared with findings after 9 and 11 years. Despite our findings, further quantification of harms and their reduction are still considered a prerequisite for the introduction of populated-based screening.

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(14)61008-4

*For the full study group see appendix

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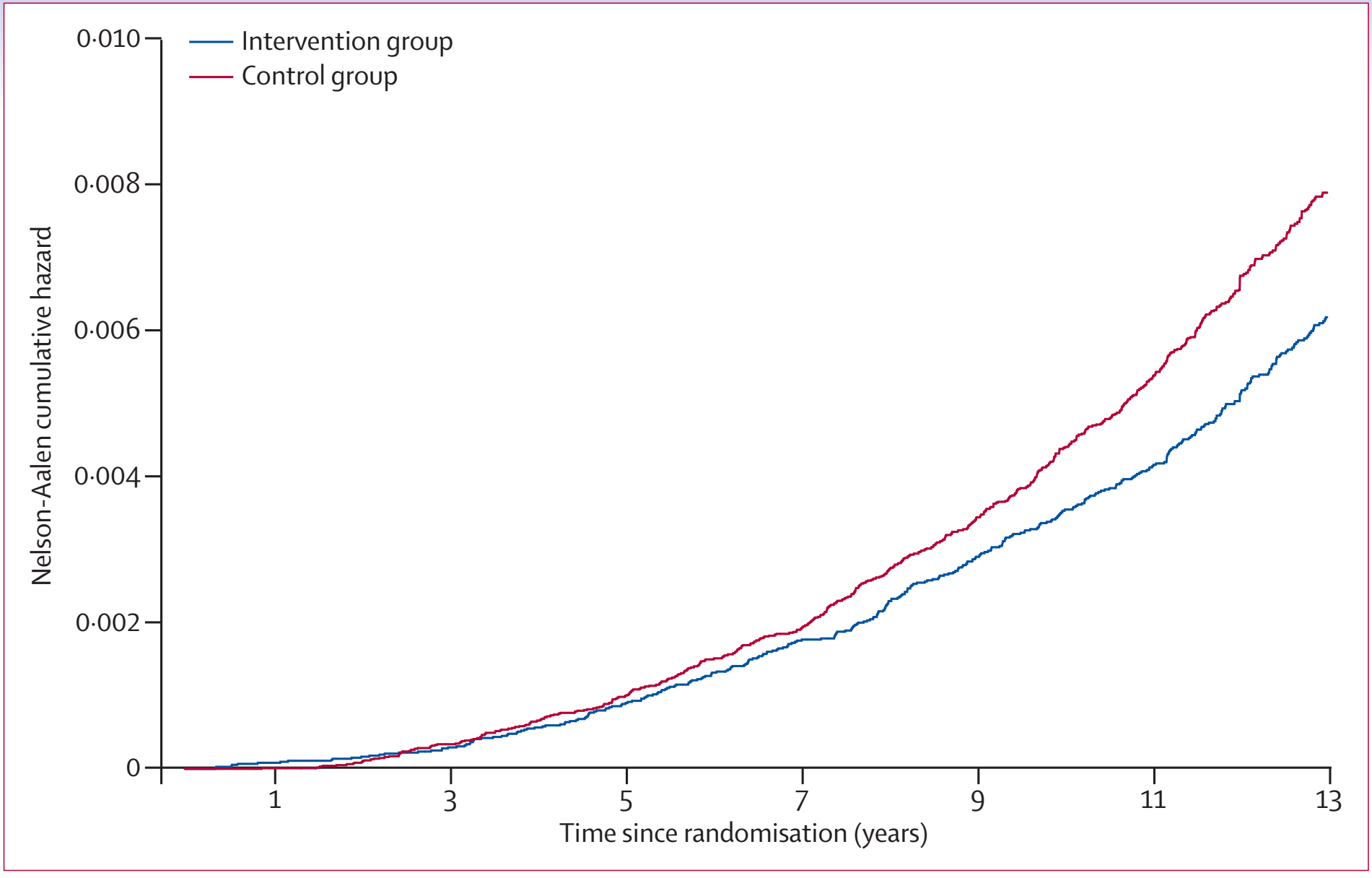

Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

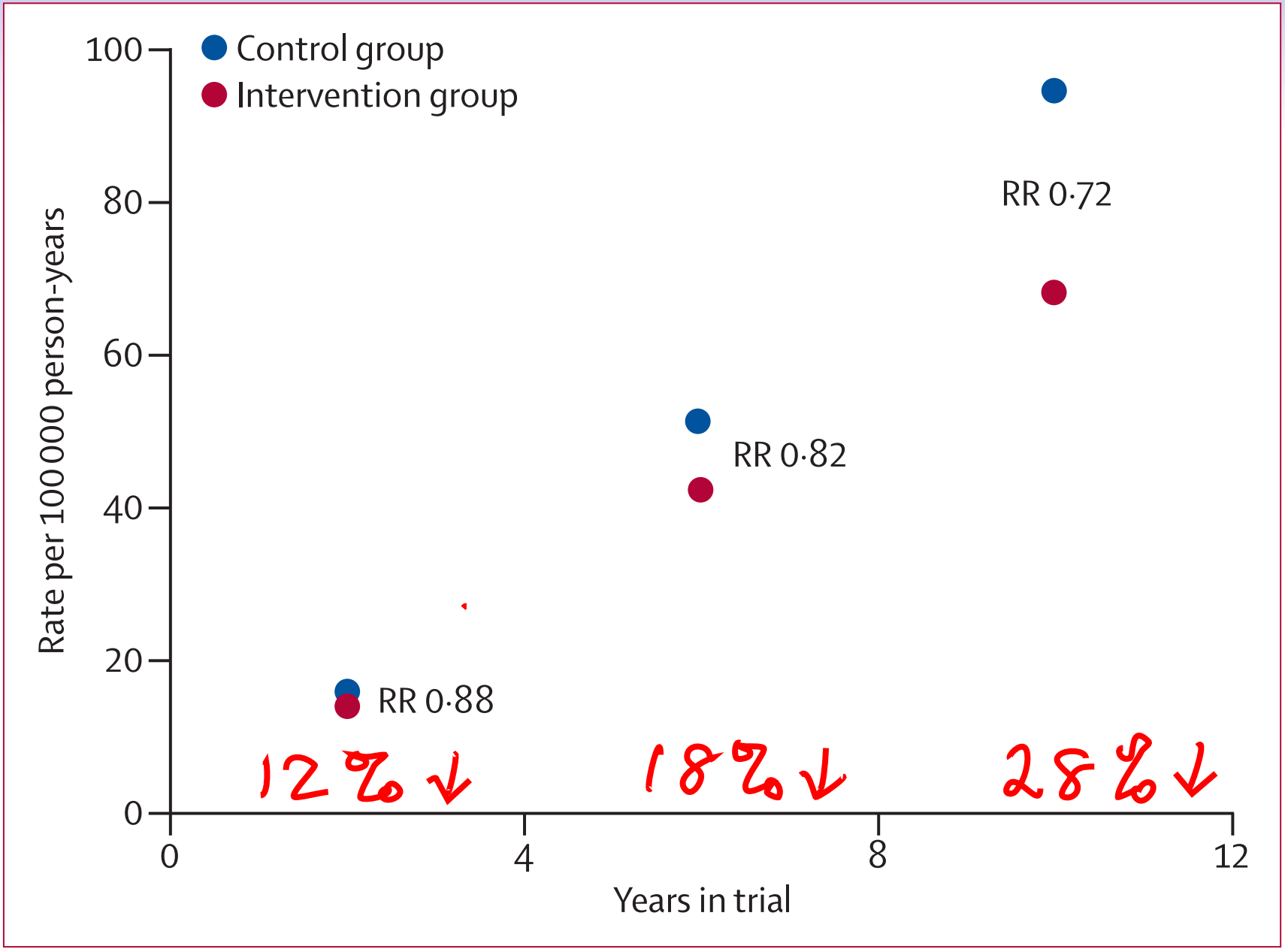

Figure 3: **Nelson-Aalen estimates of cumulative prostate cancer in both groups by 4-year periods (all centres, excluding France)**

COLON CANCER

FOBT screening for colon cancer – Minnesota Trial 1976-2008

Long-Term Mortality after Screening for Colorectal Cancer

Aasma Shaukat, M.D., M.P.H., Steven J. Mongin, M.S., Mindy S. Geisser, M.S., Frank A. Lederle, M.D., John H. Bond, M.D., Jack S. Mandel, Ph.D., M.P.H., and Timothy R. Church, Ph.D.

ABSTRACT

BACKGROUND

In randomized trials, fecal occult-blood testing reduces mortality from colorectal cancer. However, the duration of the benefit is unknown, as are the effects specific to age and sex.

METHODS

In the Minnesota Colon Cancer Control Study, 46,551 participants, 50 to 80 years of age, were randomly assigned to usual care (control) or to annual or biennial screening with fecal occult-blood testing. Screening was performed from 1976 through 1982 and from 1986 through 1992. We used the National Death Index to obtain updated information on the vital status of participants and to determine causes of death through 2008.

From the Divisions of Gastroenterology (A.S., J.H.B.) and Internal Medicine (F.A.L.), Minneapolis Veterans Affairs Health Care System, and the Department of Medicine, School of Medicine (A.S., F.A.L., J.H.B.), and the Division of Environmental Health Sciences, School of Public Health (S.J.M., M.S.G., T.R.C.), University of Minnesota — both in Minneapolis; and Exponent, Menlo Park, CA (J.S.M.). Address reprint requests to Dr. Shaukat at 1 Veterans Dr., 111-D, Minneapolis, MN 55417.

N Engl J Med 2013;369:1106-14.
DOI: 10.1056/NEJMoa1300720

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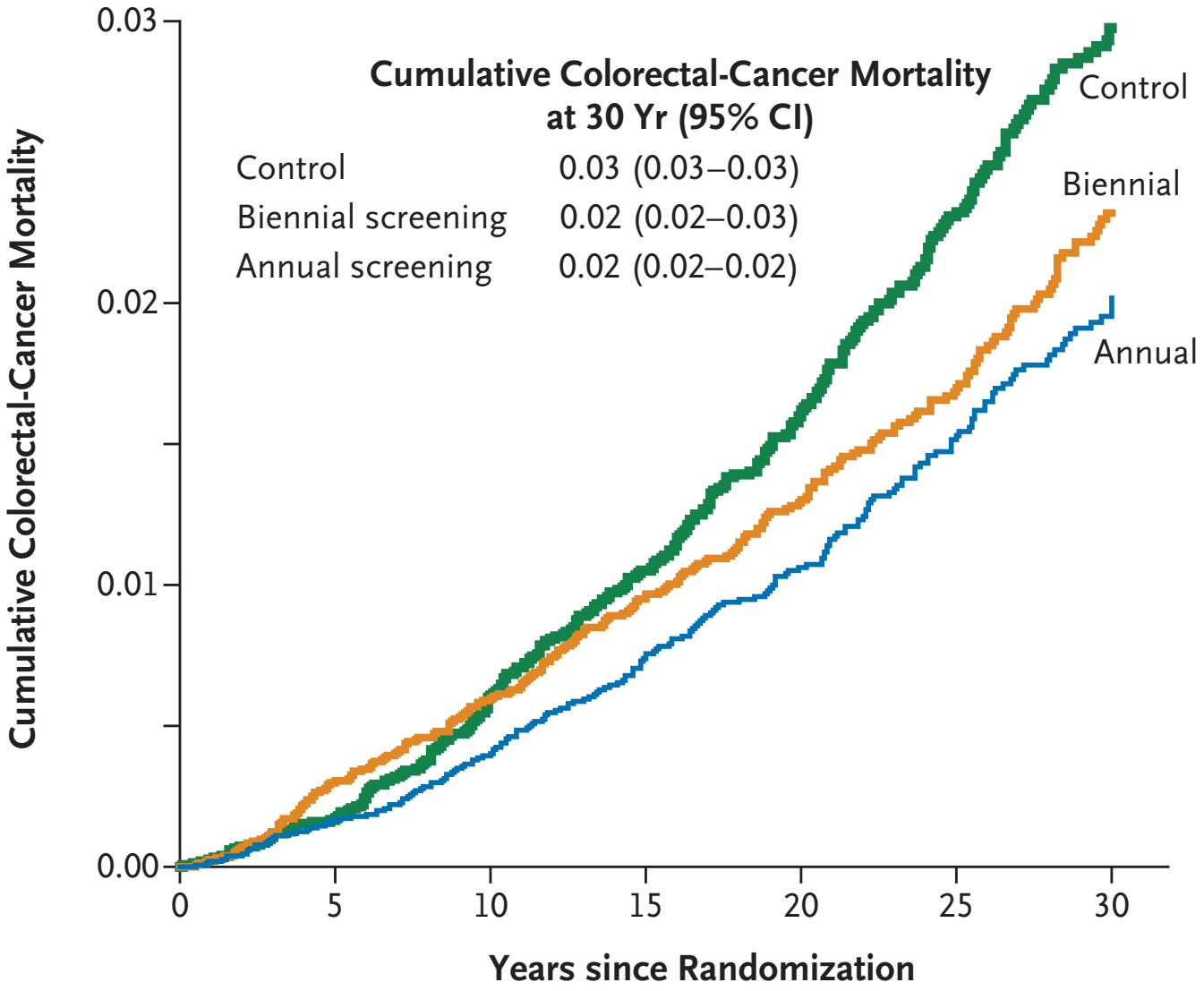
FOBT screening for colon cancer – Minnesota Trial 1976-2008

RESULTS

Through 30 years of follow-up, 33,020 participants (70.9%) died. A total of 732 deaths were attributed to colorectal cancer: 200 of the 11,072 deaths (1.8%) in the annual-screening group, 237 of the 11,004 deaths (2.2%) in the biennial-screening group, and 295 of the 10,944 deaths (2.7%) in the control group. Screening reduced colorectal-cancer mortality (relative risk with annual screening, 0.68; 32% onfidence interval [CI], 0.56 to 0.82; relative risk with biennial screening, 0.78; 22% , 0.65 to 0.93) through 30 years of follow-up. No reduction was observed in all-cause mortality (relative risk with annual screening, 1.00; 95% CI, 0.99 to 1.01; relative risk with biennial screening, 0.99; 95% CI, 0.98 to 1.01). The reduction in colorectal-cancer mortality was larger for men than for women in the biennial-screening group (P=0.04 for interaction).

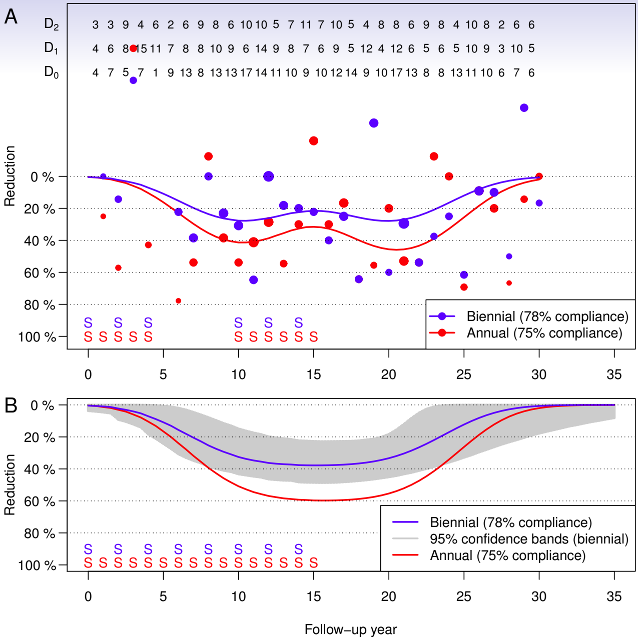
CONCLUSIONS

The effect of screening with fecal occult-blood testing on colorectal-cancer mortality persists after 30 years but does not influence all-cause mortality. The sustained reduction in colorectal-cancer mortality supports the effect of polypectomy. (Funded by the Veterans Affairs Merit Review Award Program and others.)



No. at Risk

Control	14,497	13,103	11,320	9157	6741	4450
Biennial screening	14,635	13,243	11,445	9323	6802	4583
Annual screening	14,658	13,294	11,437	9219	6802	4498



Liu, PhD Biostatistics, McGill 2014; International Statistical Review 2015.

