Measuring the Mortality Reductions due to Cancer Screening

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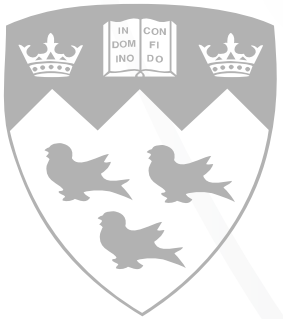
PhD Defense

3 October 2014



Cancer Screening

- "Screening for a cancer is pursuit of its early, presymptomatic diagnosis" in order to "achieve enhanced curability of the cancer". (Miettinen 2013).
- Randomized trials are often used to study whether screening serves its purpose.
- Cancer specific mortality reduction is considered as the definitive measure of the benefits.
- Screening itself is not an intervention; the benefits are due to successful early treatment.

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Objective

- Because of cost considerations, a randomized screening trial typically involves only a few (say, annual or biennial) 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**.

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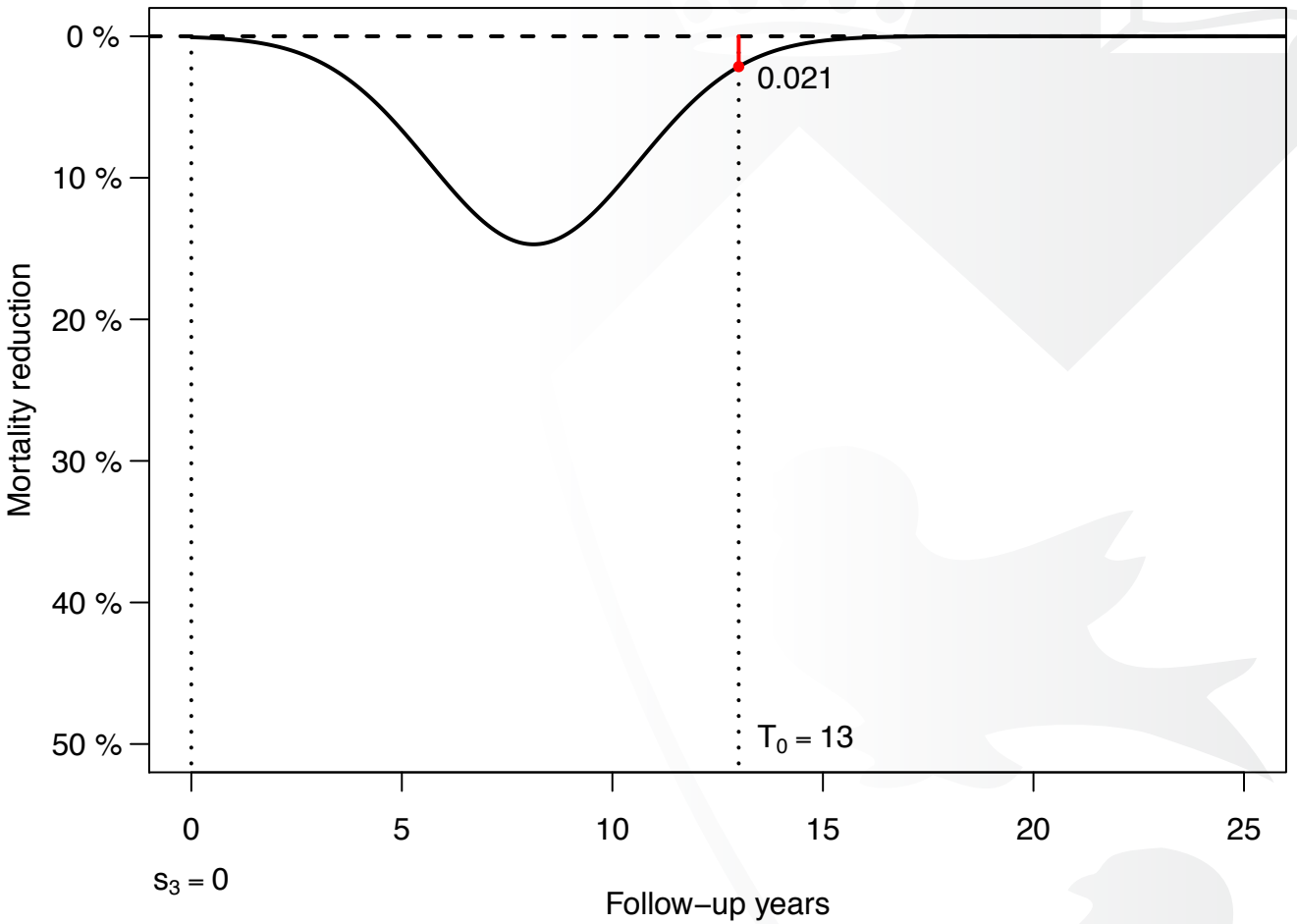
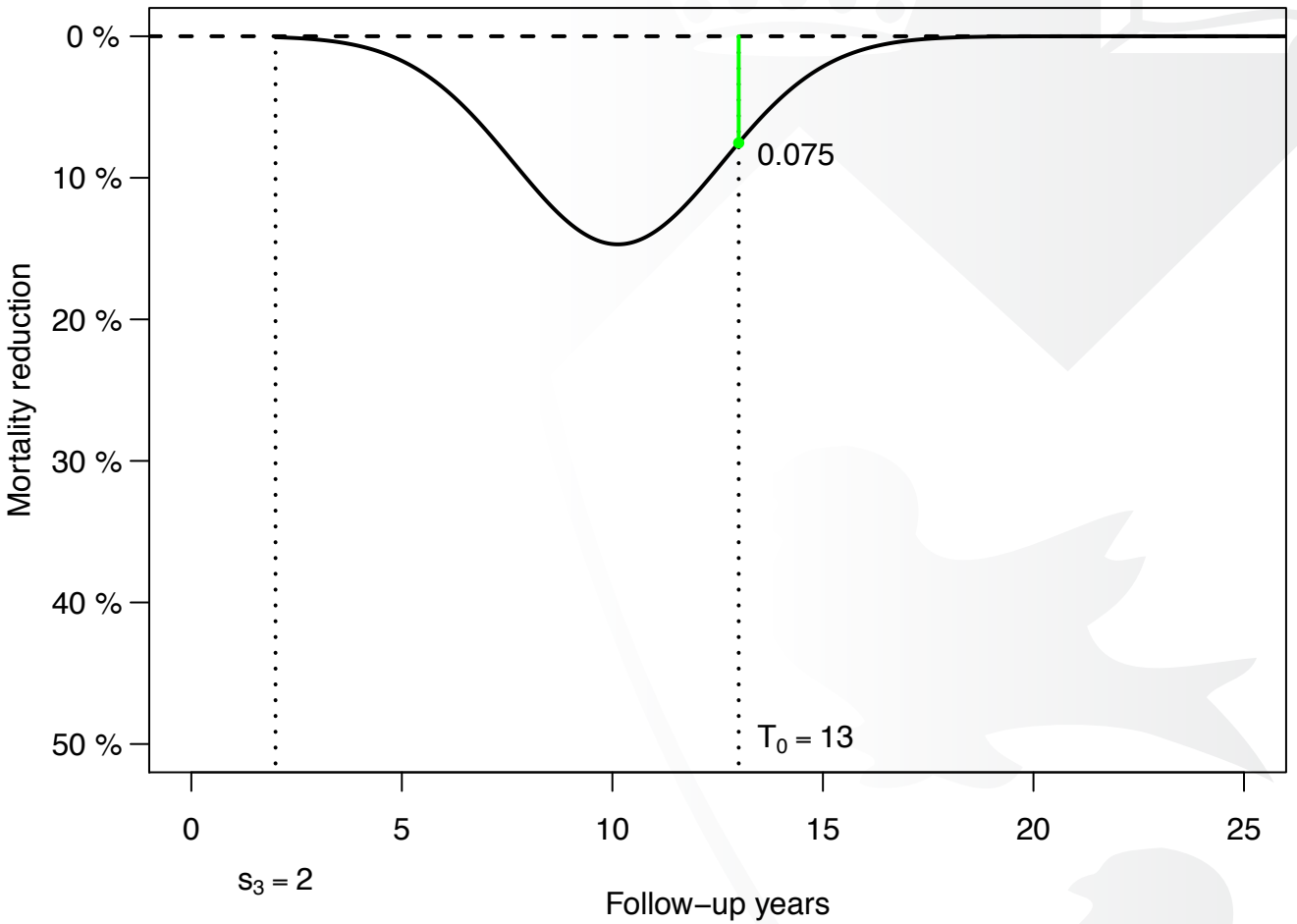
Challenge

