HOW MUCH DOES SCREENING REDUCE CANCER MORTALITY?

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McGill University

51ST ANNUAL ANDRÉ AISENSTADT MEMORIAL CLINICAL DAY
CANCER SCREENING – UPDATE 2014

A Symposium in Honour of Dr. André Lisbona
Jewish General Hospital

October 22, 2014

James A. HANLEY

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1. Comparison of response evaluation in small cell lung cancer using computerized tomography and chest radiography.
Dajczman E, **Hanley** J, **Lisbona** A, Wolkove N, Kreisman H.
Lung Cancer. 1994 Jul;11(1-2):51-60.
PMID: 8081704 [PubMed - indexed for MEDLINE]
Related citations

2. The diagnostic and prognostic value of renal allograft biopsy.
Parfrey PS, Kuo YL, **Hanley** JA, Knaack J, Xue Z, **Lisbona** R, Guttmann RD.
Transplantation. 1984 Dec;38(6):586-90.

Summary

- Harms have been (well) measured; benefits have been mis-measured
- By ignoring the delay until the reductions in mortality are expressed, the prevailing interpretations of the results of cancer screening trials ***under-estimate*** the mortality reductions that ***would be produced by a sustained screening program***
- P-value-driven RCT stopping/reporting rules exacerbate the problem
- Ways we *might* be able to avoid such misleading estimates
- Lung, Prostate, Colon: re-analysis of data from trials
- Breast : data from ~~outdated trials~~ population-screening

Outline

- Why do so many **trials** yield a 20% 'mortality reduction' ? [Theorem]
- The mortality reductions produced by a cancer screening **program**
- A way ahead? (impact of N-round program: $\sum_{i=1}^{i=N} \textit{impact of round}_i$)
- Illustrations: cancer of the **prostate**, **breast**, **colon**
- Comments: cancer of the **breast**

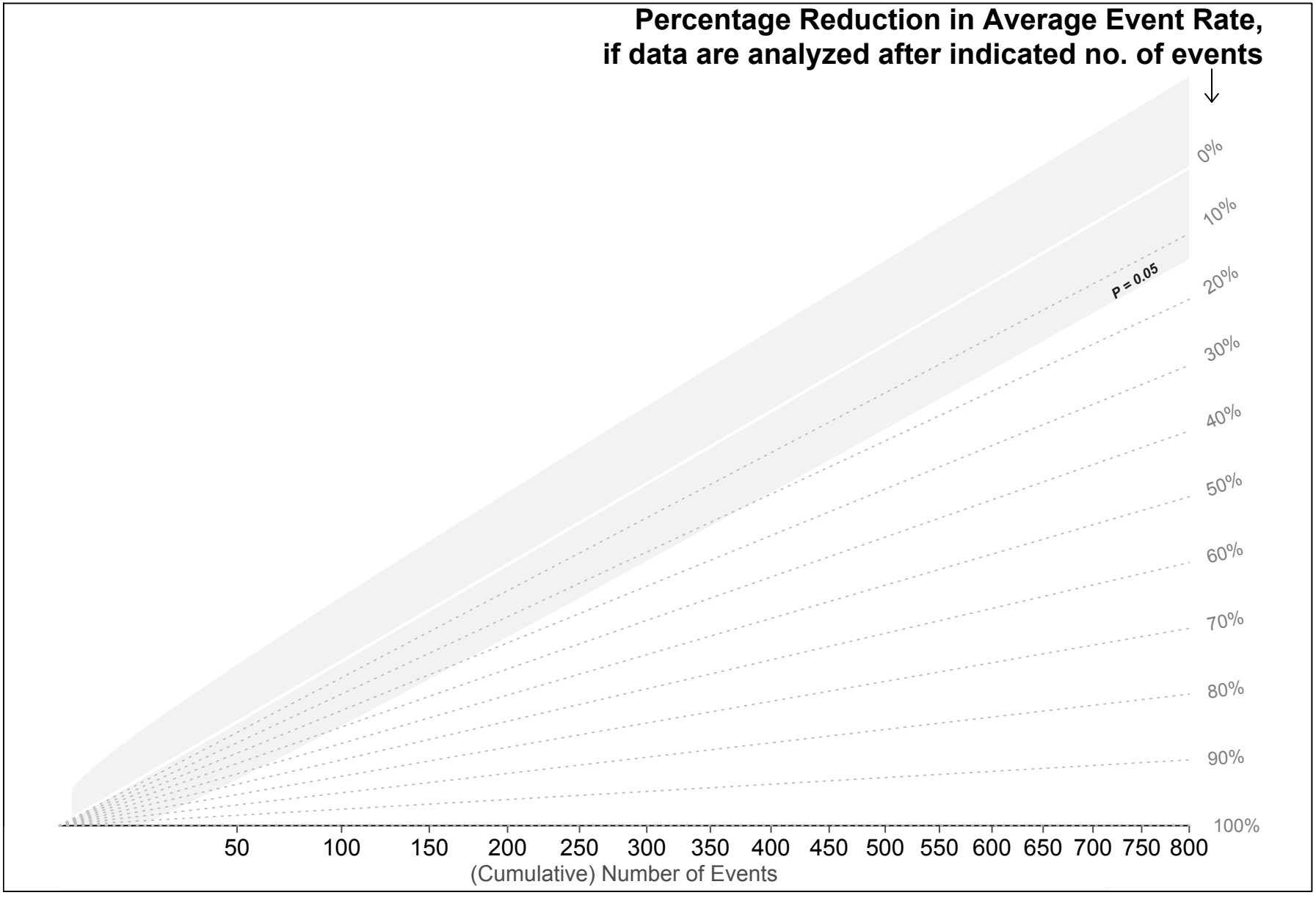
20% MORTALITY REDUCTION

A UNIVERSAL CONSTANT IN CANCER SCREENING TRIALS?

For many RCTs, single rate (hazard) ratio or risk difference is OK

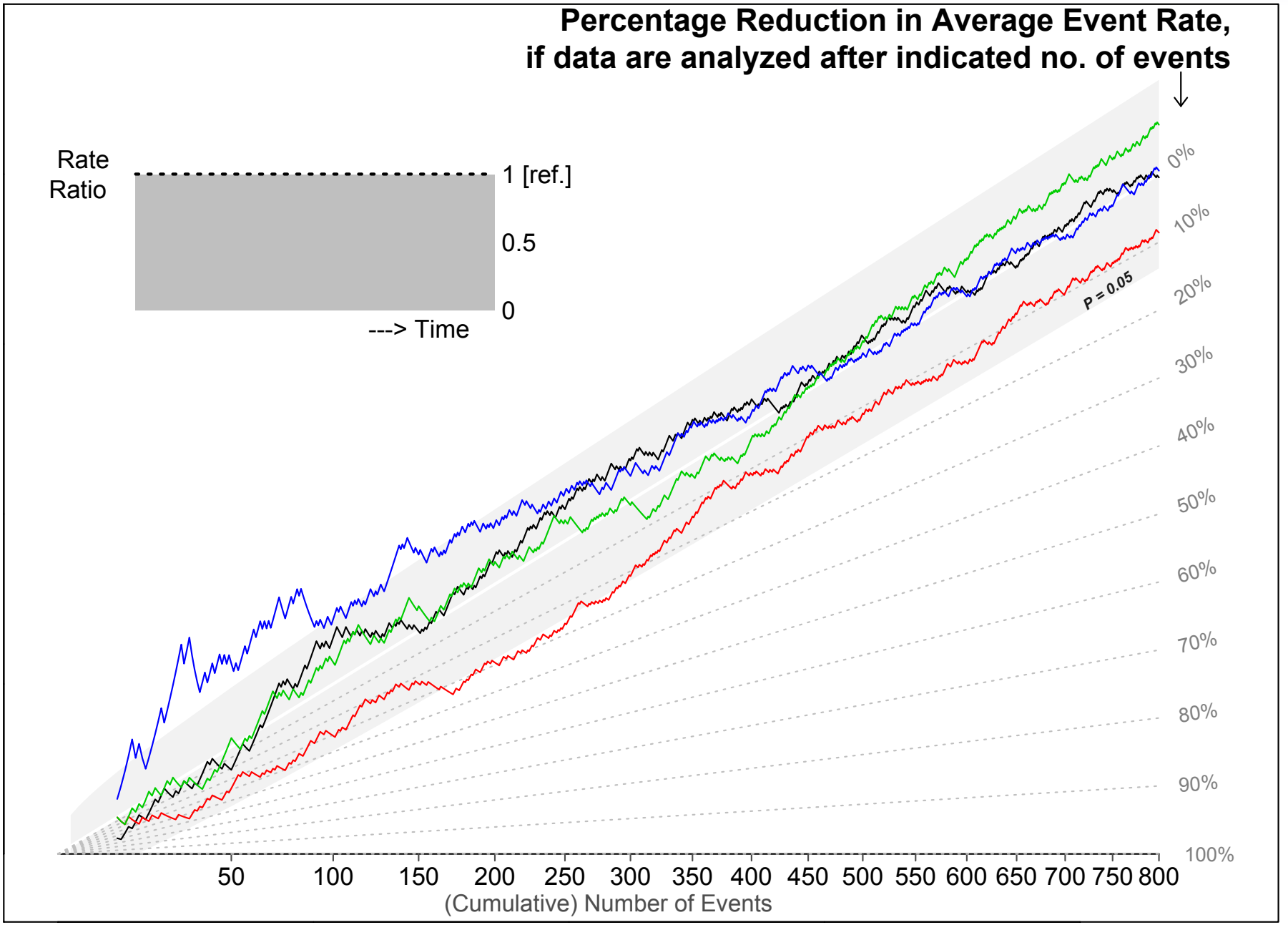
- A single (overall) Rate Reduction (i.e., single Rate Ratio), based on **all events** that have occurred (**regardless of when**) up to end of available follow-up time on each subject
- 'Regardless of when' implies **proportional hazards**, i.e., reduction is immediate & sustained (if need be, by continuing to take medications)
- **Numbers of events matter, but not their timing**:
  Q: how to have sufficient events for desired precision?
  more persons, less time? $\leftrightarrow$ more time, fewer persons?
- As amount of person time (number of events) increases, updated single Rate Reduction traces out a random walk