BREAST CANCER

Measuring the mortality reductions produced by Irish and Danish breast-cancer screening programs

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[3] National Cancer Registry Ireland [NCRI], Cork, Ireland
[4] Graduate Entry Medical School, University of Limerick, Ireland

39th Conference on Applied Statistics in Ireland, Dundalk, 2019

ESTIMANDS

- Traditional 1-number answer
- More-refined/meaningful estimands and answers

Best studies: use date of diagnosis to emulate RCT

Cancer Registry: EXCLUDE WOMEN DIAGNOSED BEFORE PROGRAM BEGAN

Original Article

Decline in breast cancer mortality: How much is attributable to screening?

Sisse Helle Njor[1], Walter Schwartz[2], Mogens Blichert-Toft[3] and Elsebeth Lynge[1]

J Med Screen
2015, Vol. 22(1) 20–27
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DOI: 10.1177/0969141314563632
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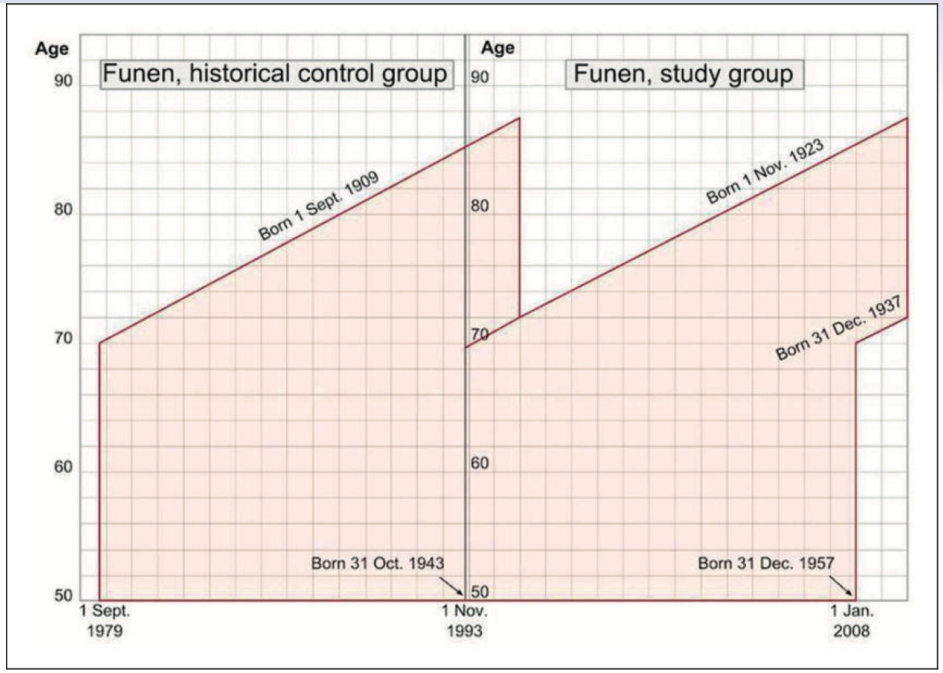
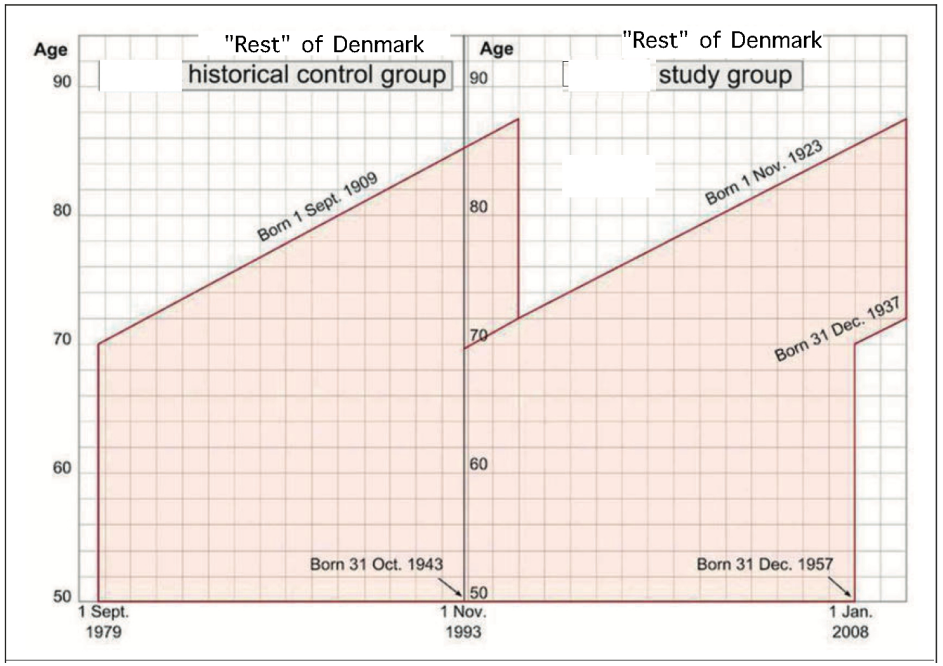
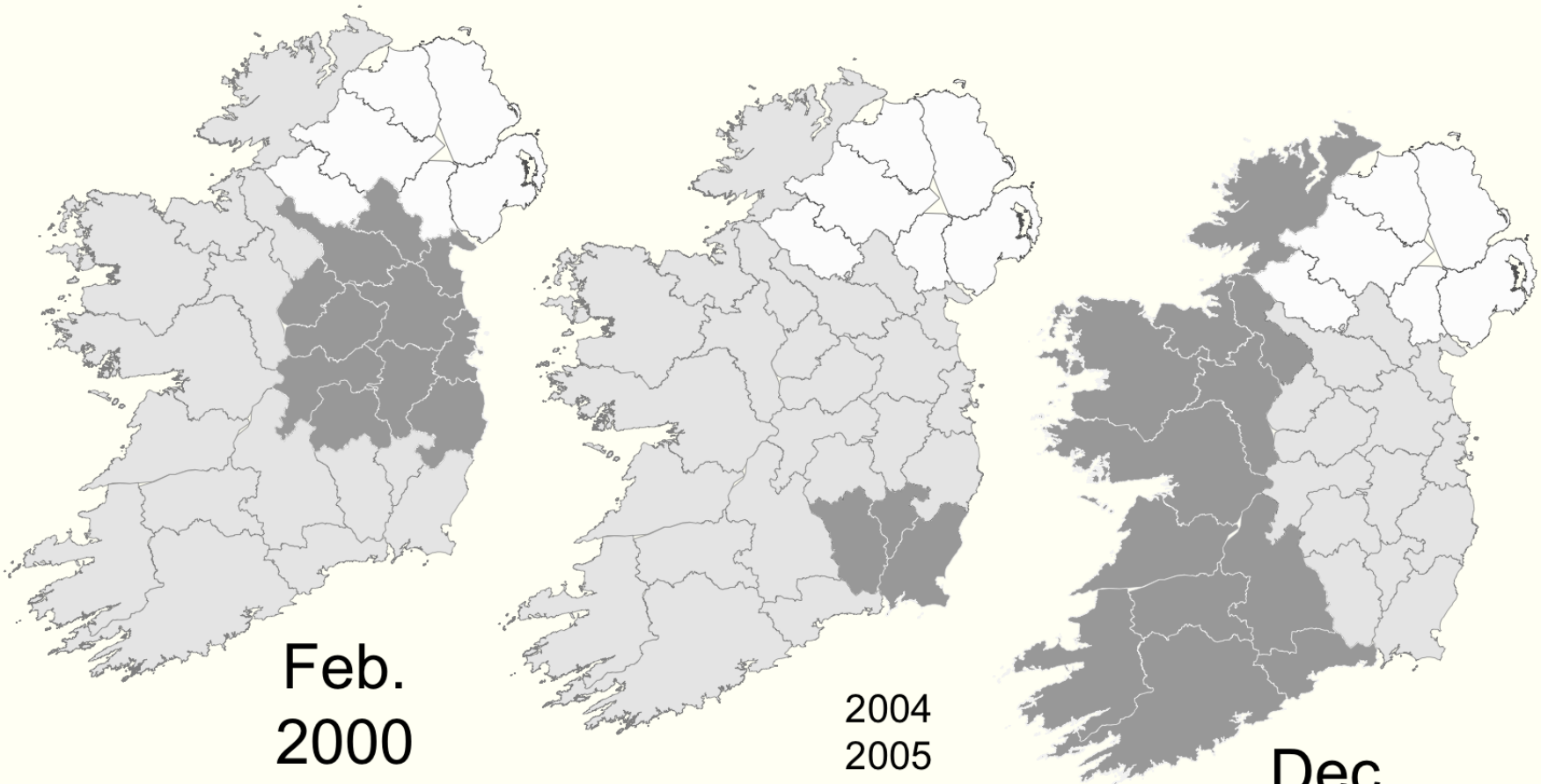
FUNEN ↓ 1993





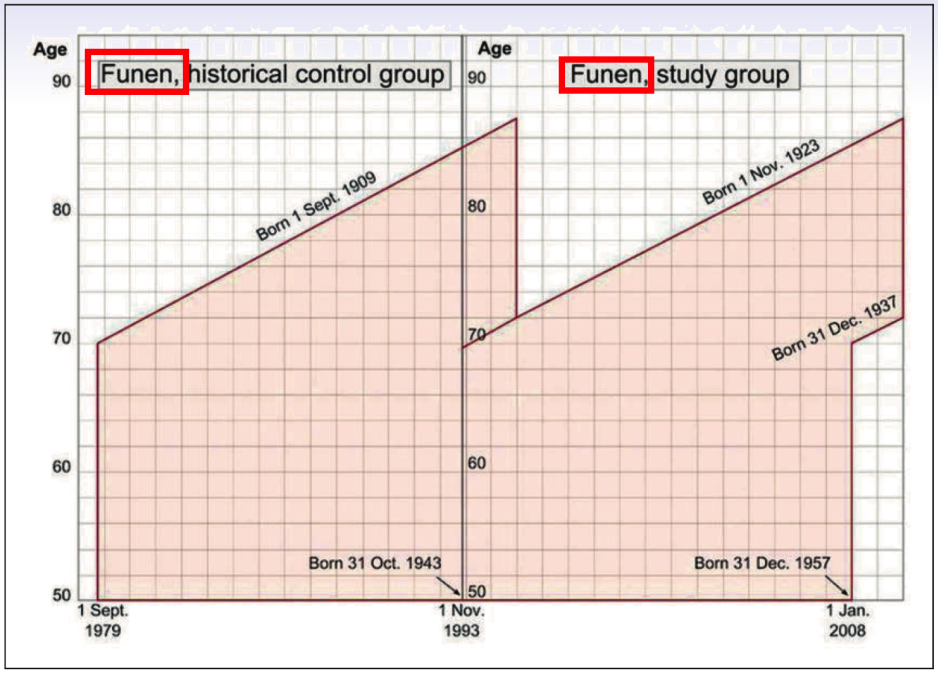
'REST' ↑ 1993

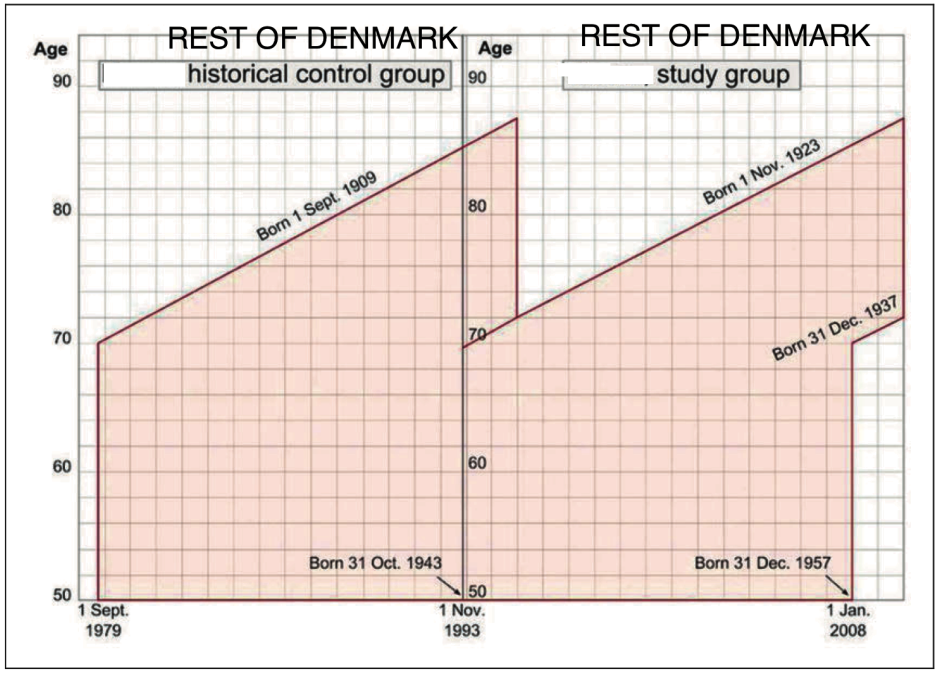


BreastCheck invitations every 2 years to women aged 50-64

RESULTS

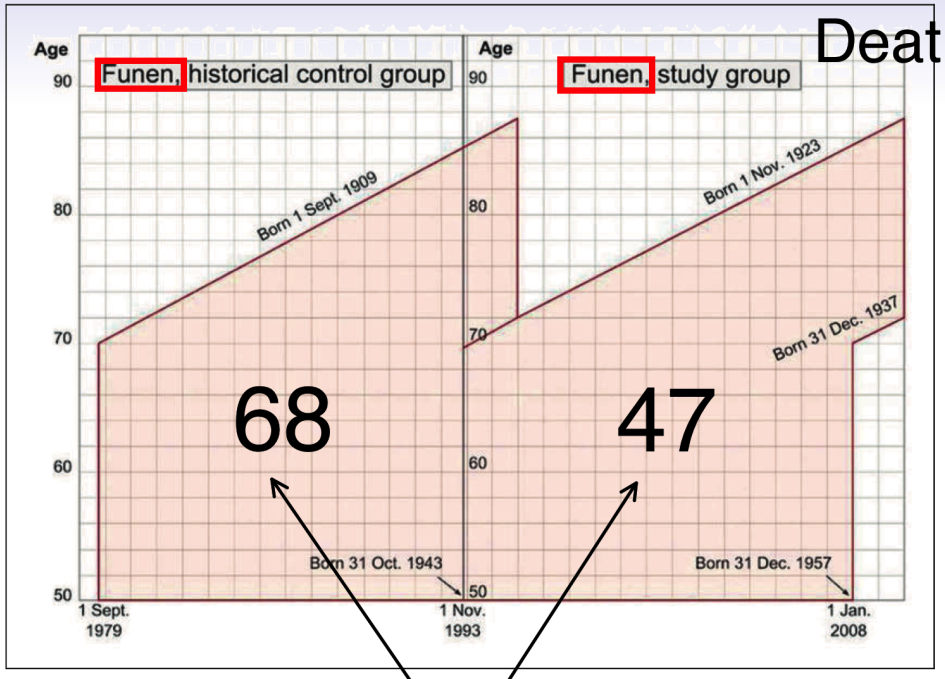
traditional
1-number summaries
(proportional hazards model)