- To project the mortality impact, we have to
  1. **decompose** the observed impact in into round-specific ones.
  2. **compound** the round-specific impacts to project that of a screening program.
- These require parametric modeling of the round-specific mortality impact.

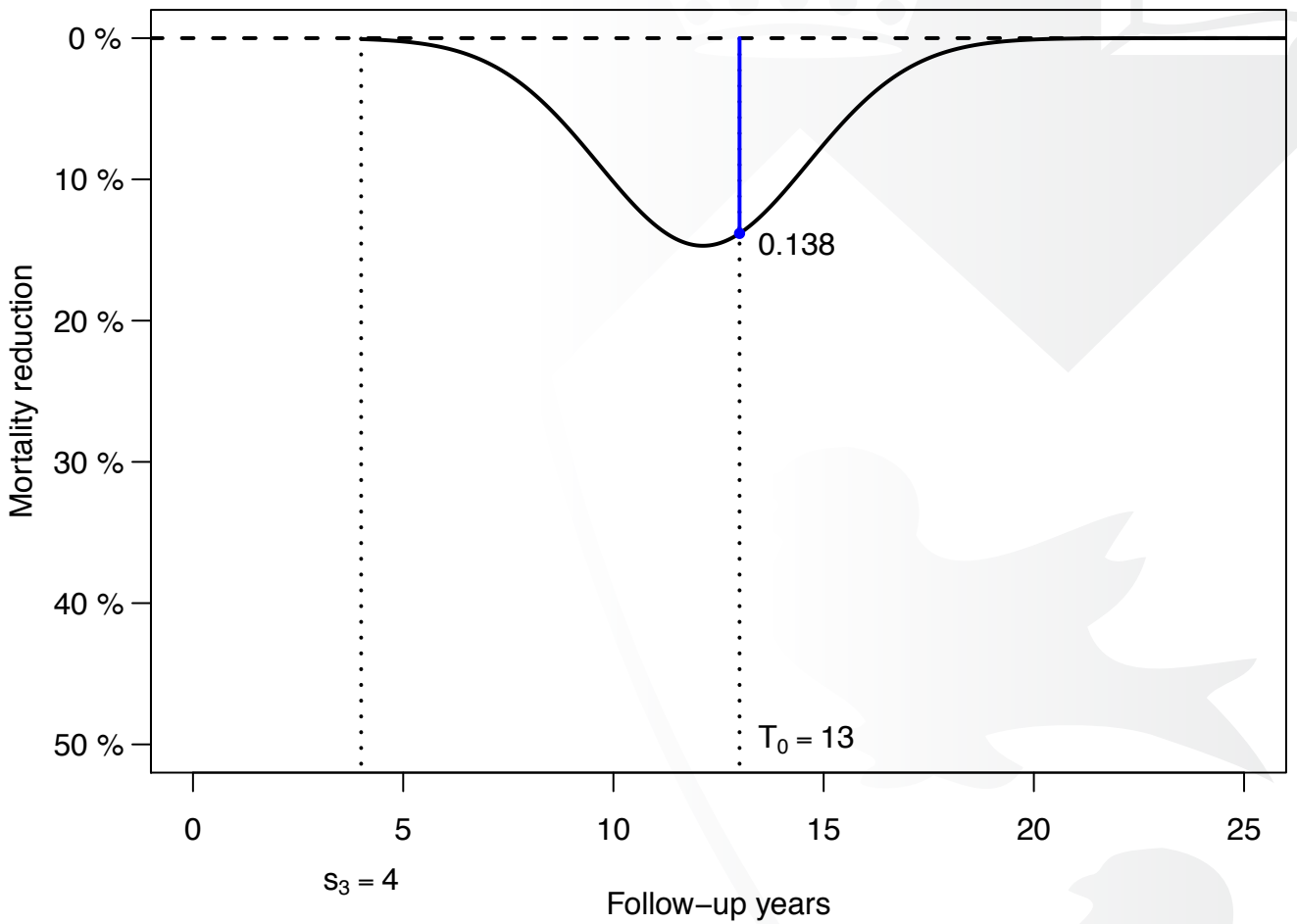
Decomposition: 1st round



