USING TRIAL DATA TO PROJECT THE MORTALITY REDUCTIONS PRODUCED BY A CANCER SCREENING PROGRAM

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Outline

- Goal of a trial *vs.* quantifying what a program might do
- Estimand in the case of a **program** with a specified schedule
- Going from trial to program:

  - disaggregate trial data: fit parameters that measure impact of 1 round;

  - then compound the impacts of the specified schedule

- Case Studies: cancer of the **lung**, **colon**
- Level of ERSPC data that would allow projection for **prostate**

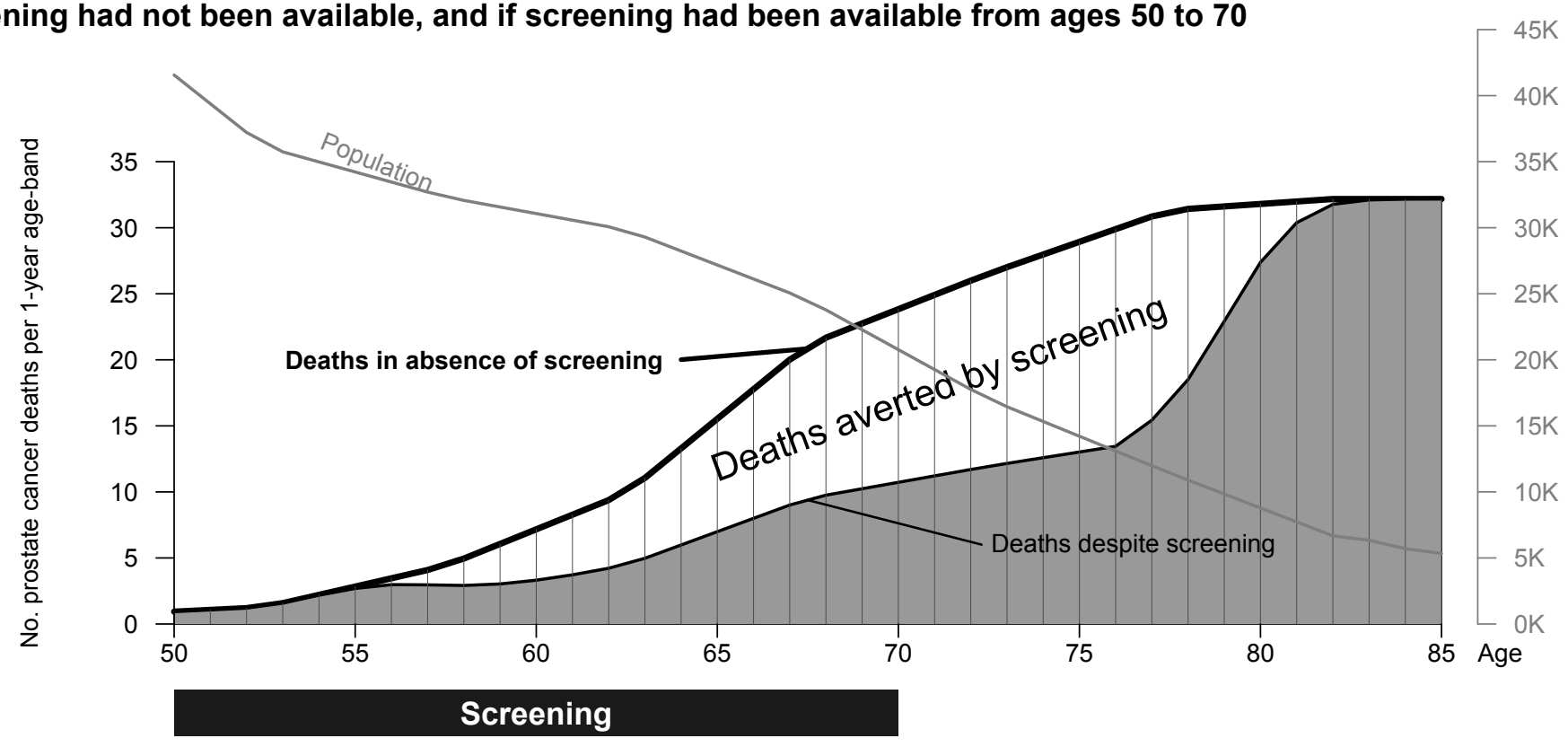
TRIAL: goal, data analysis, usual statistics

- H_0: x rounds of screening (specific spacing): no mortality reduction
- Test statistic based on # deaths at end of (ave) 8.8 y of f-up (2006.12.31)

  $\frac{326}{785585PY}$ *vs.* $\frac{214}{643401PY}$: $RateRatio = 0.8 \rightarrow$ P=0.04
- '% Reduction' statistic (at that time): $100 \times (1 - 0.8)$ = 20%.
- NLST Design: driven by power calculations (all deaths up to $T_{analysis}$)

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

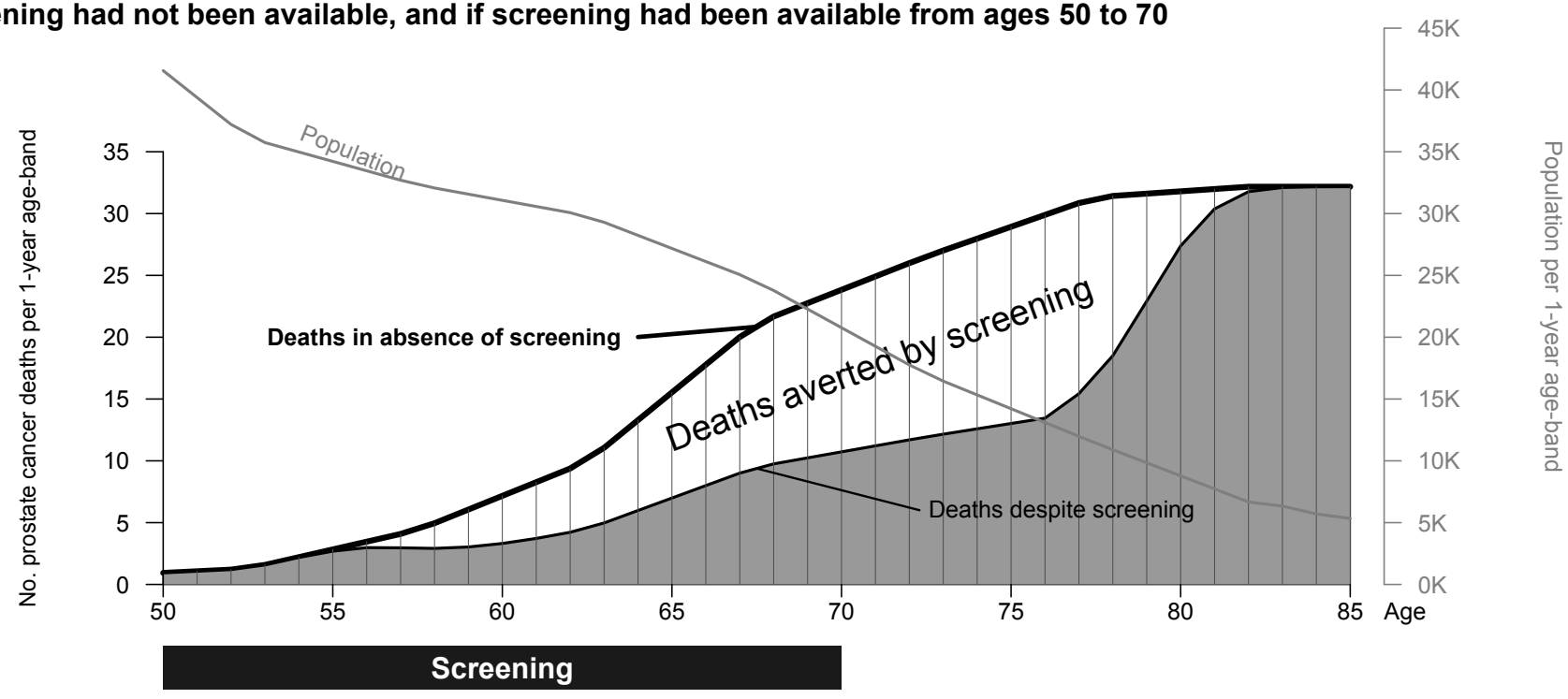


[Hypothetical, but loosely modelled after age-structure and actual numbers of deaths in Canada in 1990s.

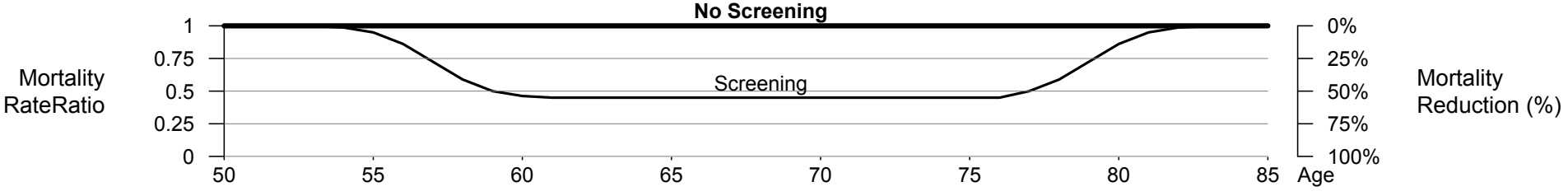
Delay between when screening starts & first mortality deficits begin, and when screening stops & last deficits end]

In relative terms: Rate Ratio (or %Reduction) **Function** for 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



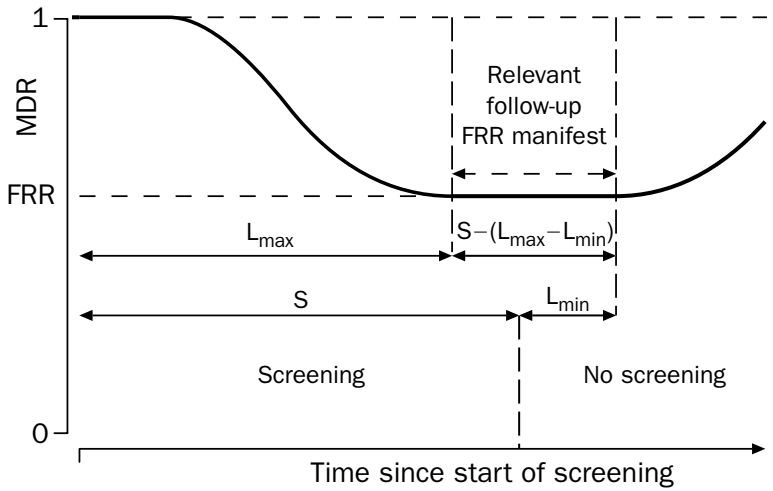
(b) The corresponding age-specific prostate cancer mortality rate ratios



‘*% 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
- For discussion, see Liu et al. J Med Scr (our website)

2002 Paradigm shift



Follow-up experience in a randomised controlled trial comparing screening for cancer with no screening in respect to cause-specific mortality: interrelations of parameters

At any given point in the follow-up there is a particular mortality density, MD, among the screened and the not screened; for an interval of t to t+dt, with dC cases expected in it, $MD_t=dC/Pdt$, where P is the size of the population. Contrasting the screened with the not screened, there is the corresponding mortality-density ratio, MDR. This ratio is depicted as a function of time since entry into the trial. The early excess mortality among the screened is not shown, since focus is on the intended result of reduced fatality rate, FR, quantified in terms of fatality-rate ratio, FRR. MDR coincides with FRR in a particular interval of follow-up time if the duration of screening, S, exceeds the difference between the maximum, L_{max}, and minimum, L_{min}, of the time lag from early diagnosis to the death prevented by early intervention but not by late intervention (ie, in the absence of screening).

Miettinen et al. 2002 THE LANCET http://image.thelancet.com/extras/1093web.pdf (on our website)

{Morrison has simpler version in his 198x book}

Why %reduction function is the shape it is

ORIGINAL ARTICLE

Analysis of Mortality Data From Cancer Screening Studies

Looking in the Right Window

James A. Hanley

Background: Appropriate statistical analysis is required to measure the impact of early detection and treatment of cancer. The current practice of using cumulative mortality ignores both (1) the delay between early treatment and the time that any averted deaths would have otherwise occurred, and (2) cessation of these delayed benefits some time after screening is discontinued.

Methods: We use time-specific mortality density ratios to estimate the mortality ratio in the "window of influence." We then use time-specific incidence density ratios to assess the extent to which the removal of polyps and other possibly precancerous lesions detected by fecal occult blood screening reduces the incidence of colorectal cancer.

In the design of trials to assess the mortality reduction resulting from screening-induced early interventions against cancer, considerable care is taken to generate high-quality data. The statistical analyses of these data usually measure the reduction in cumulative mortality. Unfortunately, by mixing "irrelevant experience with the relevant experience,"[1] these analyses underestimate the impact of early intervention. We discuss a data analysis principle, long established but seldom practiced until recently,[1–3] and illustrate its sharpness by an unusual example.

The purpose of cancer screening is to detect and treat a lesion now that if left to present itself at a later date would

Epidemiology, Vol 16, No. 6, November 2005, pp 786-790 (our website)

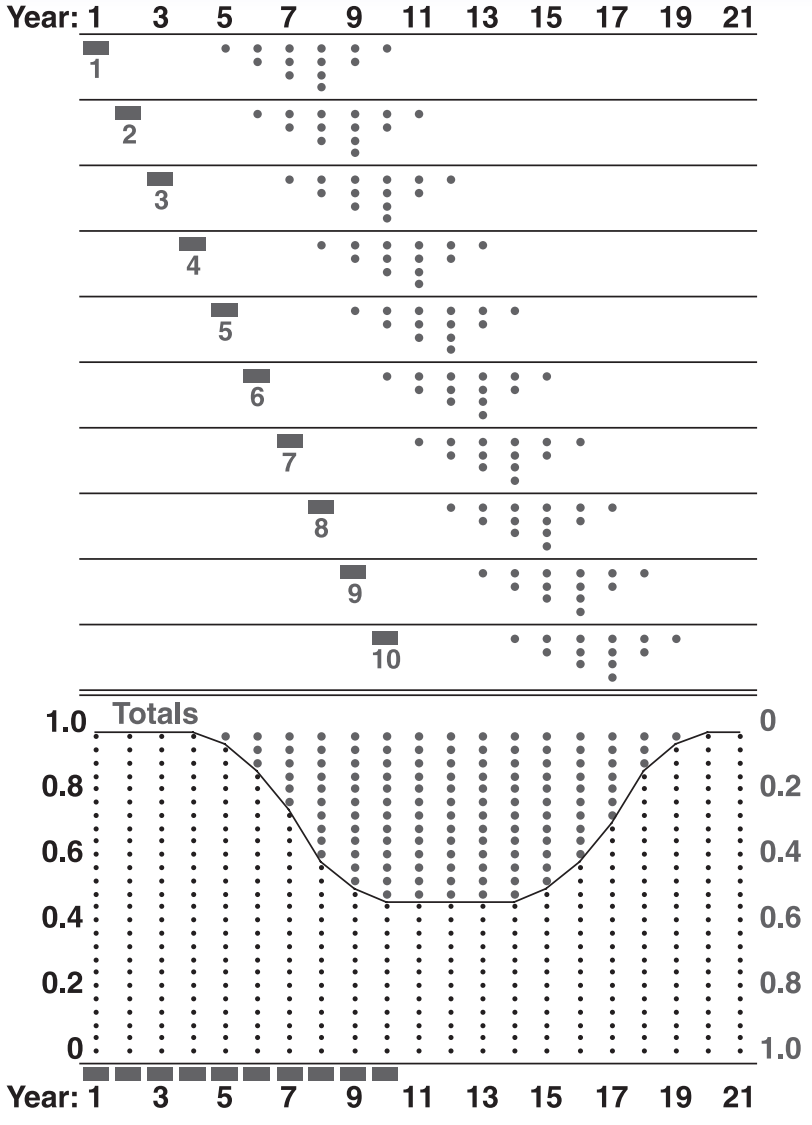


FIGURE 1: Reductions in cancer deaths in a hypothetical situation in which screening is carried out for 10 years. The dots in a specific row in the upper part of the figure represent the deaths averted by that year’s screening; the dots in the region entitled “totals” in the lower portion of the figure represent the aggregated numbers of deaths averted, whereas the smaller dots represent deaths that are not averted. The curve represents the mortality rate ratio (left vertical axis) and its complement (right vertical axis). { same 2005 article }

This theoretical example compounds the round by round impacts.