Reductions in ‘event rates’ as follow-up time unfolds

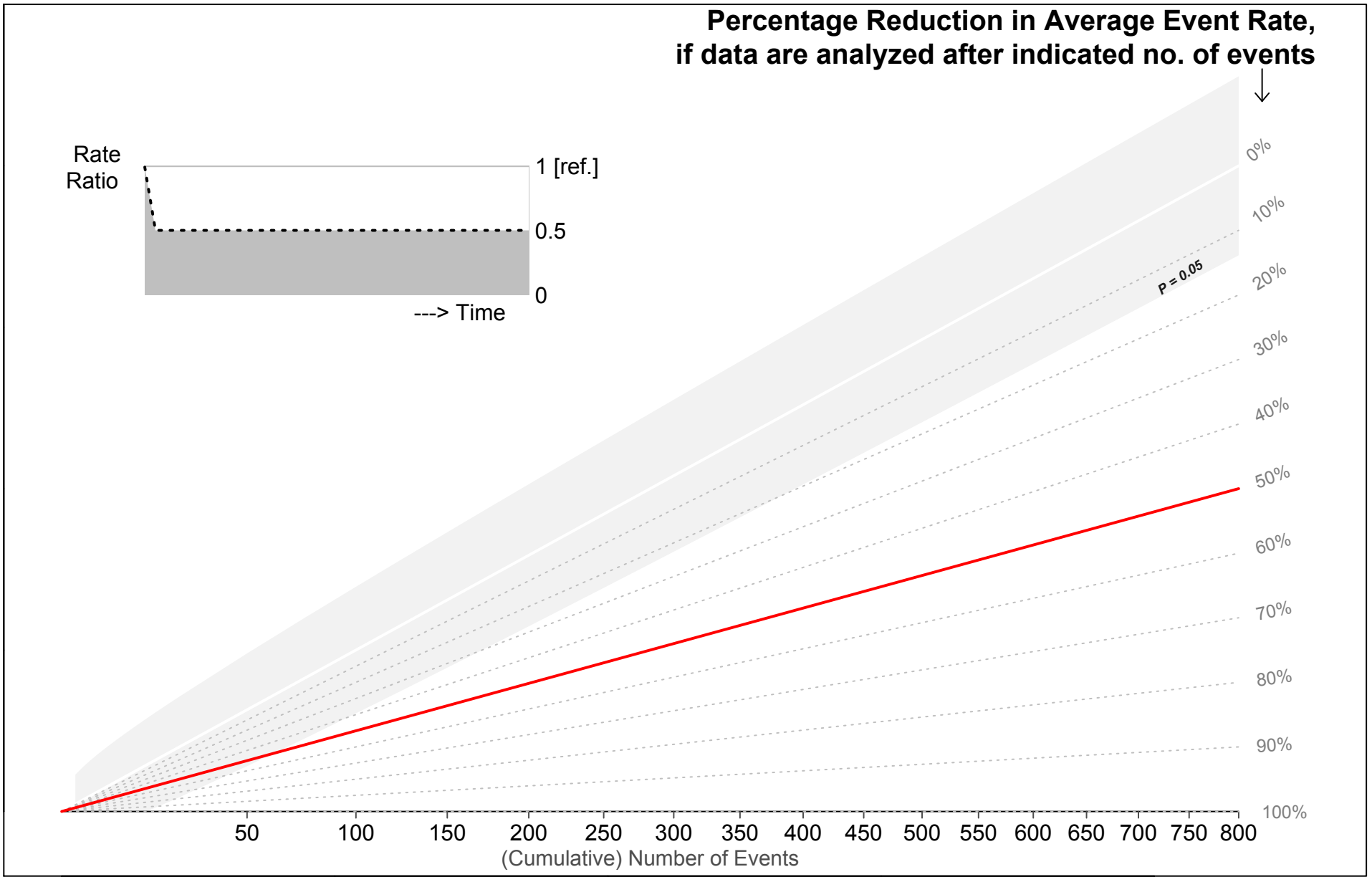


Examples of ‘prevention’ / ‘early detection’ studies

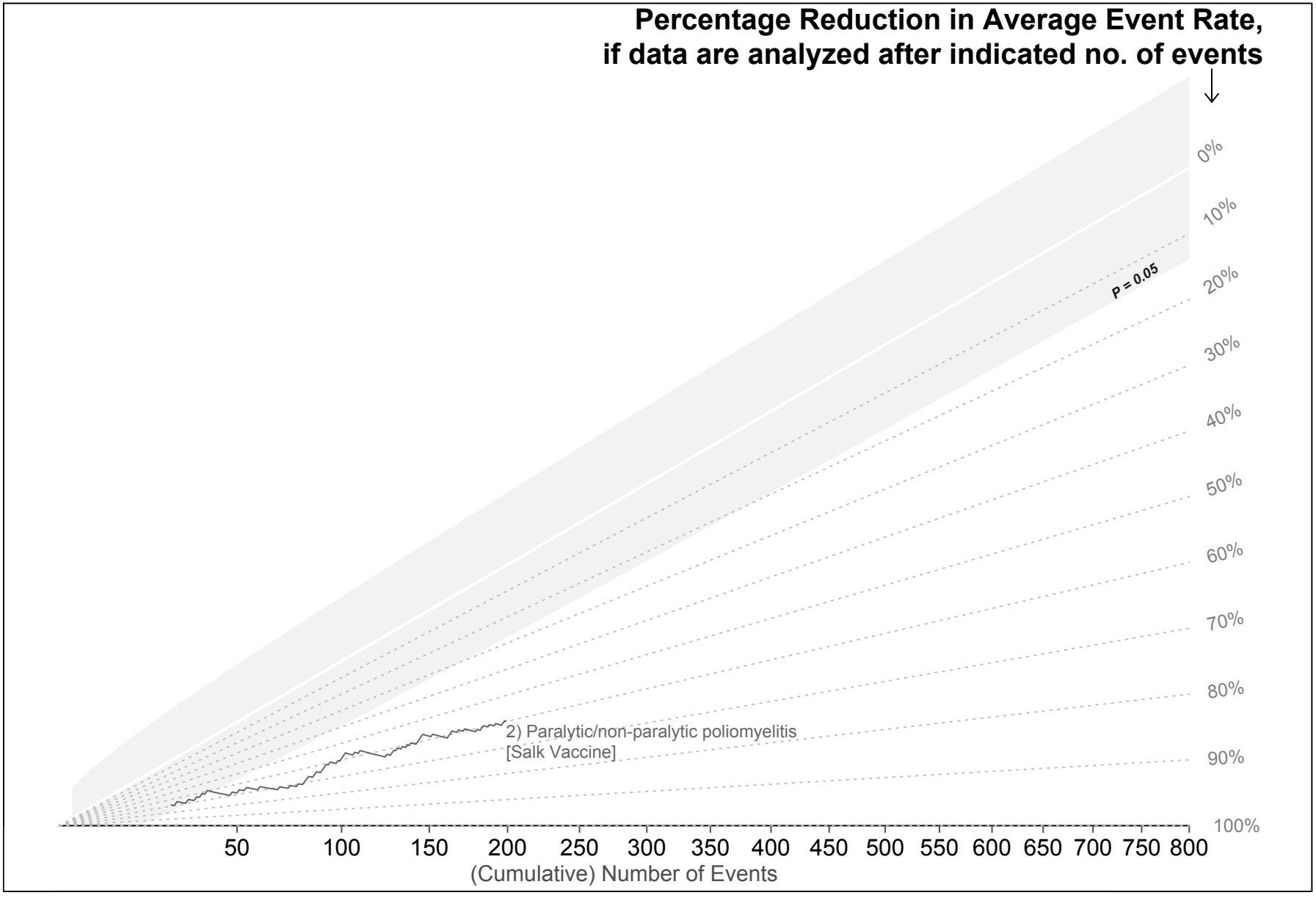
HIV: if ‘intervention’ ineffective



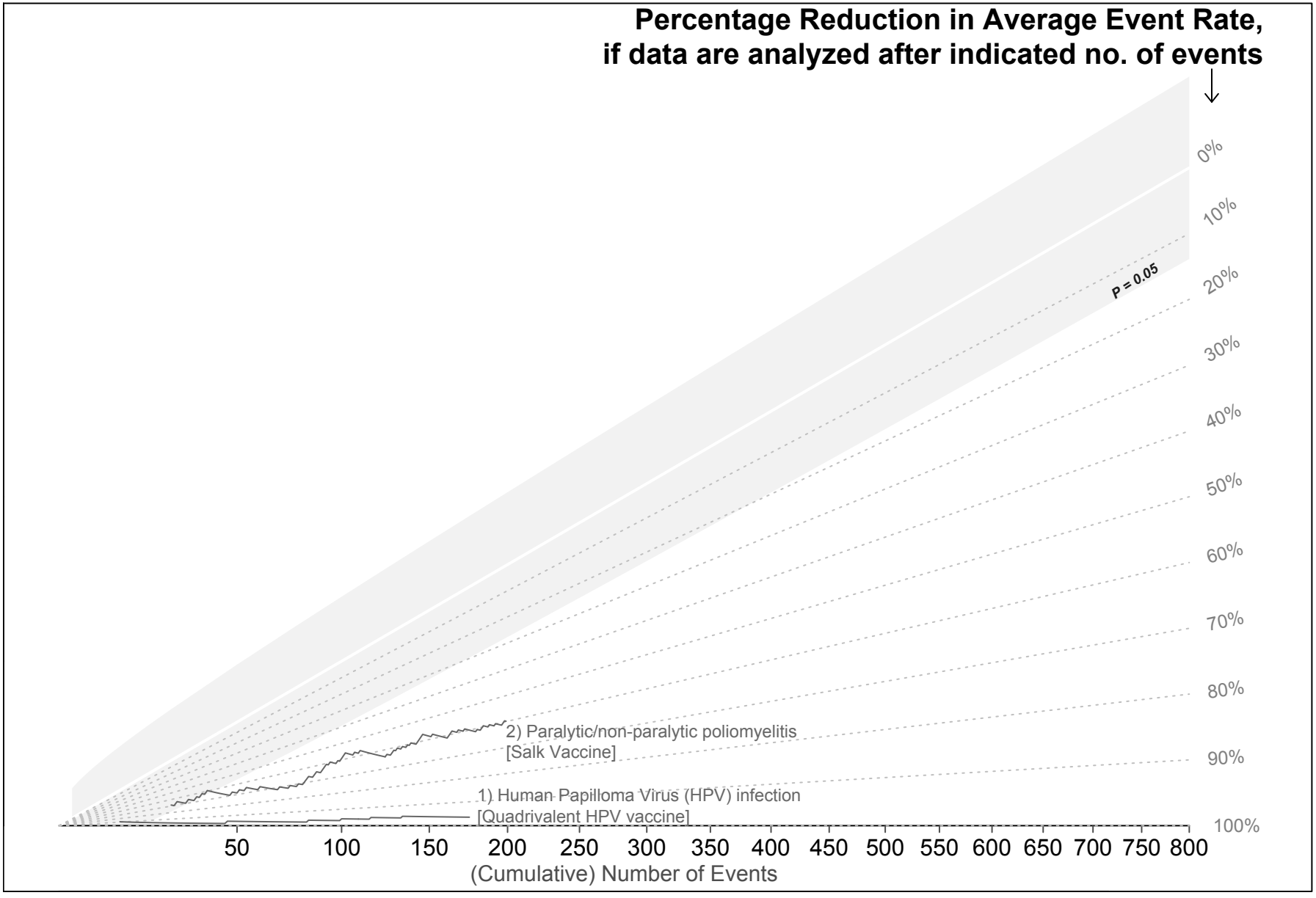
HIV: Adult circumcision



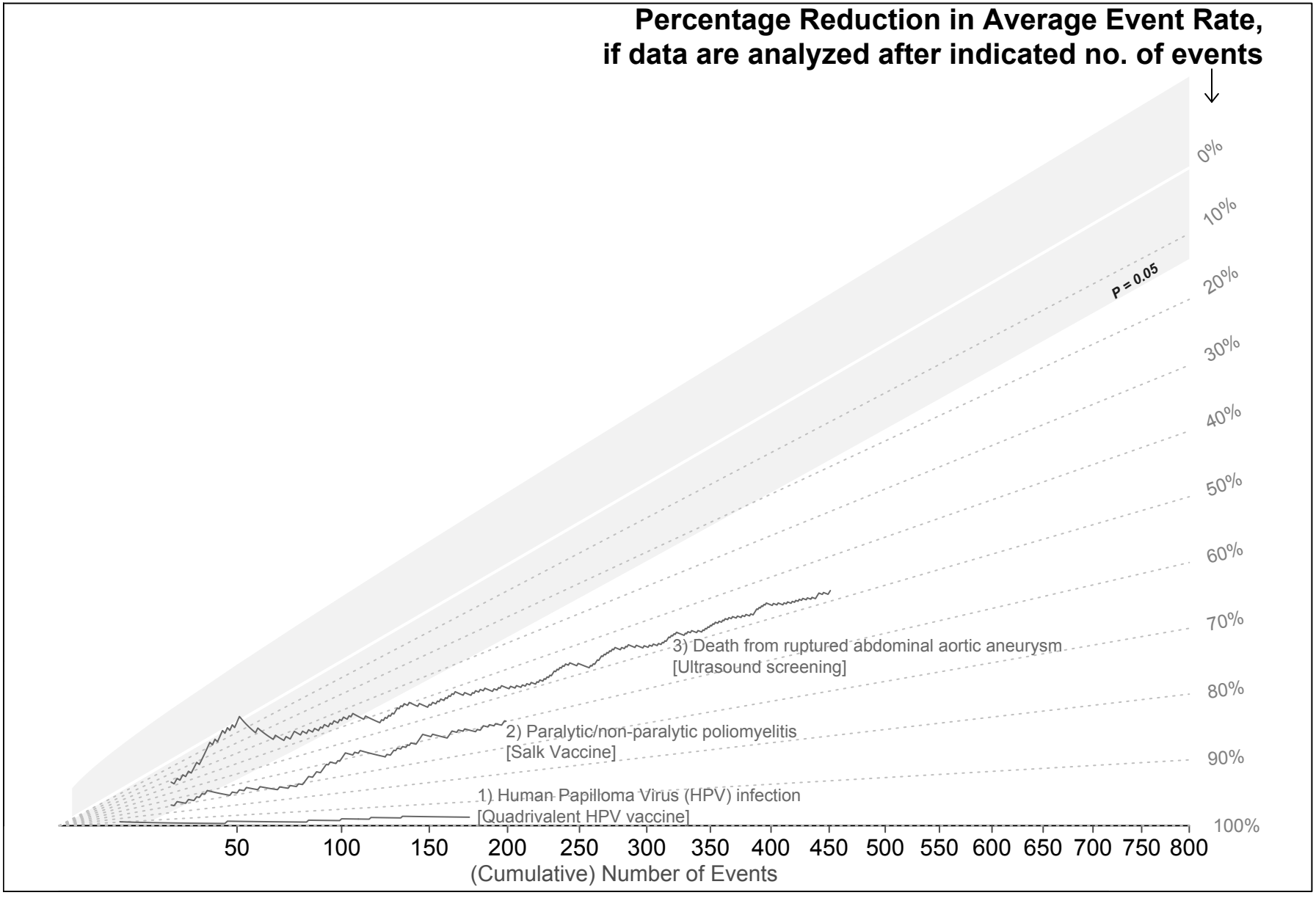
Paralytic or non-paralytic poliomyelitis: Salk Vaccine



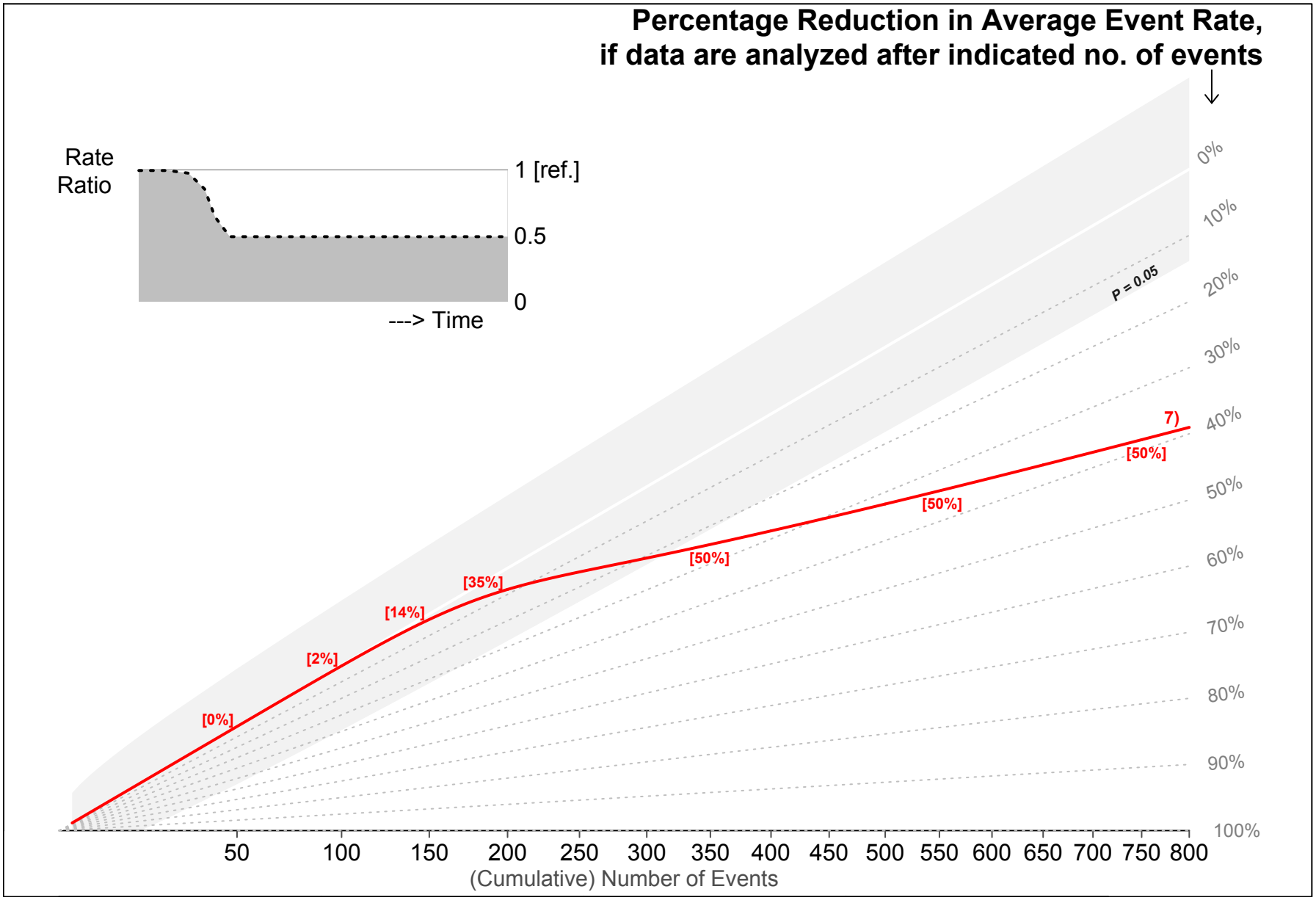
$HPV_{6,11,16,18}$ infection: Quadrivalent HPV Vaccine



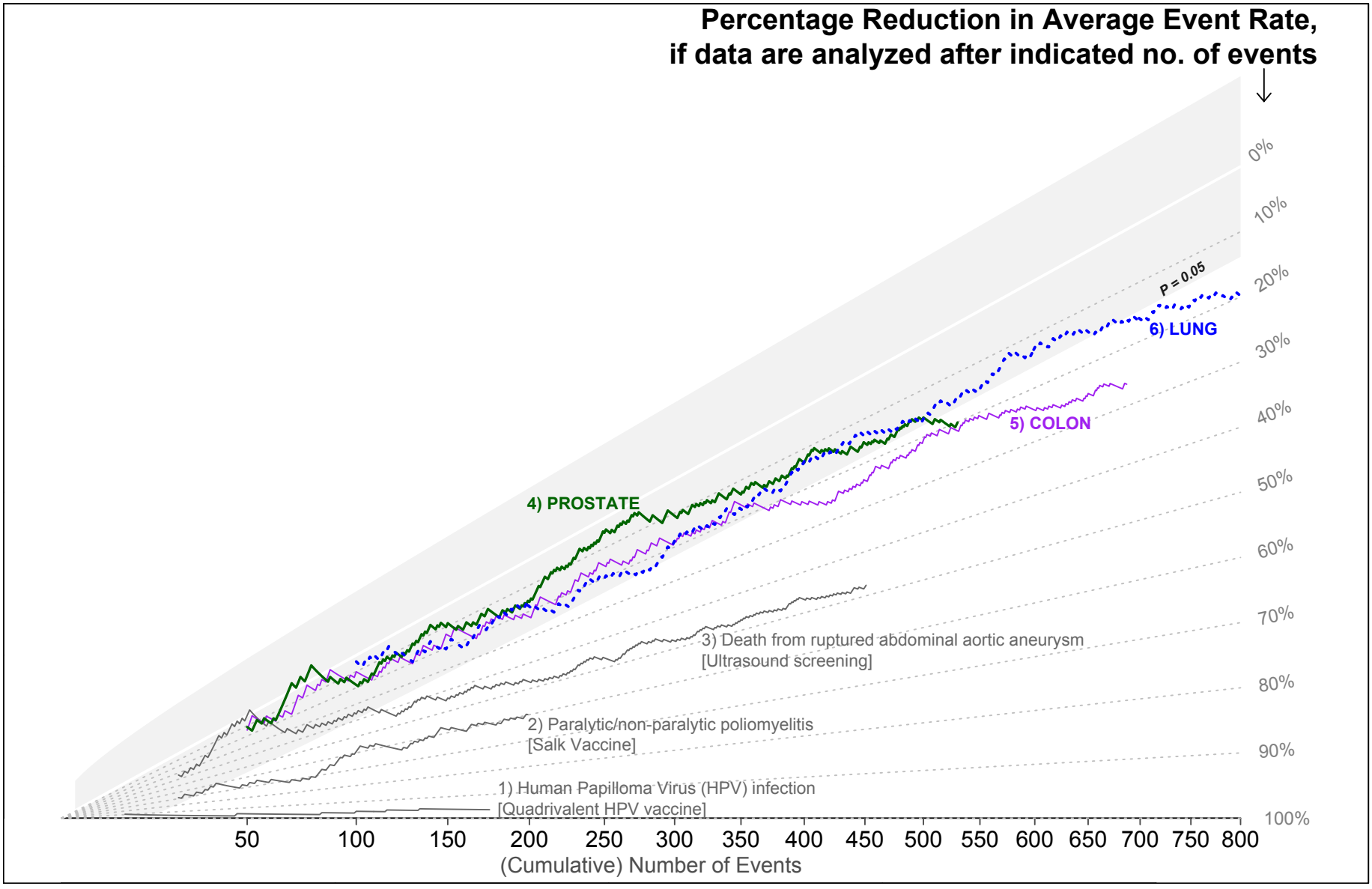
Death from ruptured abdominal aneurym: Ultrasound screening