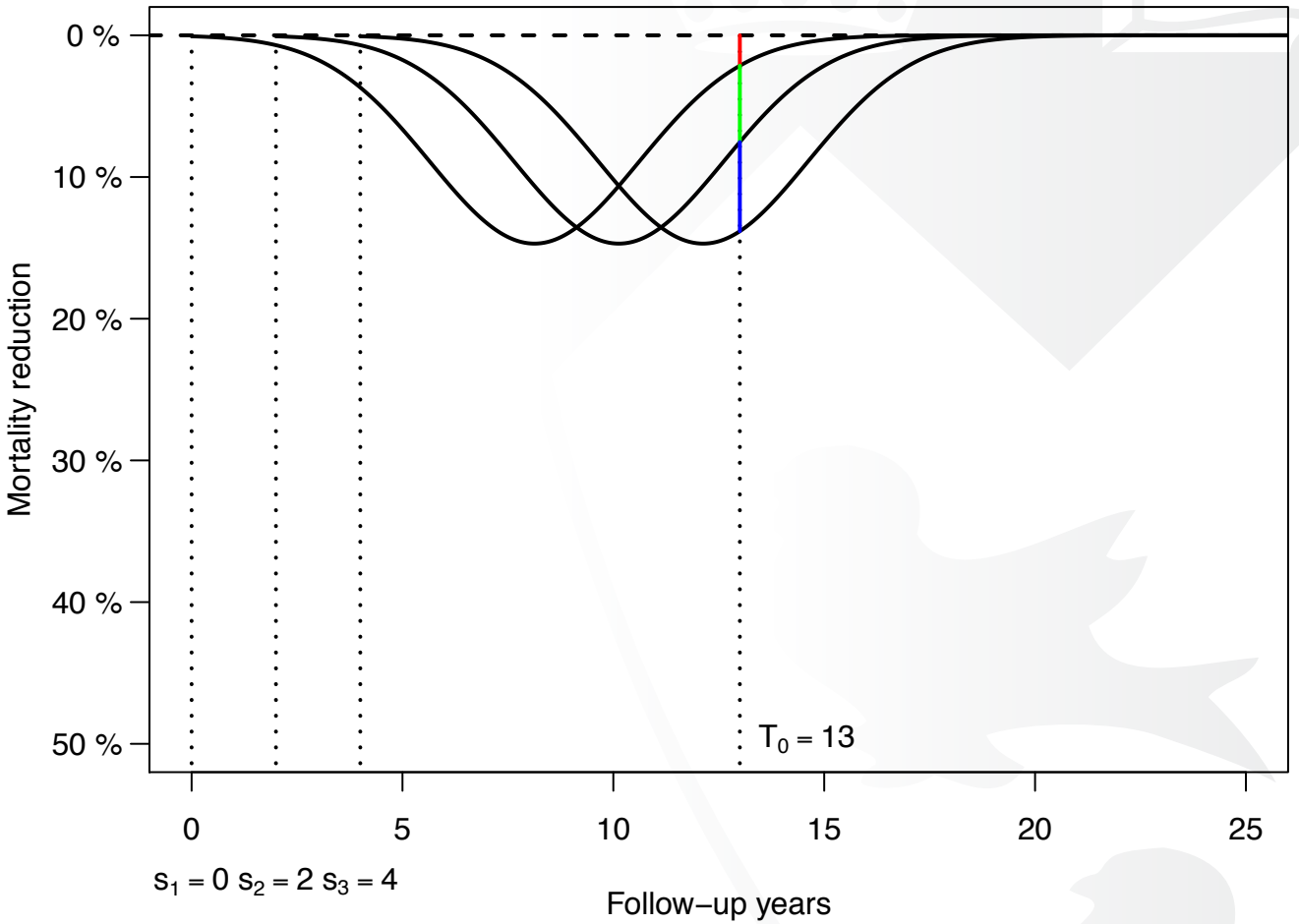
2nd round


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
0.075
$T_0 = 13$
0
5
10
15
20
25
$s_3 = 2$
Follow−up years

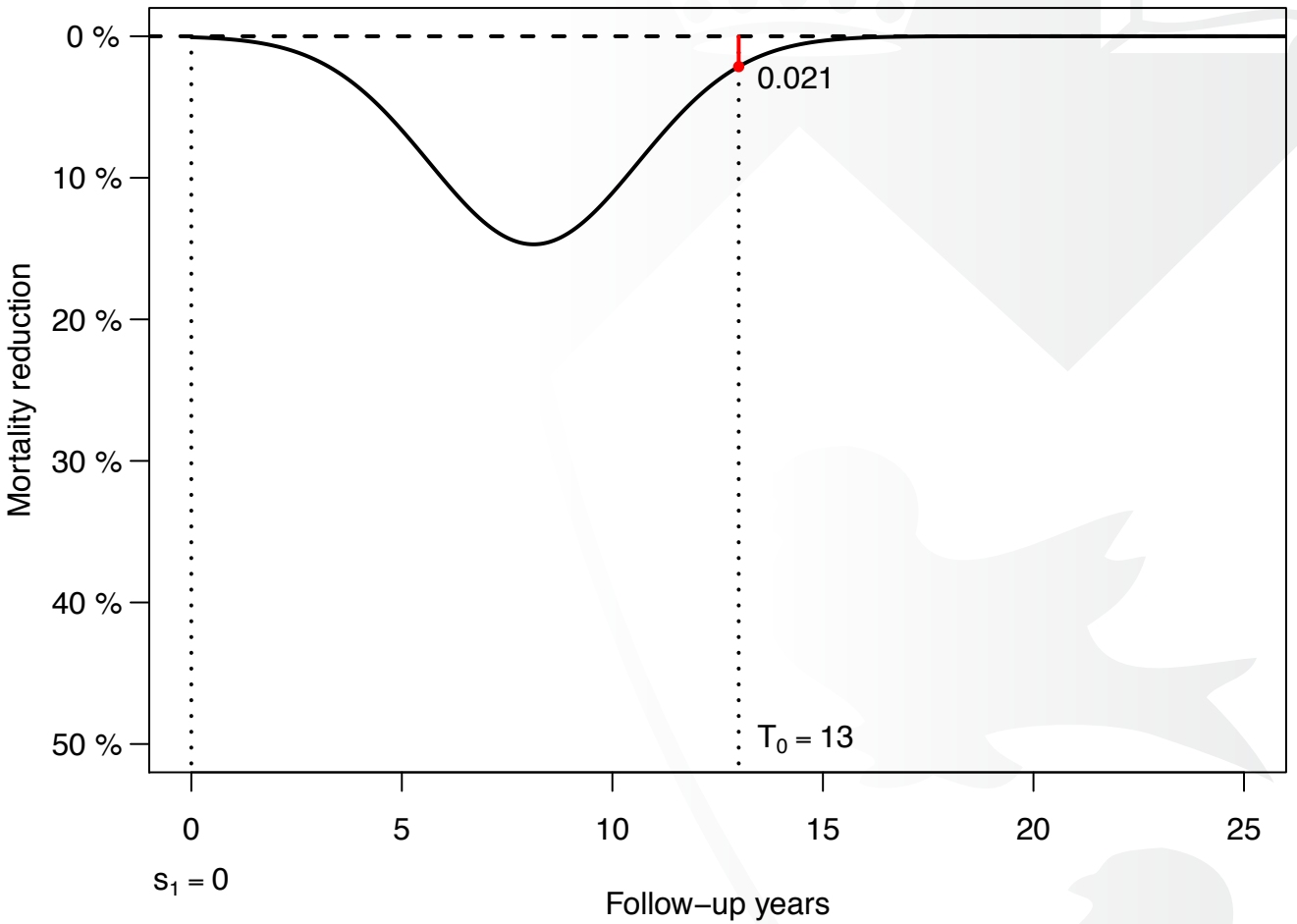
3rd round


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
0.138
$T_0 = 13$
0
5
10
15
20
25
$s_3 = 4$
Follow−up years