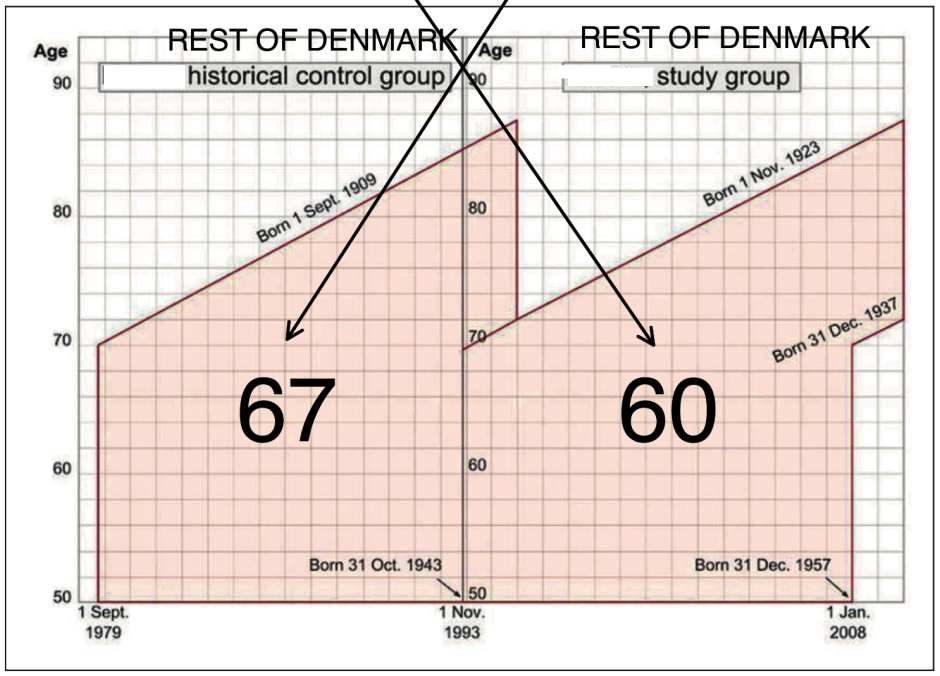

Age
Funen, historical control group
Age
Funen, study group
90
80
70
60
50
Born 1 Sept. 1909
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Oct. 1943
Born 31 Dec. 1957
1 Sept. 1979
1 Nov. 1993
1 Jan. 2008


Age
REST OF DENMARK
historical control group
Age
REST OF DENMARK
study group
90
80
70
60
50
Born 1 Sept. 1909
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Oct. 1943
Born 31 Dec. 1957
1 Sept. 1979
1 Nov. 1993
1 Jan. 2008

(8 x Funen)

Deaths per 100,000 WY





22% reduction

HR = 0.78

Republic of Ireland

2 phases, 8 years apart

RESEARCH ARTICLE

Mortality reductions due to mammography screening: Contemporary population-based data

James A. Hanley[1☯]*, Ailish Hannigan[2☯], Katie M. O'Brien[3☯]

1 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Québec, Canada, **2** Graduate Entry Medical School, University of Limerick, Limerick, Ireland, **3** National Cancer Registry Ireland, Cork, Ireland

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Check for updates

OPEN ACCESS

Citation: Hanley JA, Hannigan A, O'Brien KM (2017) Mortality reductions due to mammography screening: Contemporary population-based data. PLoS ONE 12(12): e0188947. https://doi.org/10.1371/journal.pone.0188947

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Abstract

Our objective was to compare breast cancer mortality in two regions of the Republic of Ireland that introduced a screening programme eight years apart, and to estimate the steady-state mortality deficits the programme will produce. We carried out age- and year-matched between-region comparison of breast cancer mortality rates, and of incidence rates of stage 2–4 breast cancer, in the eligible cohorts. The regions comprised counties that, beginning in early 2000 (region 1) and late 2007 (region 2), invited women aged 50–64 to biennial mammography screening. The data were supplied by the National Cancer Registry, Central Statistics Office. As impact measures, we used age-and-year-matched mortality (from breast cancers diagnosed from 2000 onwards), rate ratios and incidence rate ratios in the compared regions from 2000 to 2013. Ratios were adjusted for between-region differences in background rates. In cohorts too old to be invited, death rates in regions 1 and 2 were 702 per 0.91 and 727 per 0.90 million women-years respectively (Ratio 0.96). In the eligible cohorts, they were 1027 per 2.9 and 1095 per 2.67 (Ratio 0.88). Thus, rates in cohorts that could have benefitted were 9% lower in region 1 than region 2: (95%CI: -20%, +4%). The

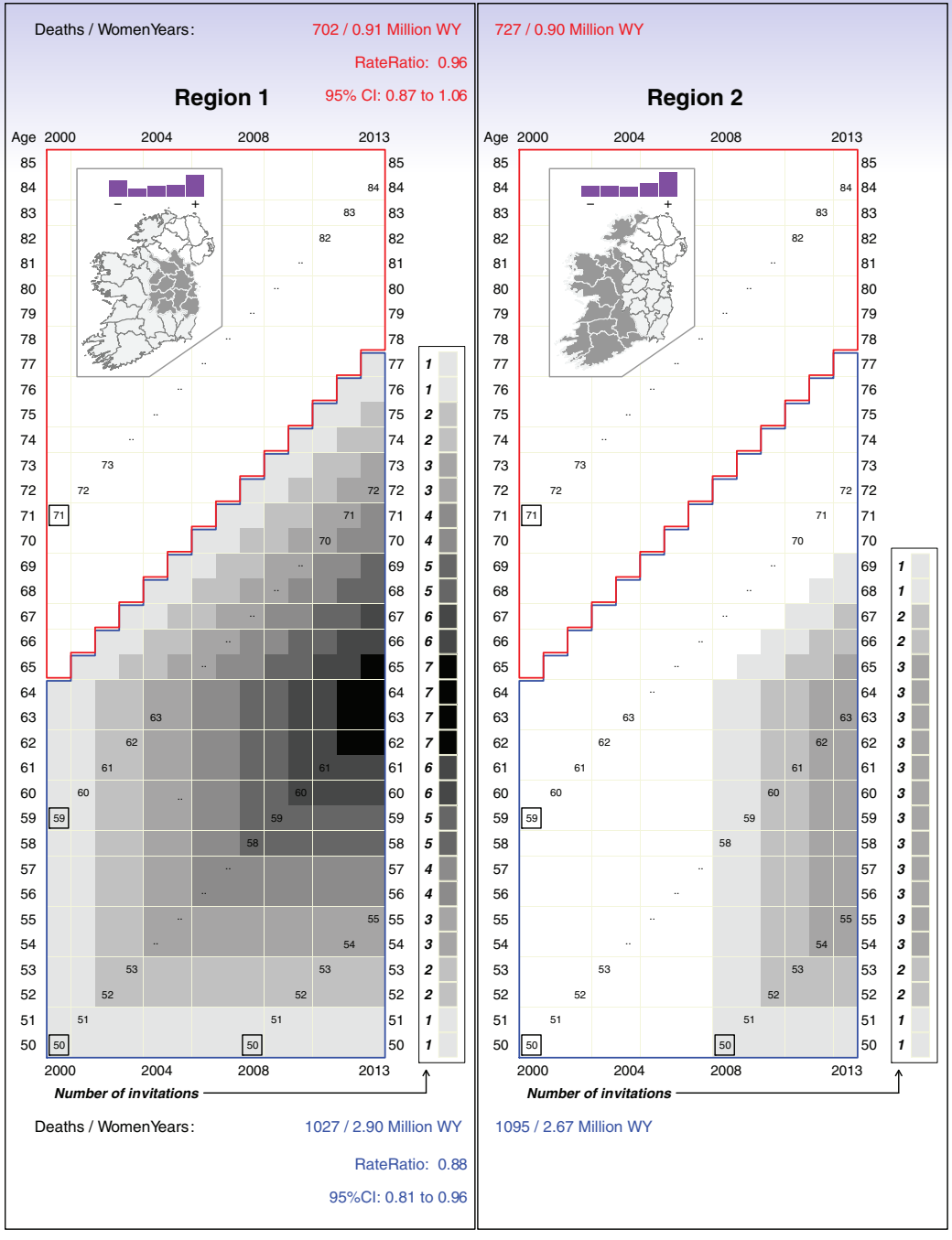


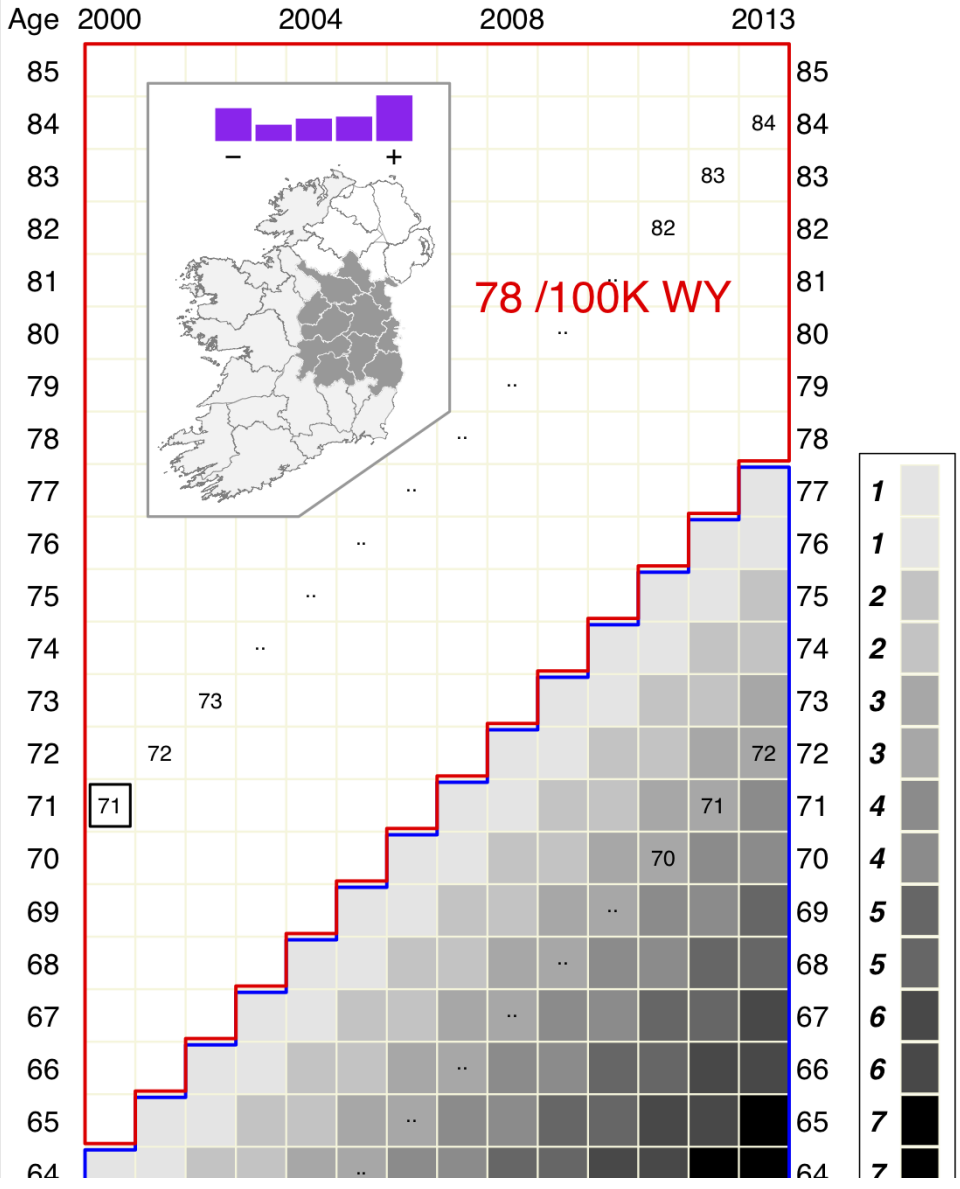
Fig 2. Numbers of screening invitations received by women in various birth-cohorts in regions 1 and 2, together with mortality rates and their ratios. Insets show the extent of each region, and (in purple) the fractions of those aged 50–85 in each quintile of the deprivation index, with '-' denoting the least and '+' the most deprived. For each birth cohort, the numbers of screening invitations received by the end of the indicated years are indicated by squares ranging in colour from white (0) to black (7), and the numbers received by the end of 2013 are shown to the right of their last follow-up year. The *Region 1 vs. Region 2*