Cancer Screening Trial - theoretical

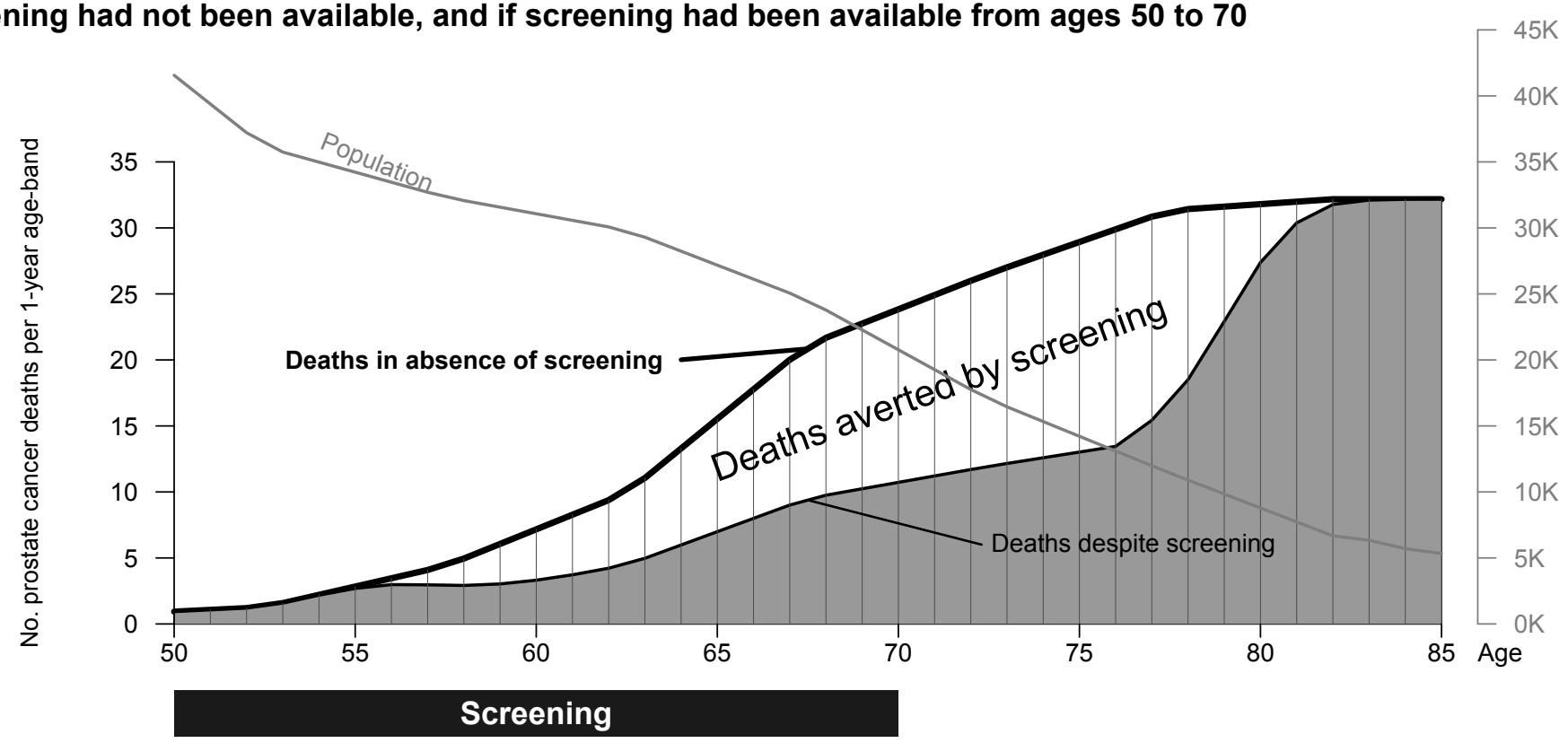


3 actual cancer screening trials



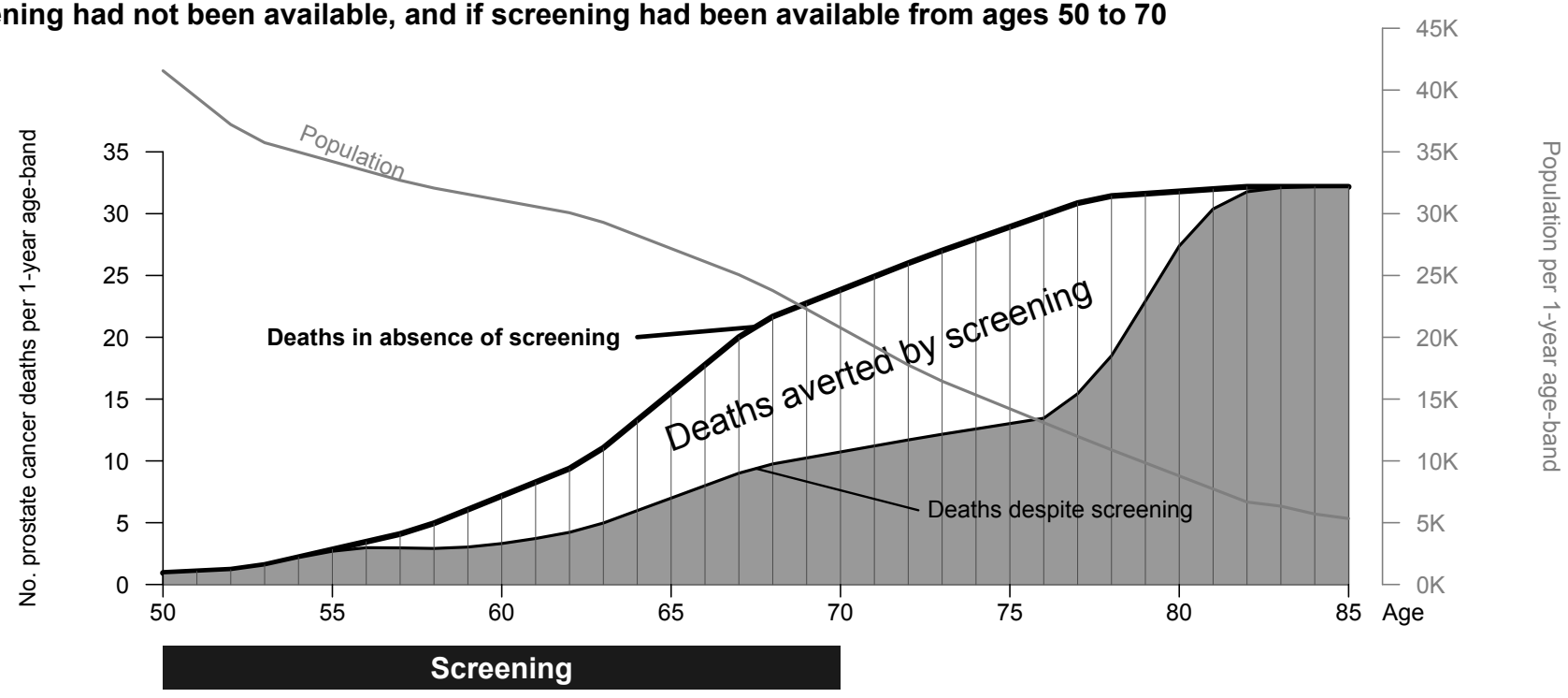
What payers would like to know about a PROGRAM

(a) Age-specific numbers of prostate cancer deaths in a steady state population with a given age-structure, if screening had not been available, and if screening had been available from ages 50 to 70

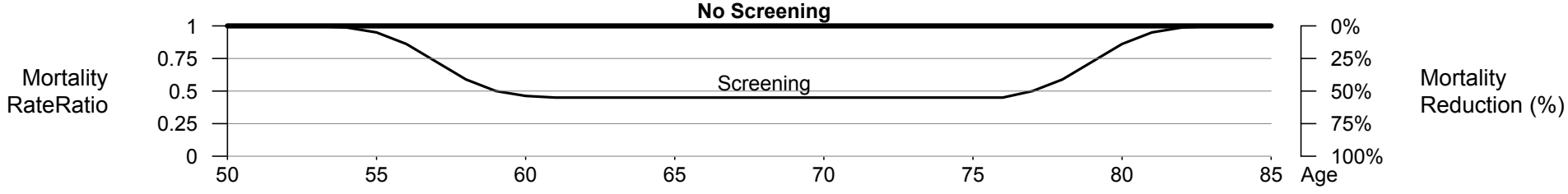


or (b) the Rate Ratio (or %Reduction) **Function** ...

(a) Age-specific numbers of prostate cancer deaths in a steady state population with a given age-structure, if screening had not been available, and if screening had been available from ages 50 to 70



(b) The corresponding age-specific prostate cancer mortality rate ratios



'*% Reduction function*' (bathtub shape)

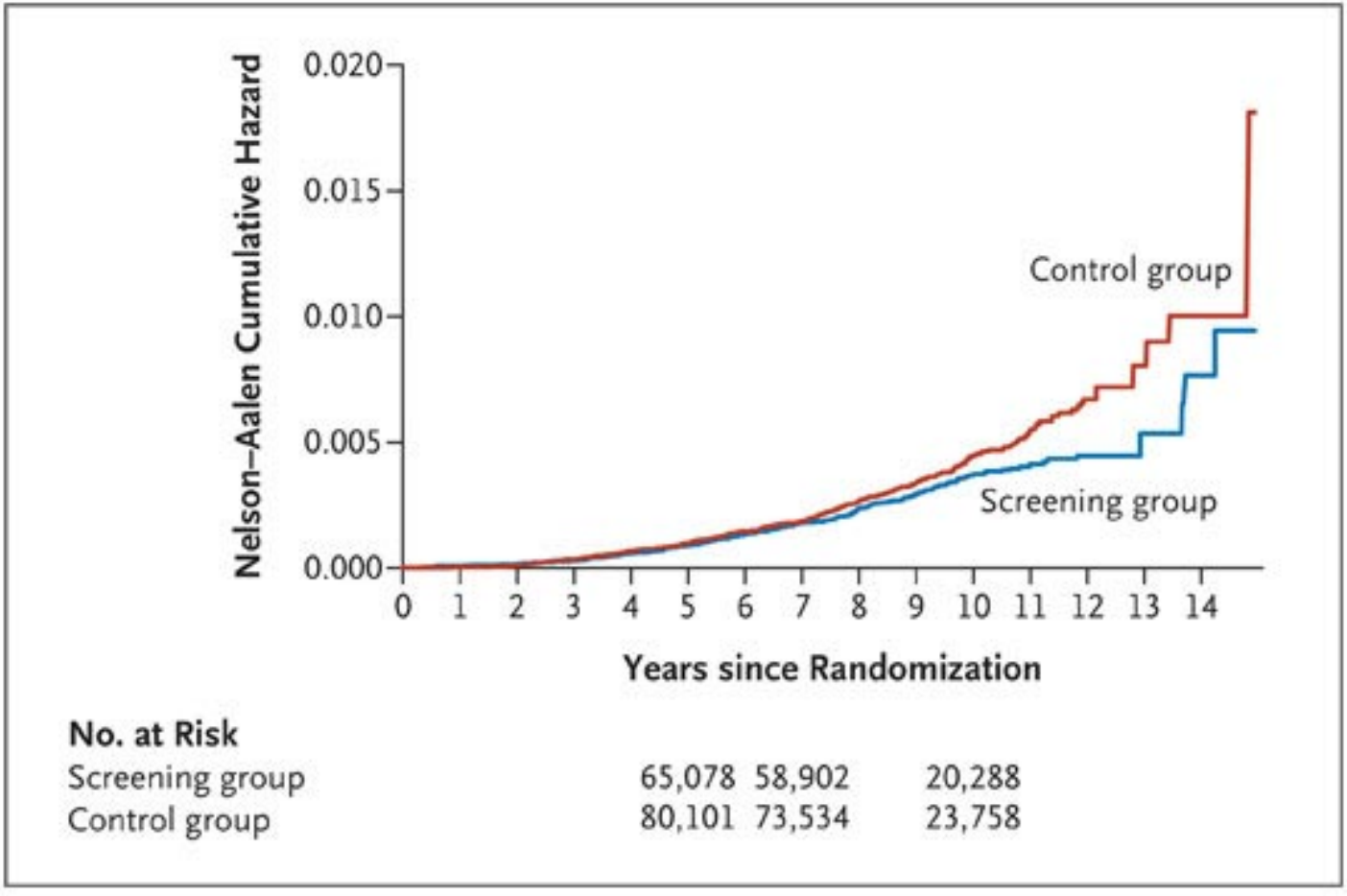
- The asymptote is the ultimate estimand
- It is determined by ...
  - number and spacing of rounds, and
  - the contribution of each round of screening
- From published trials, can one ..
  - estimate the % Reduction function ?
  - estimate contribution of each round ?
    (?? function shape if different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

PROSTATE CANCER

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

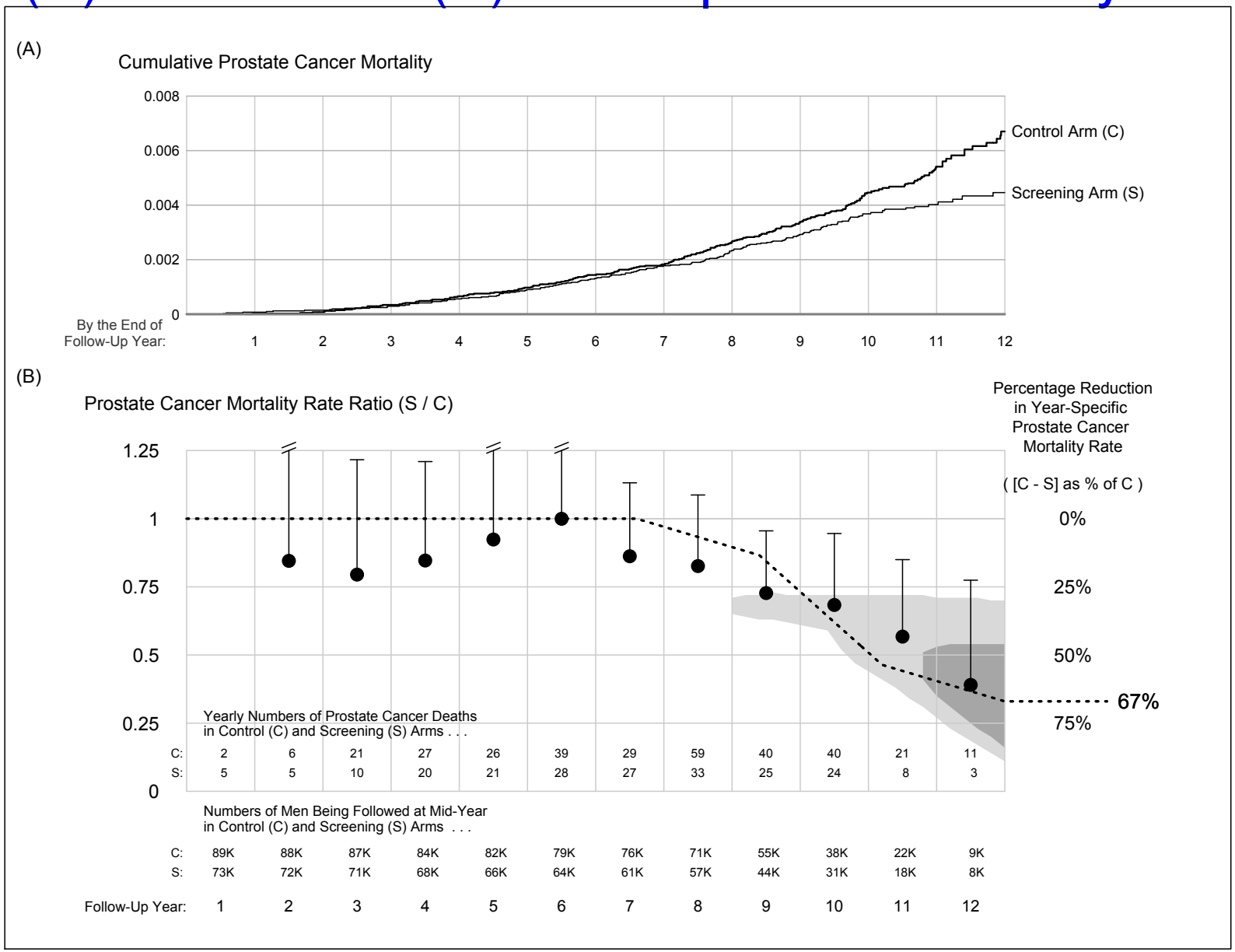
As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. (...) The adjusted **rate ratio** for death from prostate cancer in the screening group was **0.80** (95% CI, 0.65 to 0.98; P=0.04).

"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.

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.