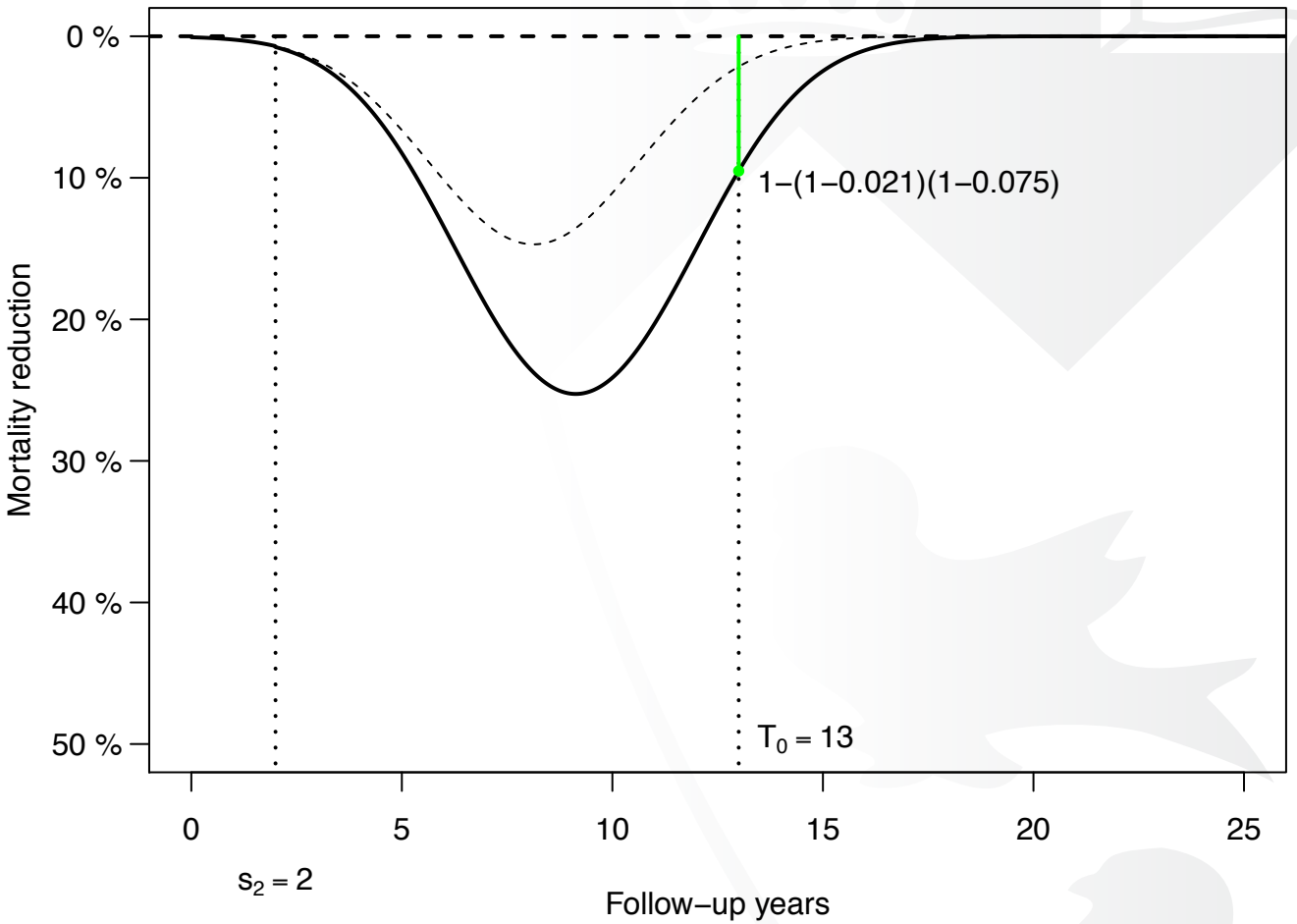
All 3 rounds


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
$T_0 = 13$
0
5
10
15
20
25
$s_1 = 0$ $s_2 = 2$ $s_3 = 4$
Follow−up years