Deaths / WomenYears : 702 / 0.91 Million WY

RateRatio: 0.96

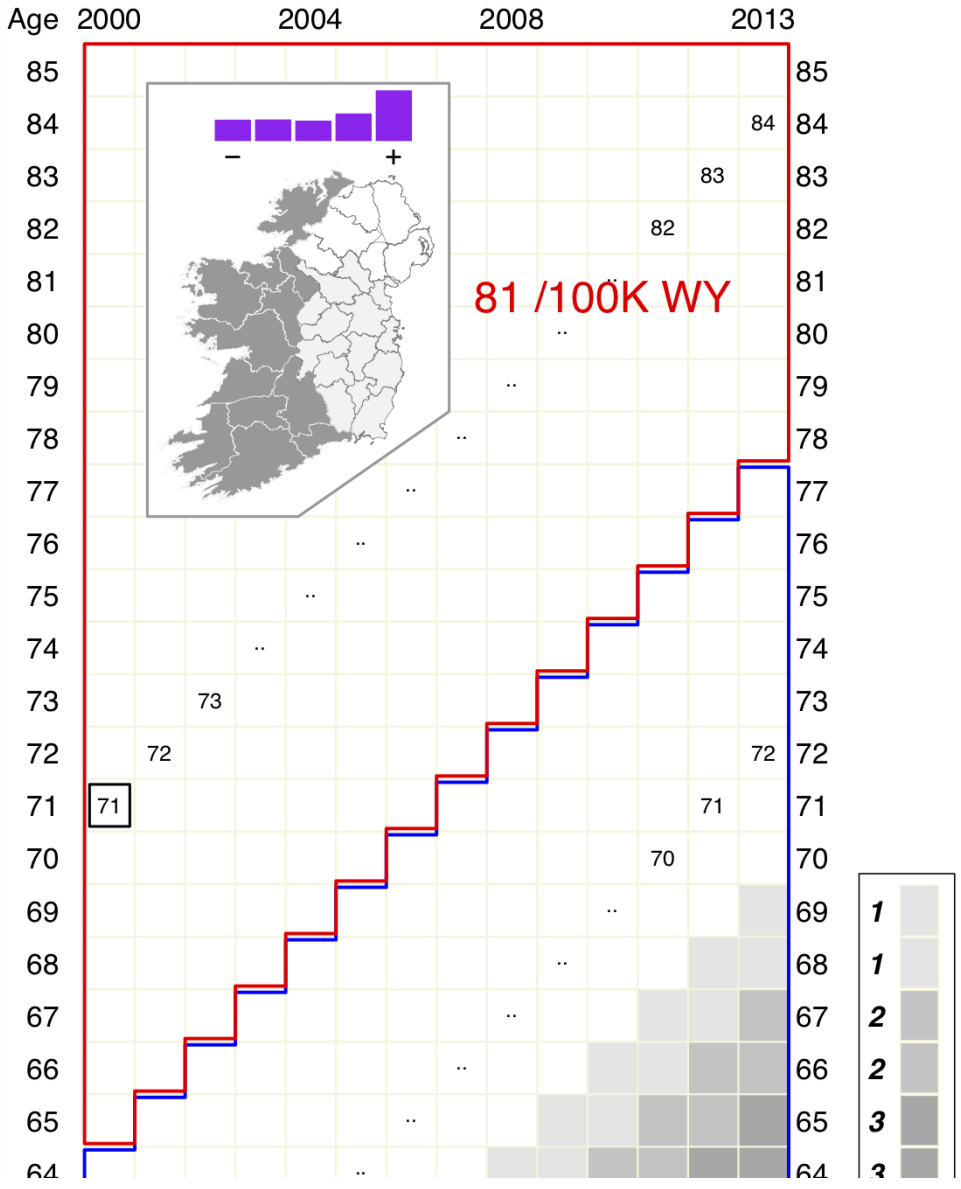
95% CI: 0.87 to 1.06

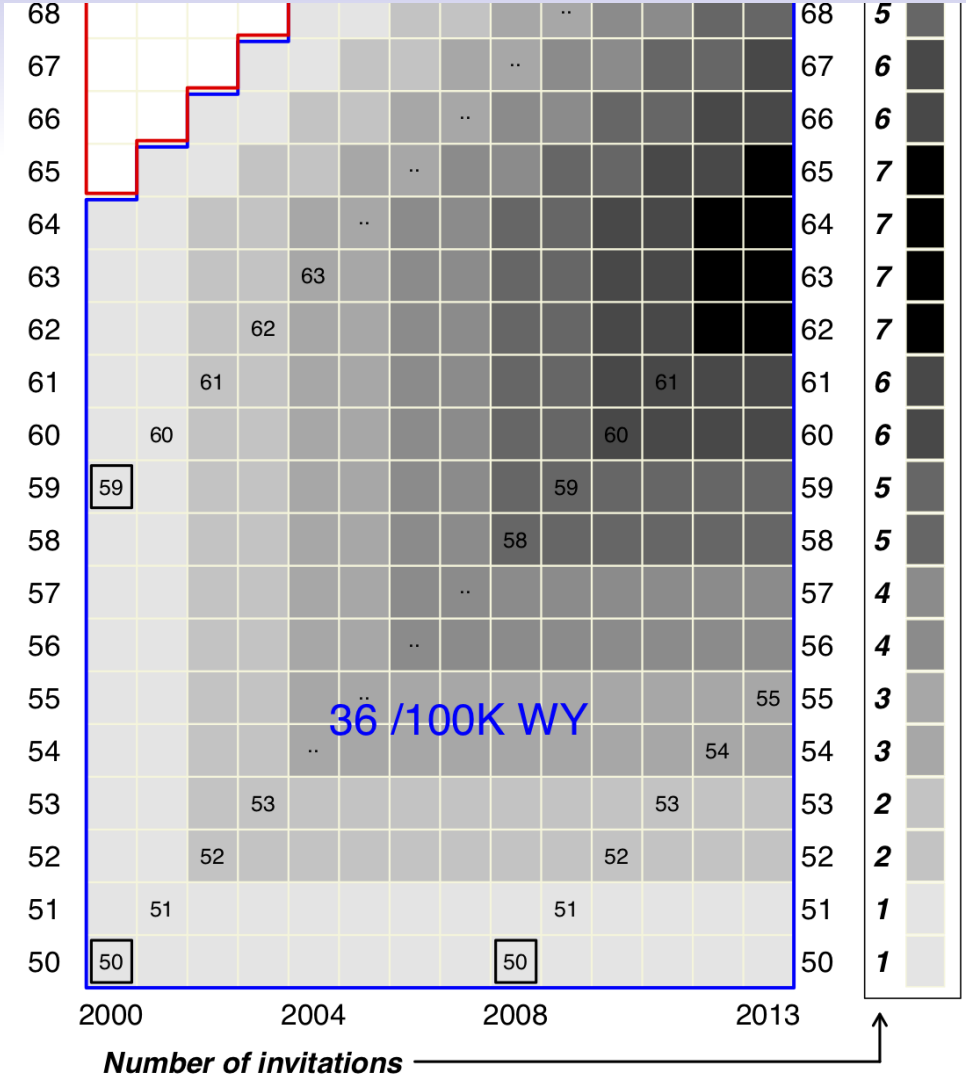
Region 1

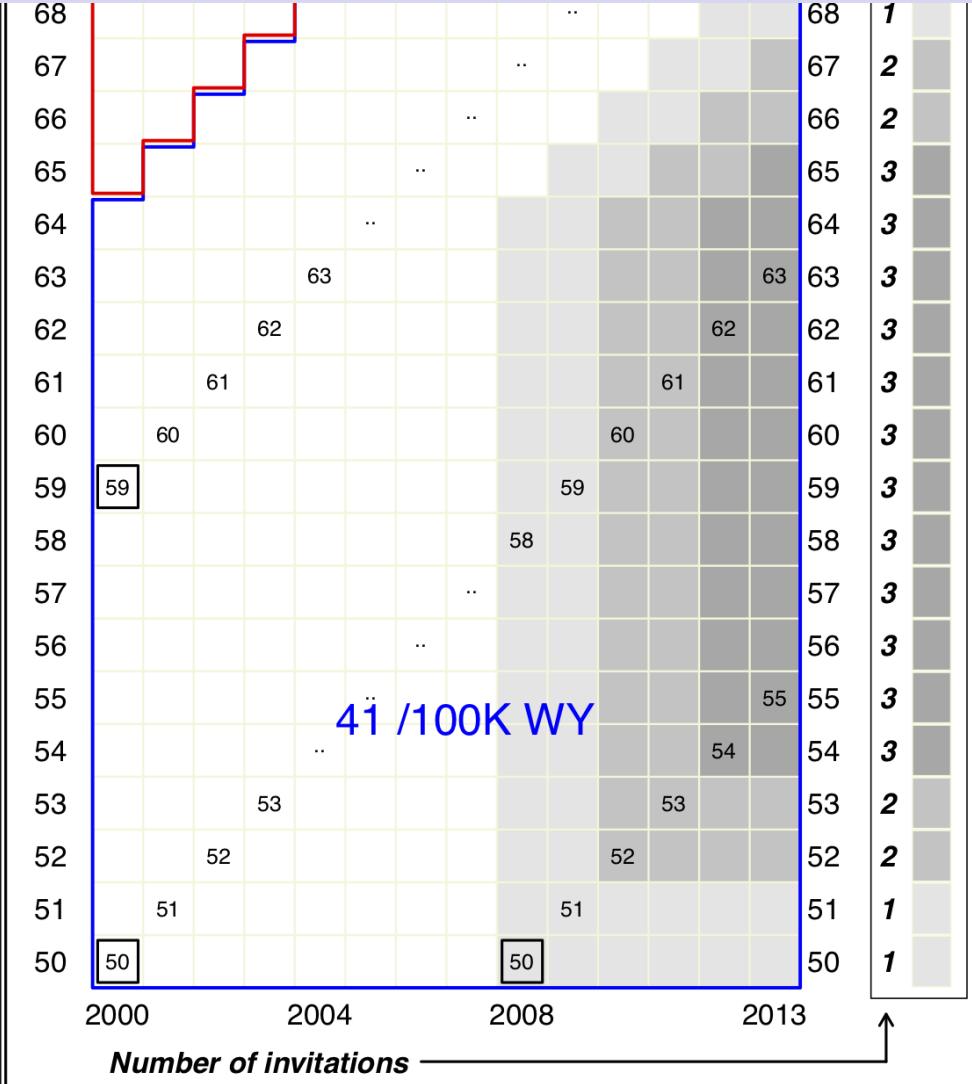


727 / 0.90 Million WY

Region 2







Deaths / WomenYears : 1027 / 2.90 Million WY

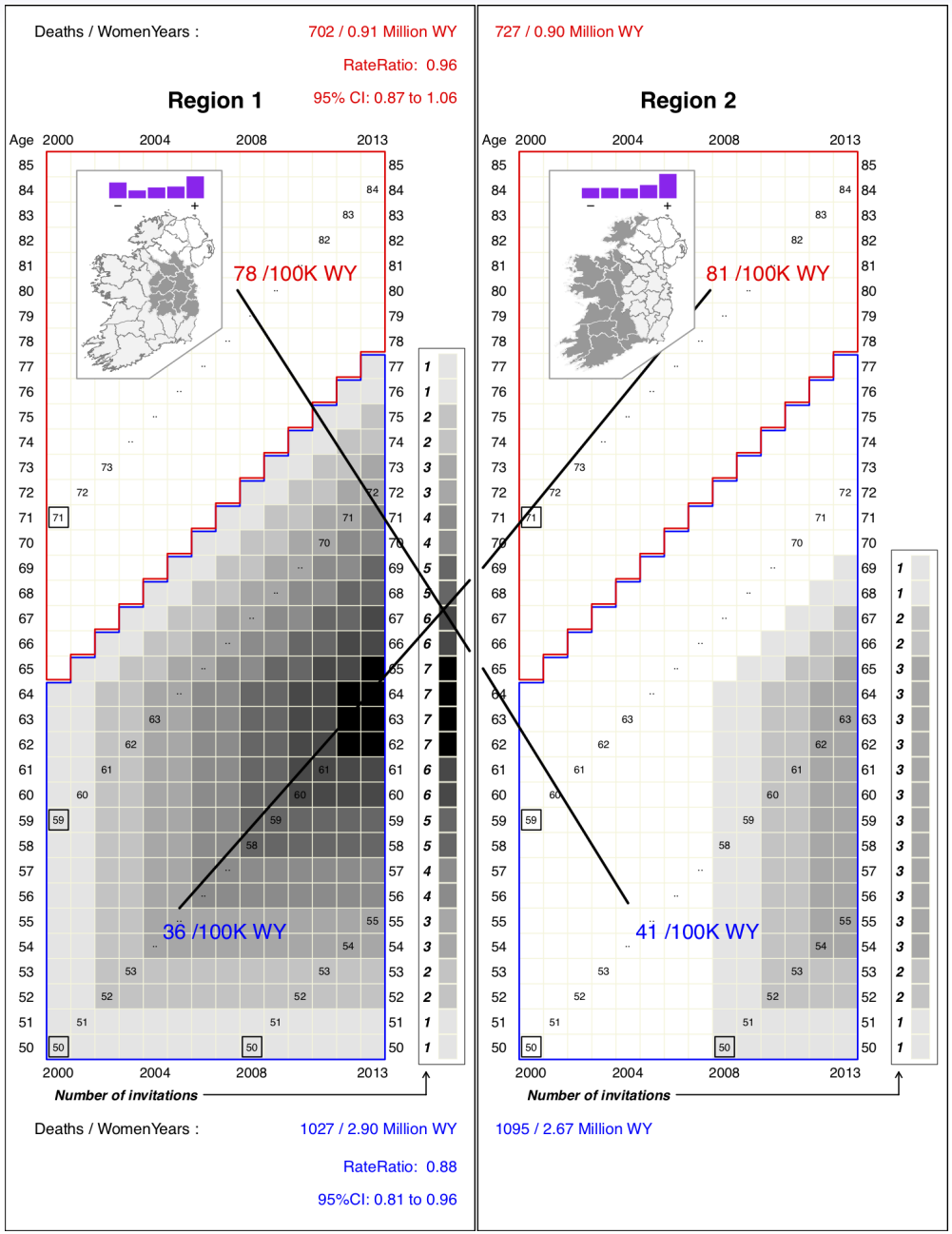
1095 / 2.67 Million WY

RateRatio: 0.88

95%CI: 0.81 to 0.96

HR = 0.91

(9% Δ)


Deaths / WomenYears :
702 / 0.91 Million WY
RateRatio: 0.96
95% CI: 0.87 to 1.06
Region 1
78 /100K WY
36 /100K WY
Deaths / WomenYears :
1027 / 2.90 Million WY
RateRatio: 0.88
95%CI: 0.81 to 0.96
727 / 0.90 Million WY
Region 2
81 /100K WY
41 /100K WY
1095 / 2.67 Million WY
Age
2000
2004
2008
2013
Number of invitations

Hazard-Ratio (% Reduction) Functions over Lexis-Space

DENMARK

European Journal of Epidemiology
https://doi.org/10.1007/s10654-017-0339-7

SCREENING

Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data

James Anthony Hanley[1] · Sisse Helle Njor[2,3]

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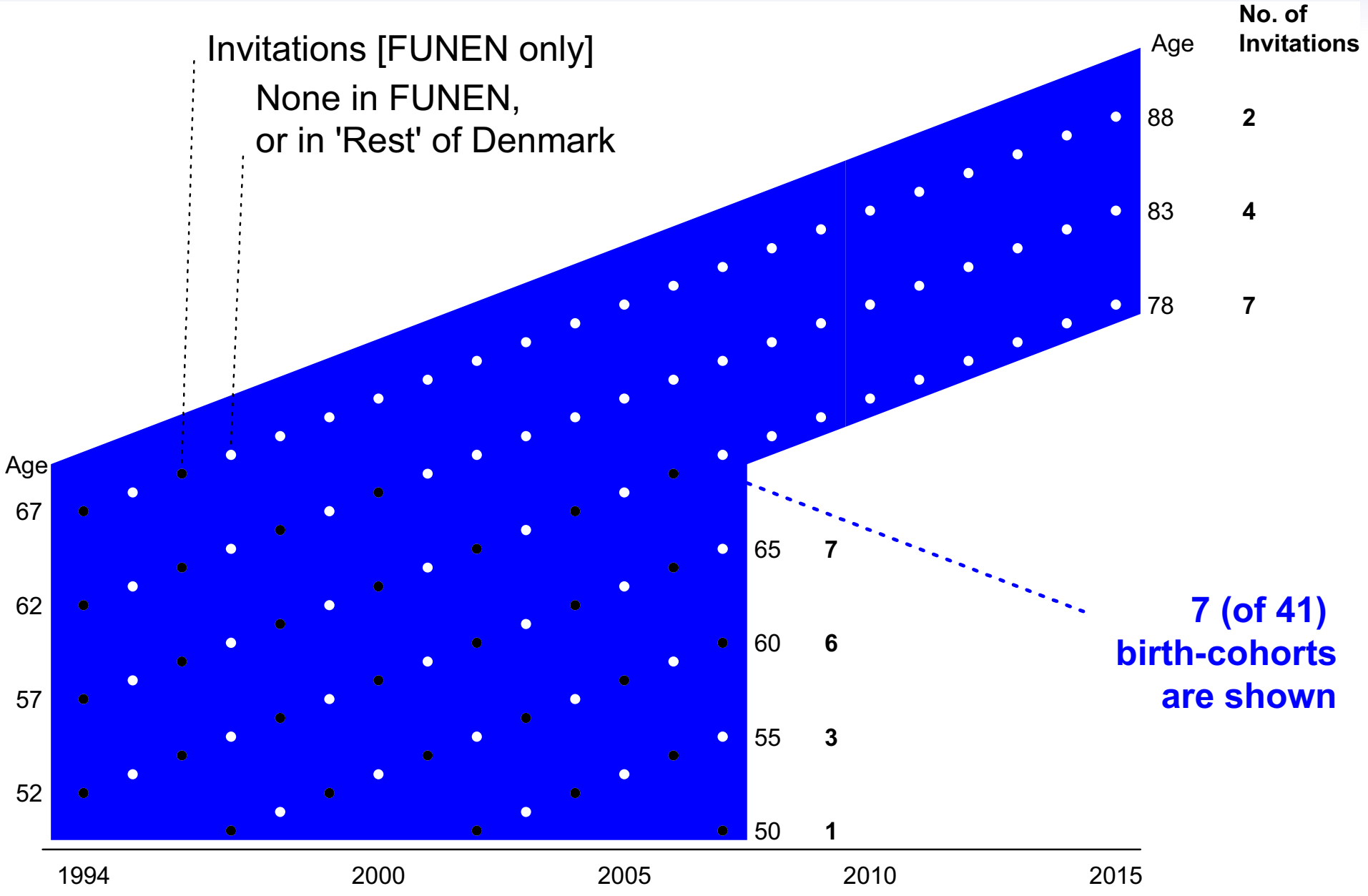
Abstract

The mortality impact in cancer screening trials and population programs is usually expressed as a single hazard ratio or percentage reduction. This measure ignores the number/spacing of rounds of screening, and the location in follow-up time of the averted deaths vis-a-vis the first and last screens. If screening works as intended, hazard ratios are a strong function of the two Lexis time-dimensions. We show how the number and timing of the rounds of screening can be included in a model that specifies what each round of screening accomplishes. We show how this model can be used to disaggregate the observed reductions (i.e., make them time-and screening-history specific), and to project the impact of other regimens. We use data on breast cancer screening to illustrate this model, which we had already described in technical terms in a statistical journal. Using the numbers of invitations different cohorts received, we fitted the model to the age- and follow-up-year-specific numbers of breast cancer deaths in Funen, Denmark. From November 1993 onwards, women aged 50–69 in Funen were invited to mammography screening every two years, while those in comparison regions were not. Under the


Invitations [FUNEN only]
None in FUNEN,
or in 'Rest' of Denmark
Age
No. of Invitations
88
2
83
4
78
7
Age
67
62
57
52
65
7
60
6
55
3
50
1
7 (of 41)
birth-cohorts
are shown
1994
2000
2005
2010
2015

BASIC IDEA IN (2 parameter) MODEL

- Think of a population without a program, and the women who died of breast cancer in a certain year.
- If these women could have been offered JUST ONE SCREEN in one of the years before they were diagnosed,
- which year would have been optimal?

  what % of them would have had their deaths averted because of the earlier detection and treatment that resulted from that earlier detection?

(b) Data for, and fitting of, HR model

		No. Deaths		Person Years		Invitation History ('Design' Matrix)
Year[y]	Age[a]	D_0	D_1	PY_0	PY_1	How many years earlier
2014	87	11	1	16,827	2,101	20 18
2013	81	24	3	17,034	2,227	19 17 15 13
2012	75	18	1	19,788	2,491	17 15 13 11 9 7 5
etc.	..	..	.	..,...	.,...	etc.