Our task will be the reverse:

dis-aggregate the yearly totals into the round by round impacts

Why number & timing of screens matter

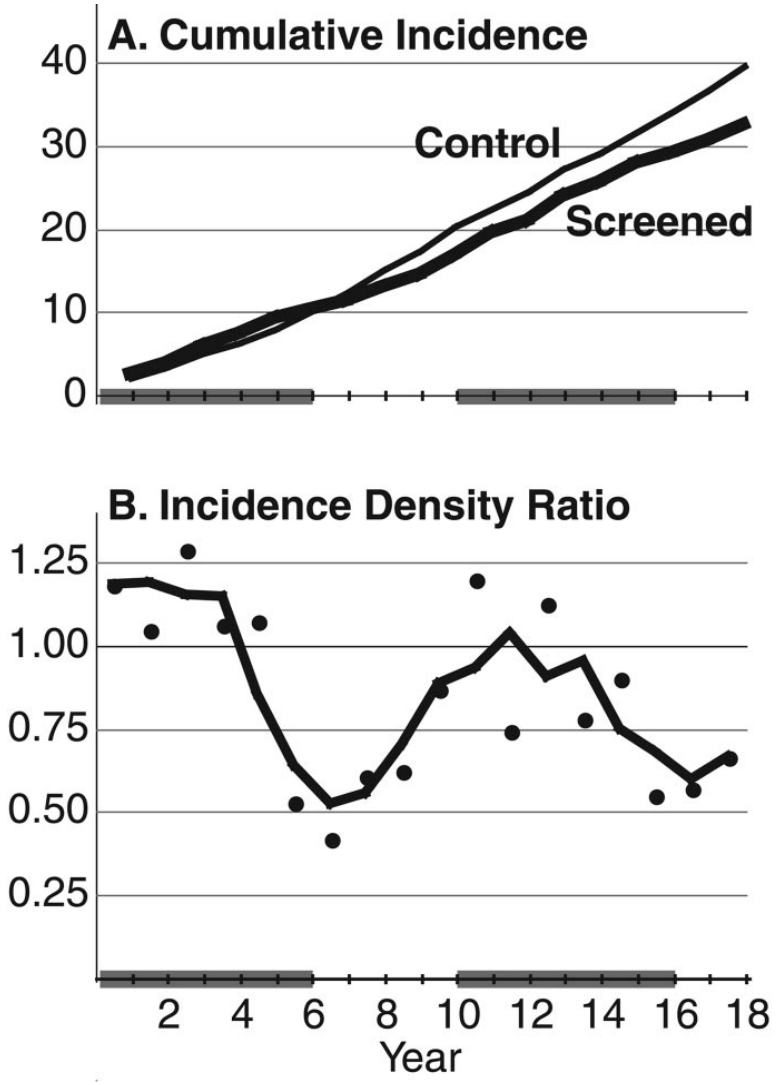


FIGURE 2. Colorectal cancer in the unscreened and screened study groups (annual and biennial combined) based on data in Mandel et al. The two 6-year periods when screening was conducted are shown as thicker lines on the time axis, and the funding-related hiatus as a gap. Cumulative incidence (A) is per 1000. Yearly incidence density ratios (B) are shown as points.

same 2005 article (our website)

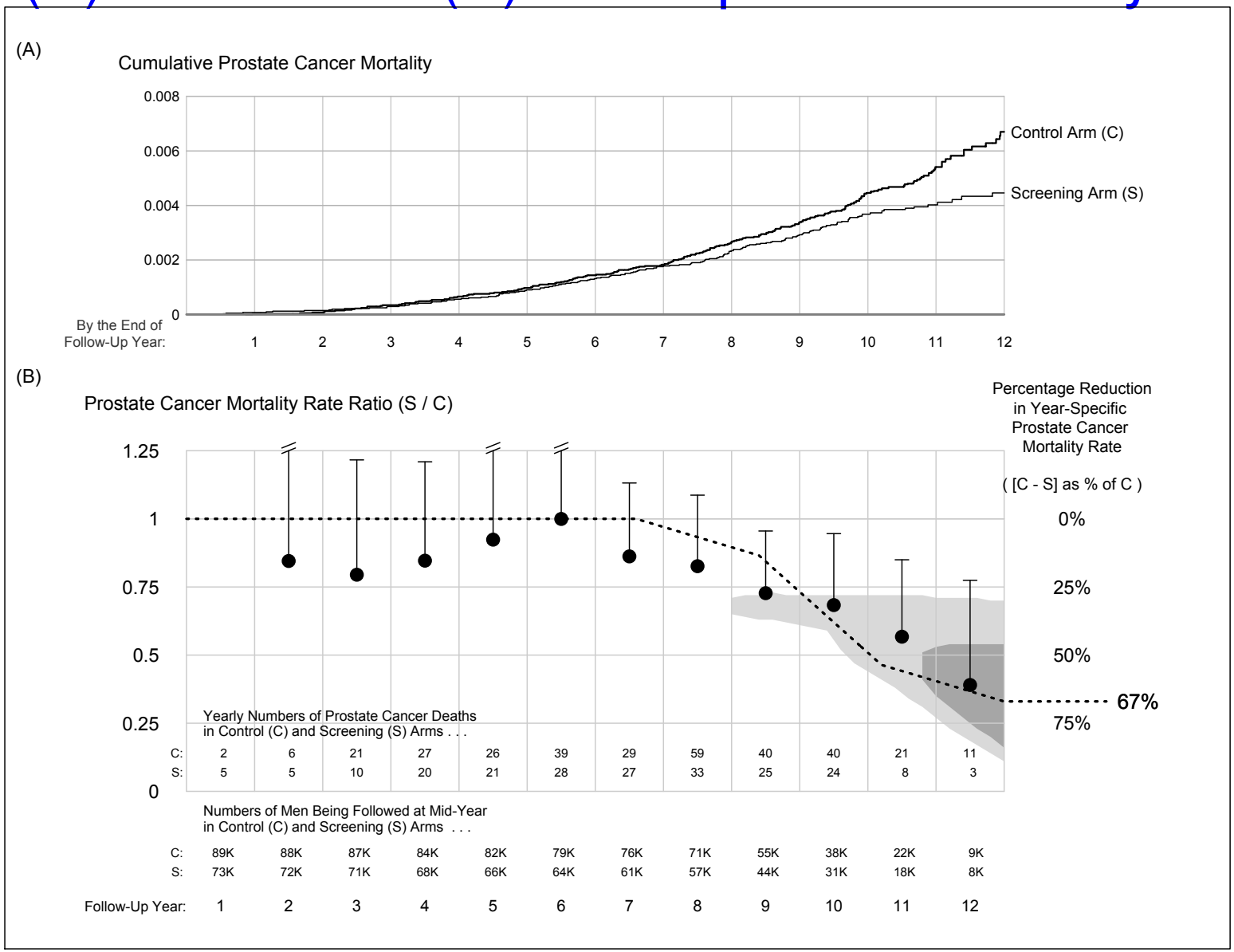
% REDUCTION FUNCTION for Prostate Cancer

(assuming same ‘average’ schedule as in ERSPC)

2010 CURVE-FITTING
(no attempt to dis-aggregate the effects)

– see 2010 J Med Scr article on our website –

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



Hanley, *J Med. Screening*, 2010. No.s deaths & men being followed: PostScript files behind pdf file, NEJM article

% REDUCTION FUNCTION

A new approach based on dis-aggregation and compounding

developed under CIHR grant

Objective

- A screening trial typically involves a few screens.
- What if screening had been continued longer?
- Objective: to obtain **probabilistic projections** for mortality reductions due to a **sustained screening program** implemented in a population, **based on trial data**.

Challenge

- To project the mortality impact, we have to

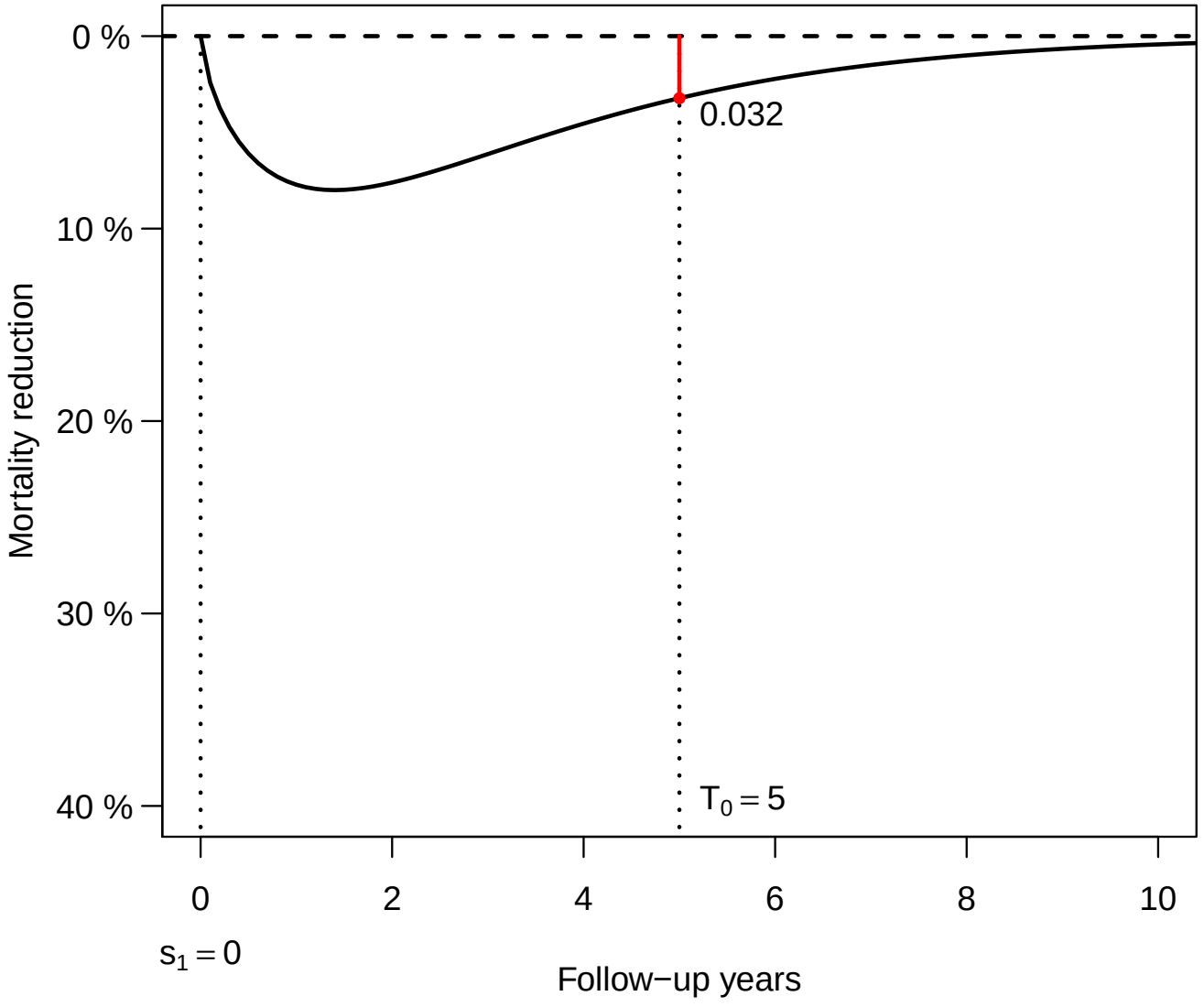
  1. **decompose** the observed impact in a trial into round-specific ones.

  2. **compound** the round-specific impacts to project that of a screening program.