Published **Online** August 7, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60525-0

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

*For the full study group see appendix

Department of Urology, Erasmus University Medical Center, Rotterdam, Netherlands (Prof F H Schröder MD, M J Roobol PhD, Prof C H Bangma MD); **Department of Urology, Sahlgrenska Academy at Goteborg University, Goteborg, Sweden** (Prof J Hugosson PhD, S Carlsson MD); **Department of Urology, Tampere University Hospital, Tampere, Finland** (Prof T L J Tammela MD); **School of Medicine, University of Tampere, Tampere, Finland** (Prof T L J Tammela); **Unit of Clinical and Descriptive Epidemiology, ISPO, Florence, Italy** (M Zappa MD, D Puliti MSc); **Provinciaal Instituut voor Hygiene, Antwerp, Belgium**

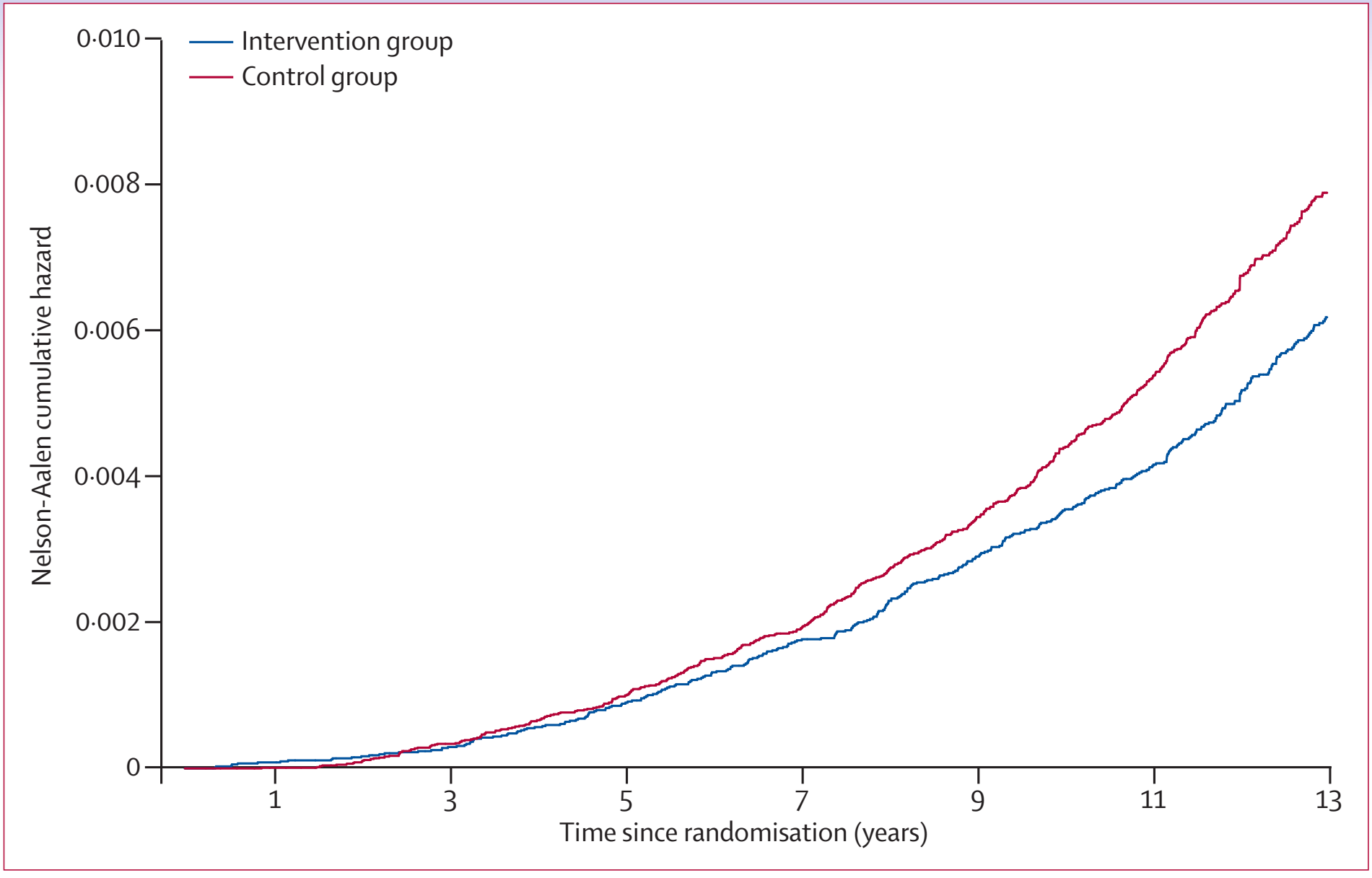


Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

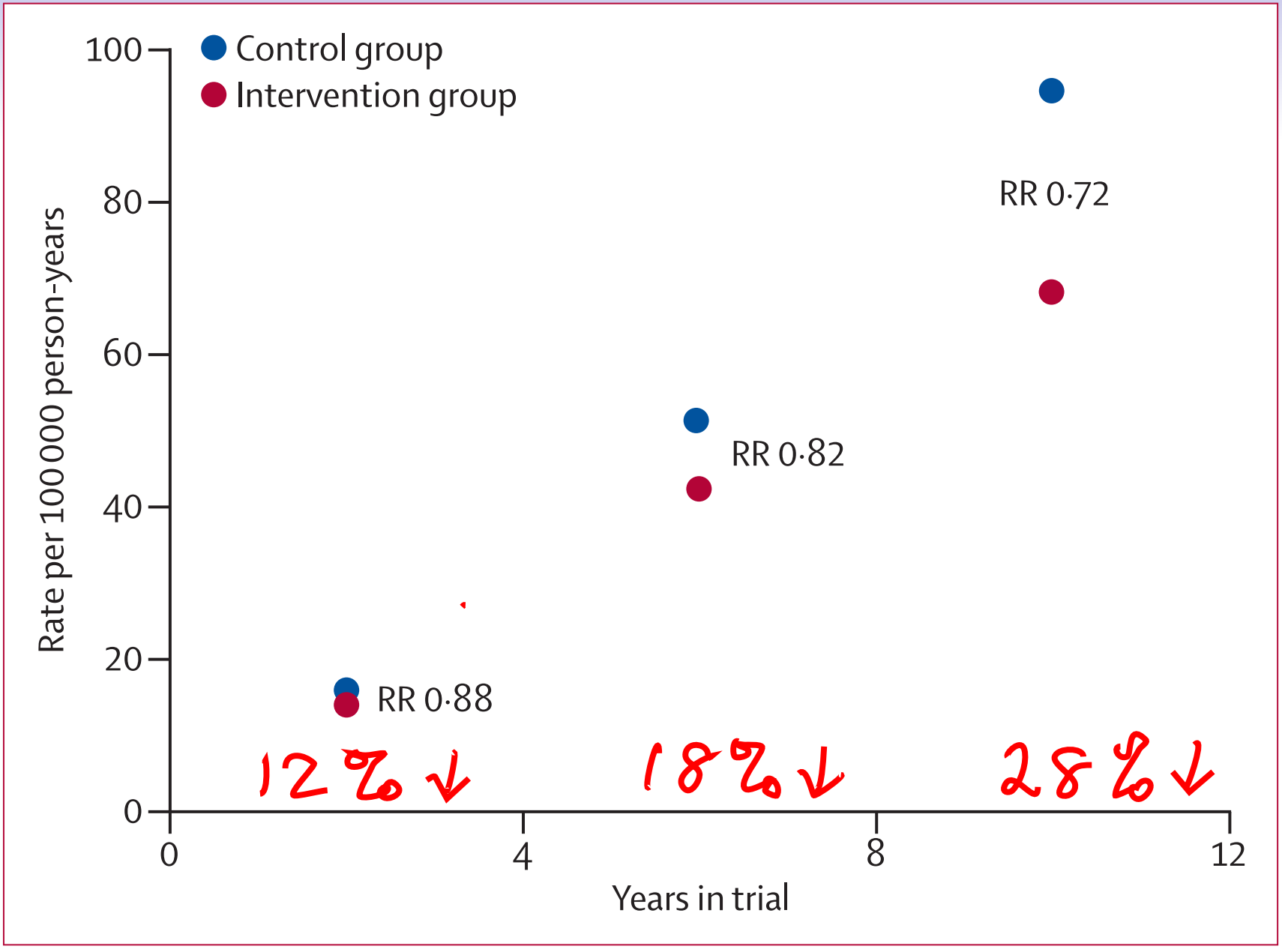


Figure 3: **Nelson-Aalen estimates of cumulative prostate cancer in both groups by 4-year periods (all centres, excluding France)**

BREAST CANCER

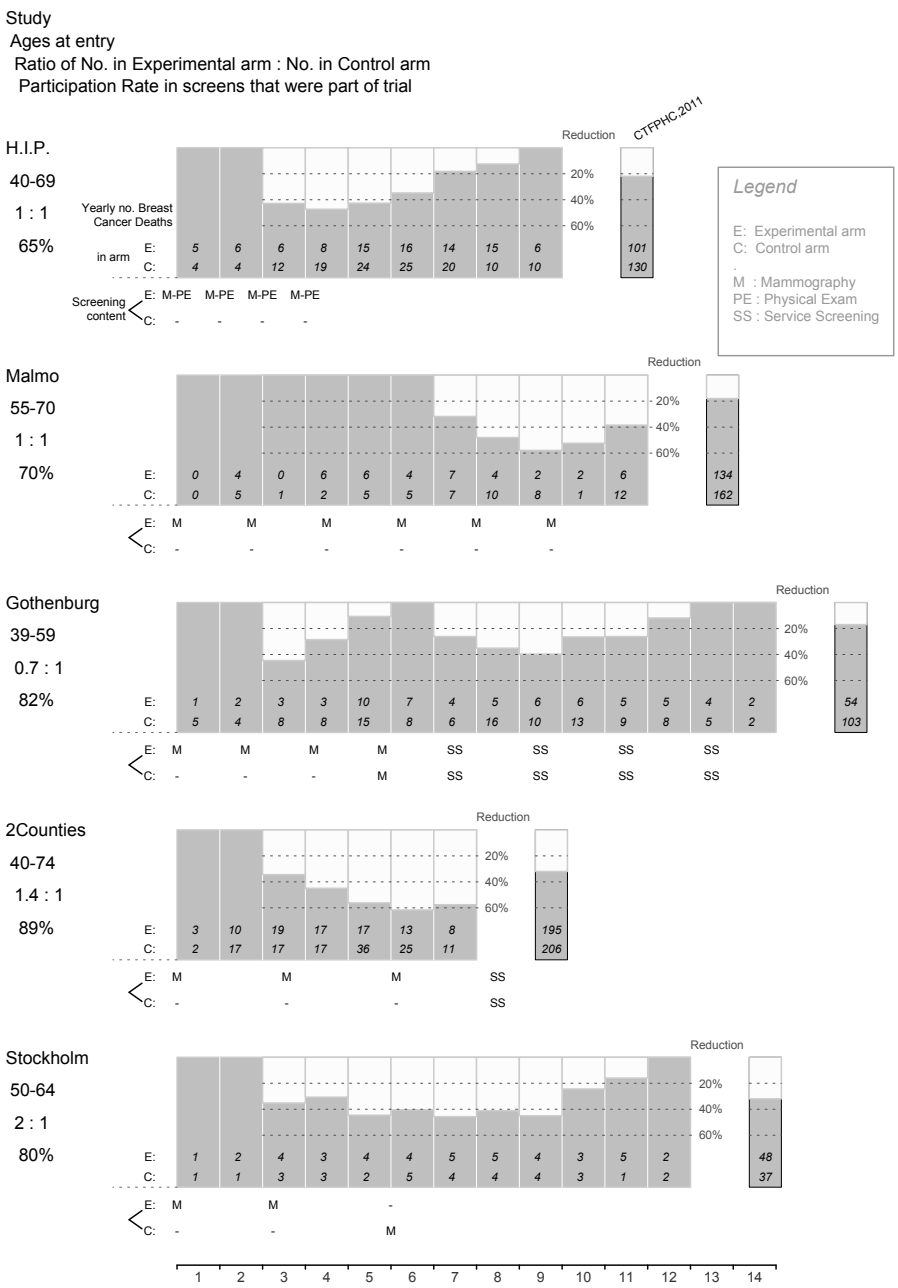
EVERY TRIAL & META-ANALYSIS:

and (nejm2010) REPORT on NORWAY NATIONAL SCREENING PROGRAM:

REDUCTION UNDER-ESTIMATED

- Miettinen et al., *Lancet* 2002.
- Hanley, *Epidemiologic Reviews* 2011.
- Hanley JA, Z Liu Z, McGregor M. The [ratio of] benefits [to] harms of breast cancer screening. Letter re the Report The Independent UK Panel on Breast Cancer Screening (*Lancet* Nov 17, 2012)
- Hanley JA, McGregor M, Liu Z, Strumpf EC, Dendukuri N. "Measuring the Mortality Impact of Breast Cancer Screening". *Can J Public Health. 2013 Sep 19;104(7):e437-42.* (Response to 2011 Canadian Task Force on Preventive Health Care)

Observed breast cancer mortality deficits in 5 Mammography Trials



- Year-specific data: trials used by Task Force.
- 20 years of screening, 50–69, would be followed by 20 years (55–74) in which the breast cancer mortality reduction in these years would be $\geq$ 40%, with smaller deficits in other years.
- Fewer than 200 women would need to participate in such a program in order to avert a breast cancer death in the age range 50-80.

Corresponding Task Force estimates:

Mortality reduction: 21% ;
Number of women: 720.

COLON CANCER

FOBT screening for colon cancer – Minnesota Trial 1976-2008

ORIGINAL ARTICLE

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.

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

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.

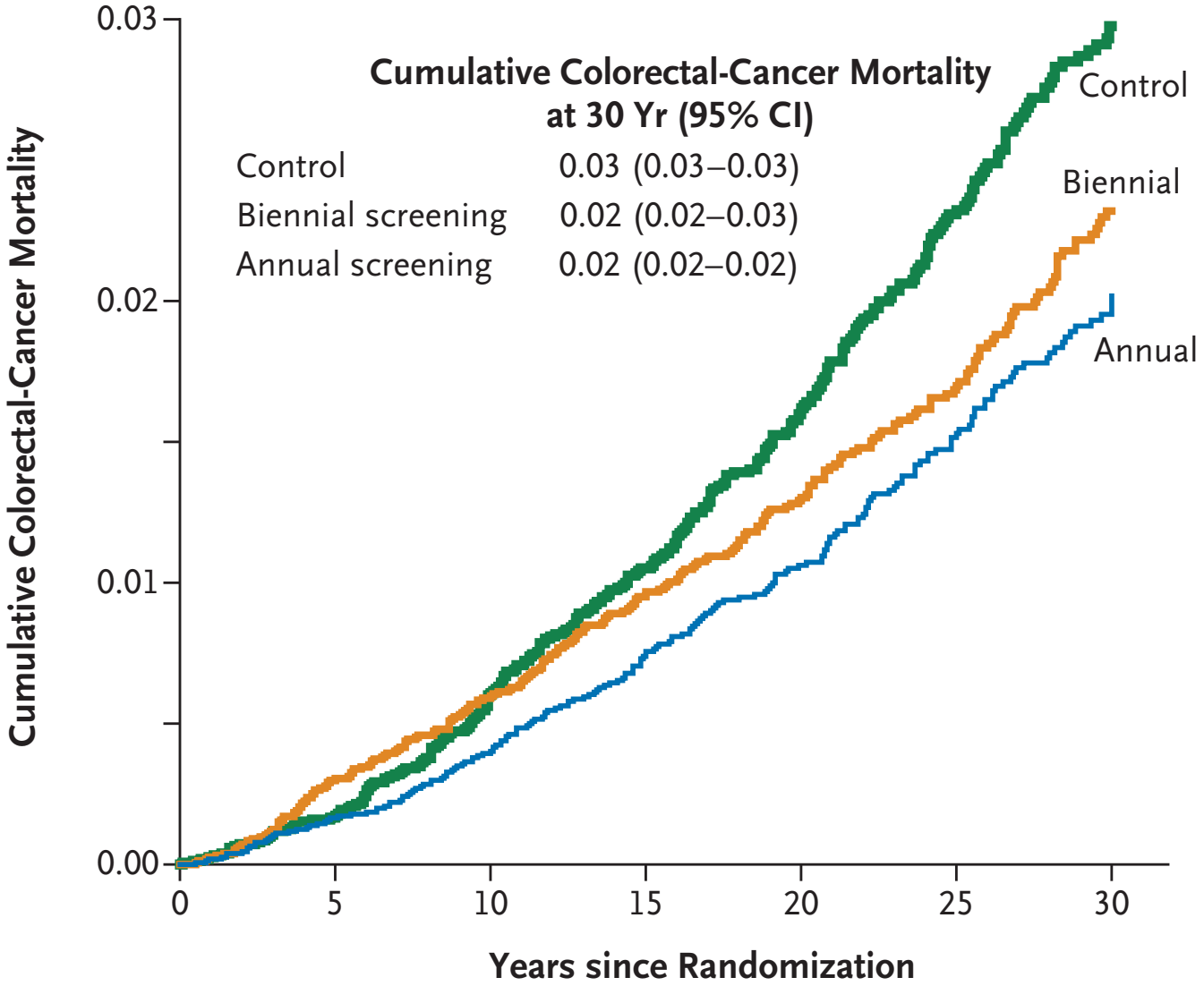
FOBT screening for colon cancer – Minnesota Trial 1976-2008

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

Radiologists as Statisticians

Figure 1. *Rep. Alexander Pirnie, R-NY, draws the first capsule in the lottery drawing held on Dec. 1, 1969. The capsule contained the date. Sept. 14.*

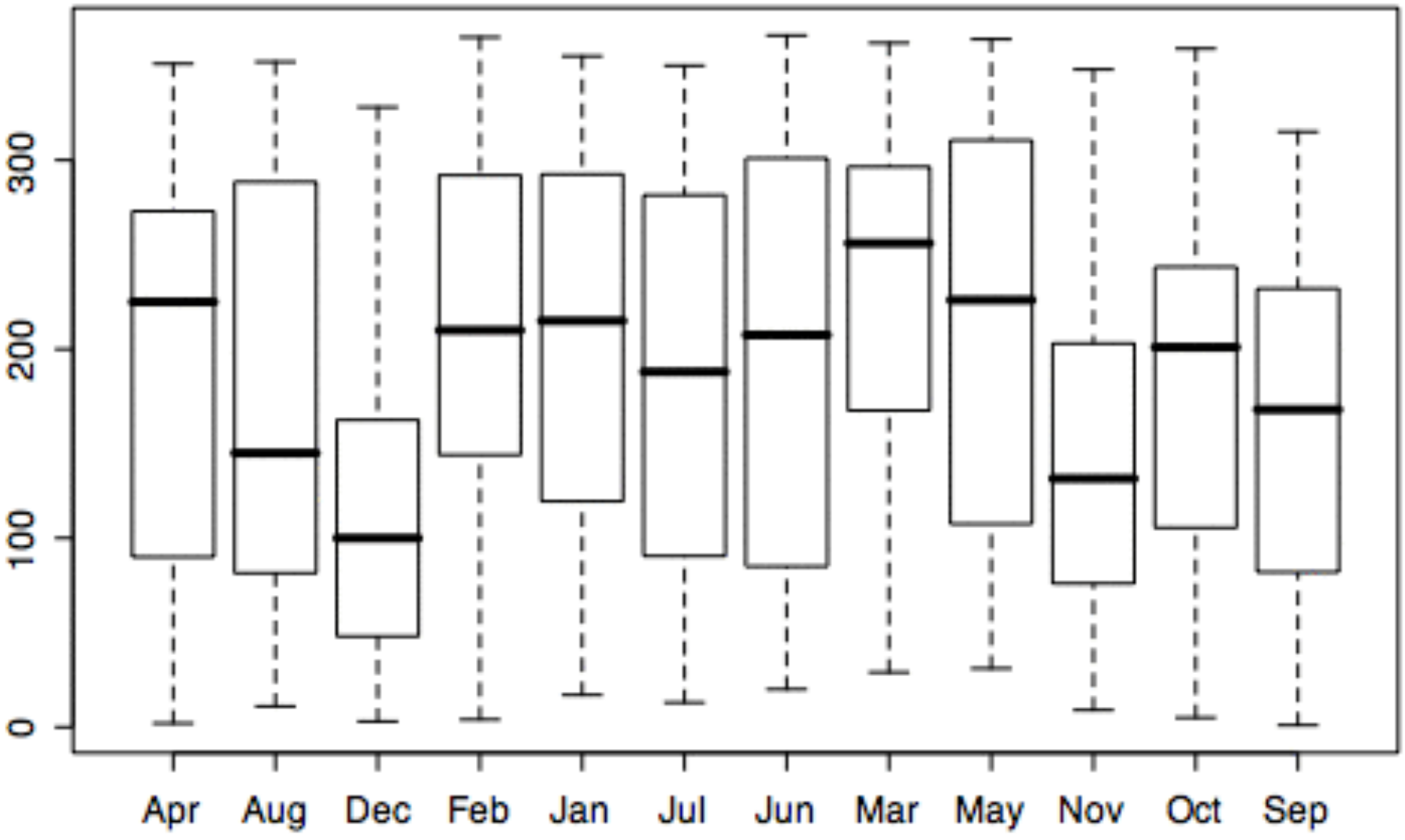


Figure 4. Side-by-side boxplots of draft numbers for each month.