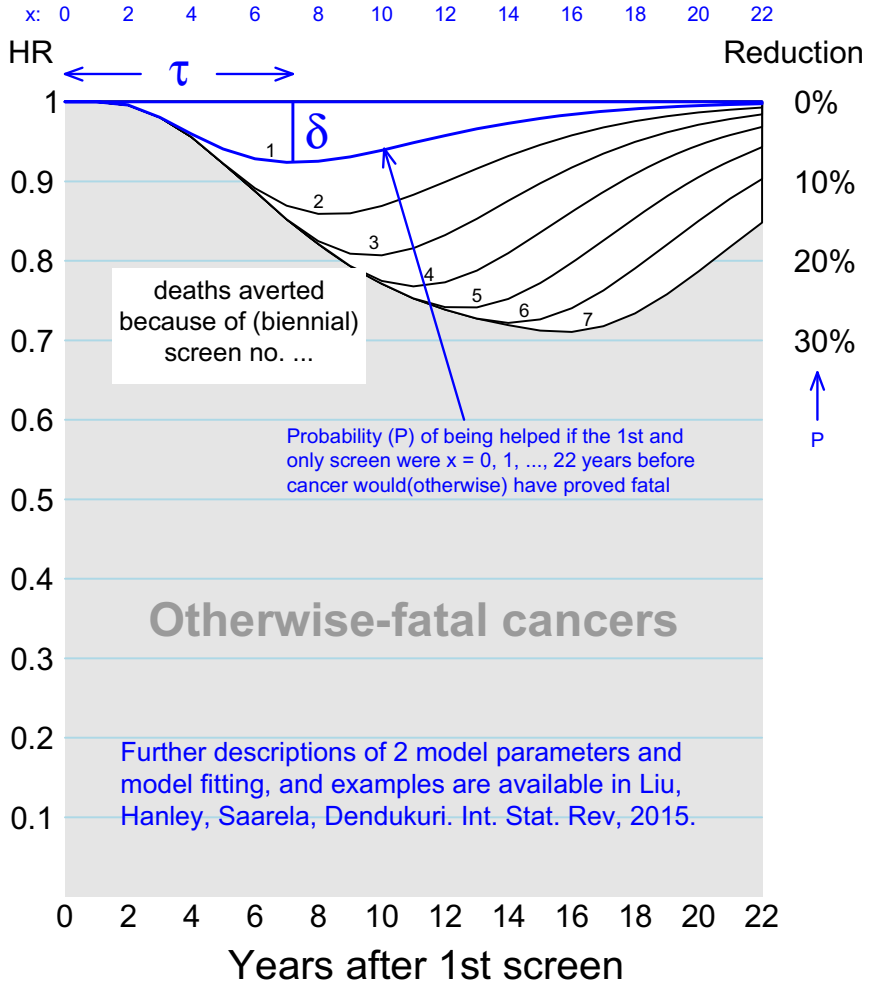
$$D_1 + D_0 = D \text{ fixed} \rightarrow D_1 \sim \text{Binomial}(D, \pi)$$

with

$$\pi = HR_{ay} \times PY_1 / (HR_{ay} \times PY_1 + 1 \times PY_0)$$

$$HR_{ay} = \prod_{AgeAtS<a} \text{Prob.not.helped.by.screen.at.age.AgeAtS}$$

(a) Model for impact of 1,2, .. ,7 rounds of screening



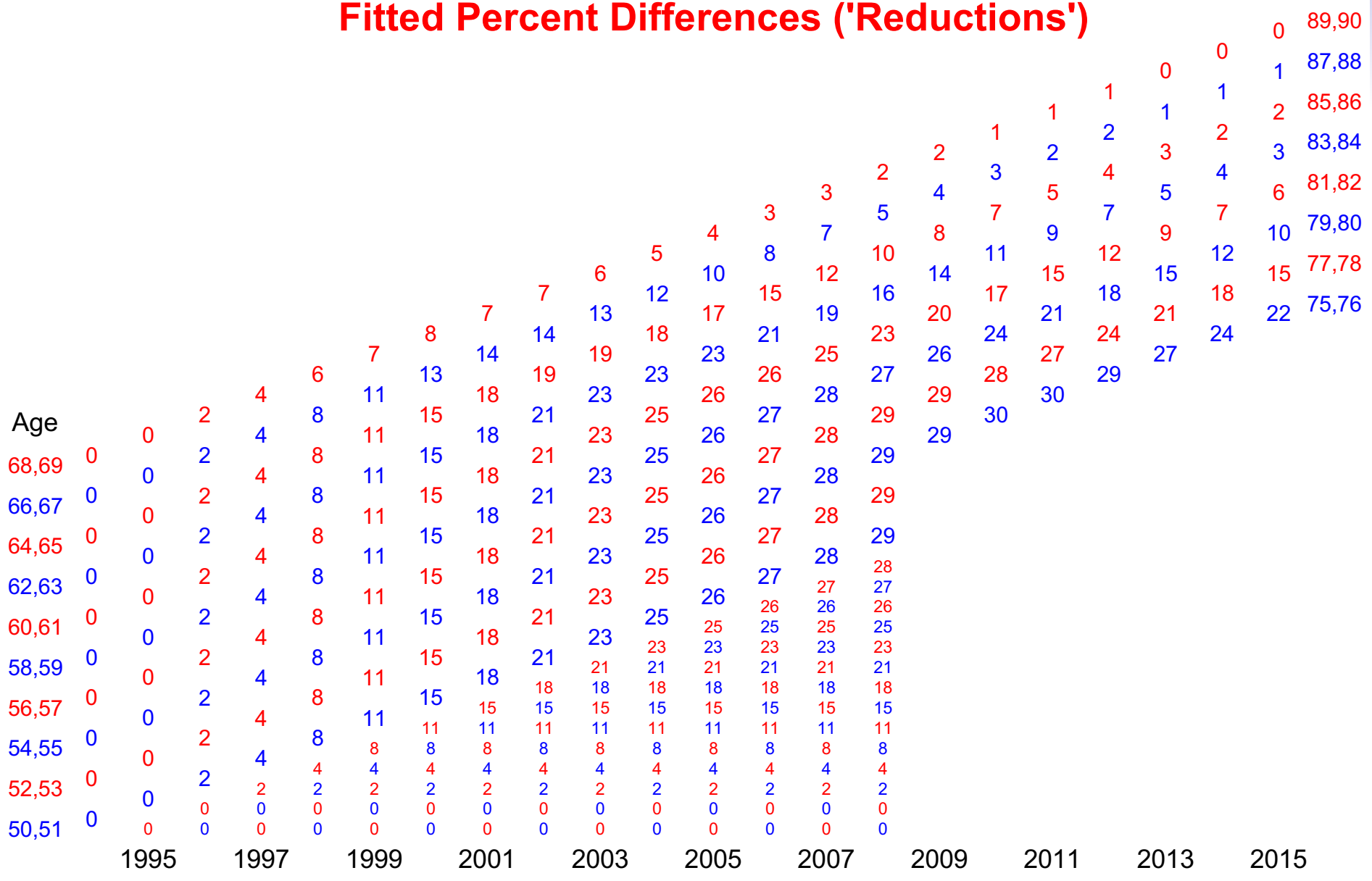
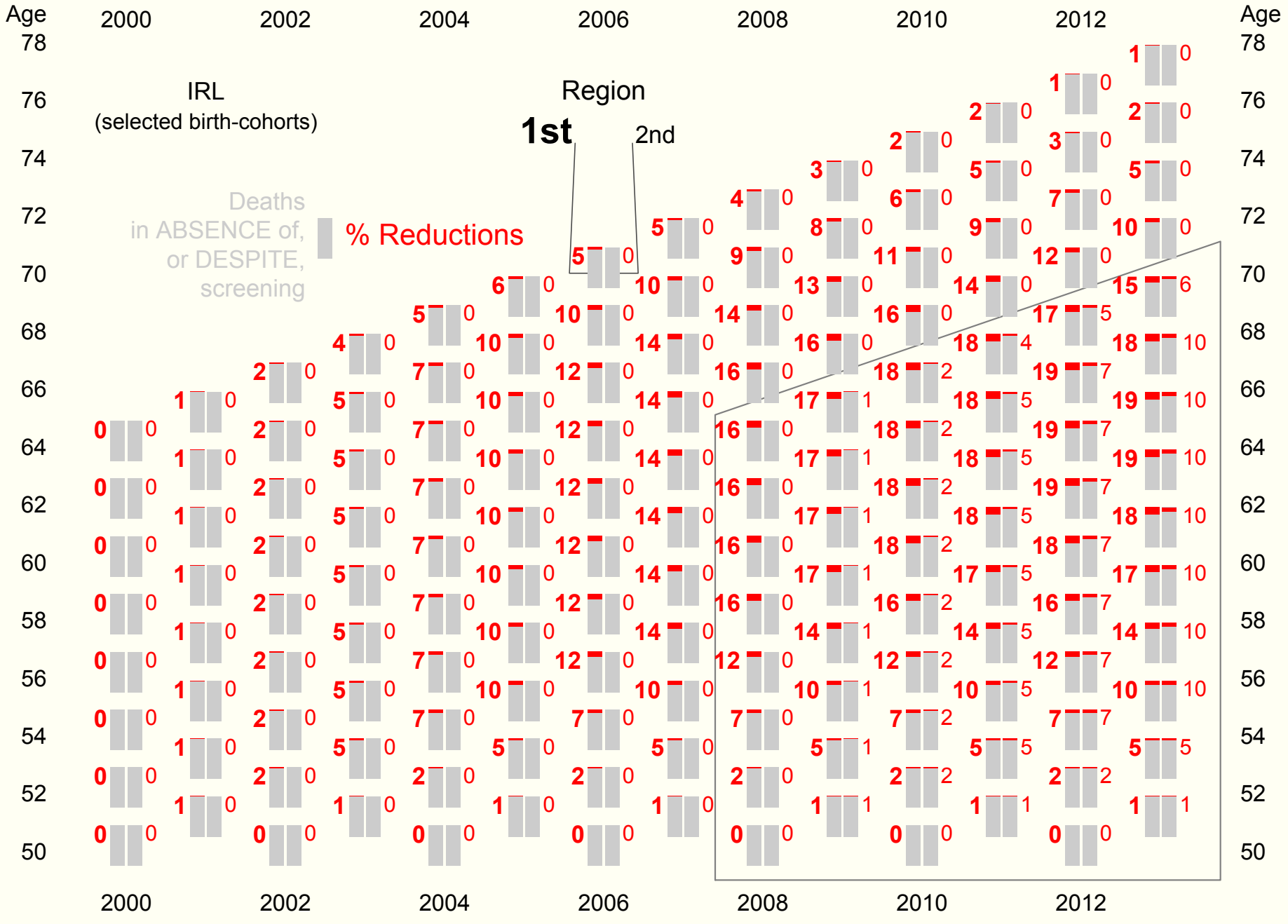
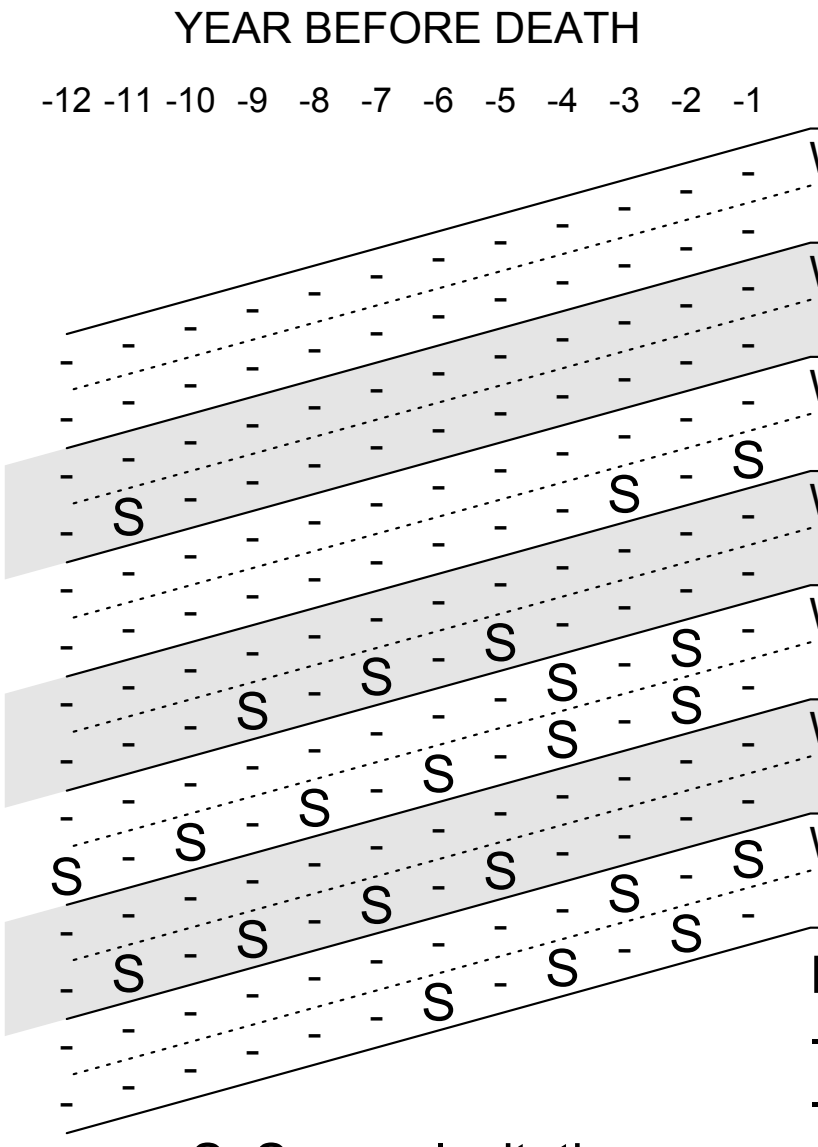


Fig. 4 For each birth cohort, the age-and year-specific fitted percentage reductions in breast cancer mortality. They were derived from the Maximum Likelihood estimates of the two model parameters (maximum probability of being helped by a single round of screening 8 years previously: 9%) and the number and timing of the preceding screening invitations

IRELAND


Age
2000
2002
2004
2006
2008
2010
2012
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
IRL
(selected birth-cohorts)
Region
1st
2nd
Deaths
in ABSENCE of,
or DESPITE,
screening
% Reductions

Design Matrix, Mortality Data, Parameter Fitting



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WEST	80	2003	2
EAST	80	2003	5
WEST	75	2011	7
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EAST	68	2009	2
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EAST	62	2012	3
WEST	68	2011	4
EAST	68	2011	5
WEST	56	2011	5
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} Binomial