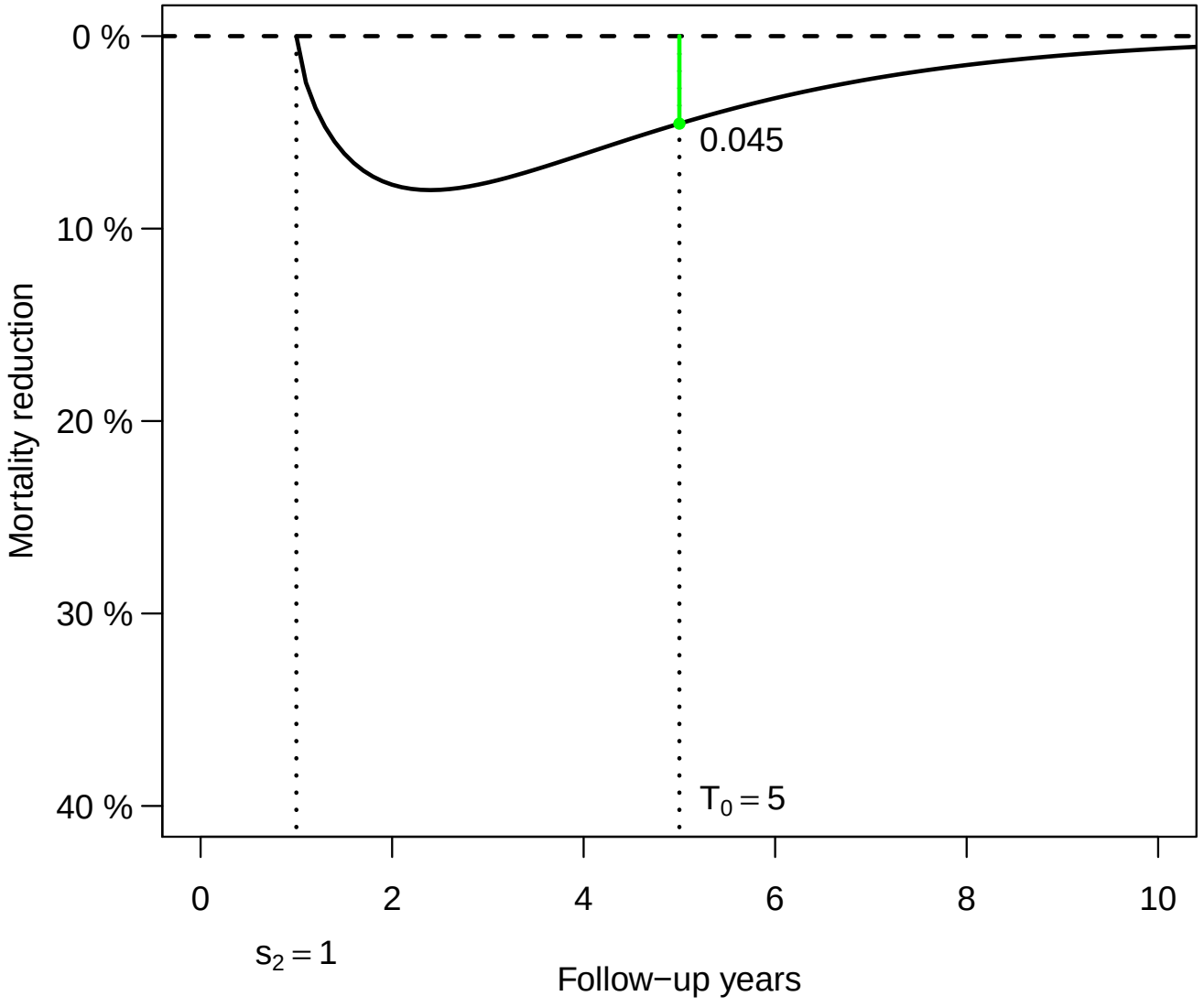
Essence of new approach

- Retrospective in spirit
- Target is those cancers that would prove fatal in absence of screening
- We parametrize and fit a model for the probability that such persons would have been helped by a round of screening

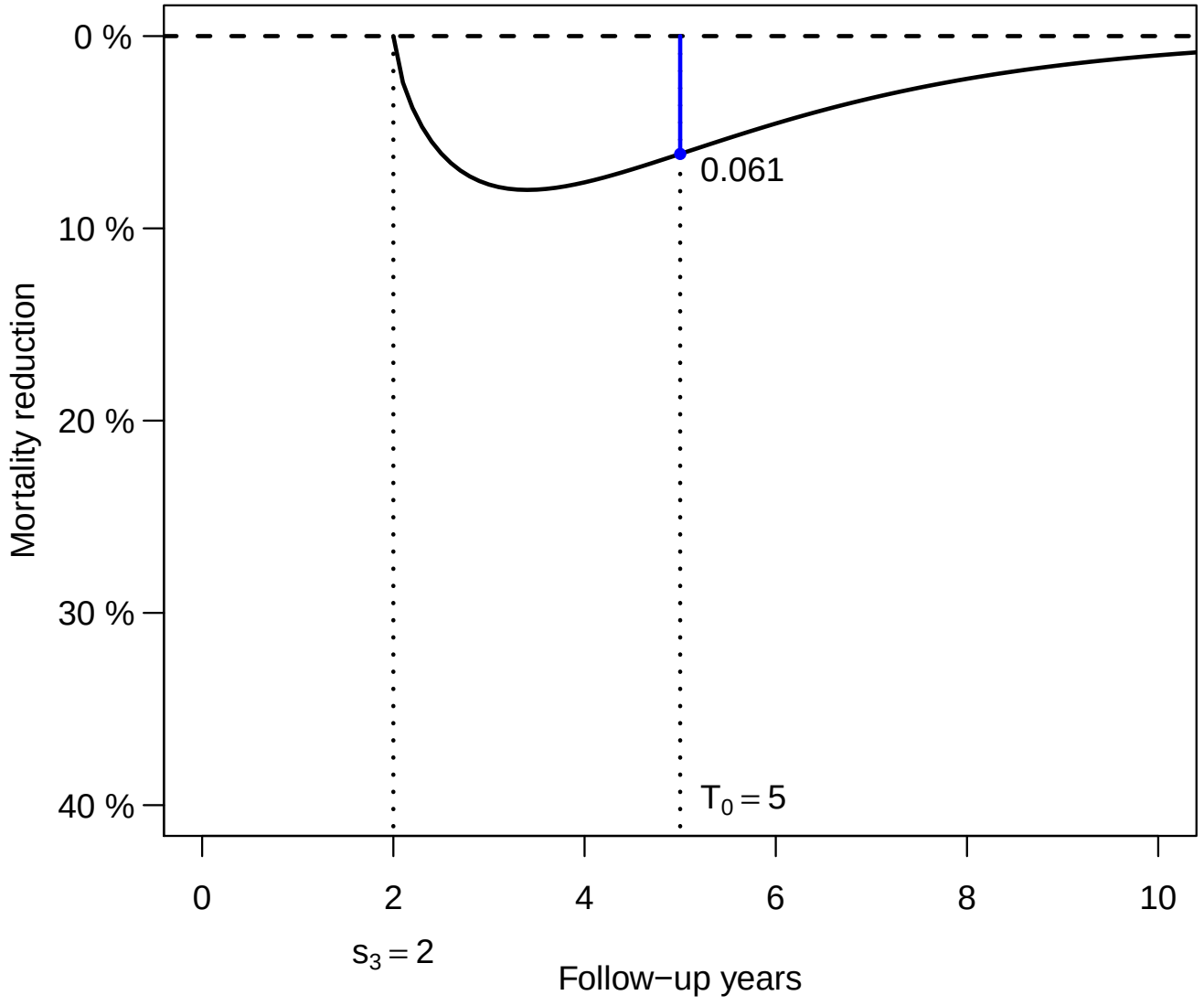
Decomposition: 1st round



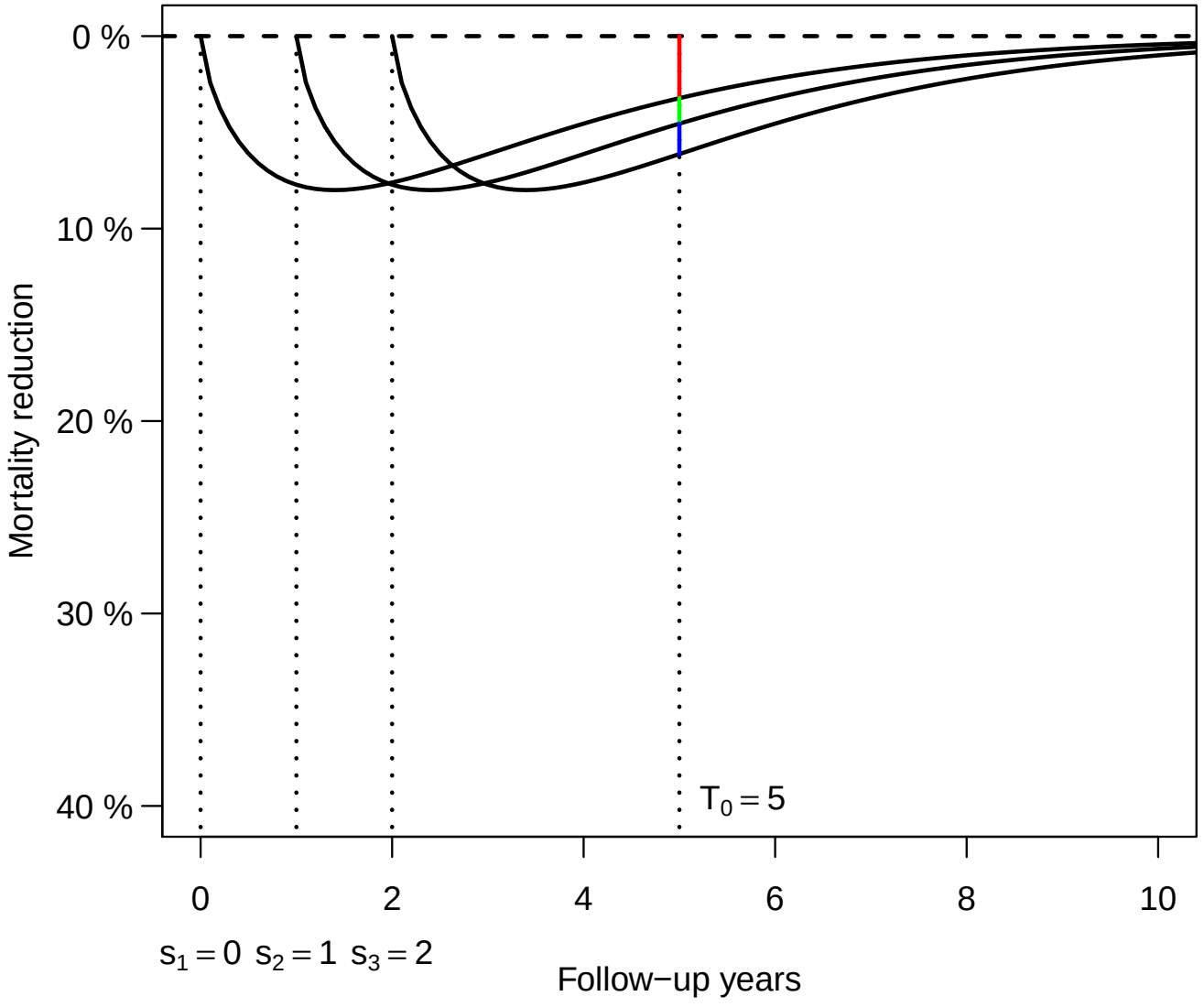
2nd round


0 %
10 %
20 %
30 %
40 %
Mortality reduction
0.045
$T_0 = 5$
0
2
4
6
8
10
$s_2 = 1$
Follow−up years

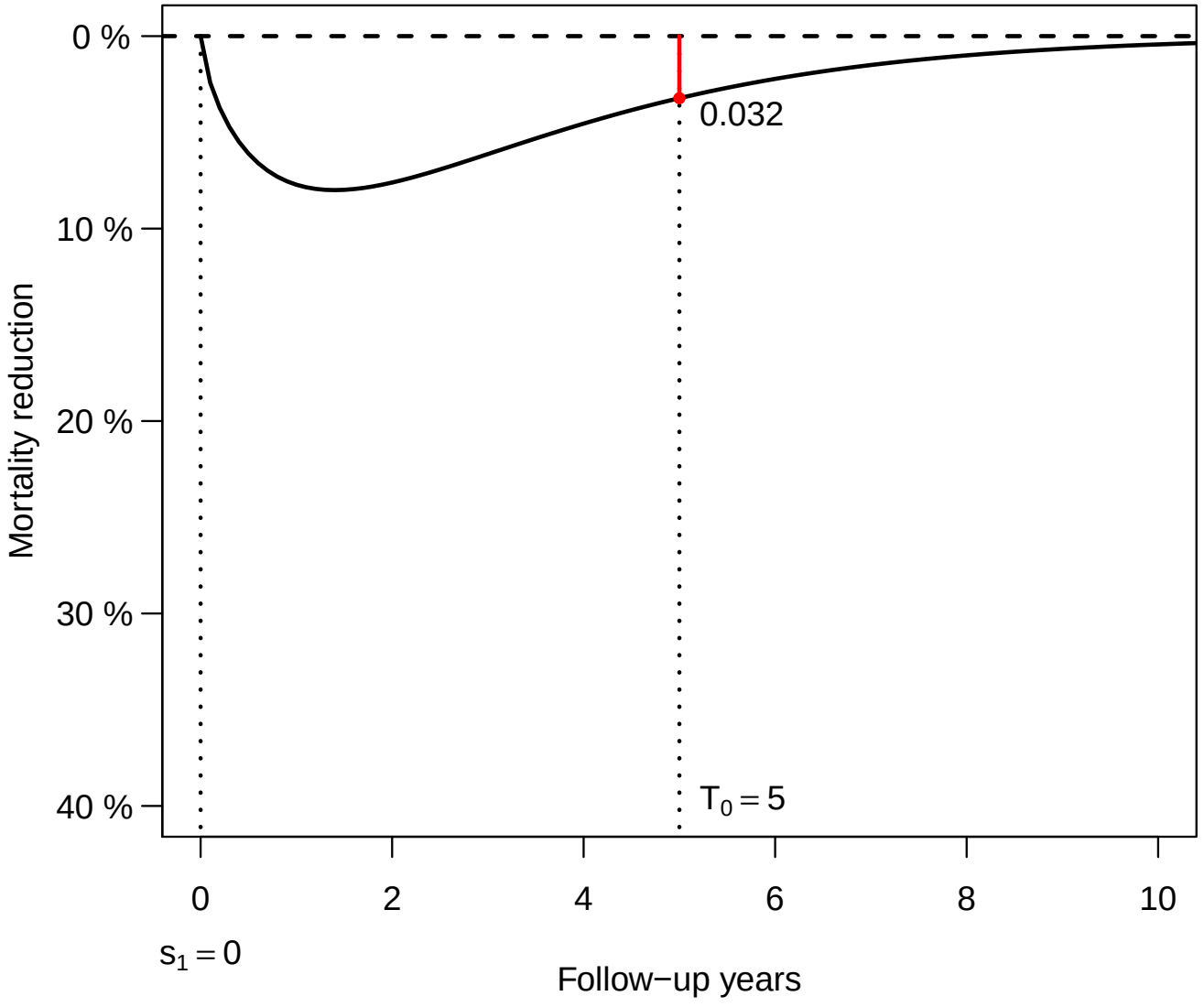
3rd round


0 %
10 %
20 %
30 %
40 %
Mortality reduction
0.061
$T_0 = 5$
0
2
4
6
8
10
$s_3 = 2$
Follow−up years