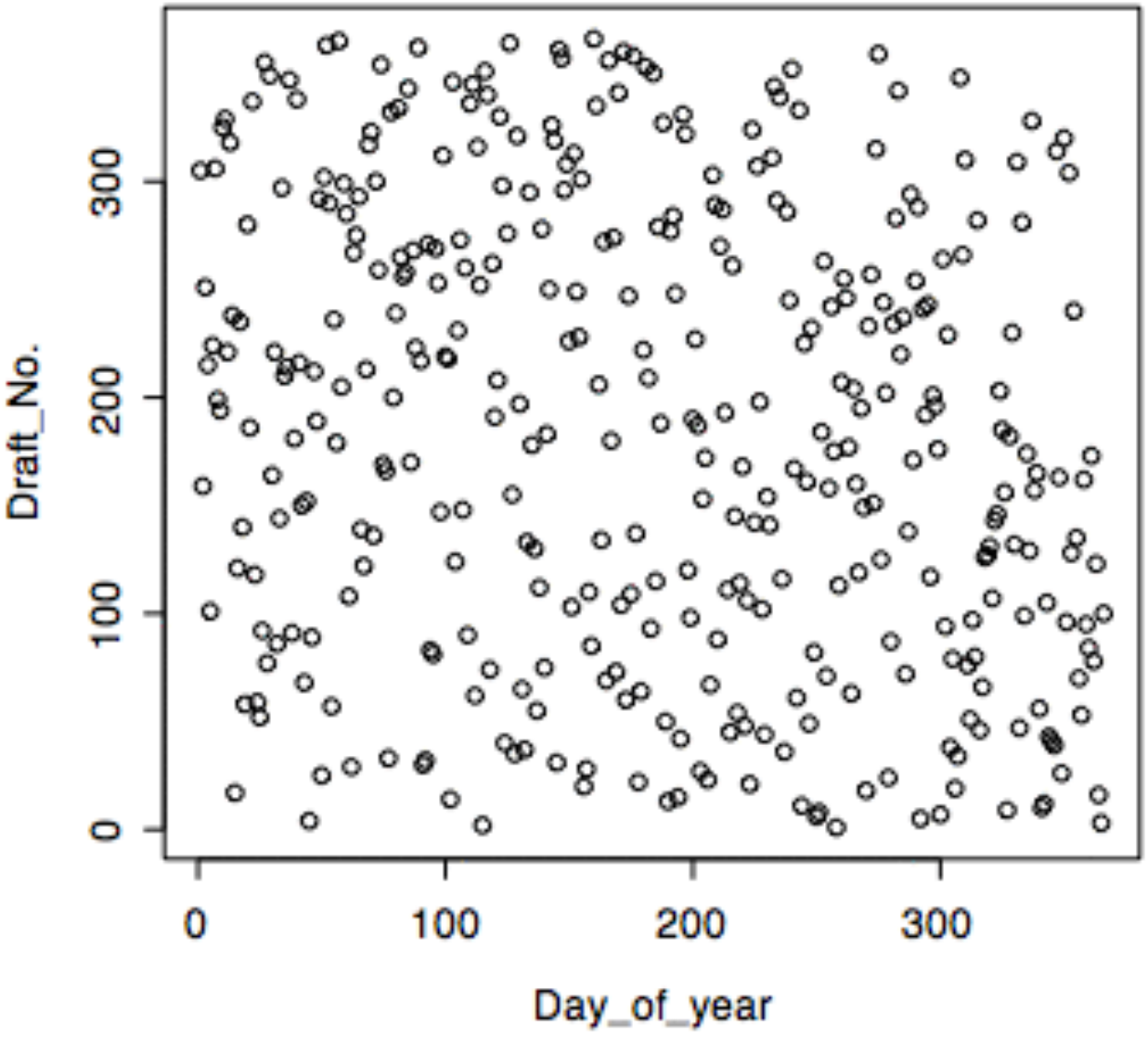


Figure 2. A scatterplot of ***Draft_No.*** *versus* ***Day_of_year****.*

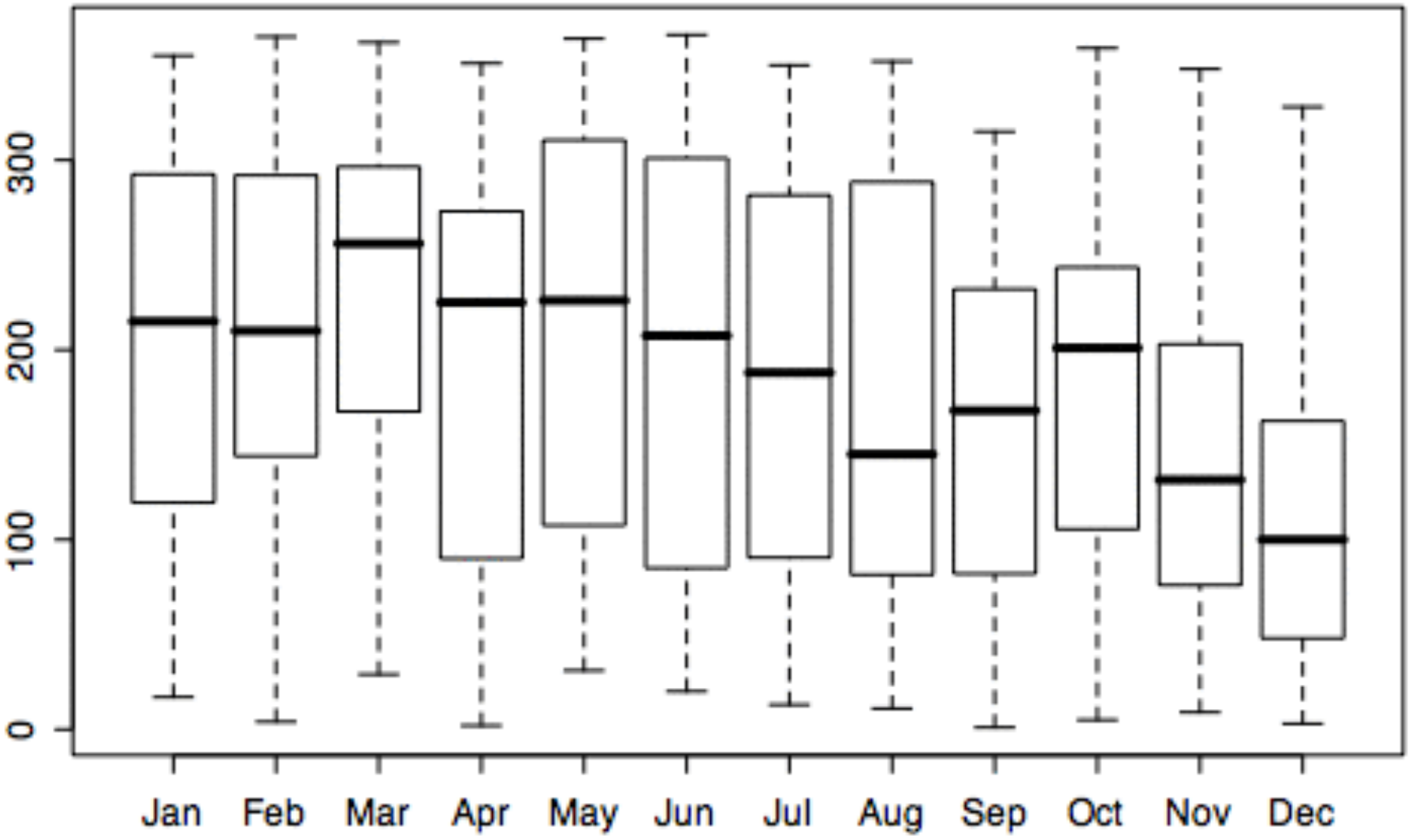
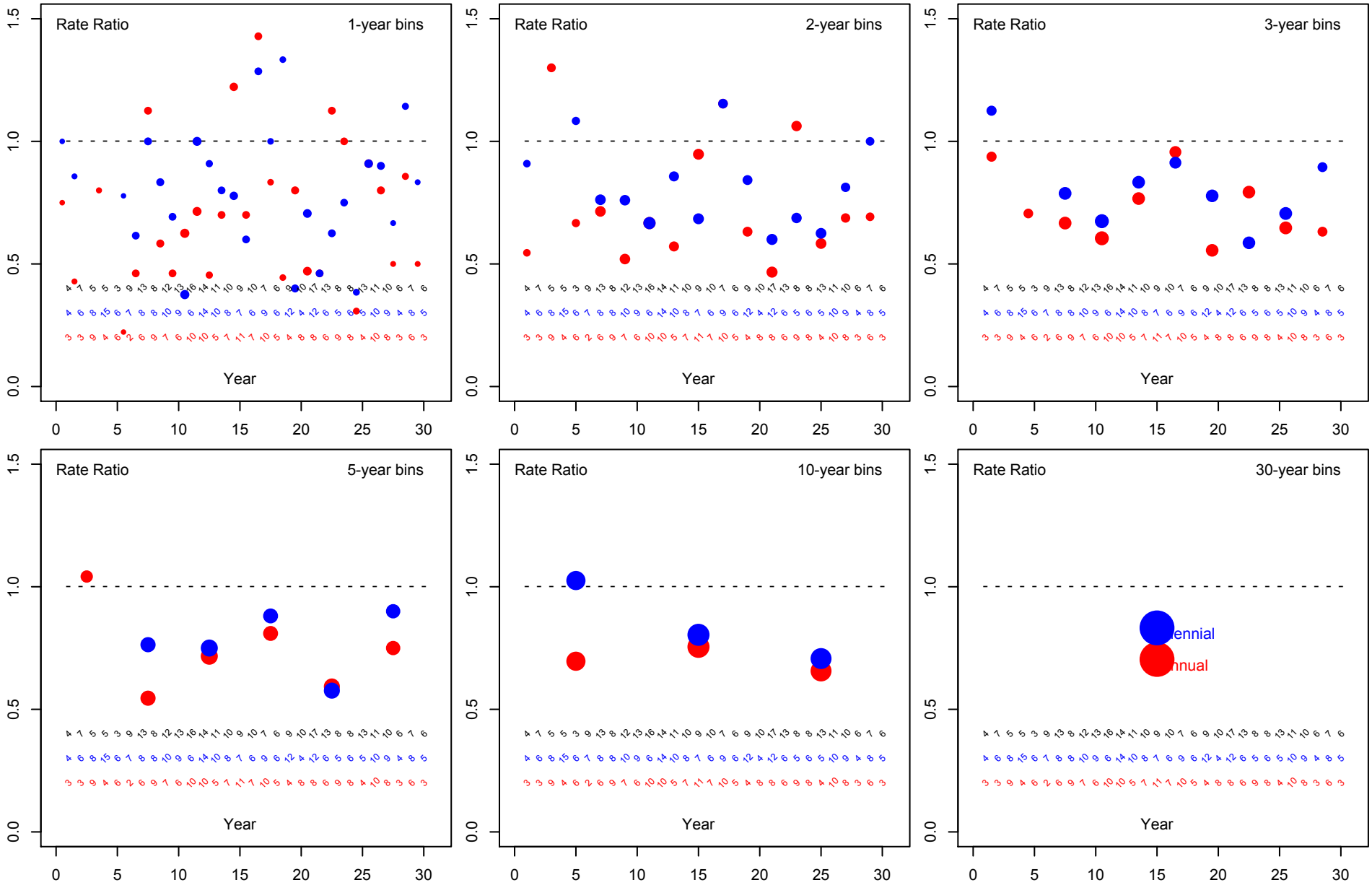
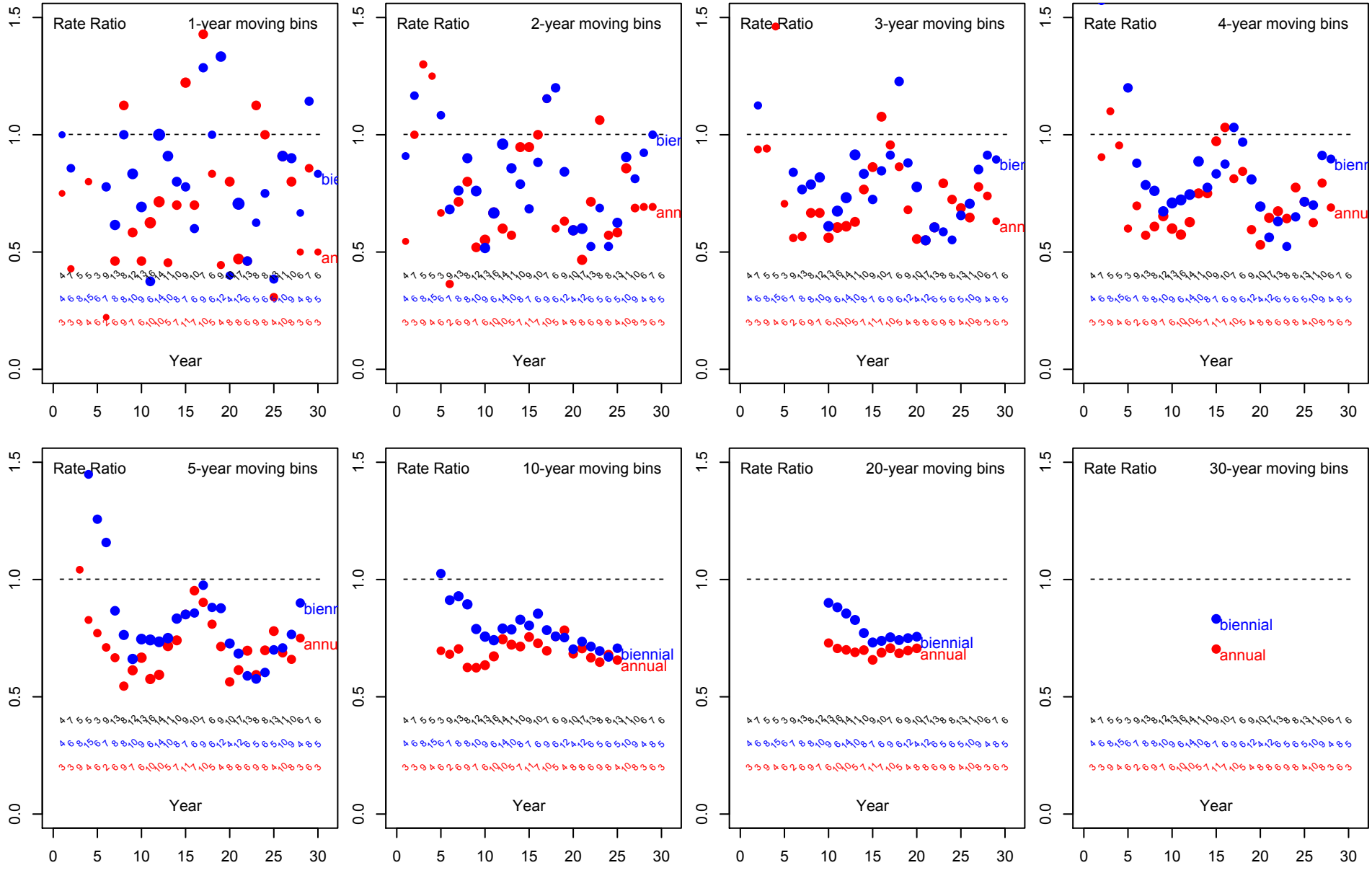


Figure 6. Side-by-side boxplots of draft numbers sorted by month.