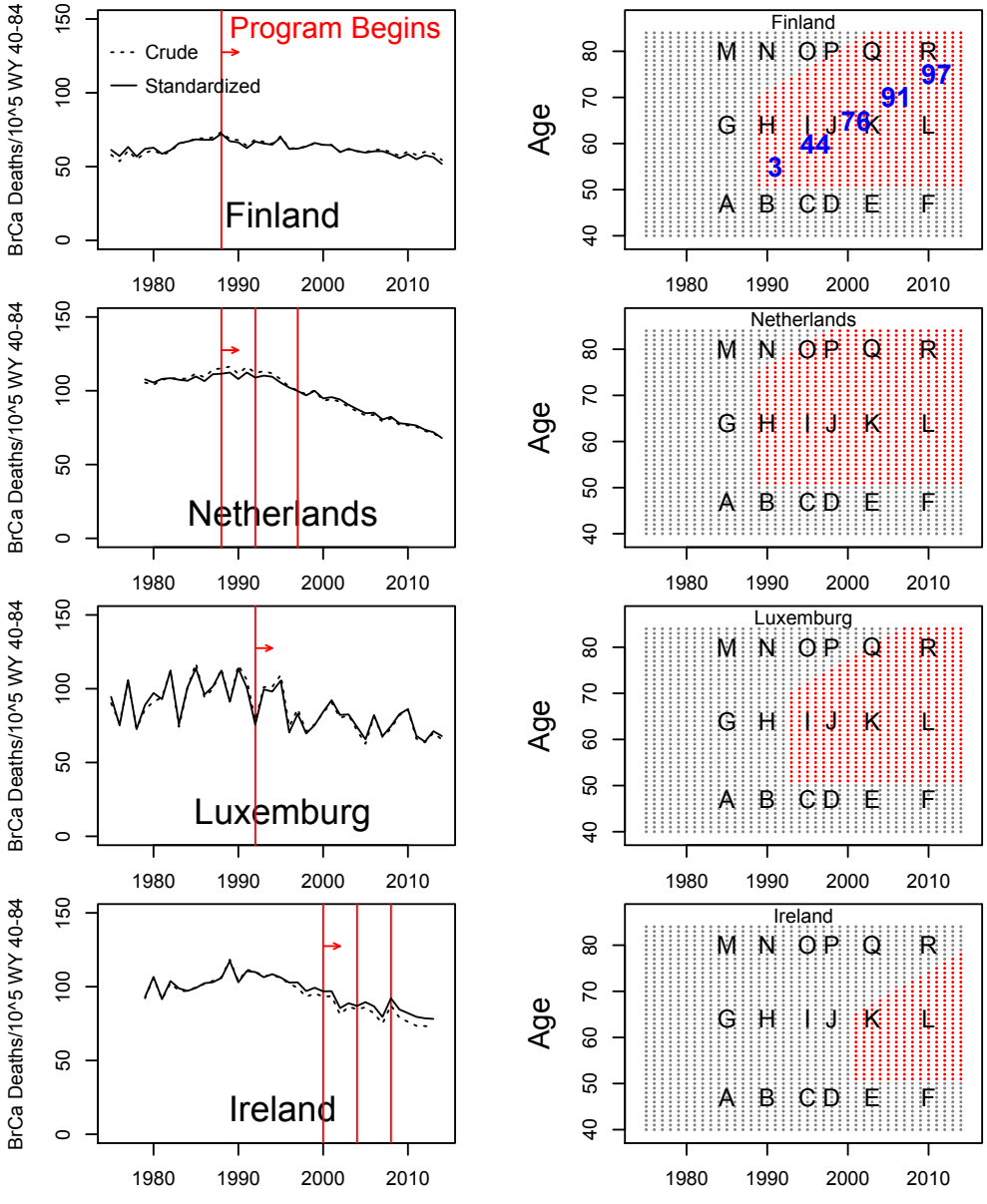
S: Screen Invitation

Binomial P = function of
- Region, Relative Population Sizes,
- NUMBER & TIMING of Screens
- IMPACT of each ROUND of SCREENING
- Participation Rate

PARAMETER ESTIMATES

Data	max[LogL(δ, τ)]	$\hat{\delta}$ (%)	$\hat{\tau}$ (yrs.)
	-1930.8	7.6%	6.7
	-1471.2	5.7%	8.0
 + 	-3402.5	6.6%	6.7

INTER-COUNTRY: WHO DATA (INCIDENT + PREVALENT)



Our Model ... in more detail (written/video)

Webpage: screening

`http://www.biostat.mcgill.ca/hanley/screening/`

Methods

`http://www.biostat.mcgill.ca/hanley/screening/section2.mov`

Applications: (TRIALS) Lung Cancer; Colon Cancer

`http://www.biostat.mcgill.ca/hanley/screening/section3.mov`

SUMMARY

- **Societal**: delayed returns vs. upfront investments, harm
- **Data analysis:** respect cancer screening principles: ~~1-number~~ $\rightarrow$ HR function, based on interpretable parameters, over Lexis space
- **Breastcheck:** "$\downarrow$ mortality from breast cancer by 20% in ten years"

  Steady state: invited from 50 onwards, followed to (say) 85, when full benefits of all invitations have been expressed, and HR reverts to 1. Estimand: depth & extent of the full bathtub-shaped HR curve.
- **Invitations, not screenings:** Reductions averaged over those who did/did not participate. Ones for those who did are presumably higher.
- **Future work**: Data to fit HR functions are hard to come by. WHO has year-and-age-specific breast cancer mortality data from 20-30 countries that introduced national mammography screening programs, starting at different times .
  - Plan to use between-country rather than within-country contrasts, but
  - (by modelling, rather than registries) first remove numbers of cases that could not have benefitted from the program.

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Liu, Z., Hanley JA, Saarela O, Dendukuri, N (2015). A conditional approach to measure mortality reductions due to cancer screening. *International Statistical Review* , **83** pp. 493 – 510.

Hanley, J.A. Hannigan, A., O'Brien, K. (2017). Mortality reductions due to mammography screening: Contemporary population-based data. *PLoS ONE*, **12(12): e0188947.**.

Hanley, J.A., Njor S.H. (2018). Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data. *Eur J Epidemiology*, **33**, pp. 465 – 472.

Some More References

1. Miettinen OS, Henschke CI, Pasmantier MW, et al. Mammographic screening: no reliable supporting evidence? *Lancet* 2002;359:404-406. and http://image.thelancet.com/extras/1093web.pdf.
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3. Olsen AH, Njor SH, Vejborg I, Schwartz W, Dalgaard P, Jensen MB, Tange UB, Blichert-Toft M, Rank F, Mouridsen H, Lynge E. Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study. BMJ. 2005 Jan 29;330(7485):220.
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5. * Hanley JA. Mortality reductions produced by sustained prostate cancer screening have been underestimated. Journal of Medical Screening. *J Medical Screening* 2010;17:147-151.
6. * Hanley JA. Measuring Mortality reductions in cancer screening studies. *Epidemiologic Reviews* 2011. Advance Access published May 30, 2011.
7. Njor S, Nystrom L, Moss S, Paci E, Broeders M, Segnan N, Lynge E; Euroscreen Working Group. Breast cancer mortality in mammographic screening in Europe: a review of incidence-based mortality studies. J Med Screen. 2012;19 Suppl 1:33-41.
8. * Liu Z, Hanley JA, Strumpf EC. Projecting the yearly mortality reductions due to a cancer screening programme. *Journal of Medical Screening*. 2013; 20(3): 156-64. doi:10.1177/0969141313504088
9. Weedon-Fekjaer, et al. Modern mammography screening and breast cancer mortality: population study BMJ 2014;348:g3701 doi: 10.1136/bmj.g3701 (Published 17 June 2014)
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* `http:www.medicine.mcgill.ca/epidemiology/hanley/` (reprints/talks)

WEB PAGE

`http://www.biostat.mcgill.ca/hanley/screening`

or Google "James Hanley McGill screening"

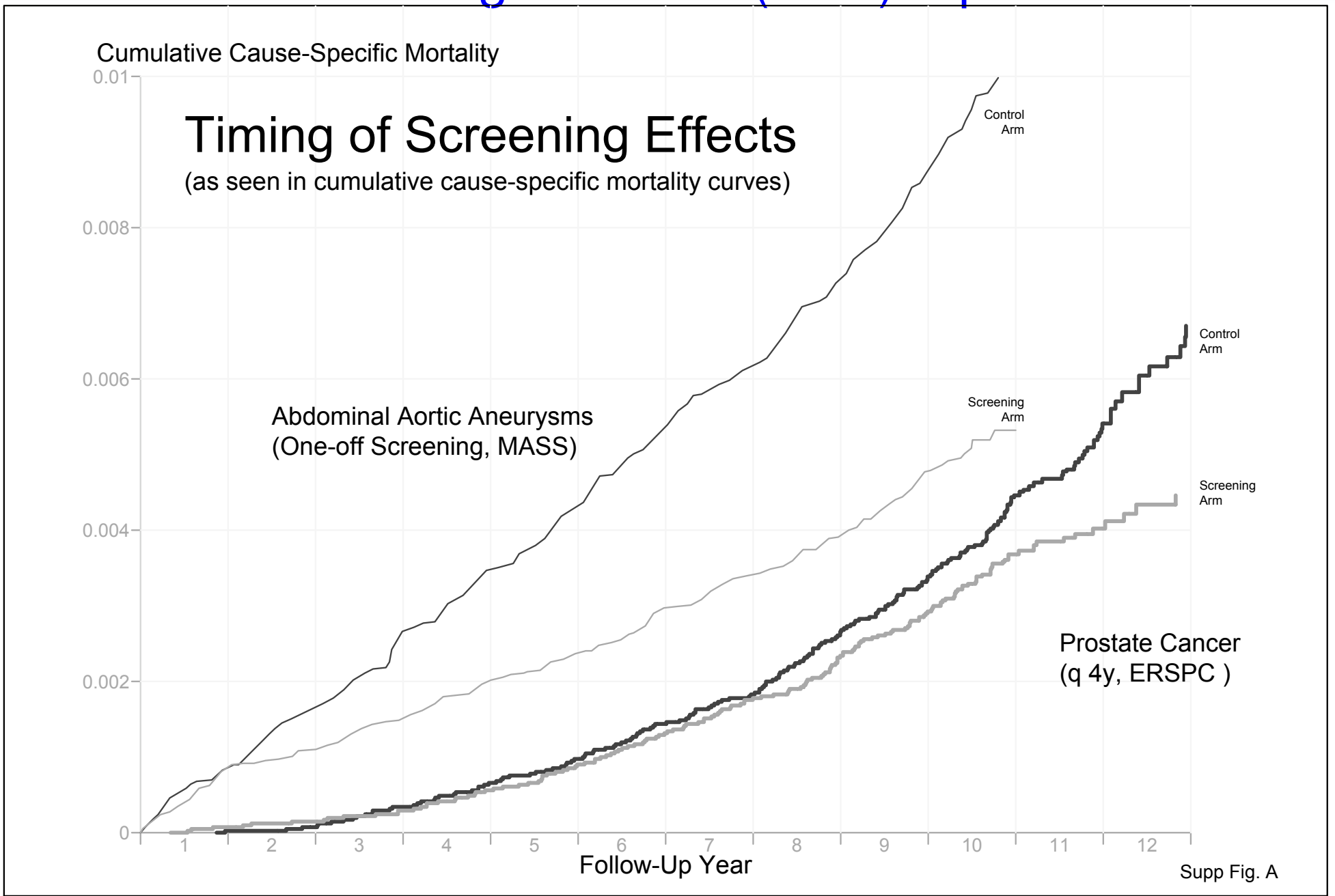
FUNDING

Canadian Institutes of Health Research
2011-2019

Economic and Social Research Institute (Ireland)
1969

https://www.esri.ie/people/james-hanley

Loneliness of Long-Distance (non-)Experimentalist



Supp Fig. A

Why do statisticians commonly limit their inquiries to Averages?

F. Galton, Natural Inheritance, 1889.

“It is difficult to understand why statisticians commonly limit their inquiries to Averages, and do not revel in more comprehensive views.

Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”

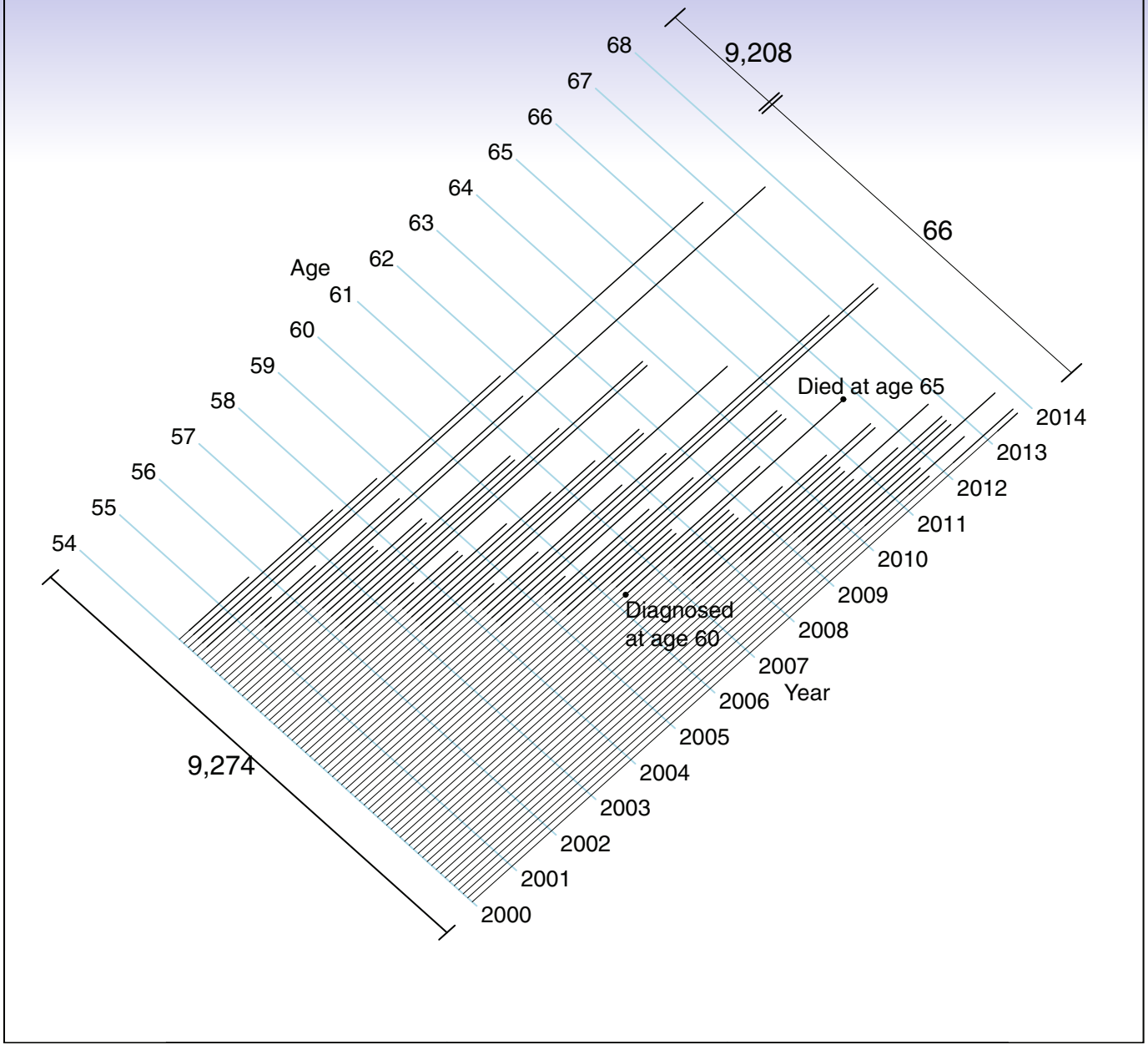


Fig 1. The ages when they were diagnosed with, and died of, breast cancer: 66 women in one selected cohort in region 2. Some 9,274 women, aged 54 in the year 2000, followed to the end of 2013. This cohort received just two screening invitations, at ages 62 and 64, too late to alter the course of these 66 fatal cancers. The lengths of the lighter portions of the lines are the maximal amounts by which screening might have advanced their diagnosis and treatment. Lines are drawn diagonally to orient readers to the full Lexis diagrams used in Figs 2 and 3.

Year and Age: Usefulness of (2-D) Lexis Diagram

OVERLOOKED PRINCIPLES

How not to conduct population-based studies

BMJ

BMJ 2011;343:d4411 doi: 10.1136/bmj.d4411

RESEARCH

Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database

Philippe Autier *research director*[1], Mathieu Boniol *senior statistician*[1], Anna Gavin *director*[2], Lars J Vatten *professor*[3]

[1]International Prevention Research Institute, 95 Cours Lafayette, 69006 Lyon, France; [2]Northern Ireland Cancer Registry, Belfast, Northern Ireland, UK; [3]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Objective To compare trends in breast cancer mortality within three pairs of neighbouring European countries in relation to implementation of screening.

Design Retrospective trend analysis.