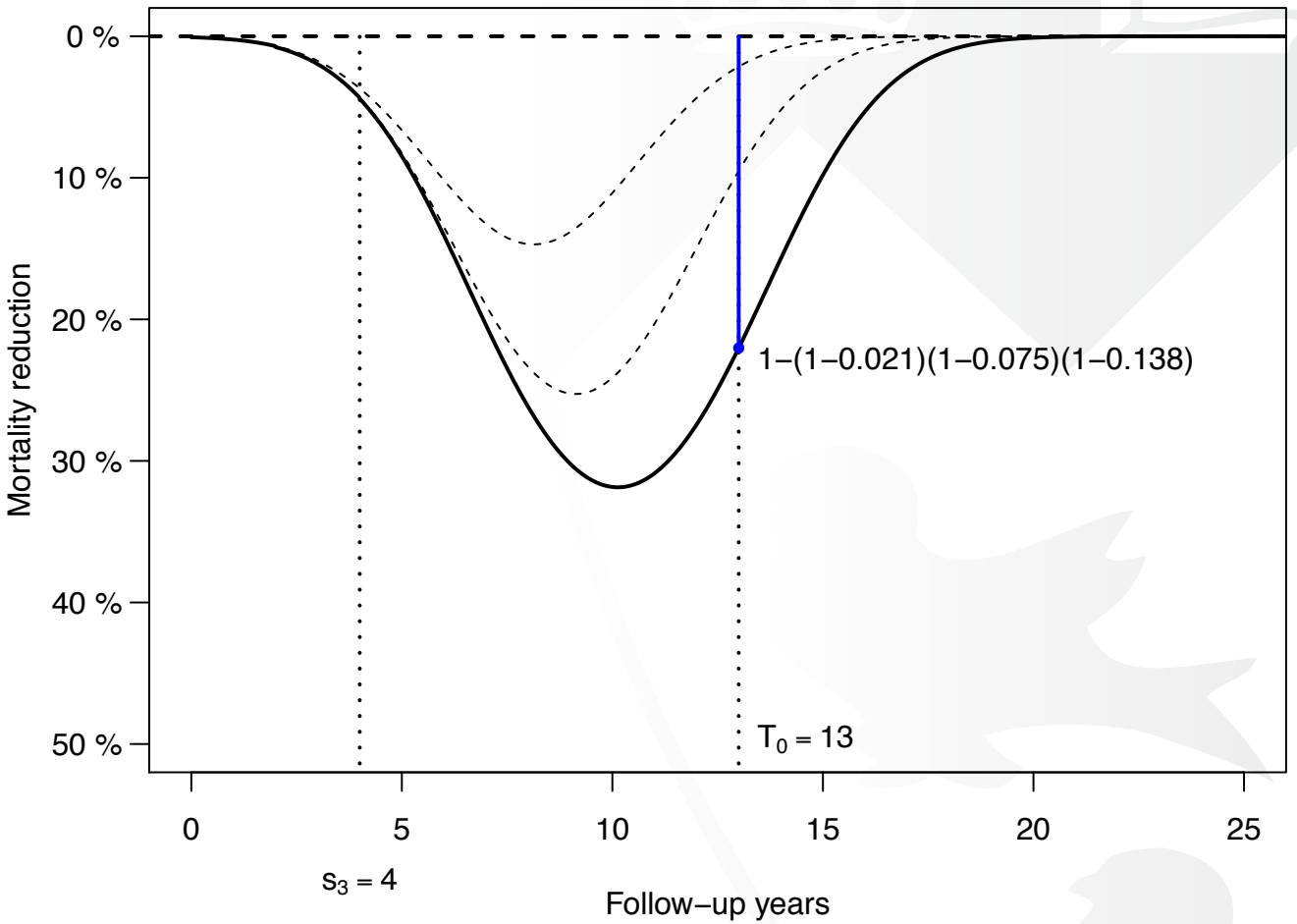
Compound: 1st round



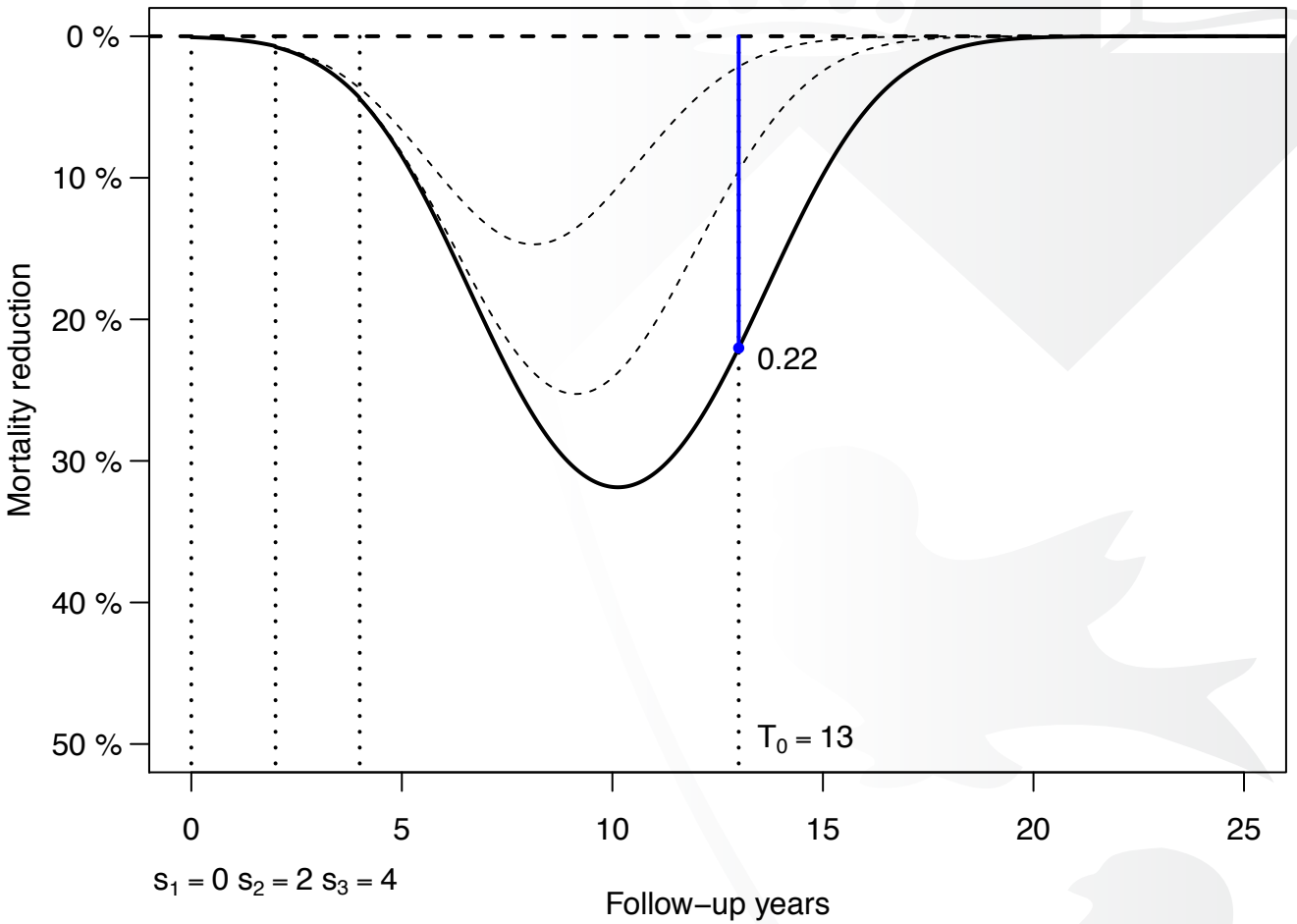
2nd round


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
1−(1−0.021)(1−0.075)
$T_0 = 13$
0
5
10
15
20
25
$s_2 = 2$
Follow−up years