Time-**split** versus time-**lumped** Rate Ratios

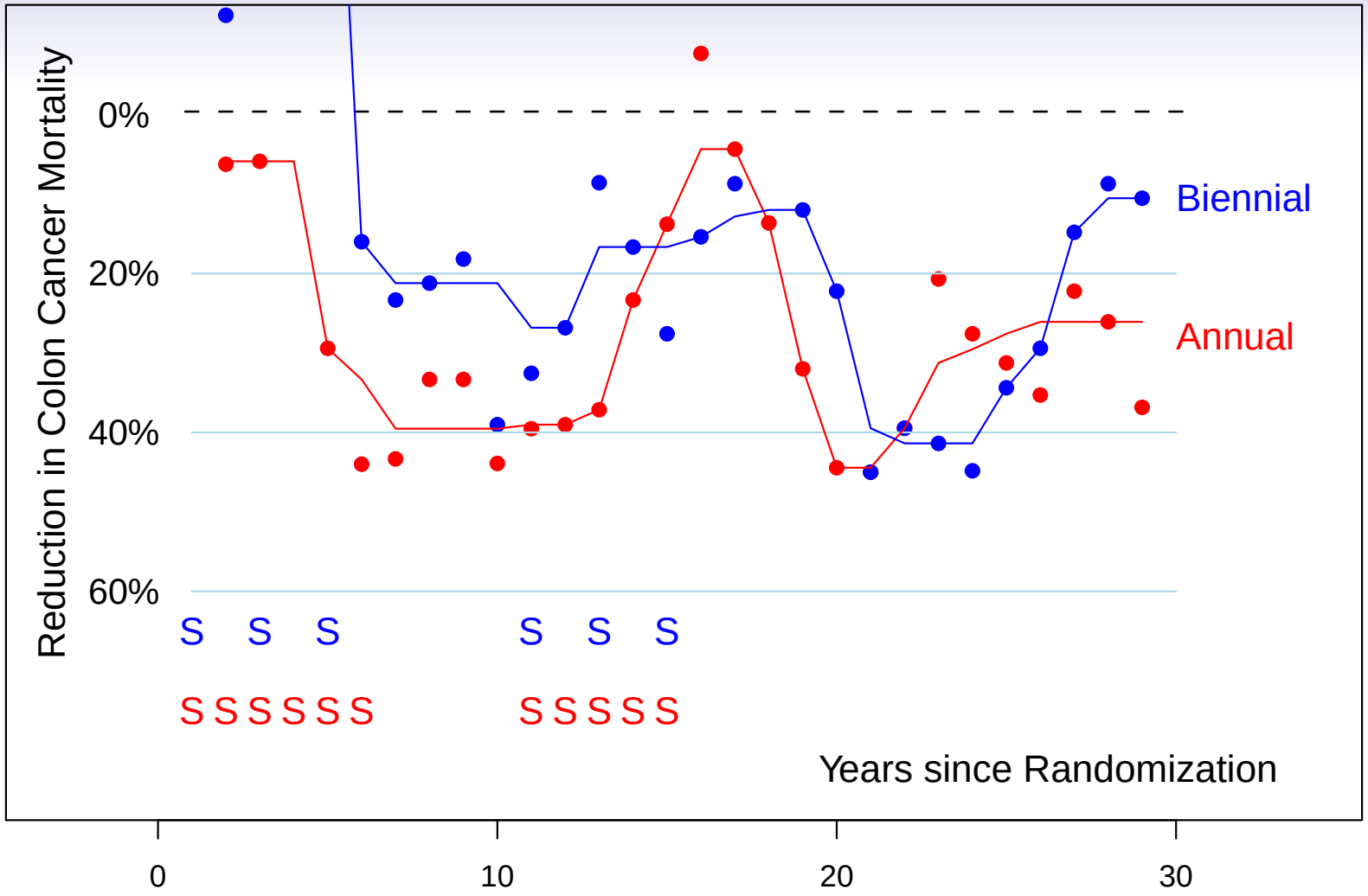


Time-**split** versus time-**lumped** Rate Ratios



Dear Editor

- Shaukat et al. report reductions of 32% and 22% in colon cancer mortality in those offered 11 annual and 6 biennial FOB screens, respectively. These reductions were achieved despite a 4-year hiatus in screening, and averaging over all 30-years of follow-up.
- What would the reductions have been without such an interruption? To answer this, we extracted the yearly numbers of deaths from the published Figure 1, and instead calculated yearly mortality reductions. Because of the unusual schedule, the resulting reduction curve has a 'W' shape, showing the lagged responses to the two phases of screening: after a delay of some years, mortality reductions reached a nadir of around 40% before reverting to what they would be in the absence of screening; this pattern is repeated when screening is resumed.
- Without the (funding related) hiatus, the reductions would have been around 40% for each year affected, which is substantially larger than those estimated.

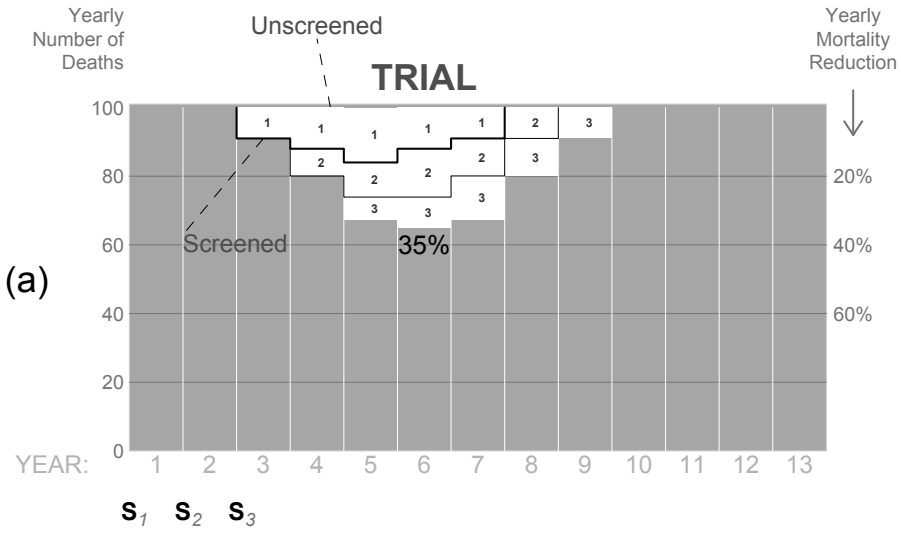


Yearly reductions in colon cancer mortality in two screening arms. Each dot is based on number of deaths in a three year moving window; smooth curves were fitted though them. Because the hiatus was in calendar-time rather than follow-up time, and entries were staggered, the timing of the screens (each denoted by an ‘S’) is only approximate.

From **Trial** to **Program**

STATISTICAL MODEL

Convolution of reductions produced by **individual** rounds



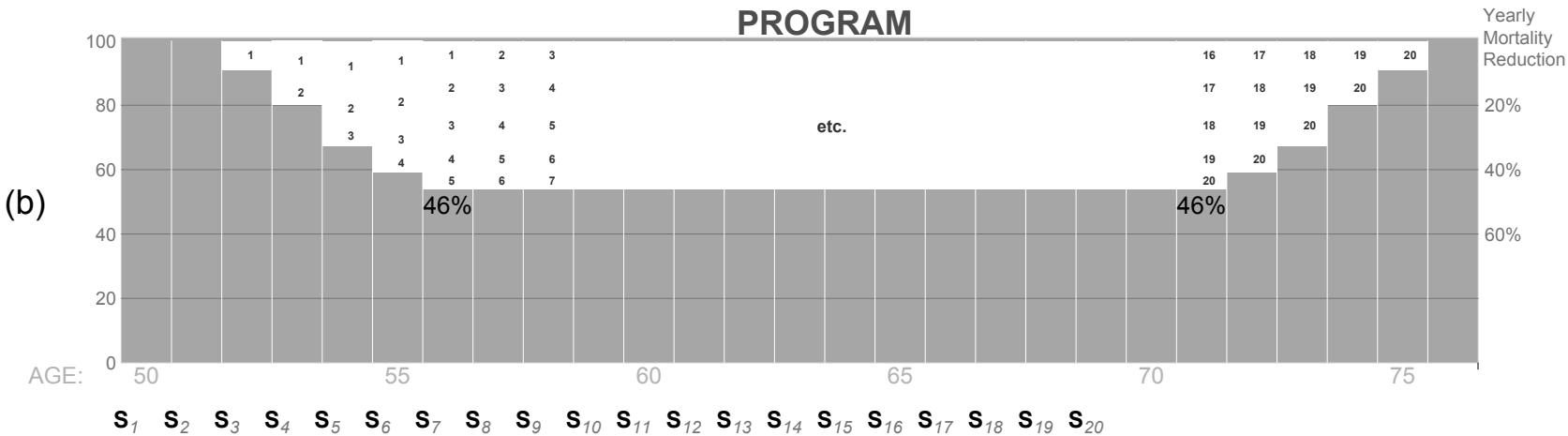
Remarks

If one round of screening reduces mortality in each of 5 future years, then in a trial, 3 rounds of screening -- S1, S2 and S3 -- would produce 3 'waves' of mortality reductions ('1', '2', '3'), each 5 years wide, over 7 years (Y3-Y9).

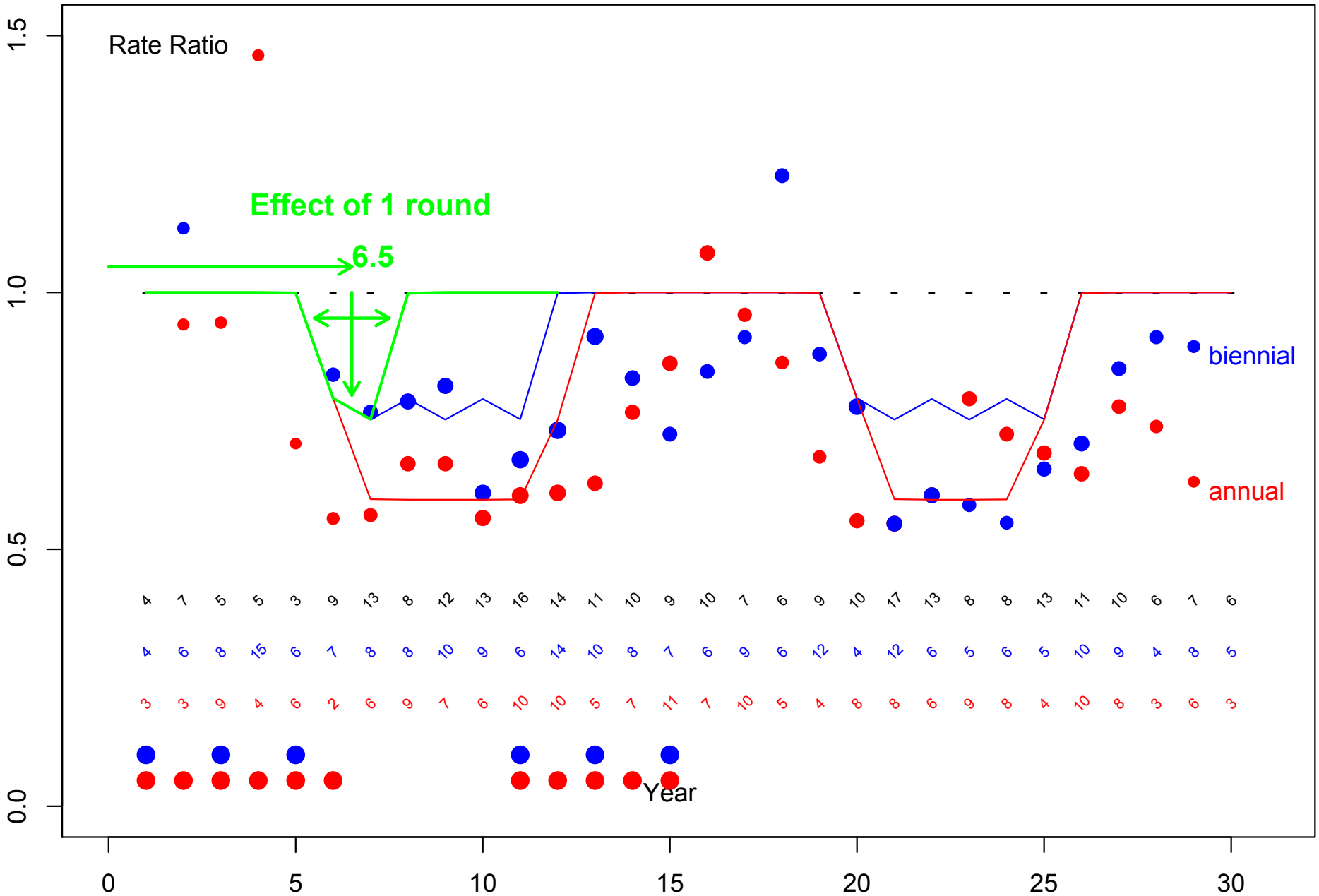
In such a trial, the maximal reduction (35%, year 6) would be smaller than the sustained (46%) reductions produced by a 20-year screening program.

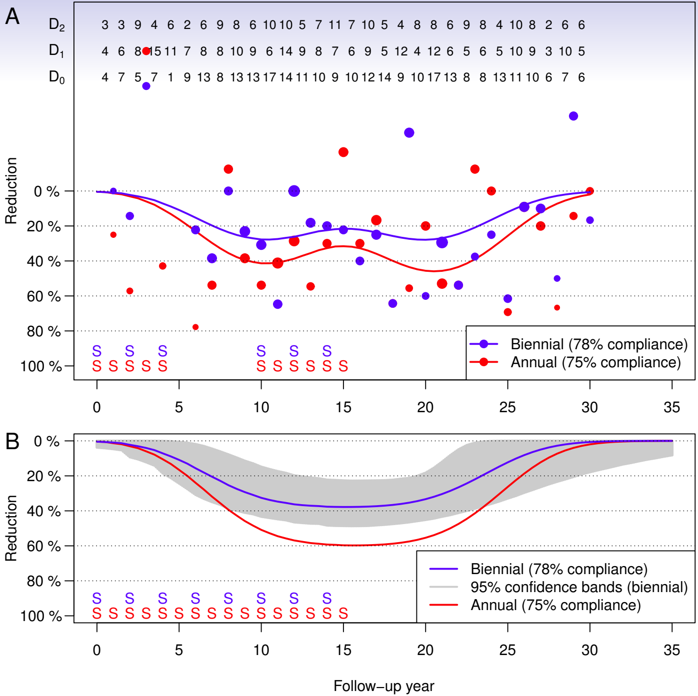
The average reduction, computed over 13 years of follow-up in such a trial would be an even more serious underestimate of the impact of a 20-year program.

Annual mortality reductions produced by once-a-year screening that begins when women reach 50, and ends when they reach 69



Fitted Model (each round) & Resulting Fits for 6 and 11 Rounds (JH)




A
D_2 3 3 9 4 6 2 6 9 8 6 10 10 5 7 11 7 10 5 4 8 8 6 9 8 4 10 8 2 6 6
D_1 4 6 8 15 11 7 8 8 10 9 6 14 9 8 7 6 9 5 12 4 12 6 5 6 5 10 9 3 10 5
D_0 4 7 5 7 1 9 13 8 13 13 17 14 11 10 9 10 12 14 9 10 17 13 8 8 13 11 10 6 7 6
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
S S S S S S
S S S S S S S S S S S
Biennial (78% compliance)
Annual (75% compliance)
0 5 10 15 20 25 30 35
B
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
S S S S S S S S
S S S S S S S S S S S S S S S S
Biennial (78% compliance)
95% confidence bands (biennial)
Annual (75% compliance)
0 5 10 15 20 25 30 35
Follow–up year

LUNG CANCER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

RESULTS

The rate of adherence to screening was more than 90%. The rate of positive screen-

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD 20892-7346, or at bergc@mail.nih.gov.

*A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102873) was published on June 29, 2011, at NEJM.org.

N Engl J Med 2011.