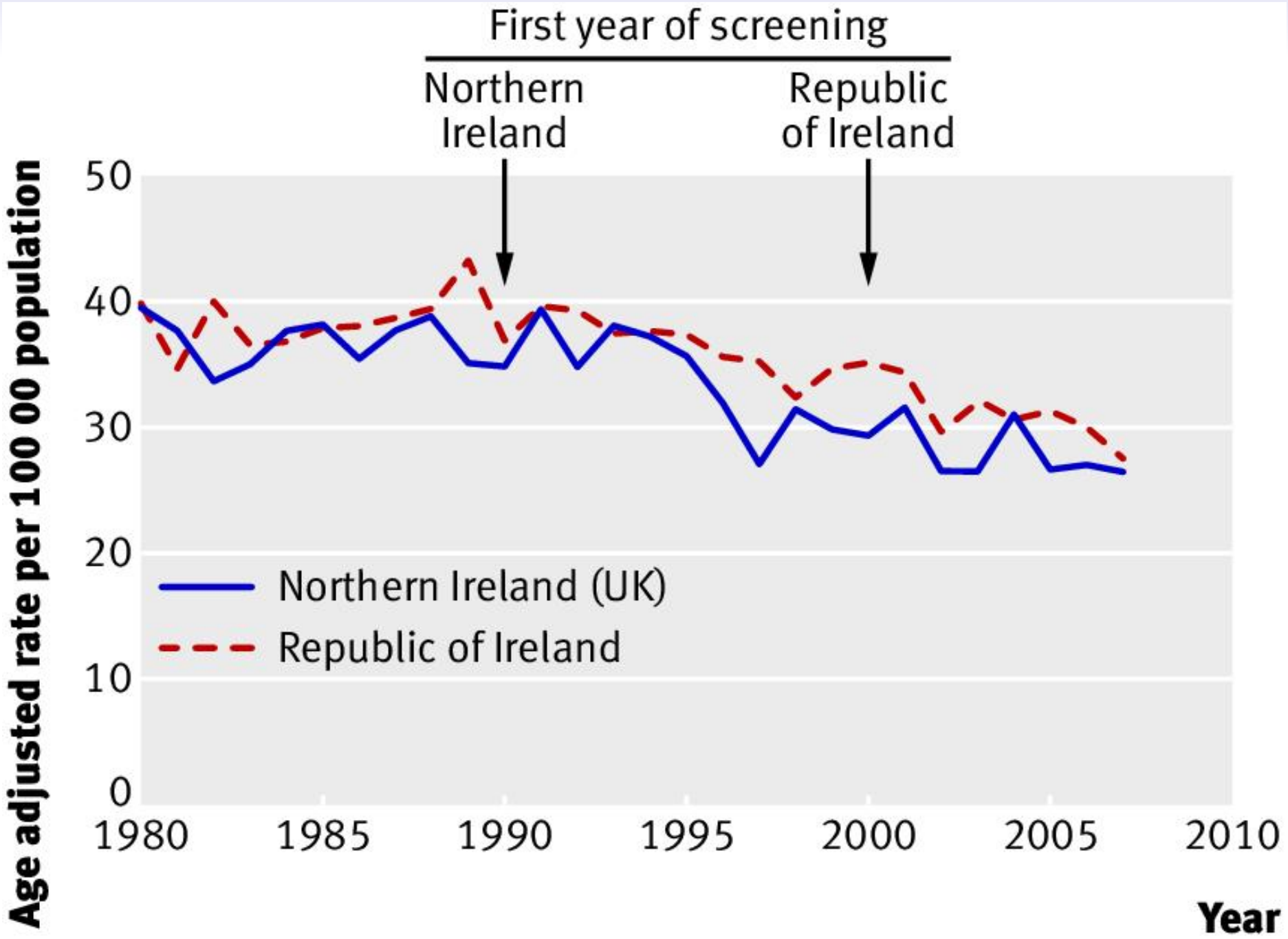
Setting Three country pairs (Northern Ireland (United Kingdom) *v* Republic of Ireland, the Netherlands *v* Belgium and Flanders (Belgian region south of the Netherlands), and Sweden *v* Norway).

Data sources WHO mortality database on cause of death and data sources on mammography screening, cancer treatment, and risk factors for breast cancer mortality.

Main outcome measures Changes in breast cancer mortality calculated from linear regressions of log transformed, age adjusted death rates. Joinpoint analysis was used to identify the year when trends in mortality for all ages began to change.

Results From 1989 to 2006, deaths from breast cancer decreased by 29% in Northern Ireland and by 26% in the Republic of Ireland; by 25% in the Netherlands and by 20% in Belgium and 25% in Flanders; and by 16% in Sweden and by 24% in Norway. The time trend and year of downward inflexion were similar between Northern Ireland and the Republic of Ireland and between the Netherlands and Flanders. In Sweden, mortality rates have steadily decreased since 1972, with no downward inflexion until 2006. Countries of each pair had similar healthcare services and prevalence of risk factors for breast cancer mortality but differing implementation of mammography screening, with a gap of about 10-15 years.

Conclusions The contrast between the time differences in implementation of mammography screening and the similarity in reductions in mortality between the country pairs suggest that screening did not play a direct part in the reductions in breast cancer mortality.


First year of screening
Northern Ireland
Republic of Ireland
Age adjusted rate per 100 00 population
50
40
30
20
10
0
1980
1985
1990
1995
2000
2005
2010
Year
Northern Ireland (UK)
Republic of Ireland

This big-data approach dilutes the measured impact

1. **WHO?** Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been diagnosed before the screening was introduced. These women could not have been helped by the program.
2. **WHEN?** Because of the 'detectability vs. curability' tradeoff, mortality deficits produced by cancer screening become evident only after some delay.
3. **HOW MUCH?** The closer to the upper screening age when the program began, the smaller the number of invitations received

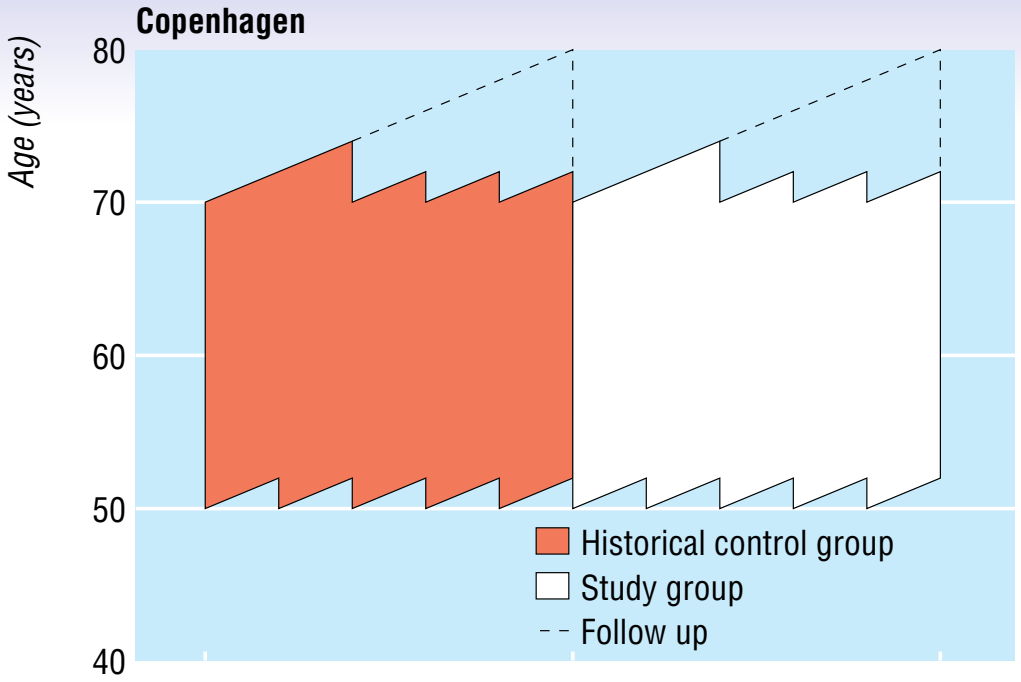
Smaller data: use date of diagnosis to emulate RCT (cancer registry data are required to do this)

Cite this article as: BMJ, doi:10.1136/bmj.38313.639236.82 (published 13 January 2005)

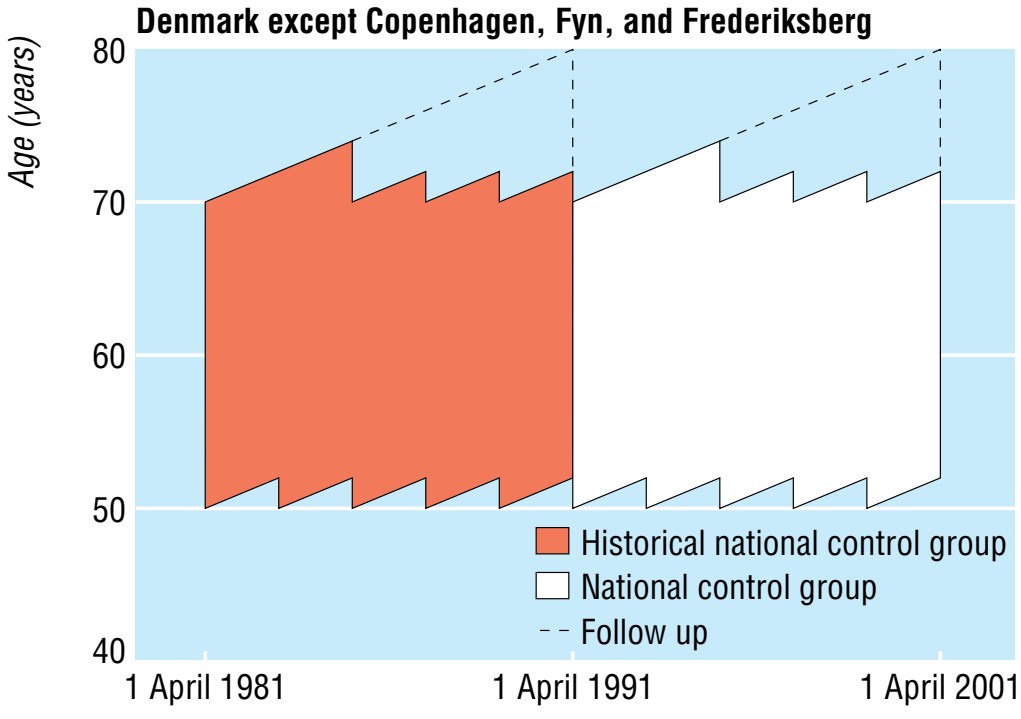
Papers

Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study

Anne Helene Olsen, Sisse H Njor, Ilse Vejborg, Walter Schwartz, Peter Dalgaard, Maj-Britt Jensen, Ulla Brix Tange, Mogens Blichert-Toft, Fritz Rank, Henning Mouridsen, Elsebeth Lynge

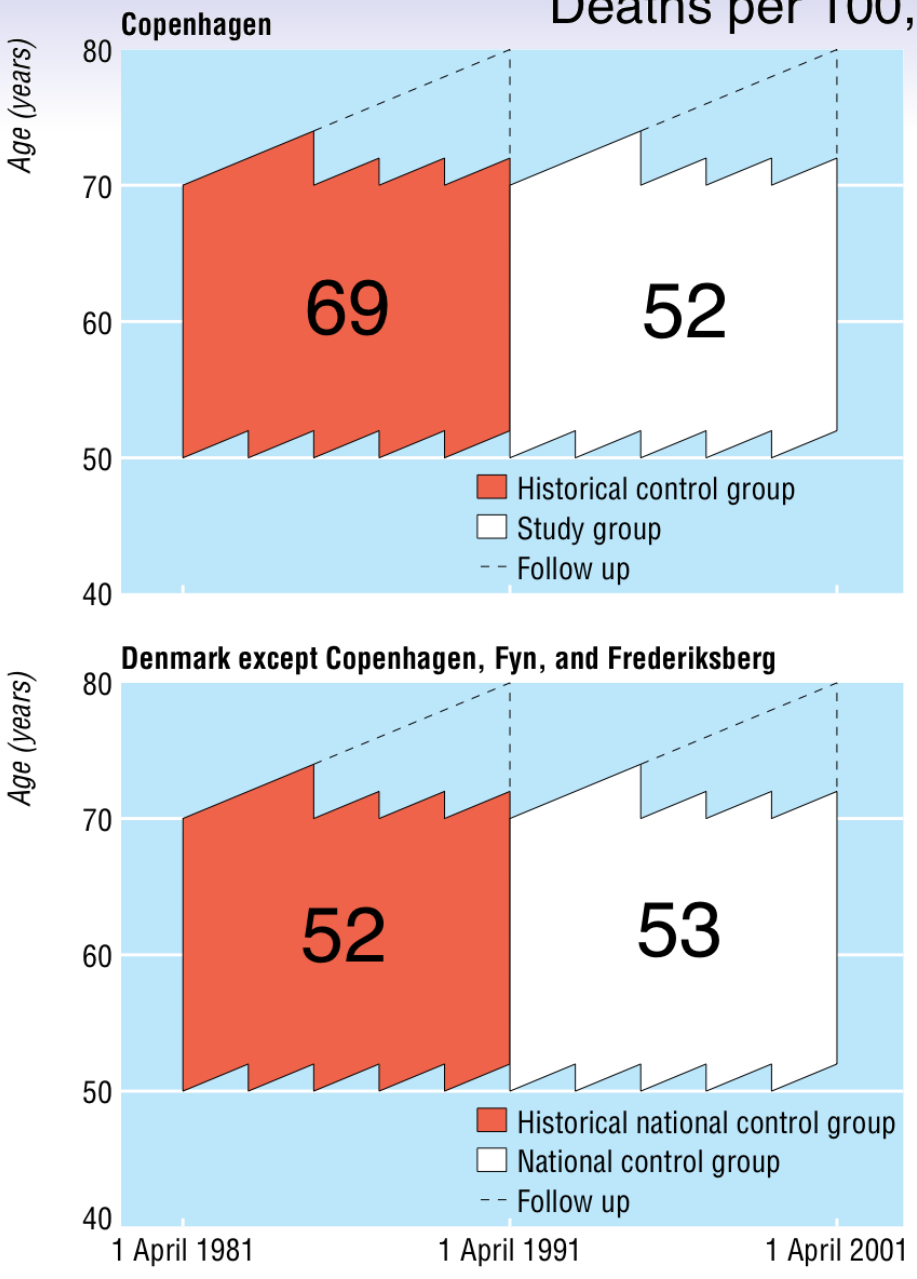


Copenhagen

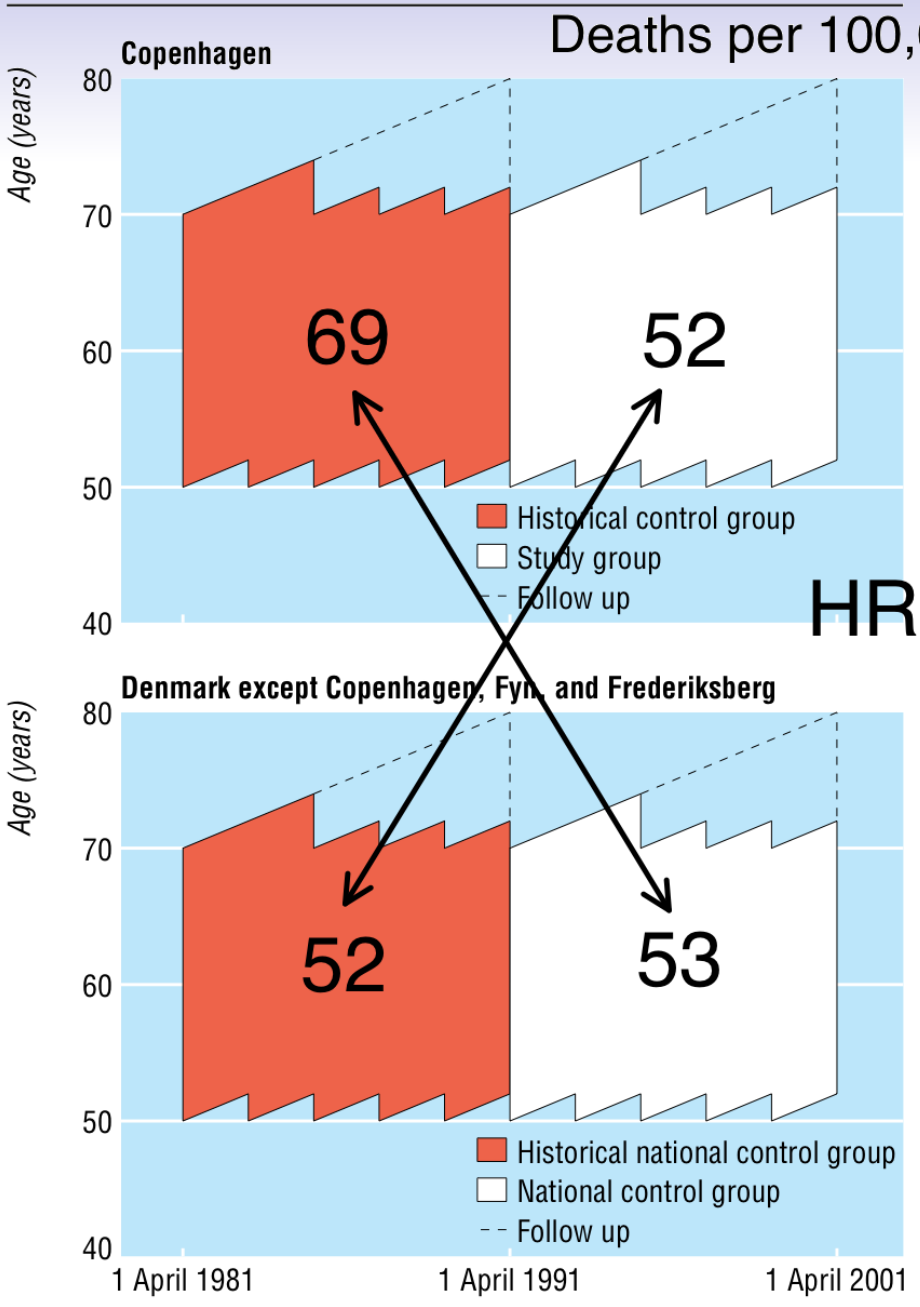


Rest of Denmark (10 x)