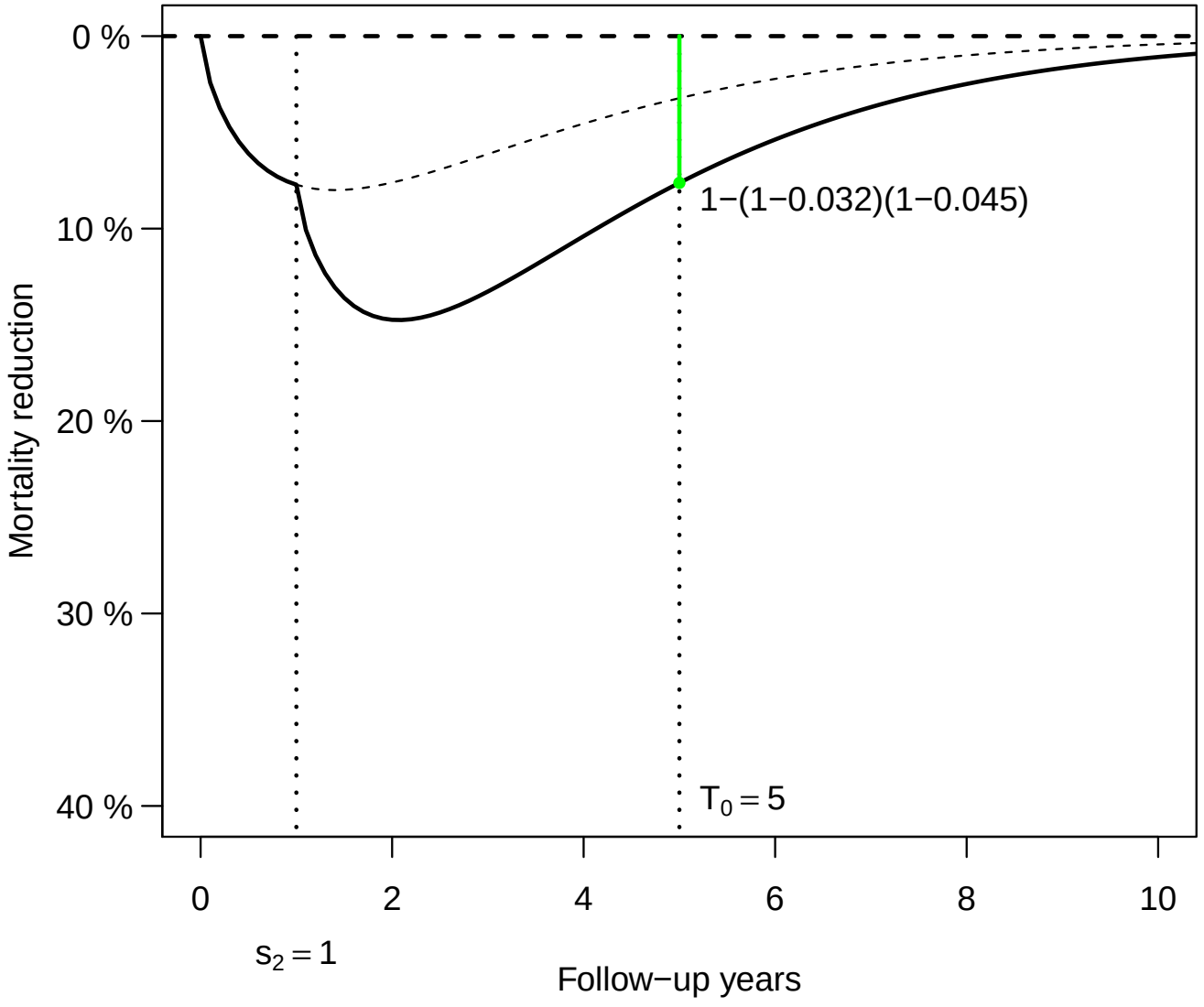
All 3 rounds


0 %
10 %
20 %
30 %
40 %
Mortality reduction
$T_0 = 5$
0
2
4
6
8
10
$s_1 = 0$ $s_2 = 1$ $s_3 = 2$
Follow−up years

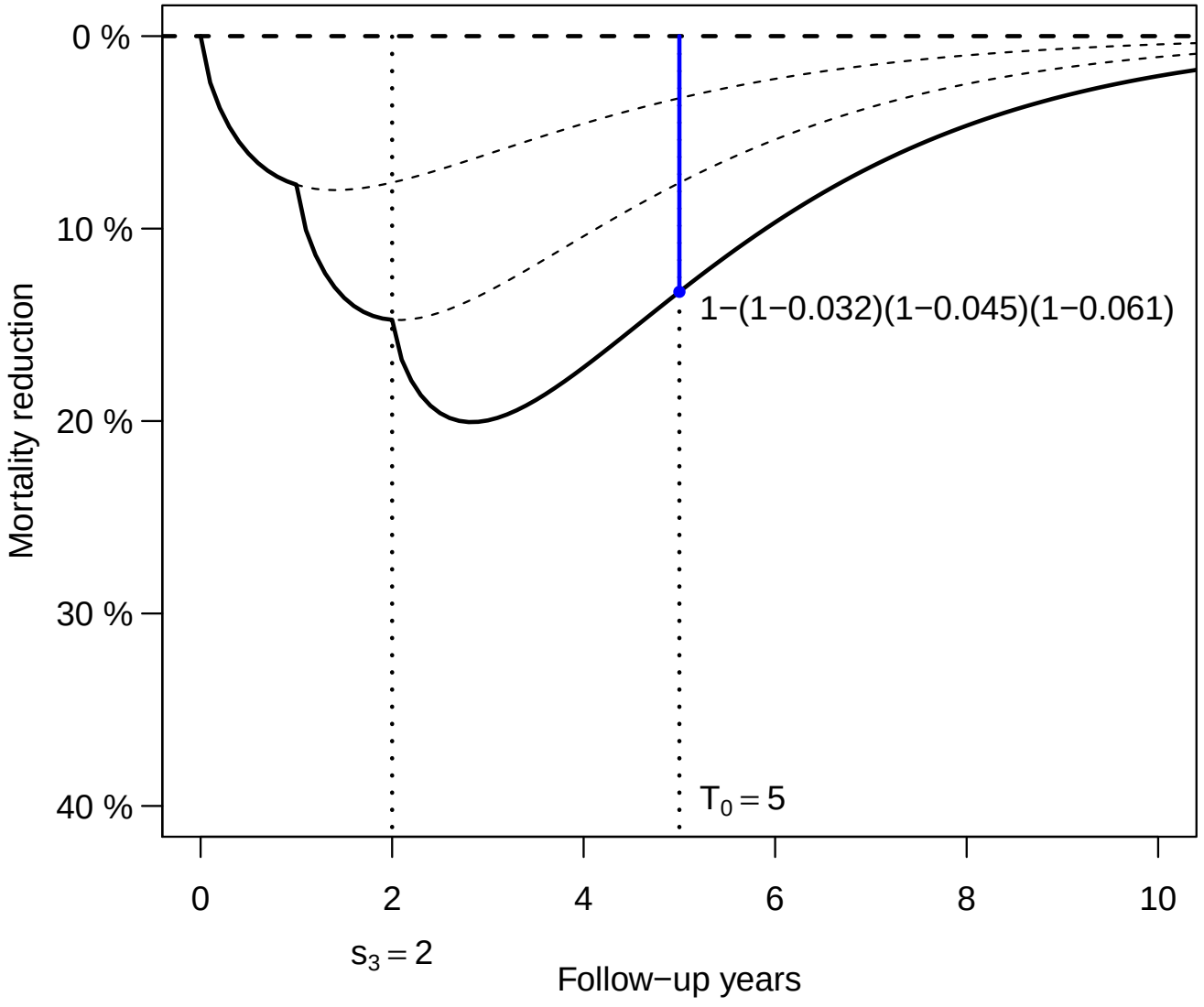
Compound: 1st round



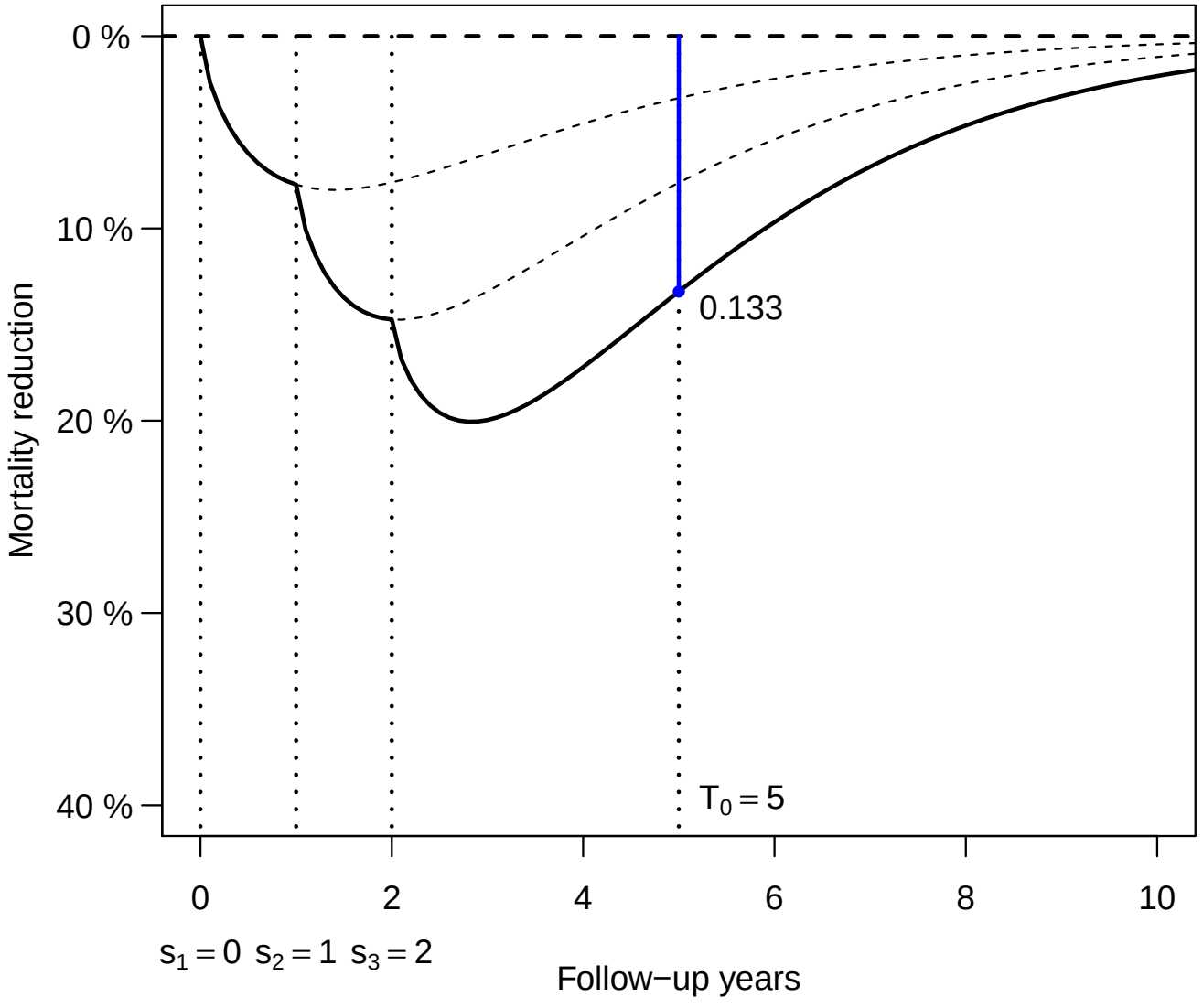
2nd round


0 %
10 %
20 %
30 %
40 %
Mortality reduction
1−(1−0.032)(1−0.045)
$T_0 = 5$
0
2
4
6
8
10
$s_2 = 1$
Follow−up years

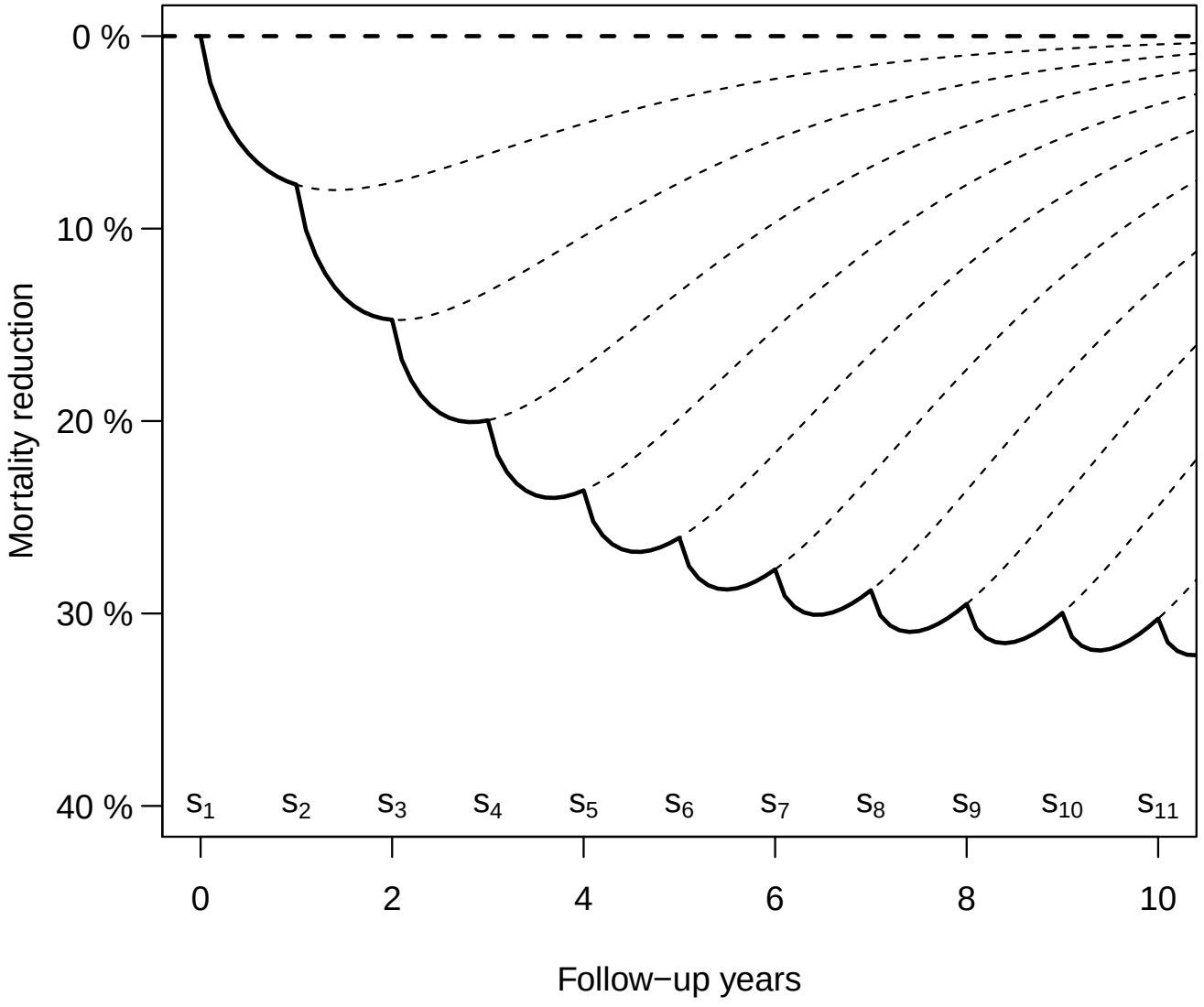
3rd round


0 %
10 %
20 %
30 %
40 %
Mortality reduction
1−(1−0.032)(1−0.045)(1−0.061)
$T_0 = 5$
0
2
4
6
8
10
$s_3 = 2$
Follow−up years

All 3 rounds


0 %
10 %
20 %
30 %
40 %
Mortality reduction
0.133
$T_0 = 5$
0
2
4
6
8
10
$s_1 = 0$ $s_2 = 1$ $s_3 = 2$
Follow−up years

And so on


0 %
10 %
20 %
30 %
40 %
Mortality reduction
s_1 s_2 s_3 s_4 s_5 s_6 s_7 s_8 s_9 s_{10} s_{11}
0
2
4
6
8
10
Follow−up years

LUNG CANCER

The US National Lung Screening Trial (NLST)

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.