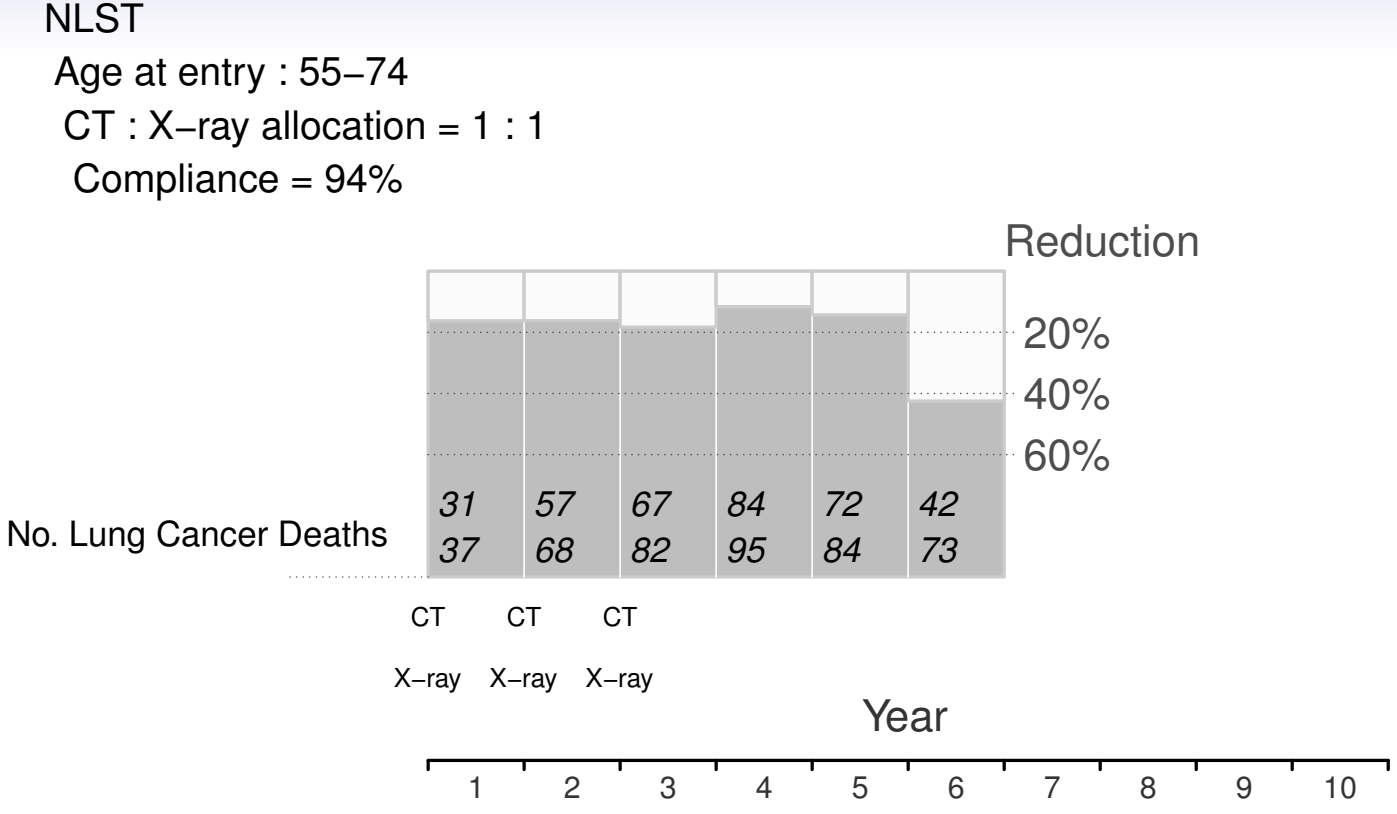


Figure 6–1: NLST yearly numbers of lung cancer deaths, extracted from published NEJM report.

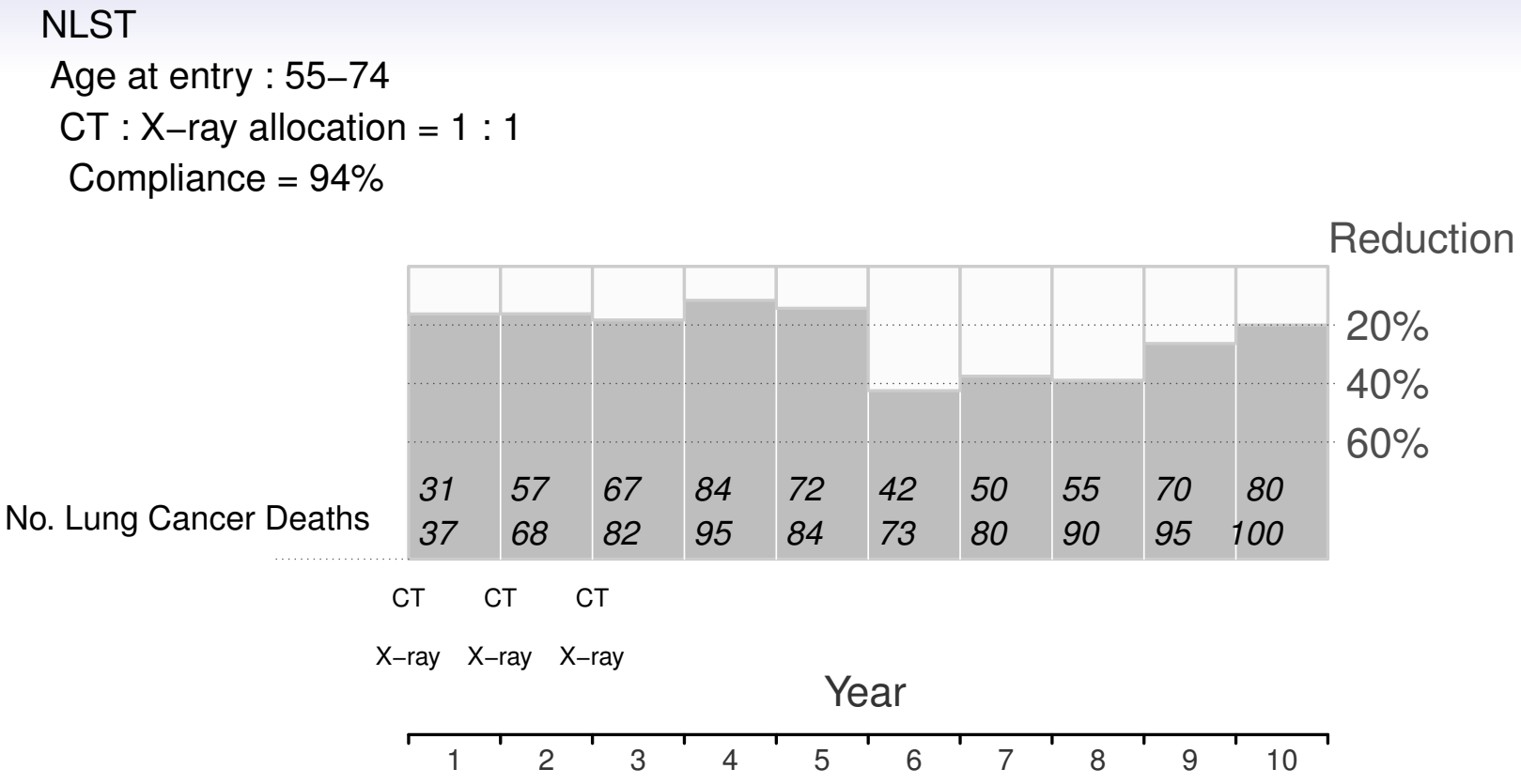


Figure 6–2: NLST yearly numbers of lung cancer deaths, with relatively large hypothetical reductions in years 7-10.

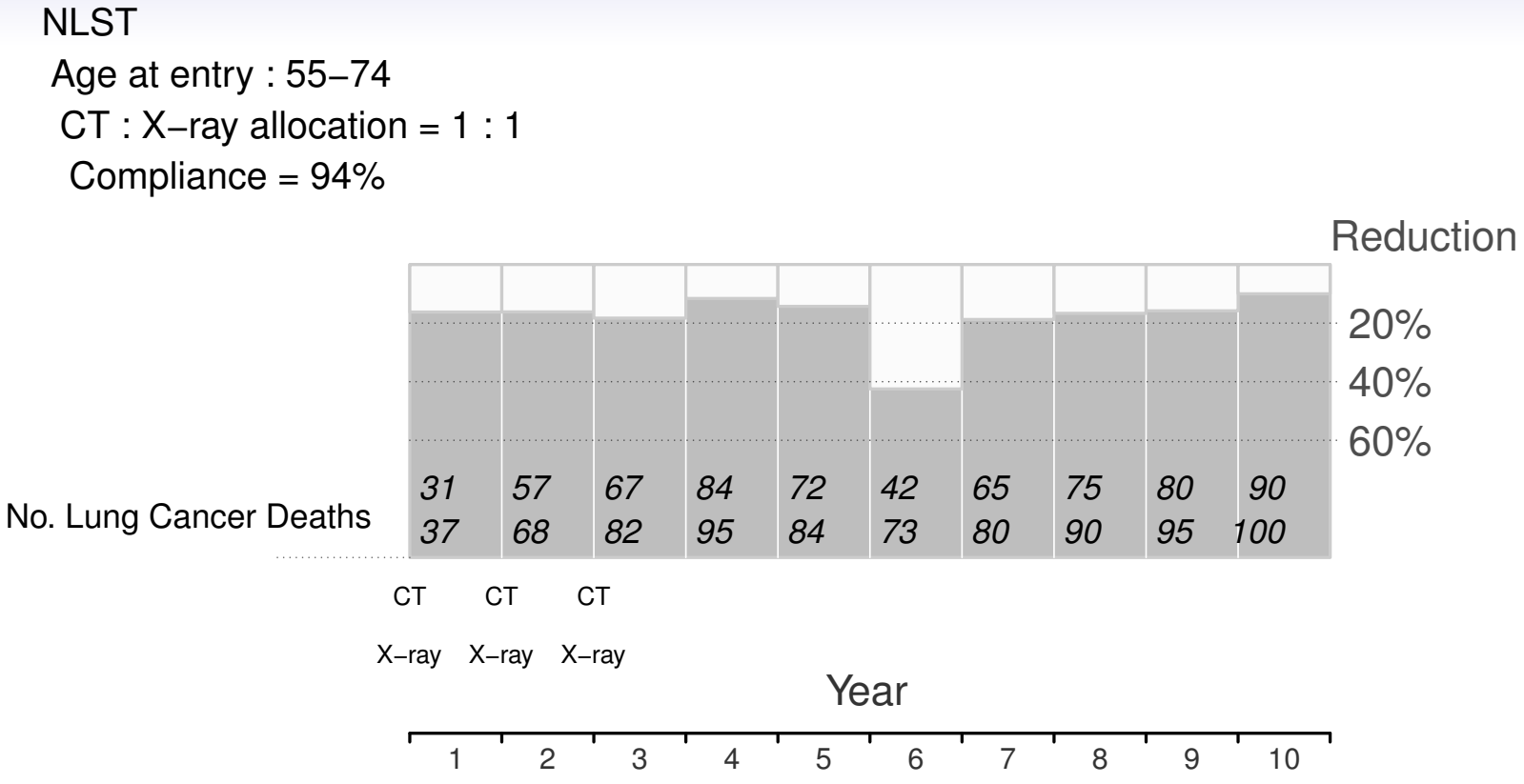


Figure 6–3: NLST yearly numbers of lung cancer deaths, with relatively small hypothetical reductions in years 7-10.

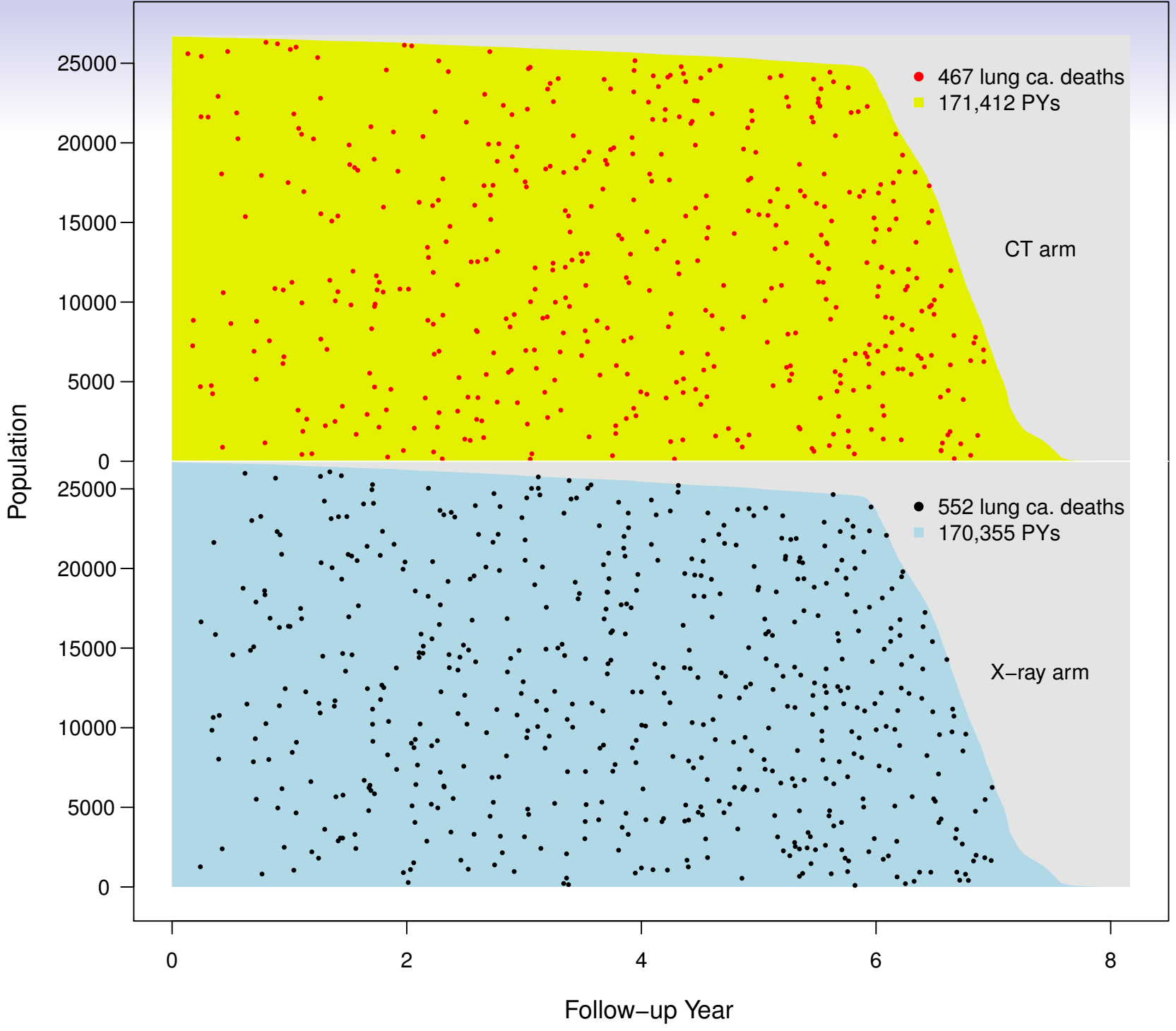

467 lung ca. deaths
171,412 PYs
CT arm
552 lung ca. deaths
170,355 PYs
X−ray arm
Population
25000
20000
15000
10000
5000
0
0
2
4
6
8
Follow−up Year

Table 6–1: Yearly numbers of lung cancer deaths in the NLST. Part (a) was based on our extraction from the NEJM report, (b) and (c) are based on the individual-level NLST data; in (b) only deaths that occurred before the cut-off (i.e. January 15th, 2009) were included, and in (c) all deaths occurred before and after the cutoff date were included.

(a) Year-specific data extracted from figure in NEJM report

Follow-up Year:	1	2	3	4	5	6	7	Total
Screens	↑	↑	↑					
X-ray Arm:	37	68	82	95	84	73	4	442
CT Arm:	31	57	67	84	72	42	3	354
Reduction:	16%	16%	18%	12%	14%	**42%**	25%	20%

(b) Year-specific data including deaths before the cutoff only

X-ray Arm:	38	70	83	91	88	74	4	448
CT Arm:	31	57	67	84	72	45	3	359
Reduction:	18%	19%	19%	8%	18%	39%	25%	20%

(c) Year-specific data including deaths before and after the cutoff

X-ray Arm:	38	70	83	91	89	116	65	552
CT Arm:	31	57	67	84	73	85	70	467
Reduction:	18%	19%	19%	8%	18%	27%	-8%	15%

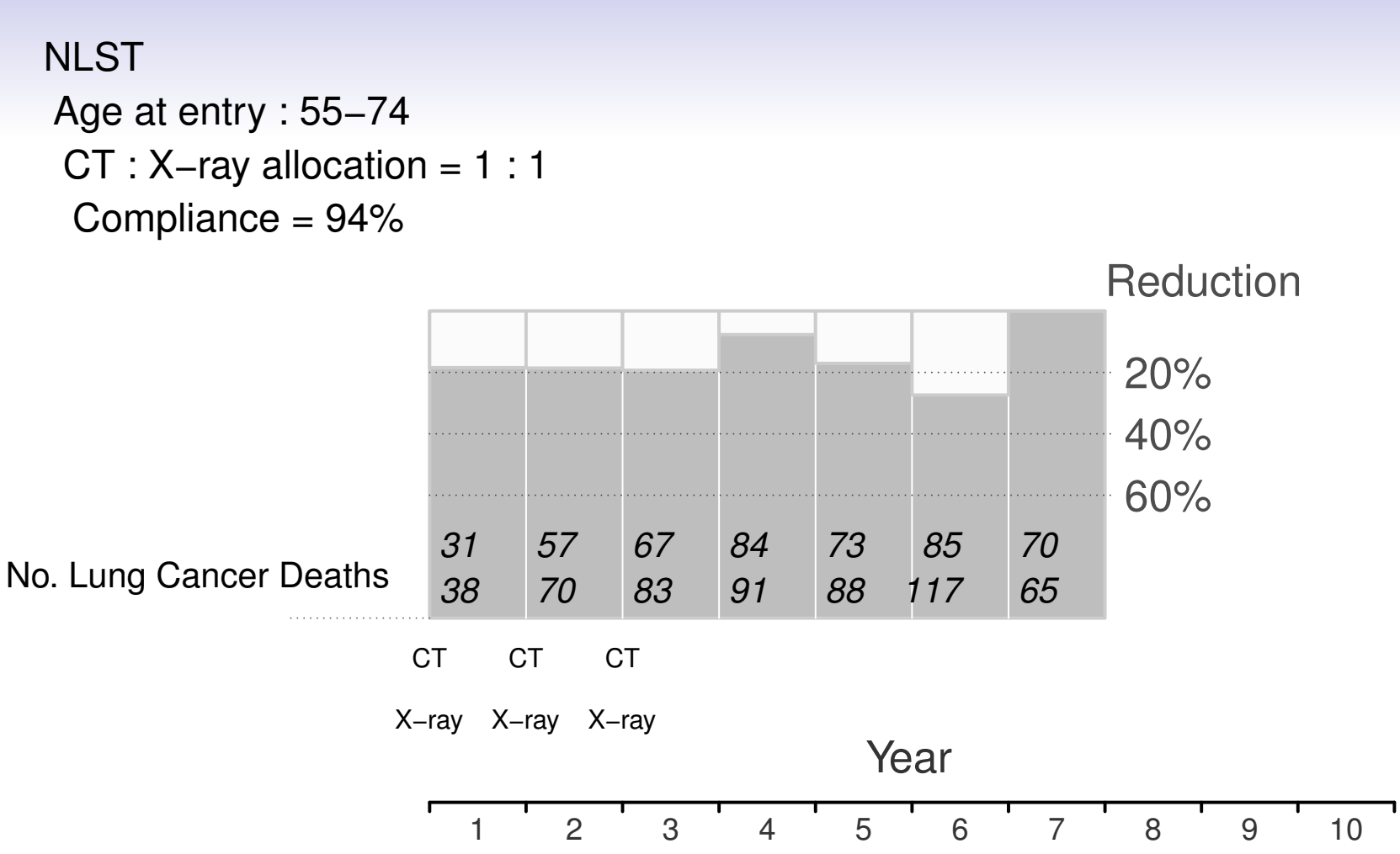


Figure 6–5: NLST yearly numbers of lung cancer deaths, correspond 6–1(c).