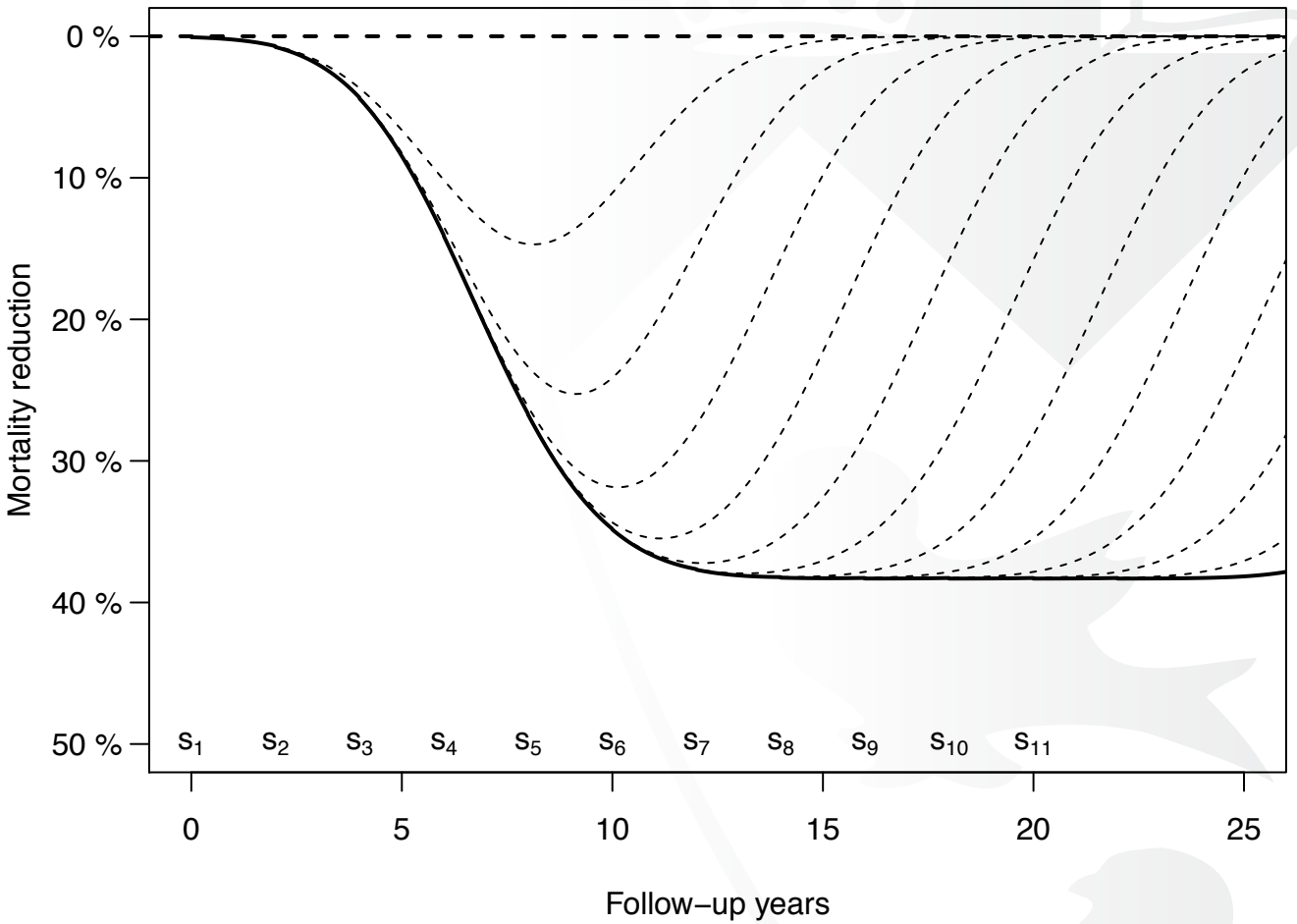
3rd round


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
1−(1−0.021)(1−0.075)(1−0.138)
$T_0 = 13$
0
5
10
15
20
25
$s_3 = 4$
Follow−up years

All 3 rounds


0 %
10 %
20 %
30 %
40 %
50 %
Mortality reduction
0.22
$T_0 = 13$
0
5
10
15
20
25
$s_1 = 0$ $s_2 = 2$ $s_3 = 4$
Follow−up years

And so on


0 %
10 %
20 %
30 %
40 %
50 %
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
5
10
15
20
25
Follow−up years

Probability model

- Let T_{1i} and T_{0i} be the **potential** times of cancer death in the presence and absence of screening, respectively.
- The **time-specific probability of being helped by screening** is decomposed into the round-specific impacts as

$$P(T_{1i} > t \mid T_{0i} = t) = 1 - \prod_{j=1}^{m(t)} \{1 - Q_j(t; \theta)\},$$

where $Q_j(t; \theta)$ is the **probability of being helped by the jth screen**, given that previous screens failed to detect the cancer.

Estimation procedure

- We use a likelihood for being randomized into the screening arm, given the time-specific cancer death.
- This involves contributions only from those who died of the cancer.
- With certain identifying assumptions, the likelihood can be expressed in terms of $Q_j(t;\theta)$.
- It then can be numerically maximized w.r.t. θ.

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

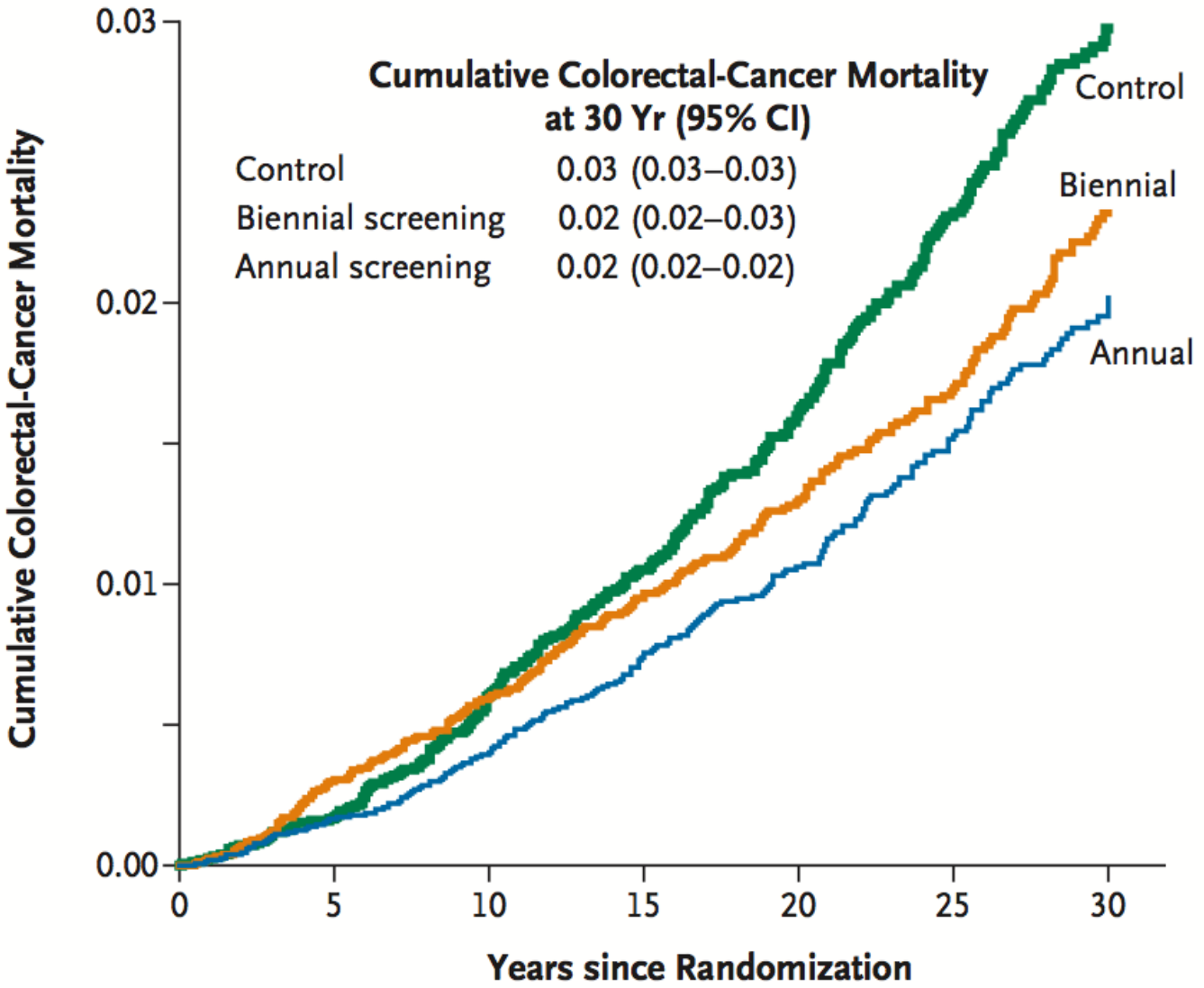
MCCCS

- 46,551 healthy volunteers randomized to either annual or biennial fecal occult blood (FOB) testing, or control (Shaukat et al. 2013).
- Cumulative colorectal cancer mortality reduction (biennial vs. control and annual vs. control) after 30 years of follow-up:

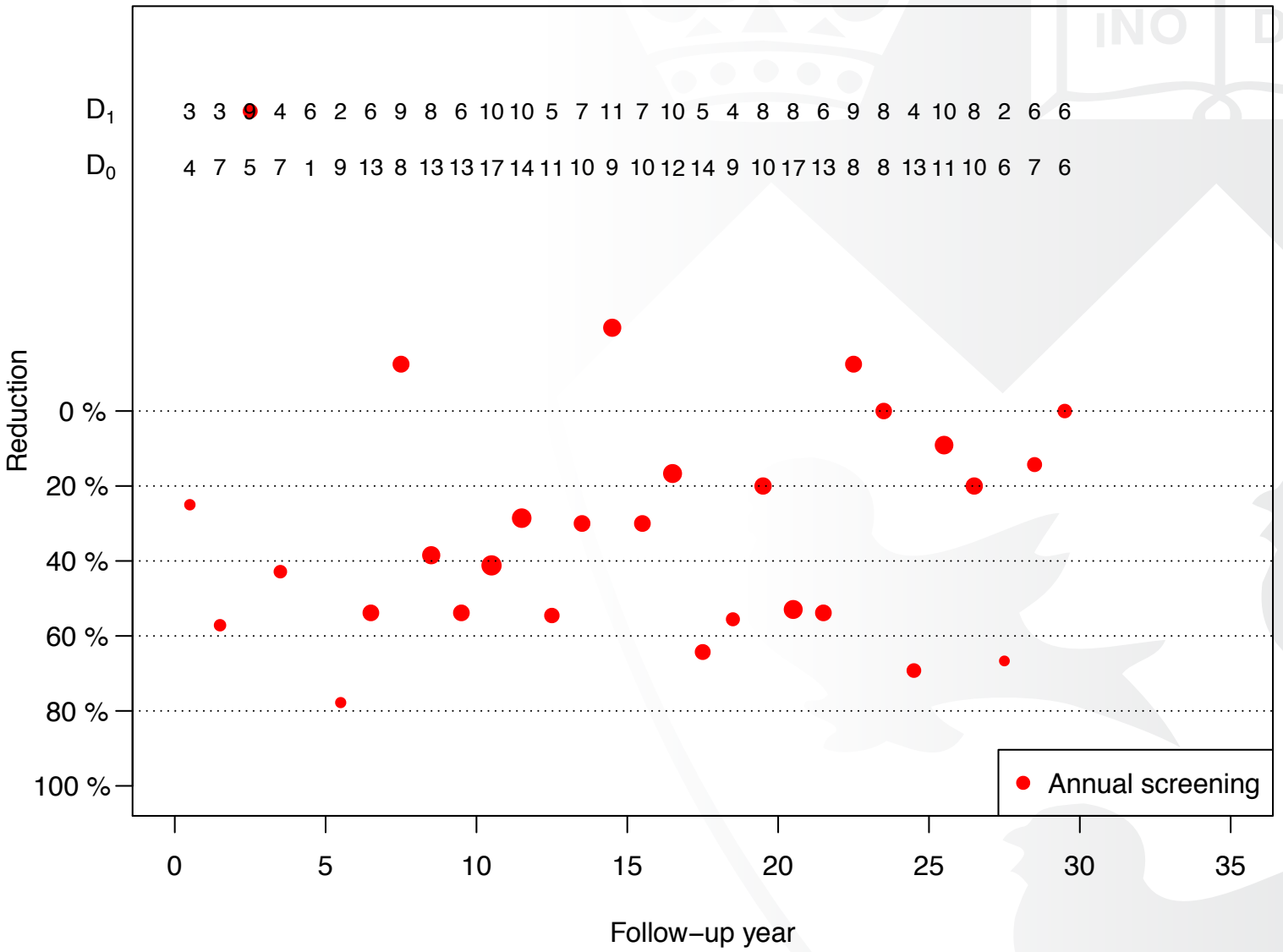
$$1 - \frac{237}{295} \approx 20\% \quad \text{and} \quad 1 - \frac{200}{295} \approx 32\%.$$