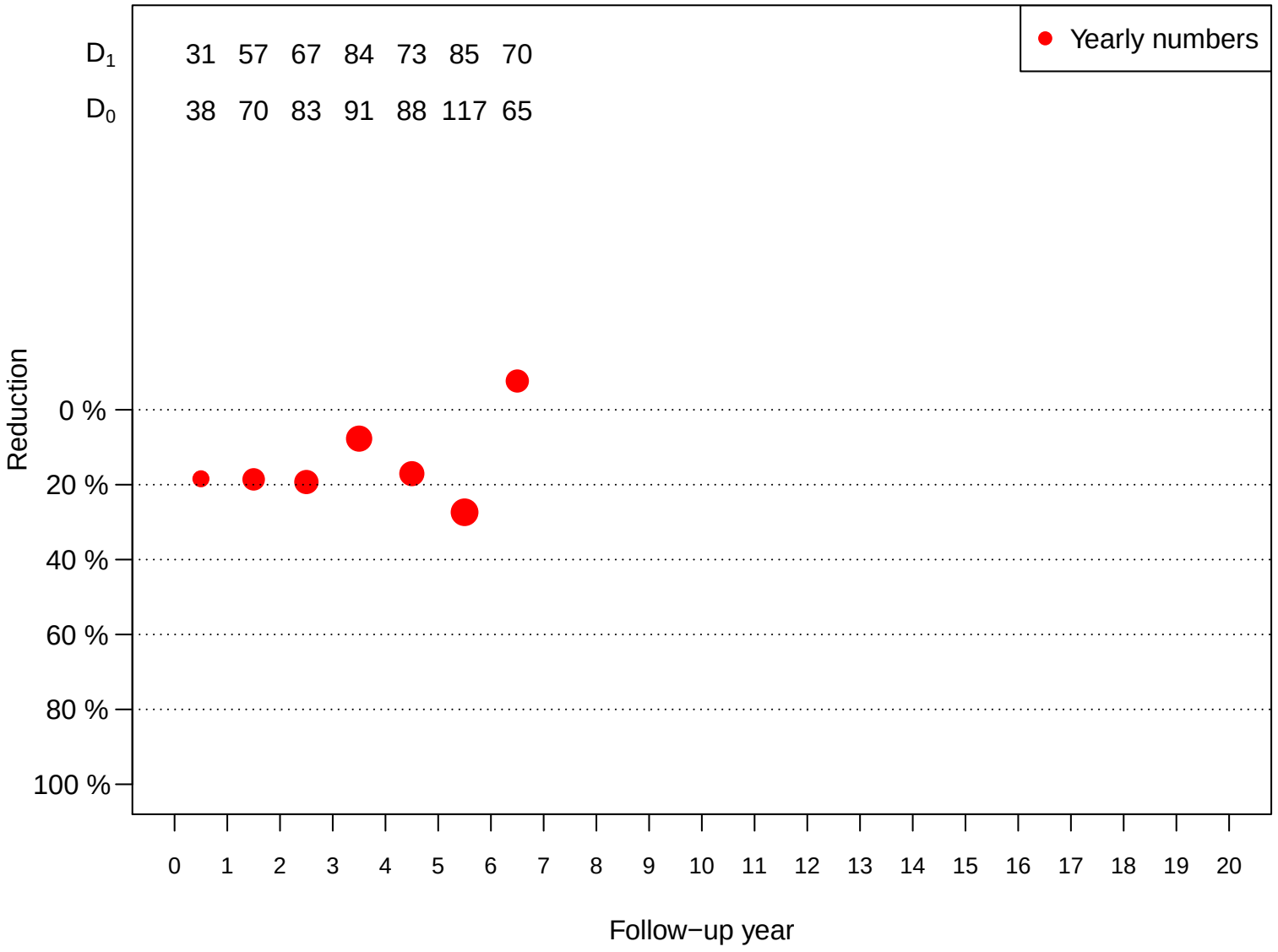
NLST

- 53,454 smokers randomized to either low-dose CT scans or chest X-rays.
- Cumulative lung cancer mortality reduction (CT vs. X-ray) after 7 years of follow-up:

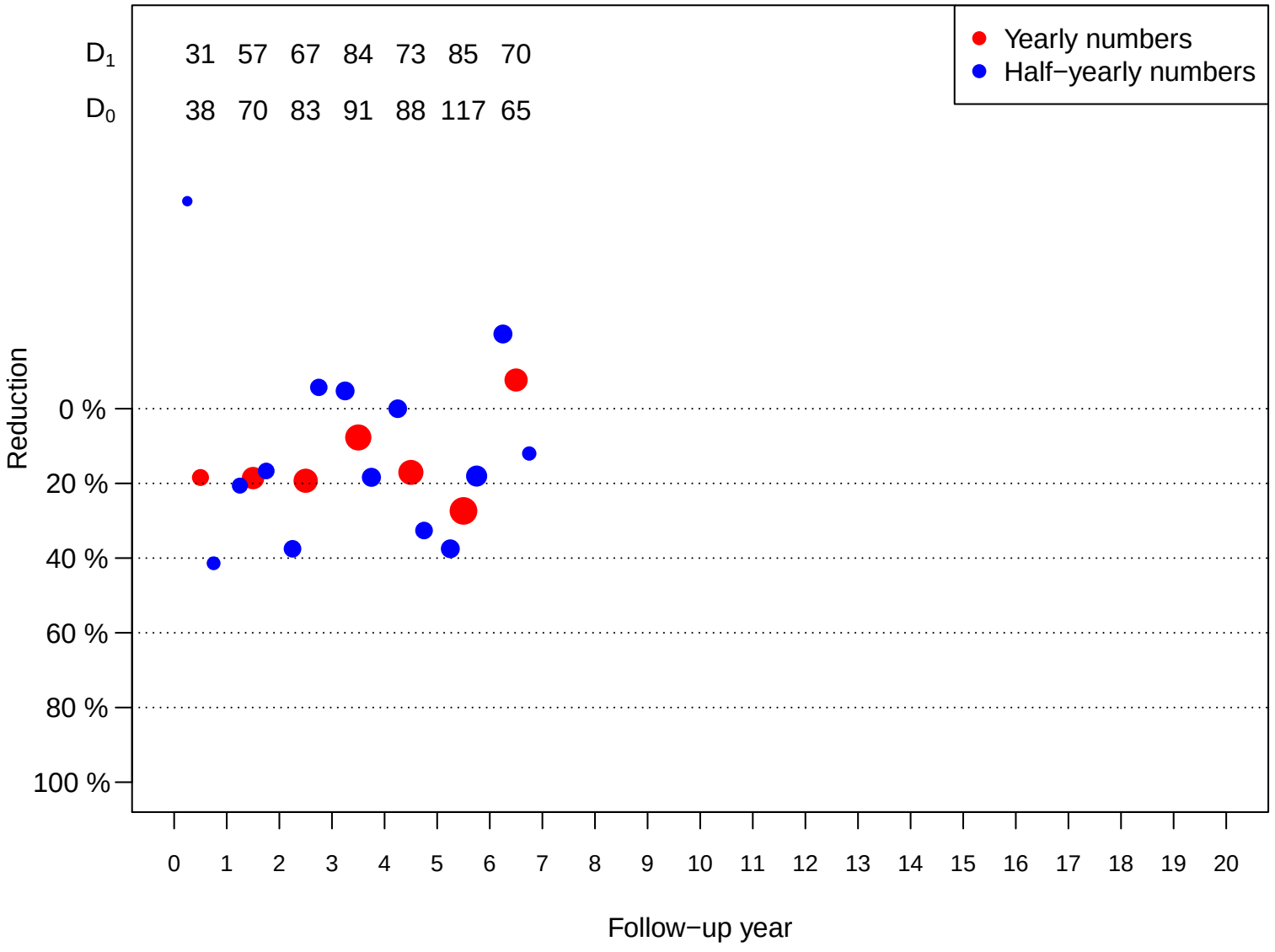
$$1 - \frac{467}{552} \approx 15\%.$$

- Screening was discontinued after 3 years; the impact on mortality had already faded by the last year of follow-up.
- What if the screening had been continued?

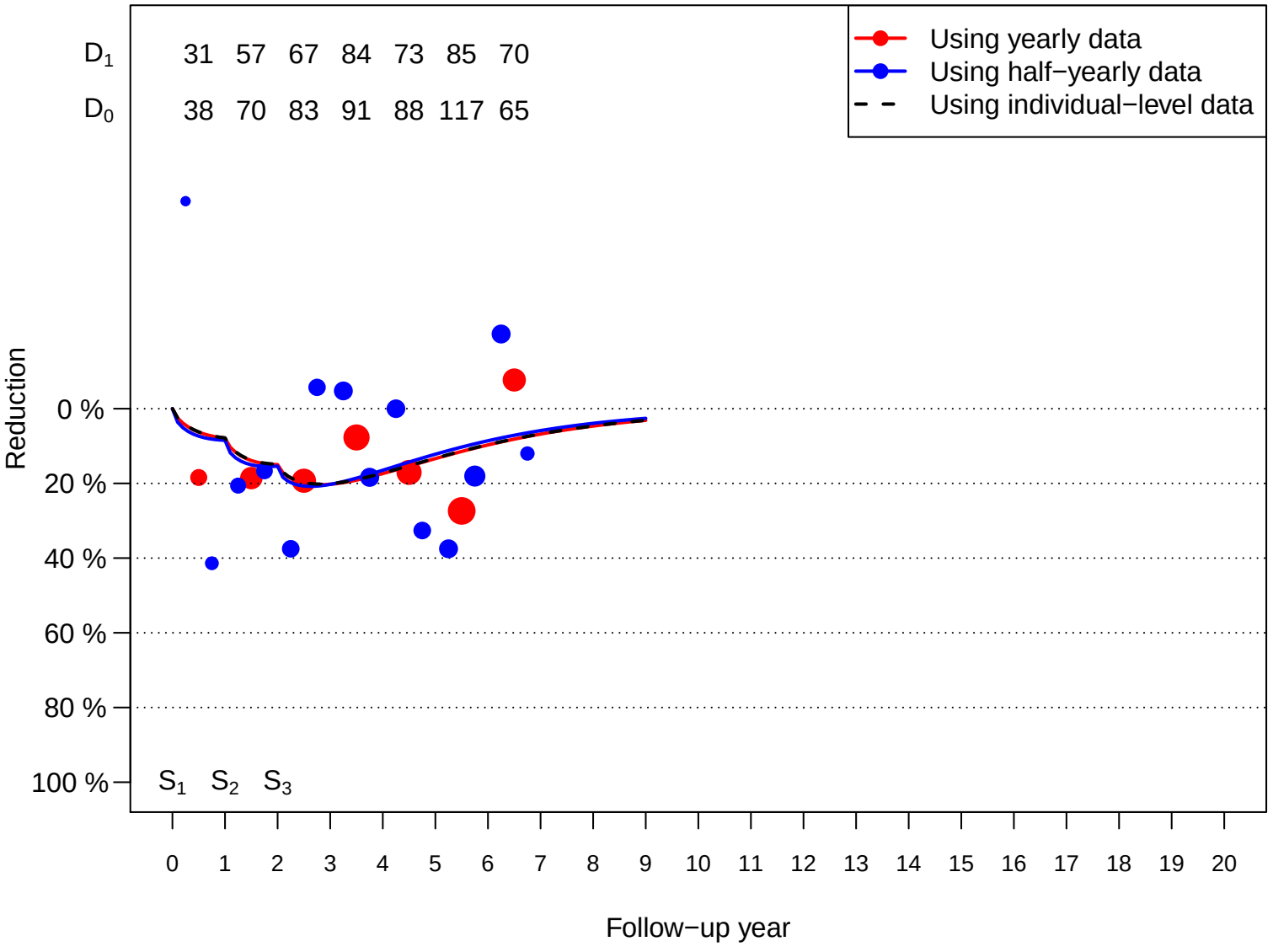
NLST data


Yearly numbers
D1 31 57 67 84 73 85 70
D0 38 70 83 91 88 117 65
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Follow−up year