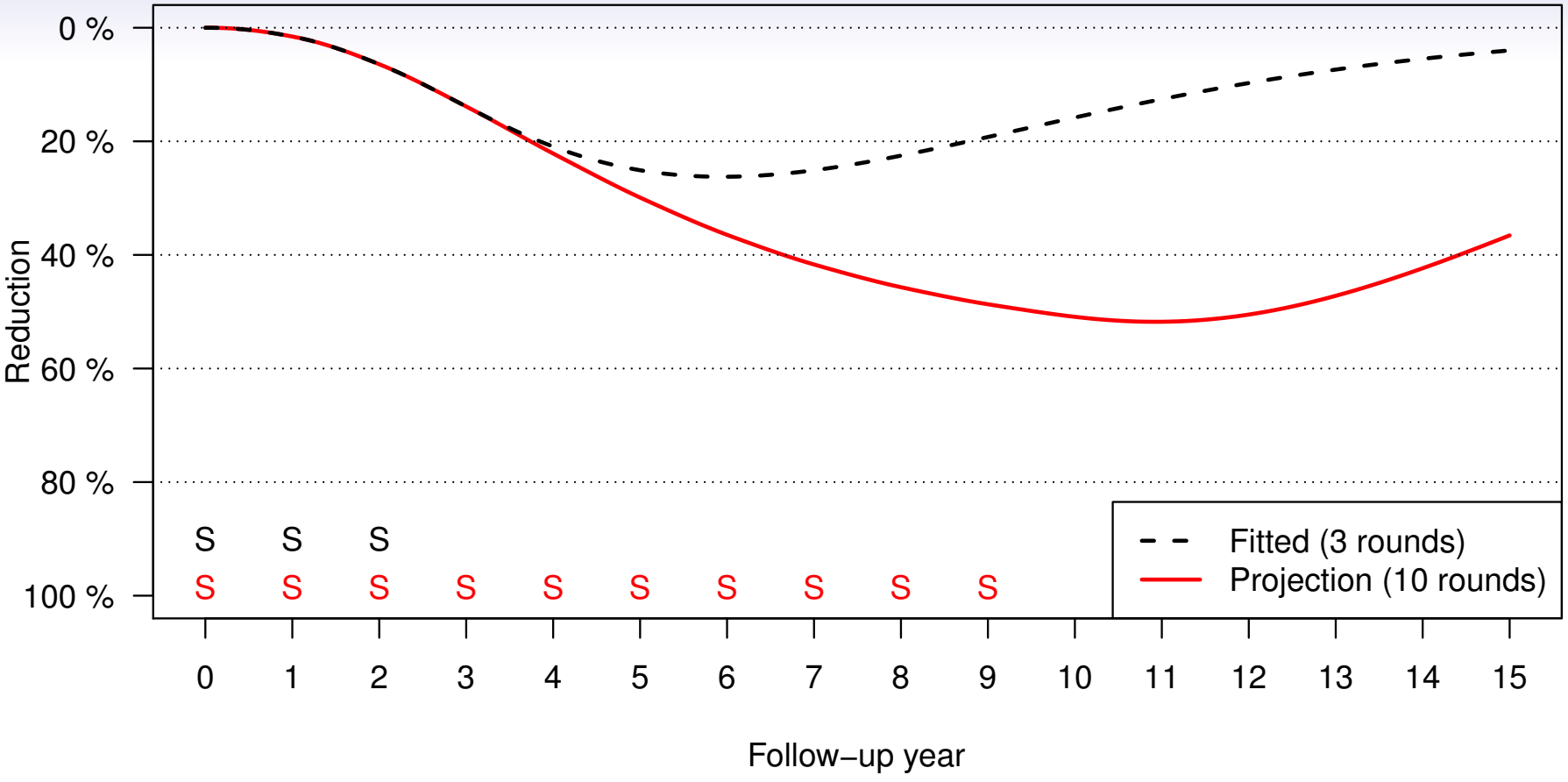


Figure 6–6: Fitted reduction curve (dotted, black) based on the NLST data for persons aged below 65 at onset of screening and projected curve based on 10 rounds of annual screenings.

Summary

- By ignoring the delay until the reductions in mortality are expressed, the prevailing interpretations of the results of cancer screening trials ***under-estimate*** the mortality reductions that ***would be produced by a sustained screening program***
- P-value-driven RCT stopping/reporting rules exacerbate the problem
- We *might* be able to avoid such misleading estimates if we . . .
  (i) distinguish a trial from a program
  (ii) run trials with sufficient rounds of screening and sufficient follow-up
  (iii) spend major portion of career waiting to measure real reductions
  (iv) analyze the data using time-specificity / non-proportional hazards
  (v) focus on parameters describing **impact of 1 round of screening**
  (vi) mammography: use data from population-screening, not old trials

FUNDING, CO-ORDINATES, DOWNLOADS

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Le Fonds québécois de la recherche sur la nature et les technologies

Canadian Institutes of Health Research (2011-2014)

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Biostatistique

Why do statisticians commonly limit their inquiries to Averages?

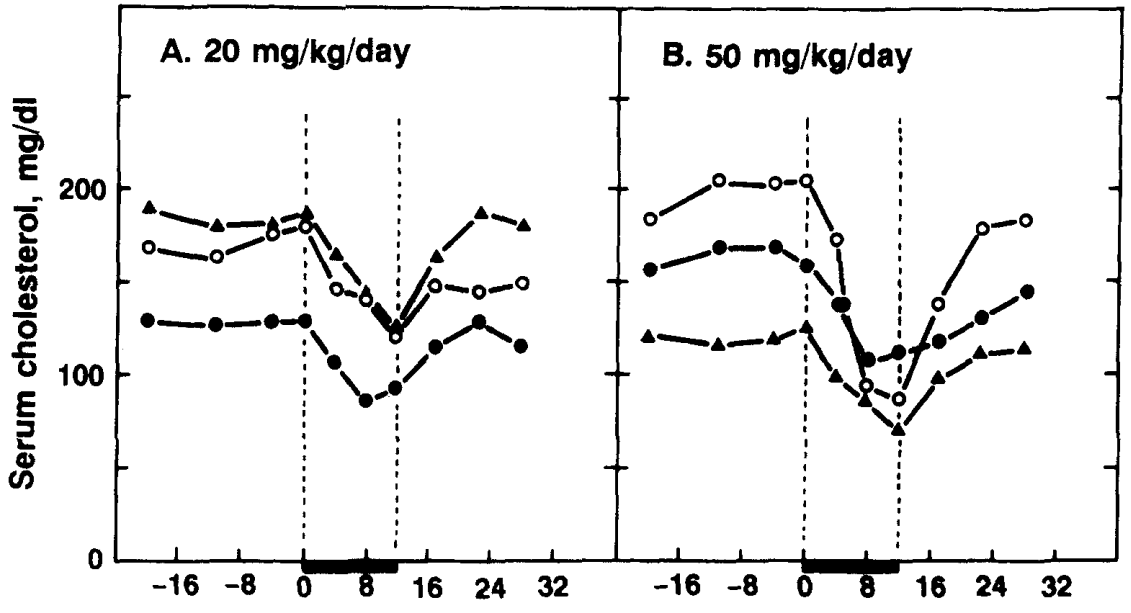
F. Galton, Natural Inheritance, 1889.

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

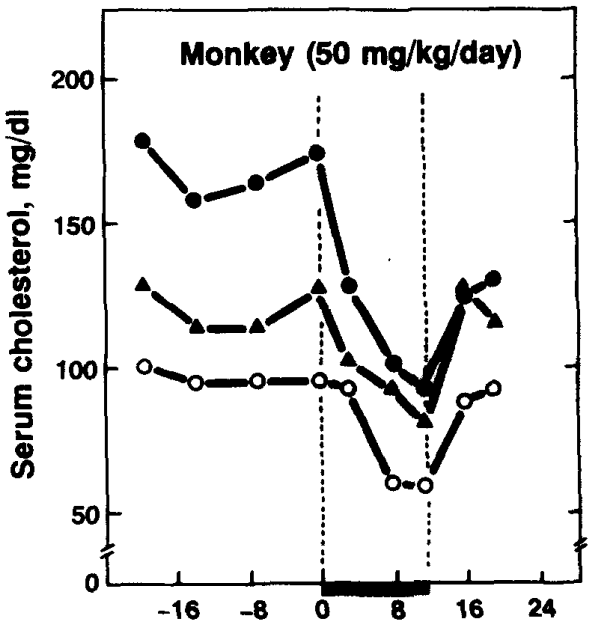
Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”

Timing of cholesterol reductions produced by statins

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

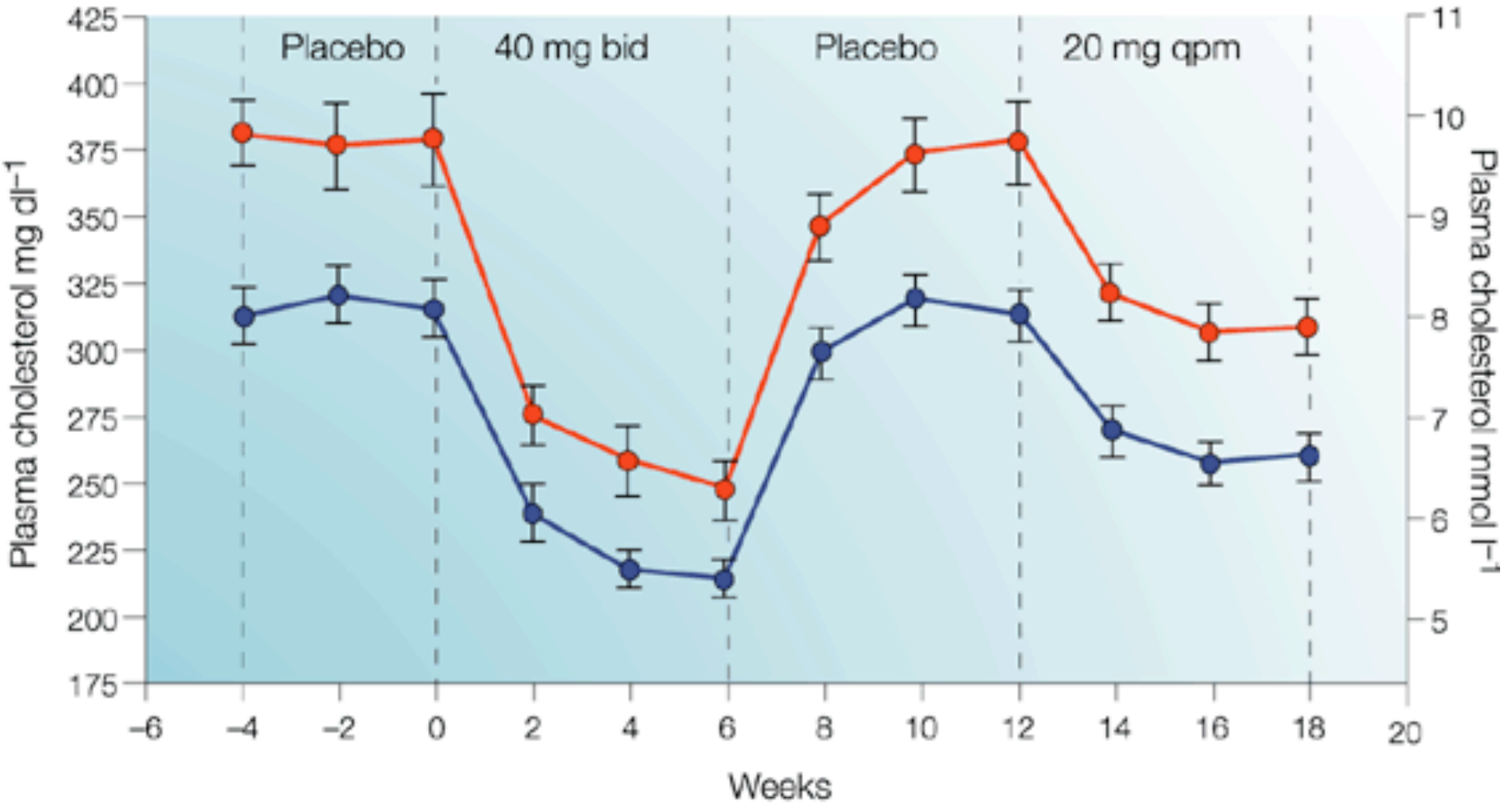


3 monkeys at 50

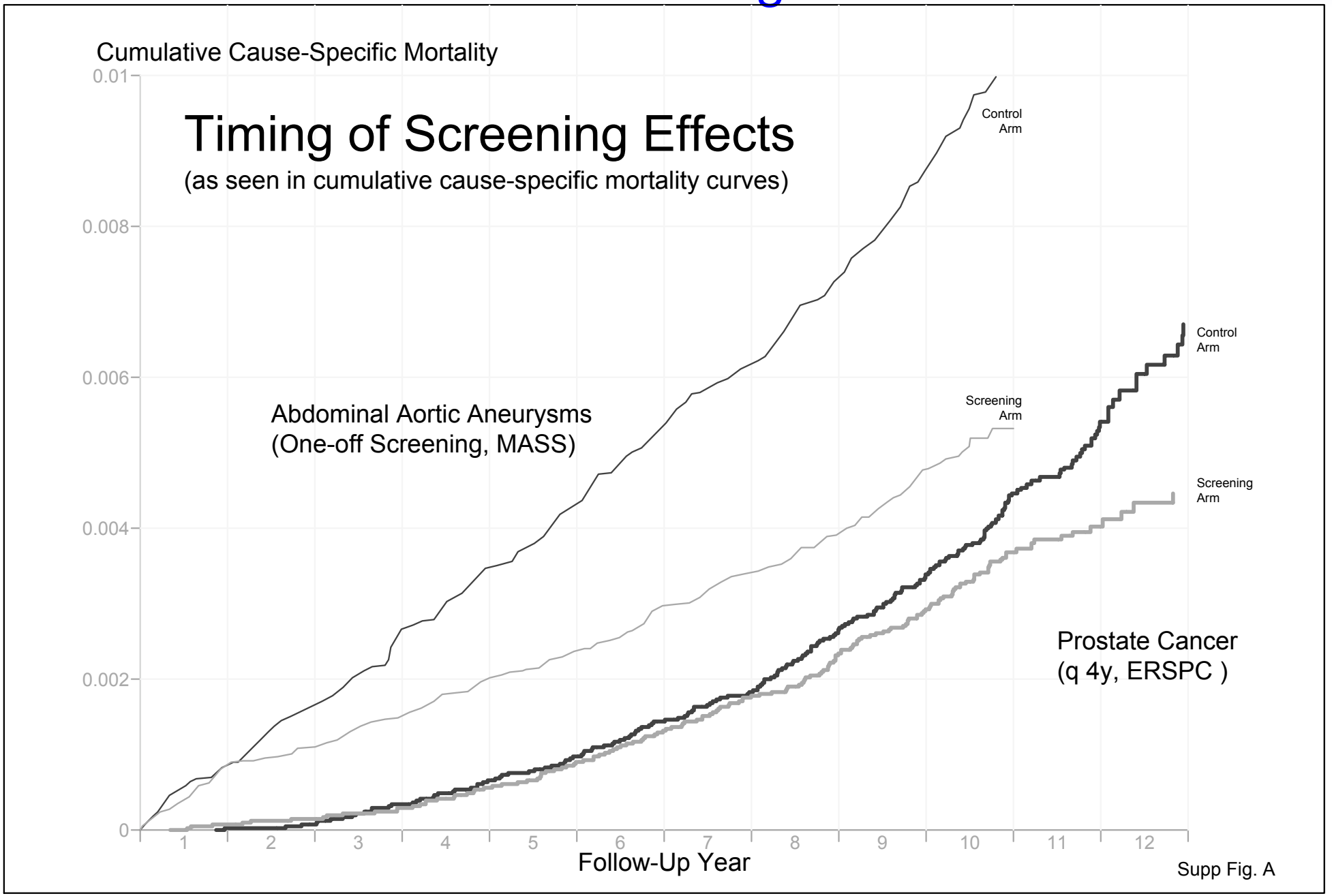


Timing of cholesterol reductions produced by statins

Humans



The loneliness of the long-distance trialist



Supp Fig. A