Deaths per 100,000 WY



Deaths per 100,000 WY



HR = 0.75 (25% ↓)

Our Model ... in more detail

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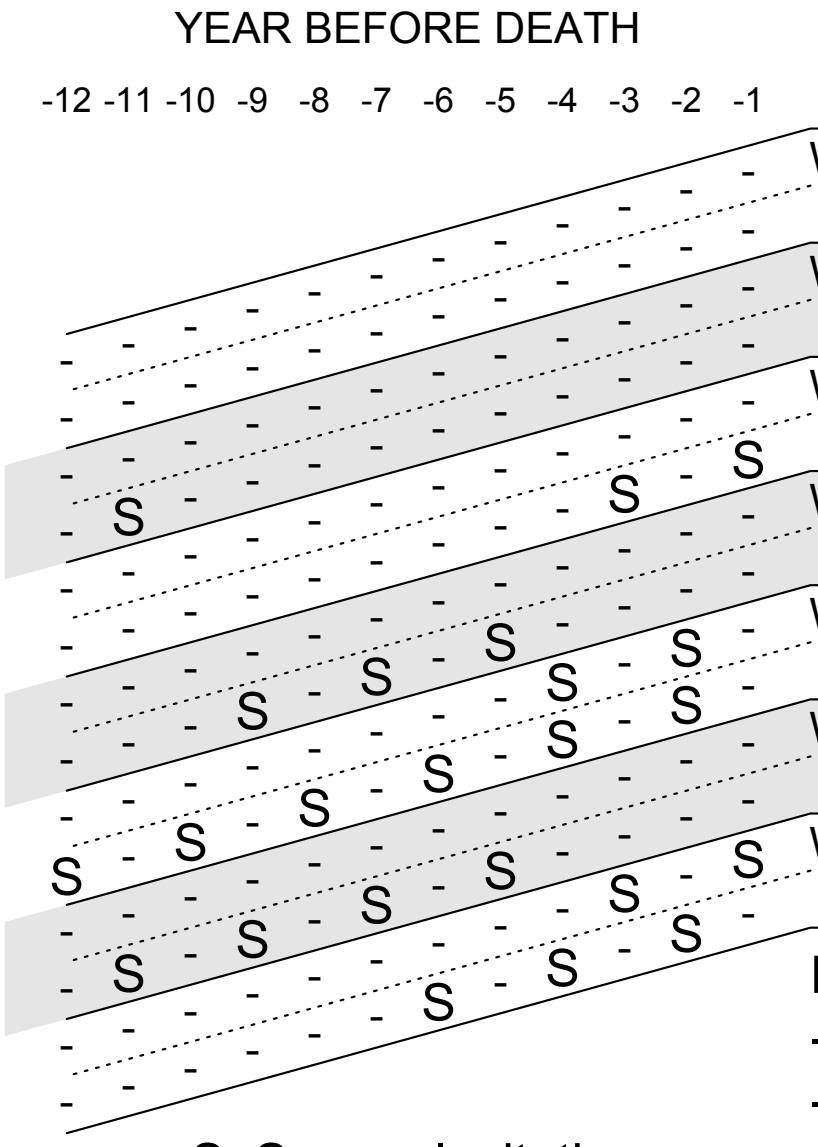

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* `http:www.medicine.mcgill.ca/epidemiology/hanley/` (reprints/talks)

FUNDING, CO-ORDINATES, DOWNLOADS

Natural Sciences and Engineering Research Council of Canada

Canadian Institutes of Health Research (2011-2015)

.....

James.Hanley@McGill.CA

www.med.mcgill.ca/epidemiology/hanley

→ **r e p r i n t s / talks**

EXTRA SLIDES

Why do statisticians commonly limit their inquiries to Averages?

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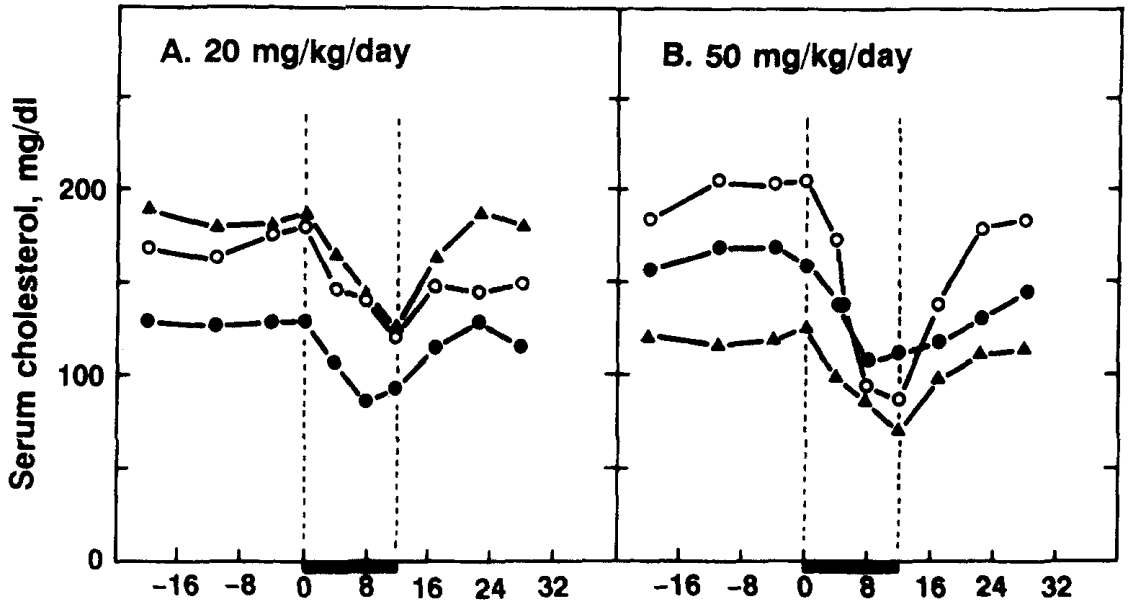
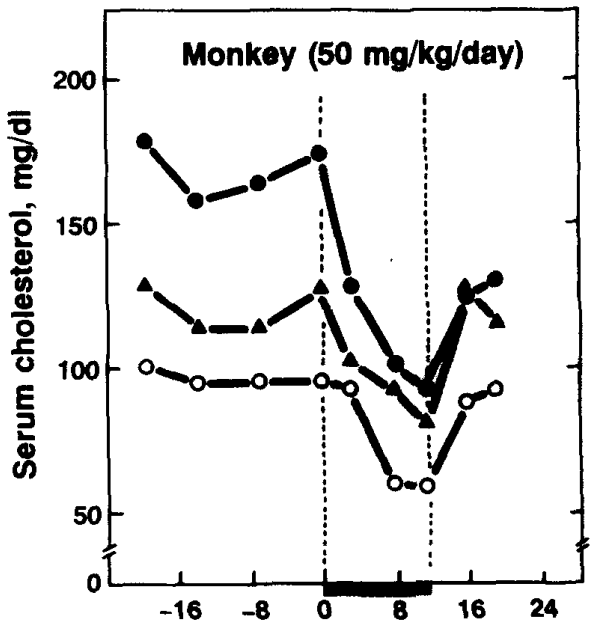
Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”

Timing of cholesterol reductions produced by statins

3 dogs at 20 mg/kg/day; 3 at 50 mg/kg/day

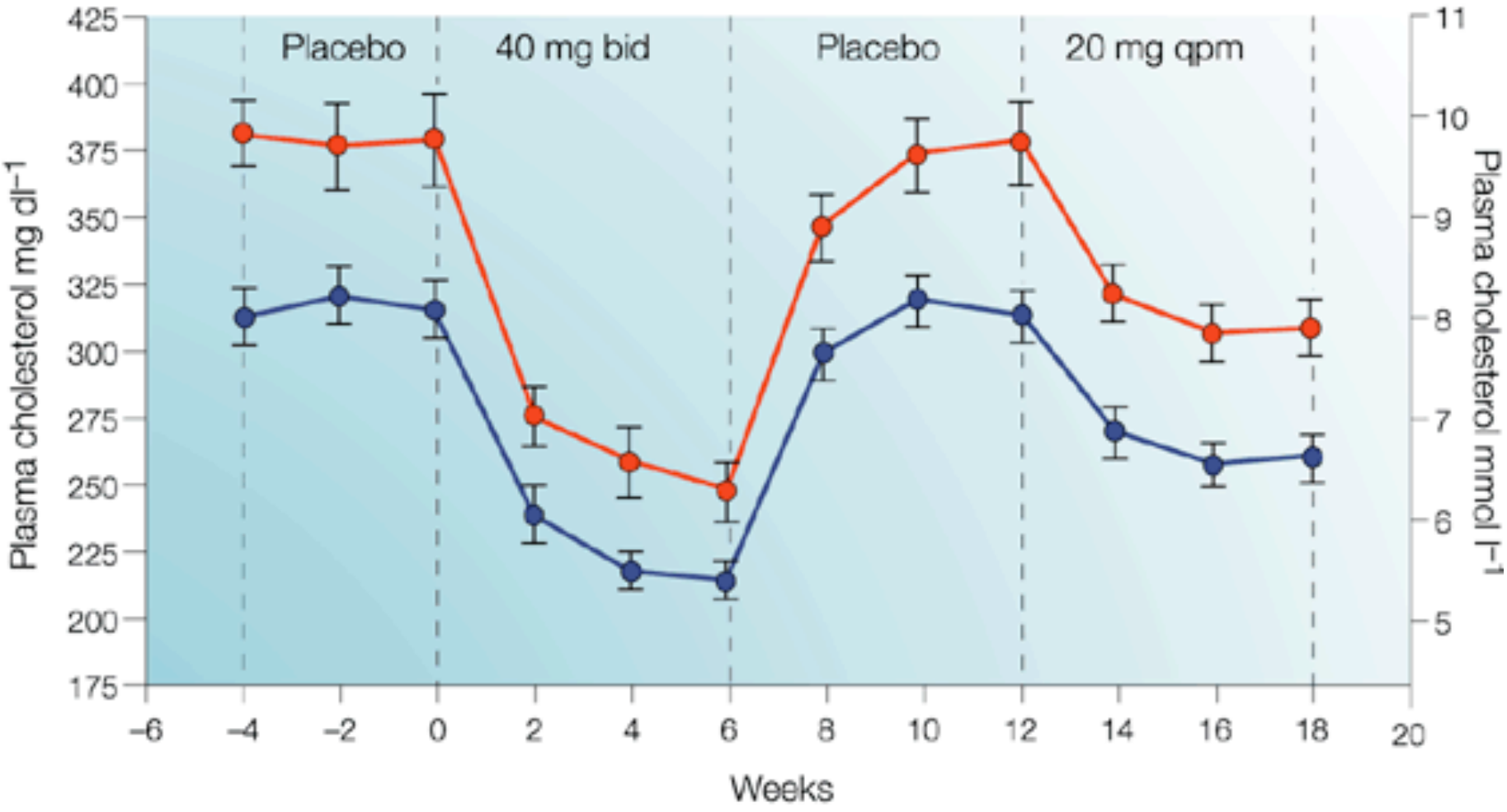


3 monkeys at 50

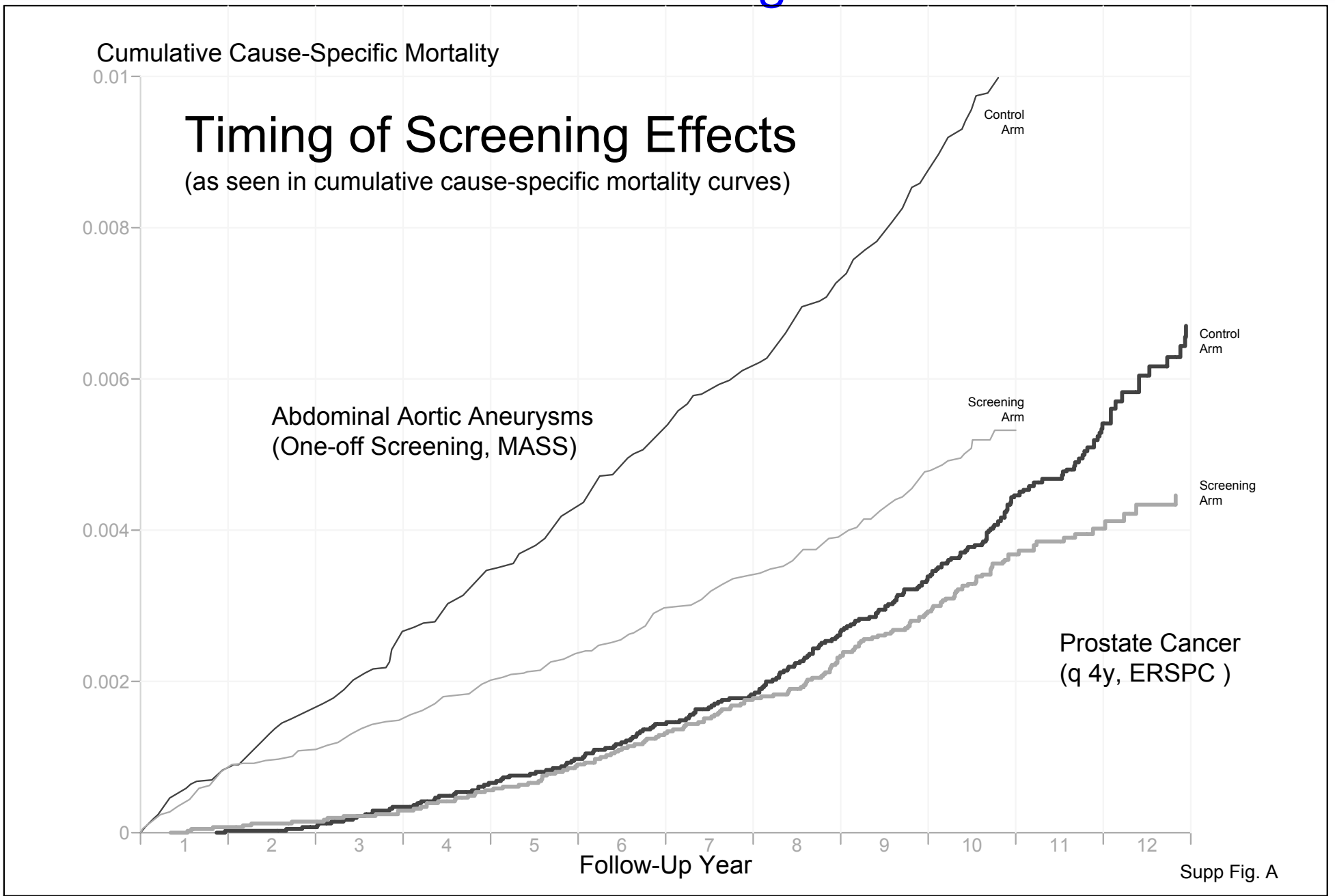


Timing of cholesterol reductions produced by statins

Humans



The loneliness of the long-distance trialist



Supp Fig. A