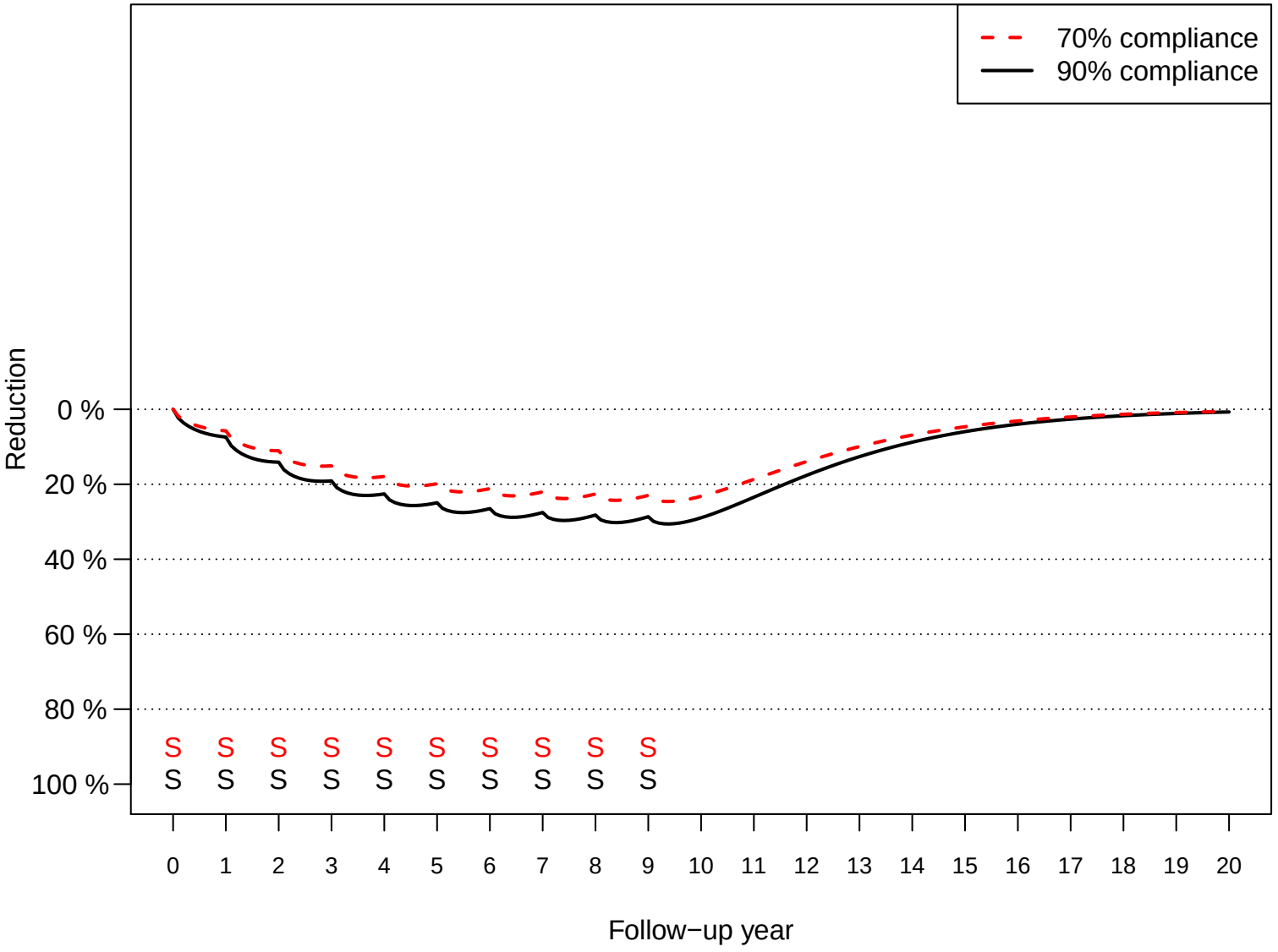
NLST data (2)


D1 31 57 67 84 73 85 70
D0 38 70 83 91 88 117 65
Yearly numbers
Half−yearly numbers
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Follow−up year

NLST fit


Using yearly data
Using half−yearly data
Using individual−level data
D1 31 57 67 84 73 85 70
D0 38 70 83 91 88 117 65
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
S1 S2 S3
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Follow−up year

NLST projection



COLON CANCER

The Minnesota Colon Cancer Control Study (MCCCS)

The NEW ENGLAND JOURNAL of MEDICINE

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.

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

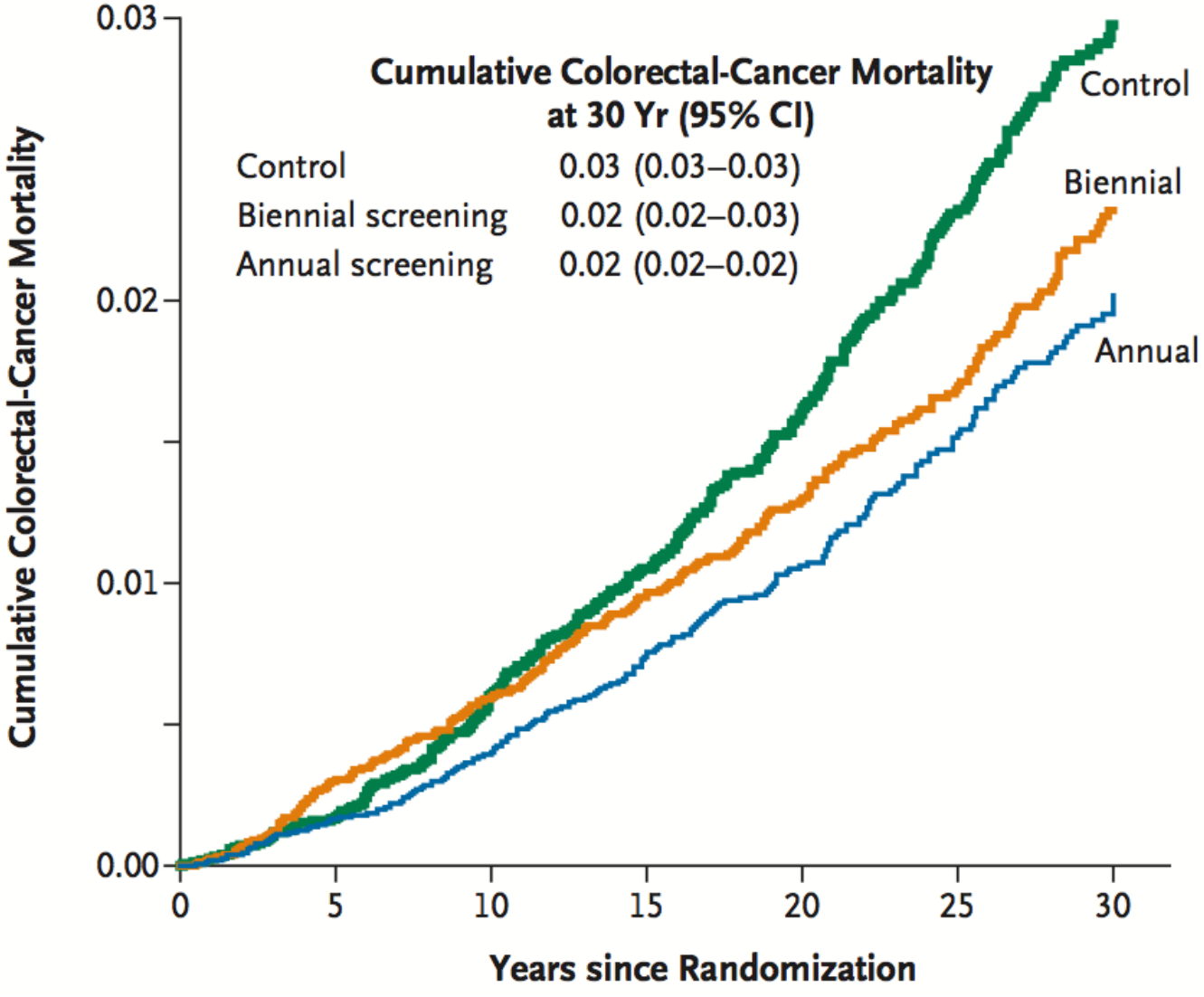
MCCCS

- 46,551 healthy volunteers randomized to either annual or biennial fecal occult blood (FOB) testing, or control.
- 30 year follow-up.
- Cumulative colorectal cancer mortality reduction (biennial vs. control and annual vs. control) after 30 years of follow-up:

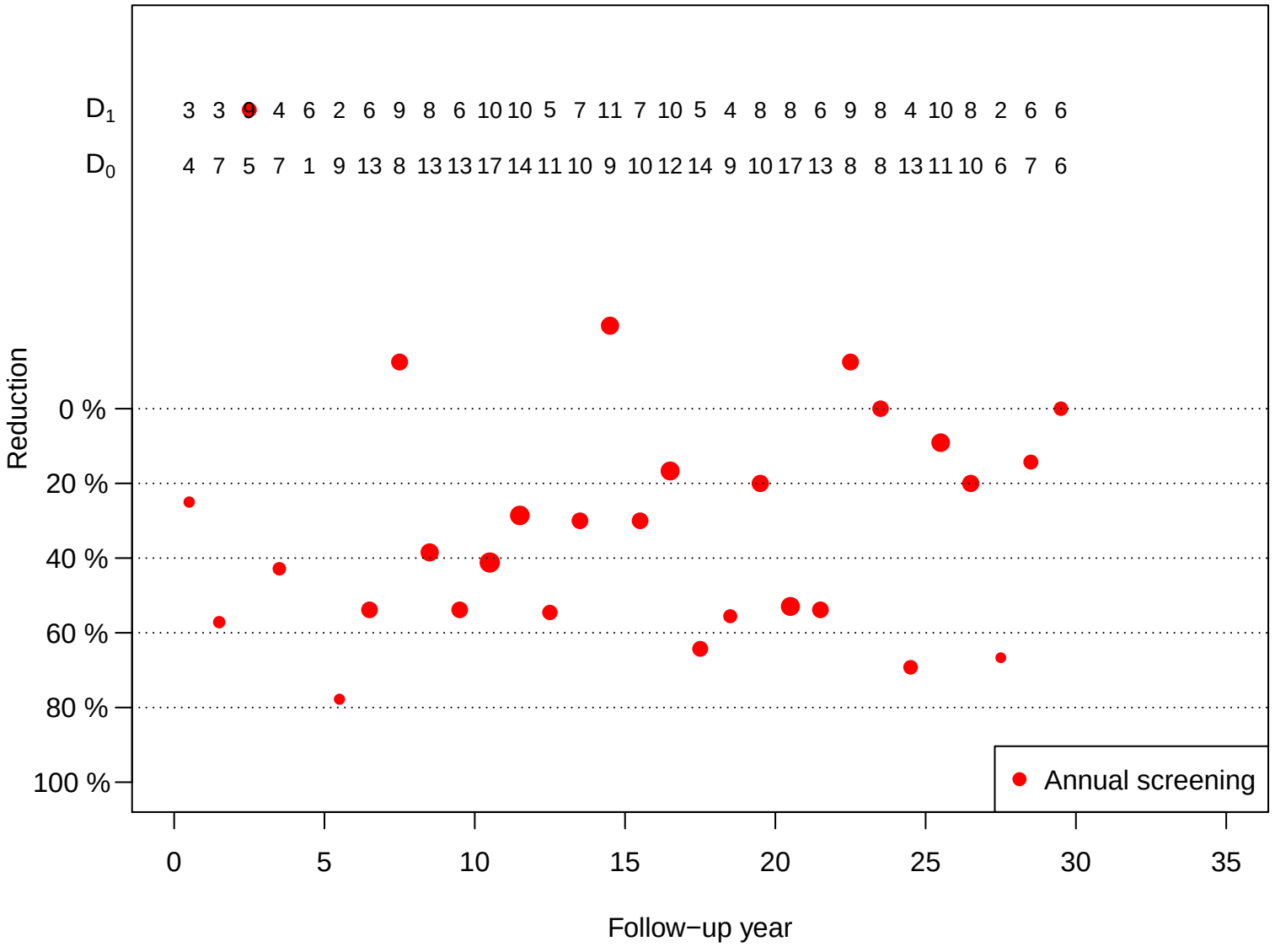
$$1 - \frac{237}{295} \approx 20\% \quad \text{and} \quad 1 - \frac{200}{295} \approx 32\%.$$

- Feature: 4-year funding-related hiatus in screening.
- Presumably, the reductions would have been larger without such an interruption.