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

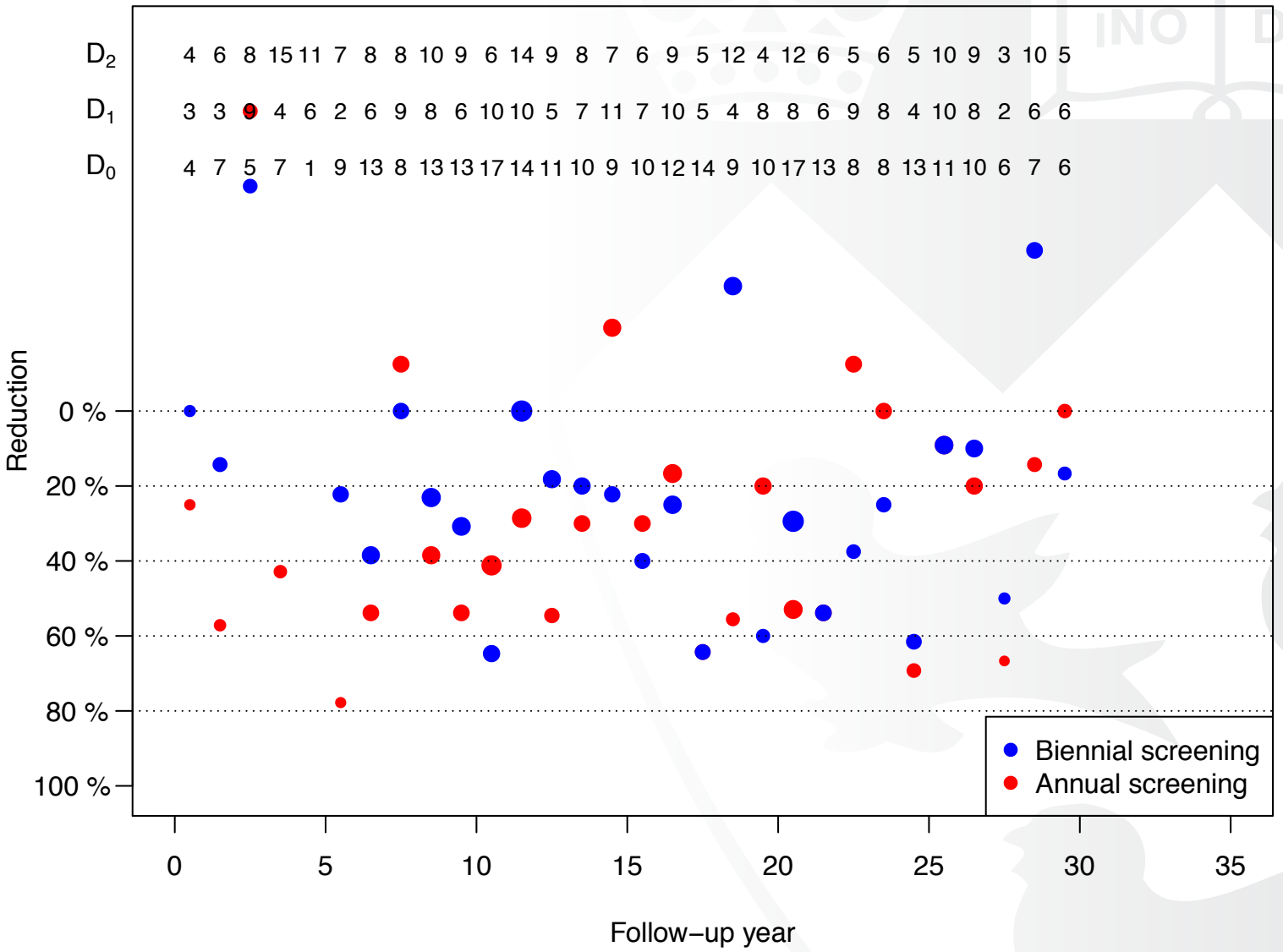
MCCCS cumulative mortality



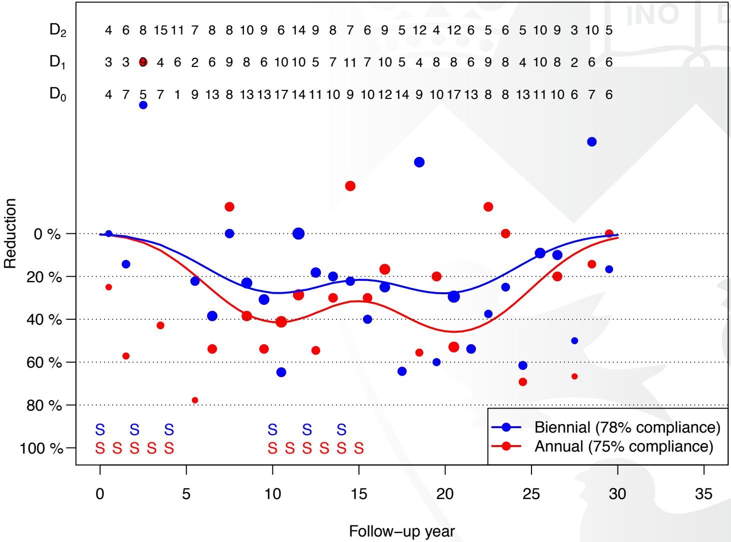
MCCCS yearly data



MCCCS yearly data (2)



MCCCS fit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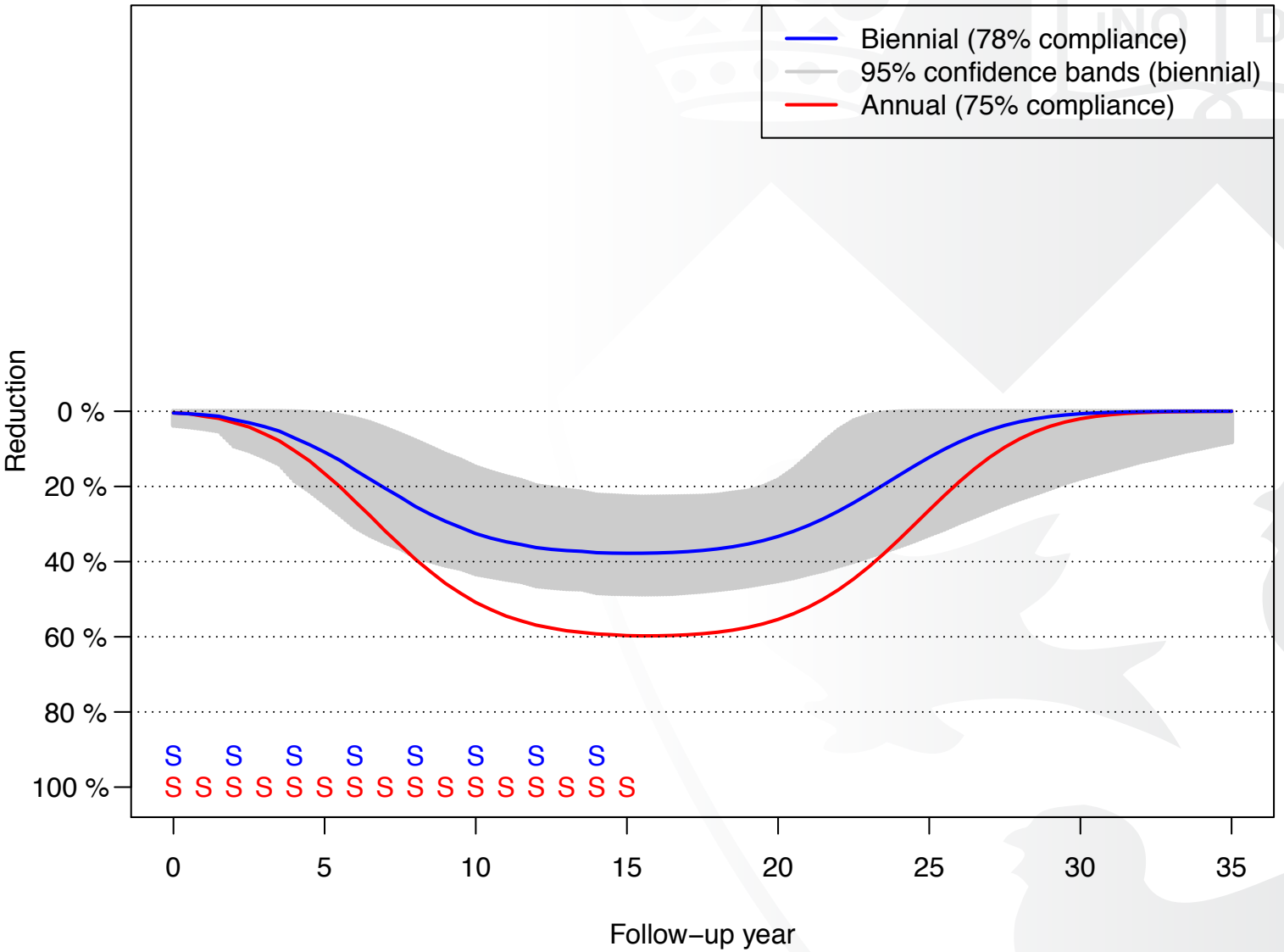
D1 3 3 9 4 6 2 6 9 8 6 10 10 5 7 11 7 10 5 4 8 8 6 9 8 4 10 8 2 6 6
D0 4 7 5 7 1 9 13 8 13 13 17 14 11 10 9 10 12 14 9 10 17 13 8 8 13 11 10 6 7 6
Reduction
0 %
20 %
40 %
60 %
80 %
100 %
S S S S S S
S S S S S S S S S S S
Biennial (78% compliance)
Annual (75% compliance)
0
5
10
15
20
25
30
35
Follow−up year

MCCCS projection



Contributions

1. Projecting the Yearly Mortality Reductions due to a Cancer Screening Program (published)
2. A Conditional Approach to Measure Mortality Reductions due to Cancer Screening (revision invited)
3. More on the National Lung Screening Trial (manuscript)
4. Recovering the Raw Data Behind a Non-parametric Survival Curve (revision invited)

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