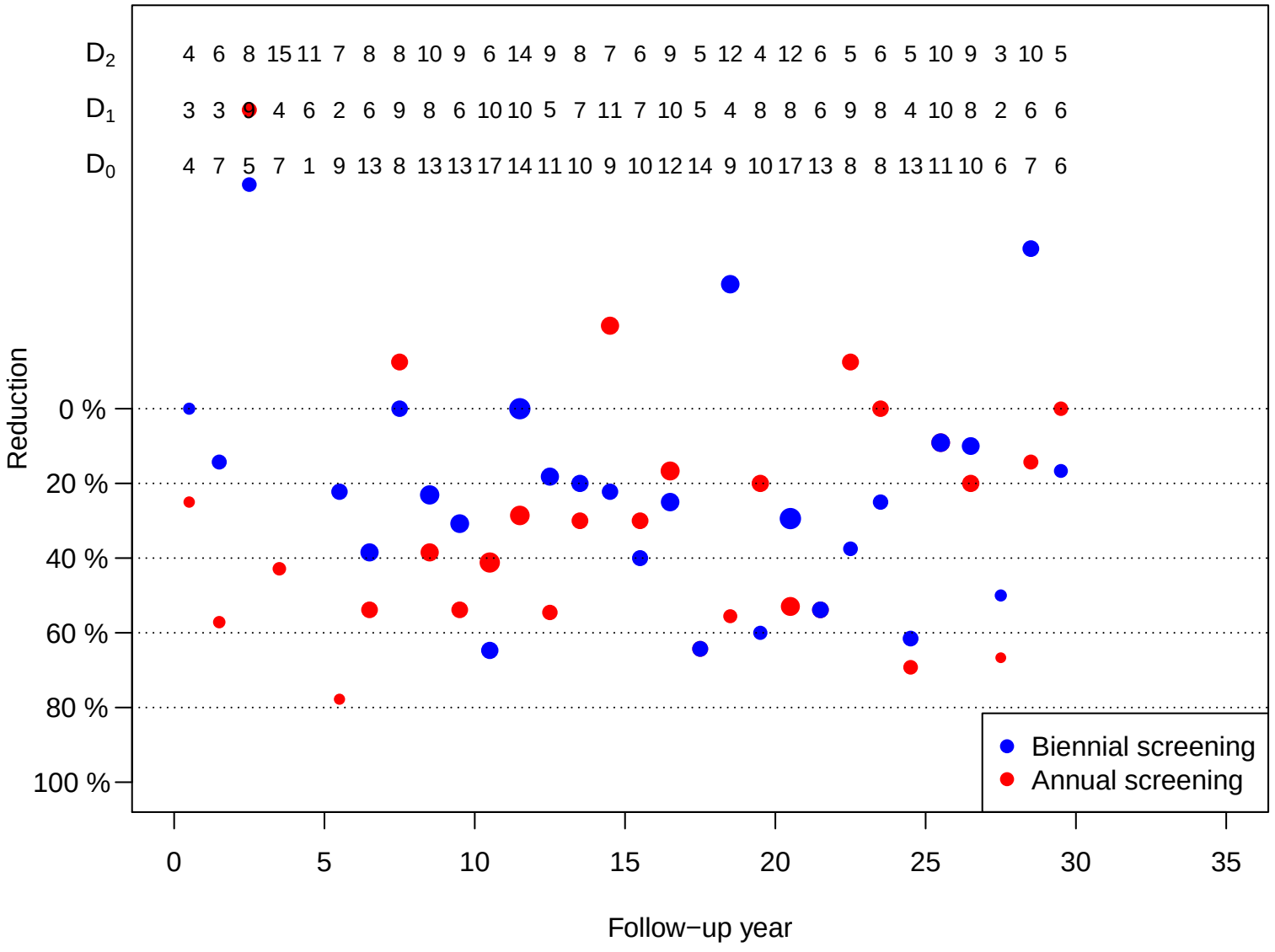
MCCCS cumulative mortality



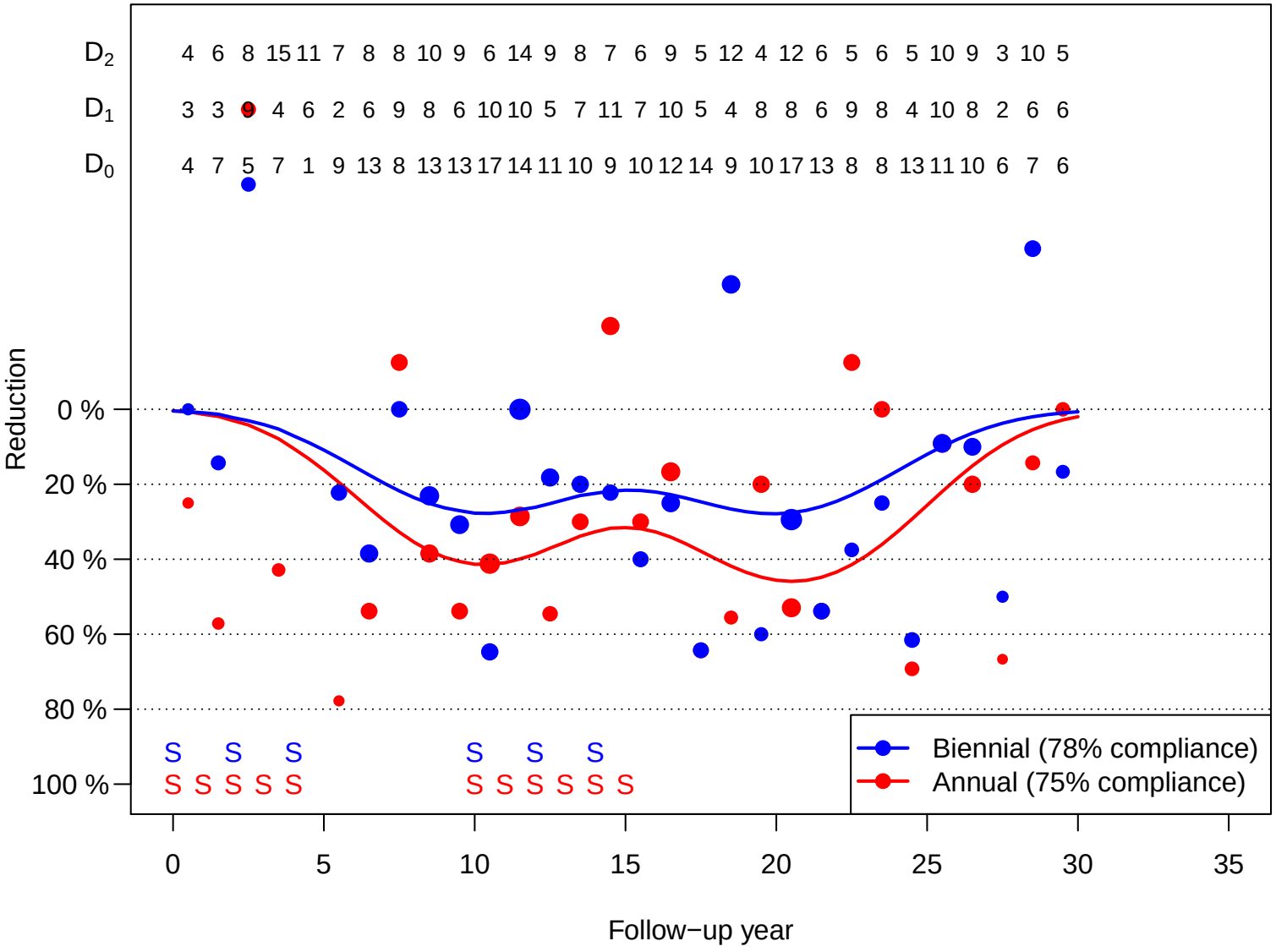
MCCCS yearly data



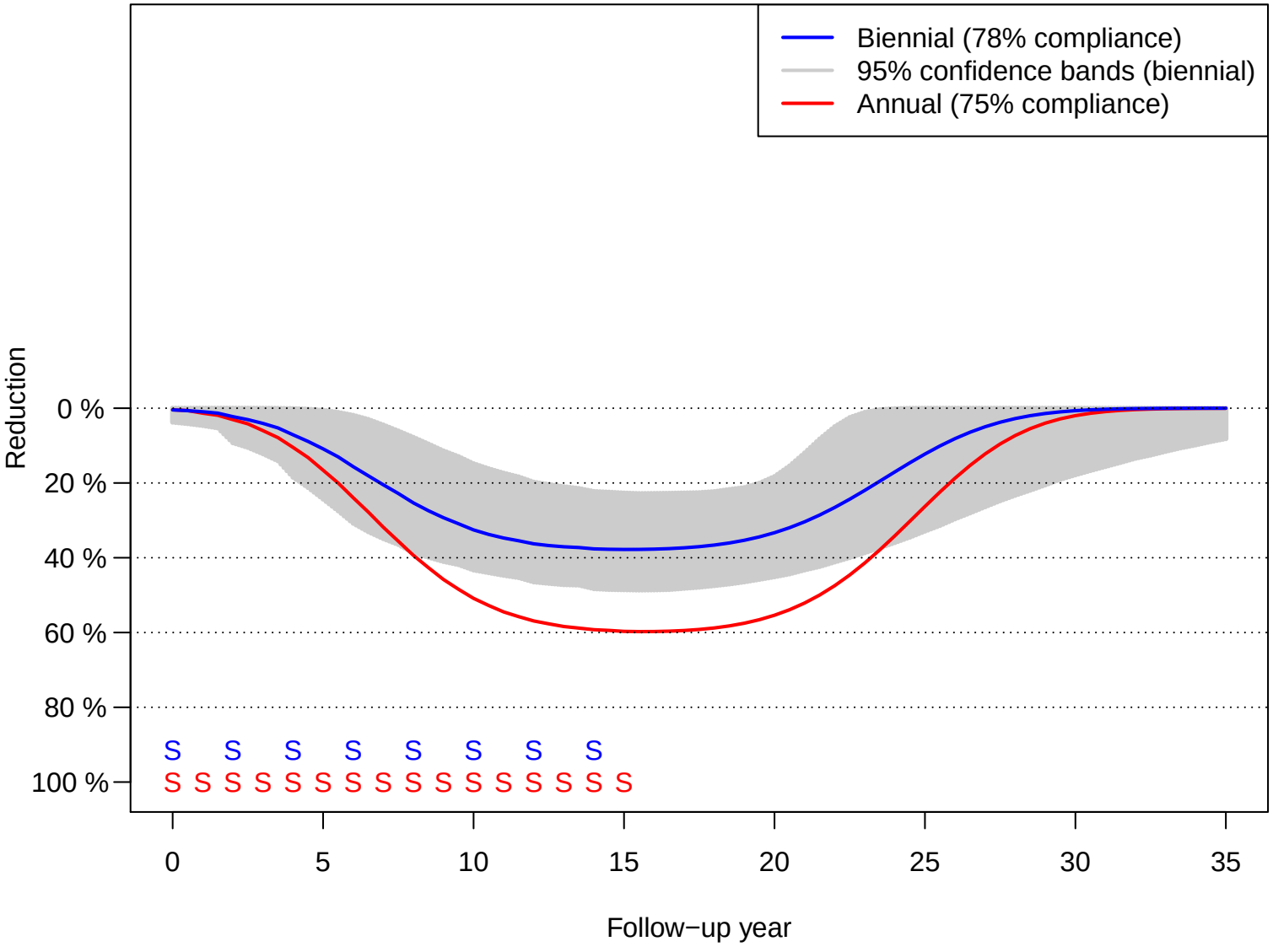
MCCCS yearly data (2)



MCCCS fit


D2 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
D1 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
D0 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 S S
Biennial (78% compliance)
Annual (75% compliance)
0 5 10 15 20 25 30 35
Follow−up year

MCCCS projection



MCCCS (and other) data

- Separate data on each of 2 screening regimens, but all 3 arms used to estimate impact of 1 round
- Could also combine log-likelihoods from different studies (with possibly different schedules) of same screening test to estimate impact of 1 round
  (like adding rows to design matrix for a regression model)

- Staggered entry, so timing of 4-year funding-related hiatus not as simple as displayed.
- Limited to data scraped from Figure in NEJM article

Parametric forms of ‘1-round reduction’ functions

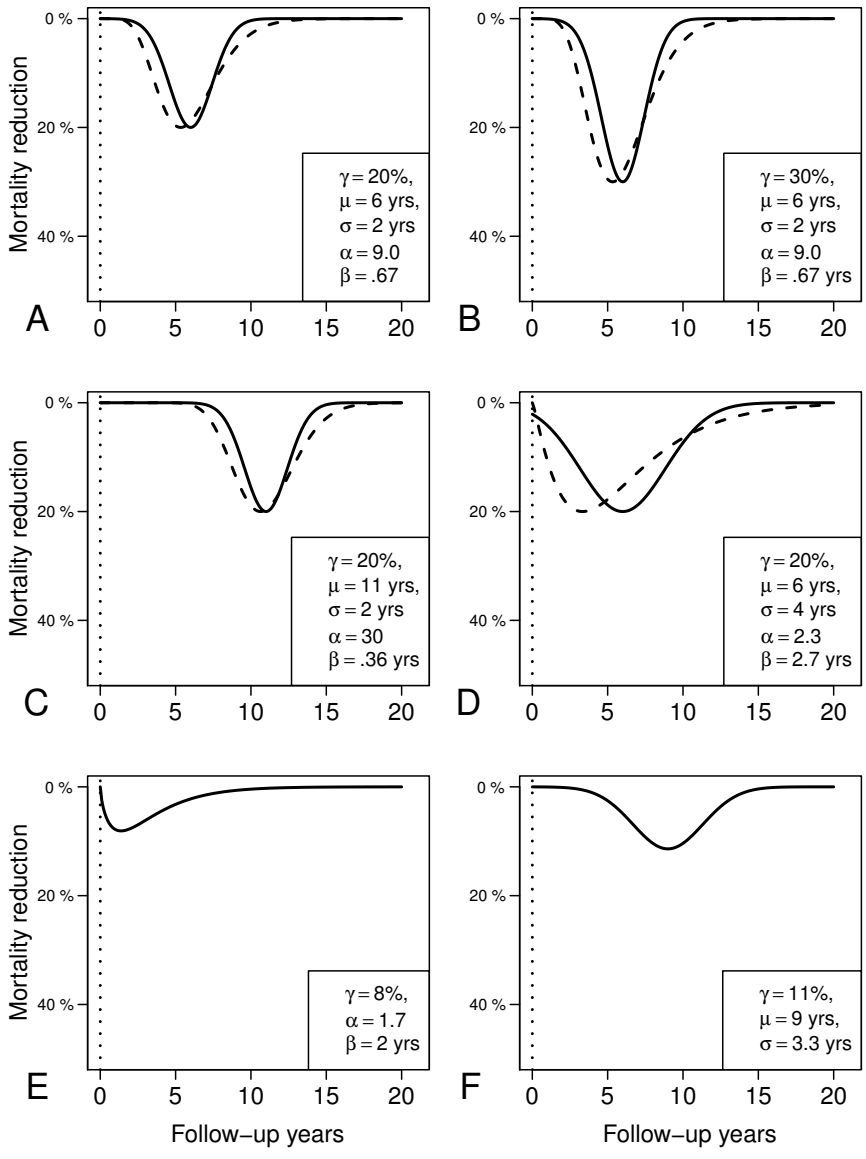


Fig. 2. Impact of a single round of screening at time $s_1 = 0$, with different patterns determined by different parameter inputs. Solid and dashed lines correspond to Gaussian-like and Gamma-like functions, respectively.

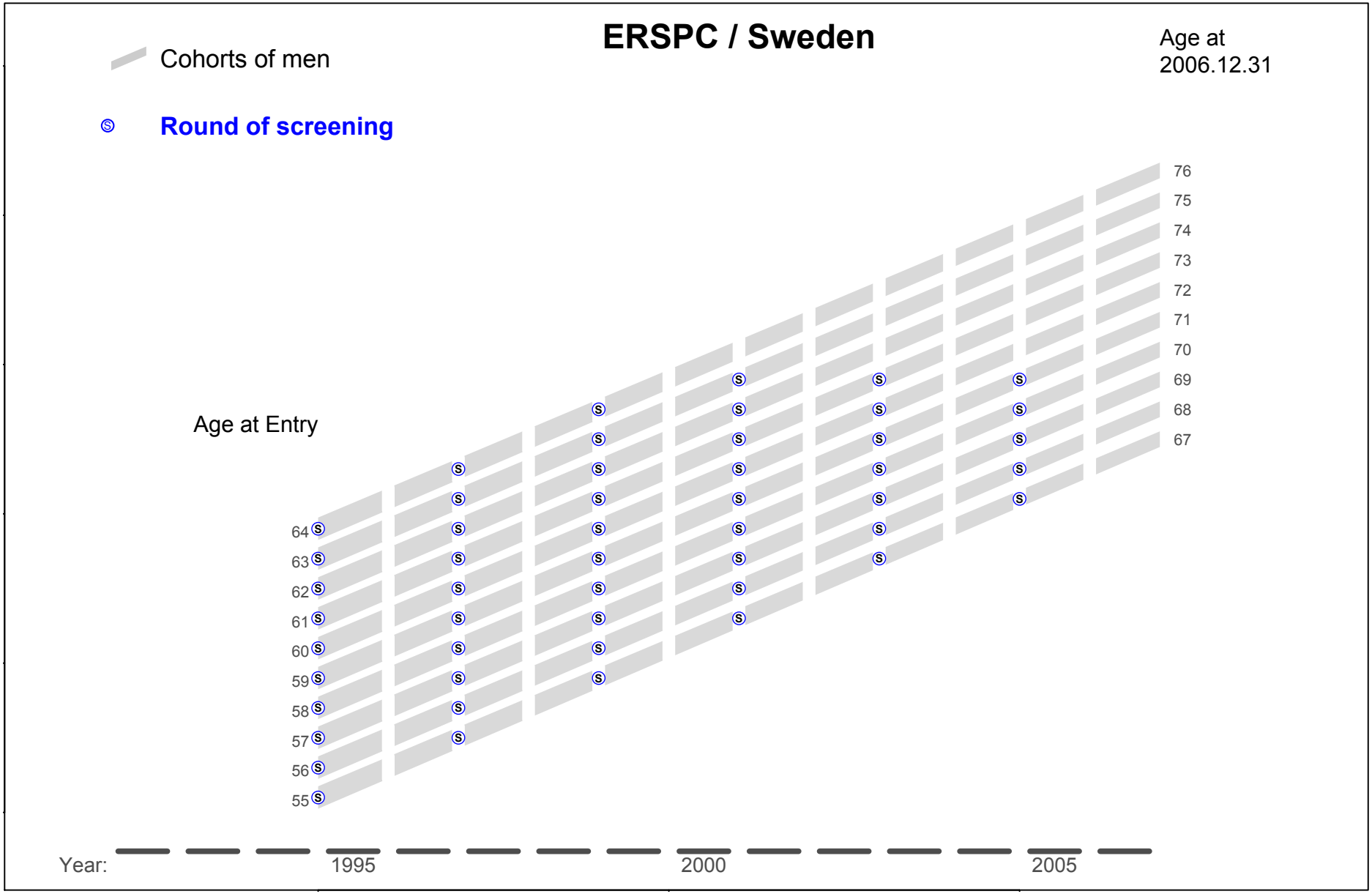
Panels A-D are hypothetical;

Panel E: fitted to the NLST data,

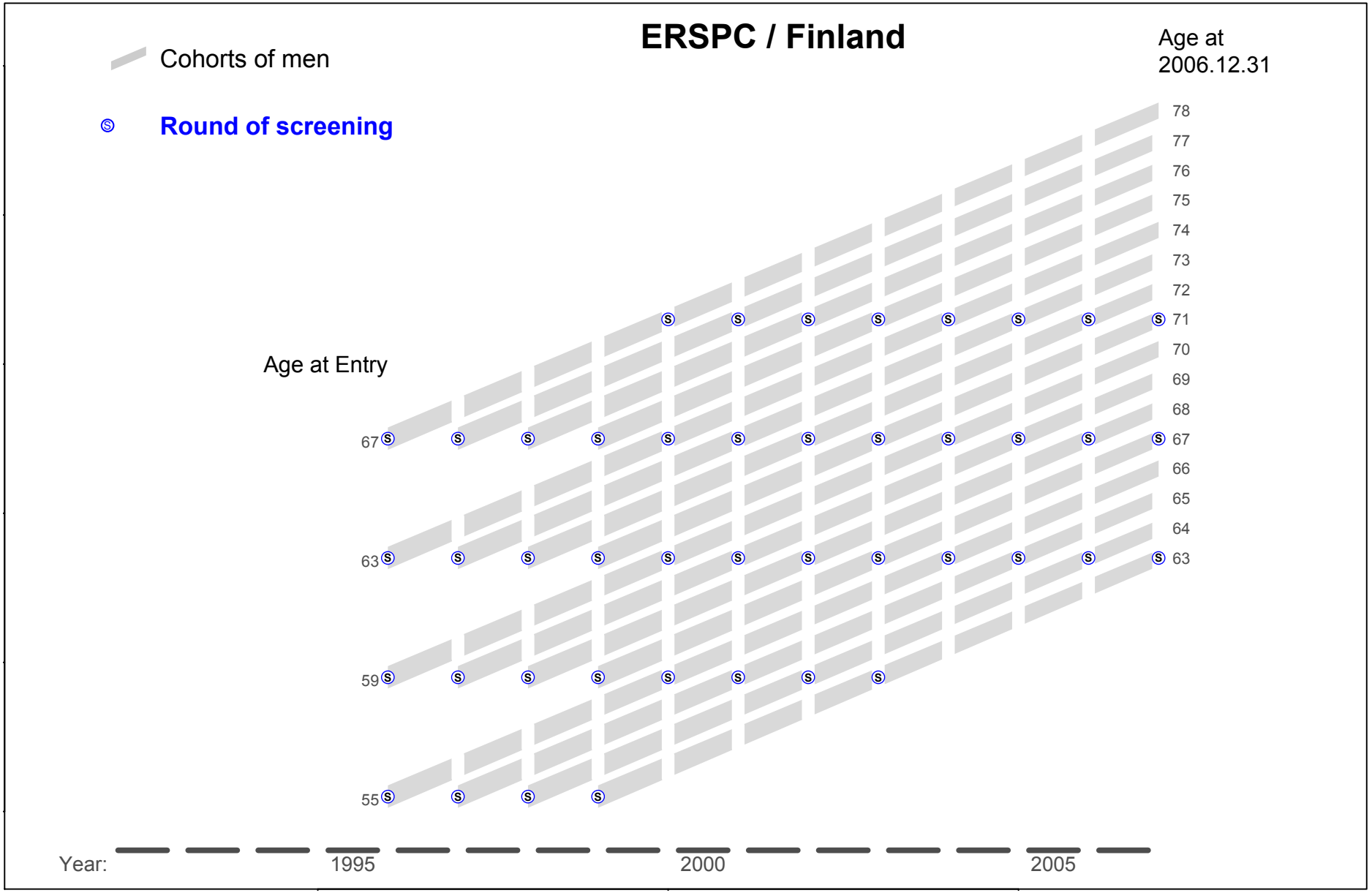
Panel F: fitted to the MCCCS data.

2014: BACK TO PROSTATE CANCER

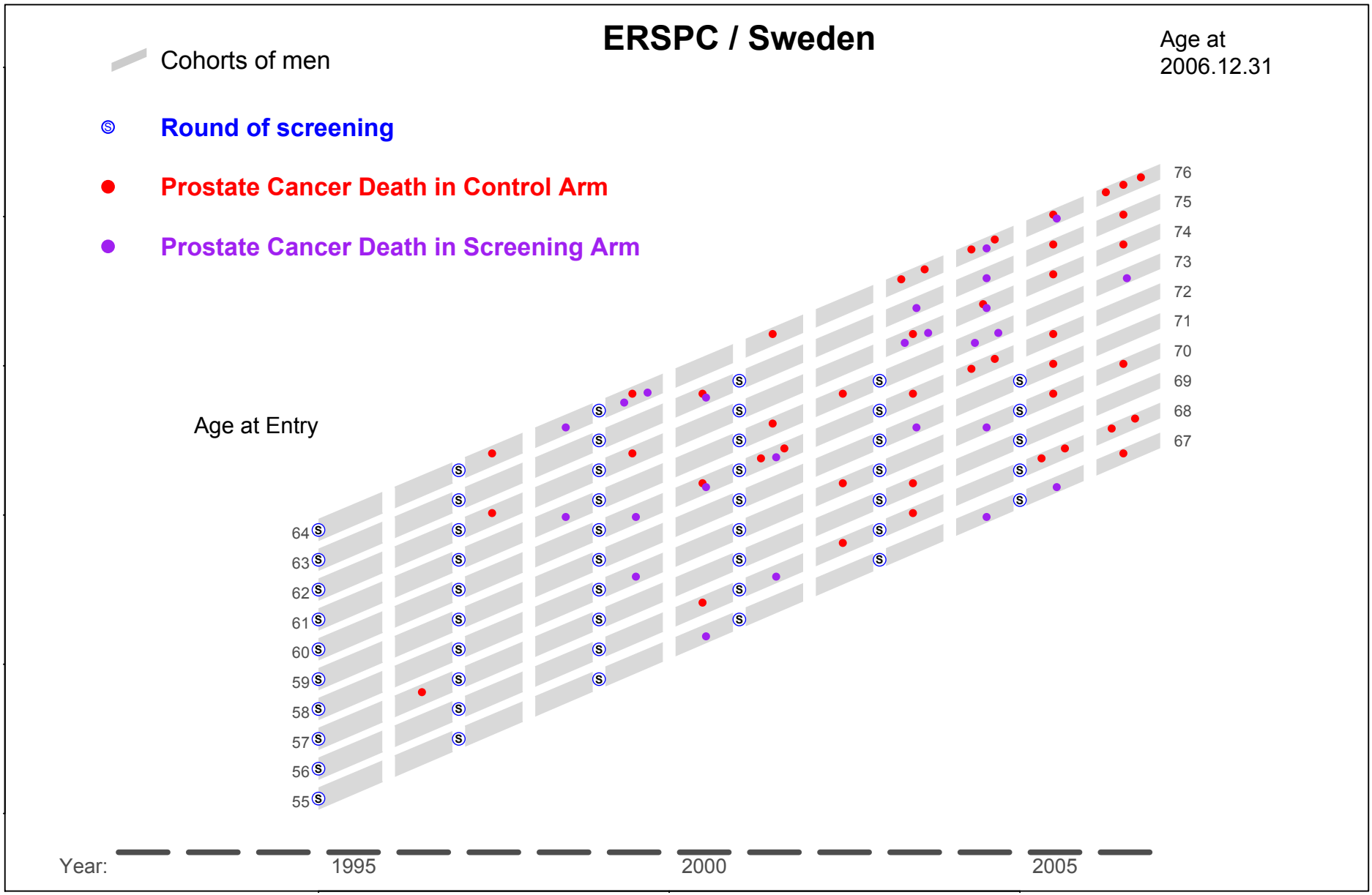
Screening schedule



Screening schedule



Numbers of Deaths



Data required to estimate 3 parameters $(\theta_1, \theta_2, \theta_3)$

Country	Lexis Rectangle		Screening History	ManYears	% Screening	No. Deaths
	Yr. in Trial	Age	(Scr. arm)	Scr. : Ctl.	Scr. : Ctl.	Scr. : Ctl.
SWEDEN	2	58	S.	1 : 1	70 / 10	0 / 1
...	3	64	S.S	1 : 1	70 / 10	0 / 1
...	3	66	S.S	1 : 1	70 / 10	0 / 1
...	4	64	S.S.	1 : 1	70 / 10	1 / 0
...	4	67	S.S.	1 : 1	70 / 10	1 / 0
...	5	62	S.S.S	1 : 1	70 / 10	1 / 0
...	5	64	S.S.S	1 : 1	70 / 10	1 / 0
...	5	66	S.S.S	1 : 1	70 / 10	0 / 1
...	5	68	S.S.S	1 : 1	70 / 10	2 / 1
...	6	60	S.S.S.	1 : 1	70 / 10	1 / 0
...	6	61	S.S.S.	1 : 1	70 / 10	0 / 1
...	6	65	S.S.S.	1 : 1	70 / 10	1 / 1
...	6	68	S.S.S.	1 : 1	70 / 10	1 / 1
...	7	62	S.S.S.S	1 : 1	70 / 10	1 / 0
...	7	66	S.S.S.S	1 : 1	70 / 10	1 / 2
...	7	67	S.S.S.S	1 : 1	70 / 10	0 / 1
...	7	70	S.S.S..	1 : 1	70 / 10	0 / 1

Country	Lexis Rectangle		Screening History	ManYears	% Screening	No. Deaths
	Yr. in Trial	Age	(Scr. arm)	Scr. : Ctl.	Scr./Ctl.	Scr./Ctl.
...	8	63	S.S.S.S.	1 : 1	70 / 10	0 / 1
...	8	65	S.S.S.S.	1 : 1	70 / 10	0 / 1
...	8	68	S.S.S.S.	1 : 1	70 / 10	0 / 1
...	9	64	S.S.S.S.S	1 : 1	70 / 10	0 / 1
...	9	65	S.S.S.S.S	1 : 1	70 / 10	0 / 1
...	9	67	S.S.S.S.S	1 : 1	70 / 10	1 / 0
...	9	68	S.S.S.S.S	1 : 1	70 / 10	0 / 1
...	9	70	S.S.S.S..	1 : 1	70 / 10	2 / 1
...	9	71	S.S.S....	1 : 1	70 / 10	1 / 0
...	9	72	S.S.S....	1 : 1	70 / 10	0 / 2
...	10	64	S.S.S.S.S.	1 : 1	70 / 10	1 / 0
...	10	67	S.S.S.S.S.	1 : 1	70 / 10	1 / 0
...	10	69	S.S.S.S.S.	1 : 1	70 / 10	0 / 2
...	10	70	S.S.S.S...	1 : 1	70 / 10	2 / 0
...	10	71	S.S.S.S...	1 : 1	70 / 10	1 / 1
...	10	72	S.S.S.....	1 : 1	70 / 10	1 / 0
...	10	73	S.S.S.....	1 : 1	70 / 10	1 / 2

Country	Lexis Rectangle		Screening History	ManYears	% Screening	No. Deaths
	Yr. in Trial	Age	(Scr. arm)	Scr. : Ctl.	Scr./Ctl.	Scr./Ctl.
...	11	65	S.S.S.S.S.S	1 : 1	70 / 10	1 / 0
...	11	66	S.S.S.S.S.S	1 : 1	70 / 10	0 / 2
...	11	68	S.S.S.S.S.S	1 : 1	70 / 10	0 / 1
...	11	69	S.S.S.S.S..	1 : 1	70 / 10	0 / 1
...	11	70	S.S.S.S.S..	1 : 1	70 / 10	0 / 1
...	11	72	S.S.S.S....	1 : 1	70 / 10	0 / 1
...	11	73	S.S.S.....	1 : 1	70 / 10	0 / 1
...	11	74	S.S.S.....	1 : 1	70 / 10	1 / 1
...	12	66	S.S.S.S.S.S.	1 : 1	70 / 10	0 / 1
...	12	67	S.S.S.S.S.S.	1 : 1	70 / 10	0 / 2
...	12	69	S.S.S.S.S.S.	1 : 1	70 / 10	0 / 1
...	12	72	S.S.S.S.....	1 : 1	70 / 10	1 / 0
...	12	73	S.S.S.S.....	1 : 1	70 / 10	0 / 1
...	12	74	S.S.S.....	1 : 1	70 / 10	0 / 1
...	12	75	S.S.S.....	1 : 1	70 / 10	0 / 3

Country	Lexis Rectangle		Screening History	ManYears	% Screening	No. Deaths
	Yr. in Trial	Age	(Scr. arm)	Scr. : Ctl.	Scr.:Ctl.	Scr./Ctl.
FINLAND	2	68	S.	1 : 1.2	75 : 5	? : ?
...	7	71	S...S..	1 : 1.2	75 : 5	? : ?
...	11	78	S...S.....	1 : 1.2	75 / 5	? : ?
...	...	...	...	...	...	...
N-LANDS	10	75	S...S....	1 : 1	70 / 10	? : ?
...	12	80	S..........	1 : 1	70 / 10	? : ?
...	12	80	S..........	1 : 1	70 / 10	? : ?
...						
BELGIUM	etc	etc	?	1 : 1	78 / 12	? : ?
...	...	...	?	1 : 1	78 / 12	? : ?
ITALY	etc	etc	?	1 : 1	72 / 11	? : ?
...	...	...	?	1 : 1	72 / 11	? : ?
SUISSE	etc	etc	?	1 : 1	74 / 13	? : ?
...	...	...	?	1 : 1	74 / 13	? : ?
SPAIN	etc	etc	?	1 : 1	70 / 10	1 : 0
...	etc	etc	?	1 : 1	72 : 12	1 : 0
...	etc	etc	?	1 : 1	72 : 12	0 : 1

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