Underestimation of Mortality Reductions in Cancer Screening Studies: The ERSPC as a Case Study

Sous-estimation des réductions de la mortalité dans les éudes de dépistage du cancer: le ERSPC comme exemple

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Outline

- Background
- European Randomized Study of Screening for Prostate Cancer
- Re-analysis of ERSPC data
- Methodologic issues applicable to all screening studies

Background

- PSA-based prostate cancer (Pr Ca) screening: media coverage

  NPR, 2009.10.21: A Rethink On Prostate and Breast Cancer Screening
  Time, 2009.10.23: Rethinking the benefits of breast and prostate cancer
  Globe and Mail, 2010.2.08: Prostate cancer dilemma
  New York Times Mar 10, 2010.3.10: The Great Prostate Mistake
  cyberpresse: 2010.3.13: Cancer de la prostate: le test de détection remis en doute
  BMJ 2010.3.17: Is the tide turning against the test?

- 1995 CETS (Québec) Report*: uncertain benefit / certain harms

- 2004 Amer. Coll. Physicians Report: likewise; 'overdiagnosis'

- 2005 RCT: Radical prostatectomy $>$ but $\not>$ watchful waiting in early Pr Ca

- 2009: European Randomized Study of Screening for Pr Ca (ERSPC)

* An Evaluation of benefits, unwanted health effect and costs. http://www.aetmis.gouv.qc.ca/site/home.phtml.

In all, 5 RCTs of Screening for Prostate Cancer

Trial:	Québec	Sweden[1]	Sweden[2]	USA	Europe
Began	1988	1987	1988	1993	1991
Last report	2004	2004	2009	2009	2009
No. men $\frac{Screening\ arm}{Control\ arm}$	$\frac{31{,}000}{15{,}000}$	$\frac{1{,}500}{7{,}500}$	$\frac{2{,}400}{24{,}000}$	$\frac{38{,}000}{38{,}000}$	$\frac{73{,}000}{89{,}000}$
Frequency of testing	?1y	3y	once	1y $\times$ 6	4y
Duration of follow-up (y)	11	15	15	10	9
Actually Screened $\geq$ 1 time(s)	$\frac{24\%}{7\%}$	$\frac{78\%}{?\%}$	$\frac{74\%}{?\%}$	$\frac{85\%}{52\%}$	$\frac{82\%}{?\%}$
No. Pr Ca deaths	$\frac{153}{75}$	$\frac{20}{97}$	$\frac{53}{506}$	$\frac{92}{82}$	$\frac{214}{326}$

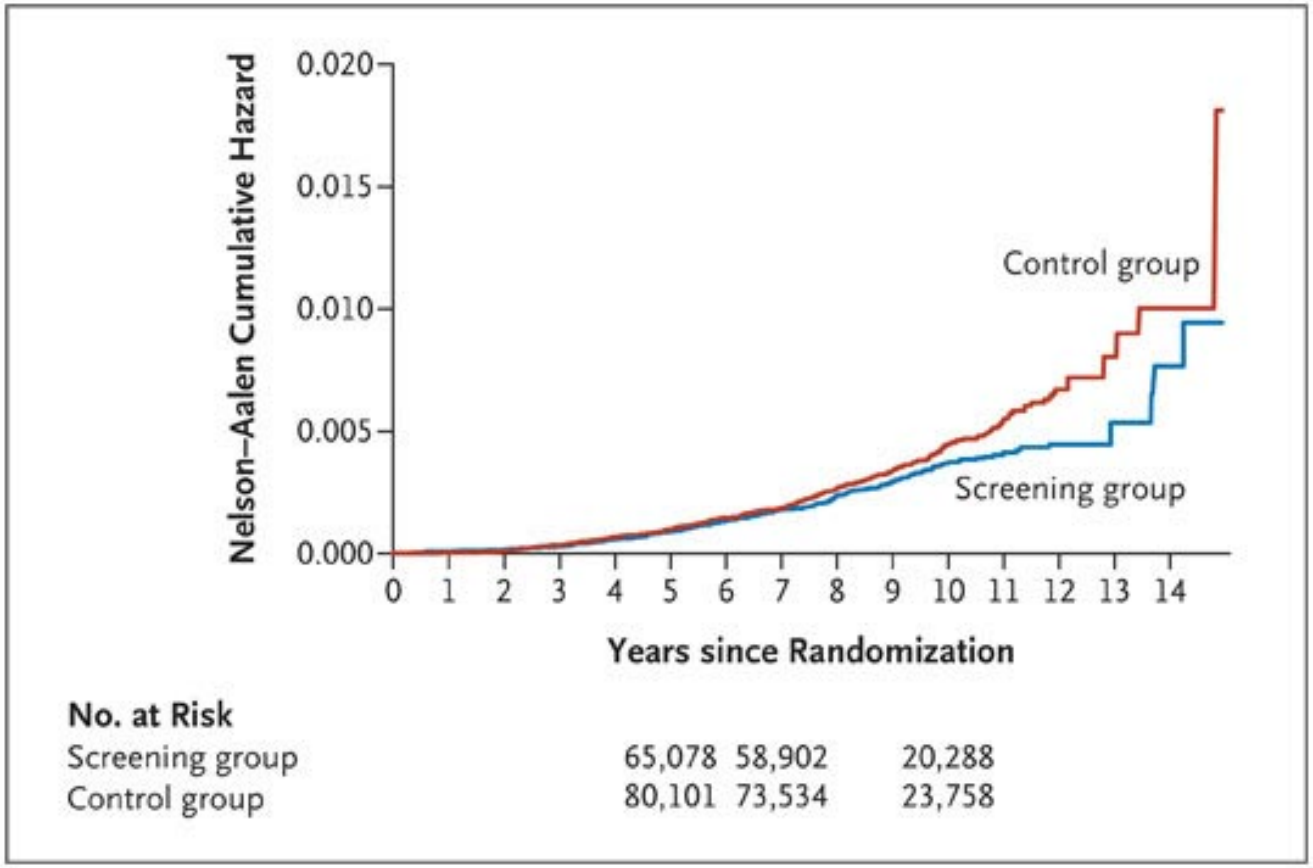
[1] Norrköping [2] Stockholm

Prostate-Cancer Mortality in ERSPC

"During a median follow-up of 9 years, the rate ratio in the screening group, as compared with the control group, was 0.80 (95% confidence interval [CI], 0.65 to 0.98; adjusted P=0.04). The absolute risk difference was 0.71 death per 1000 men."

"The analysis of men who were actually screened during the first round (excluding subjects with noncompliance) provided a rate ratio of 0.73 (95% CI, 0.56 to 0.90)."

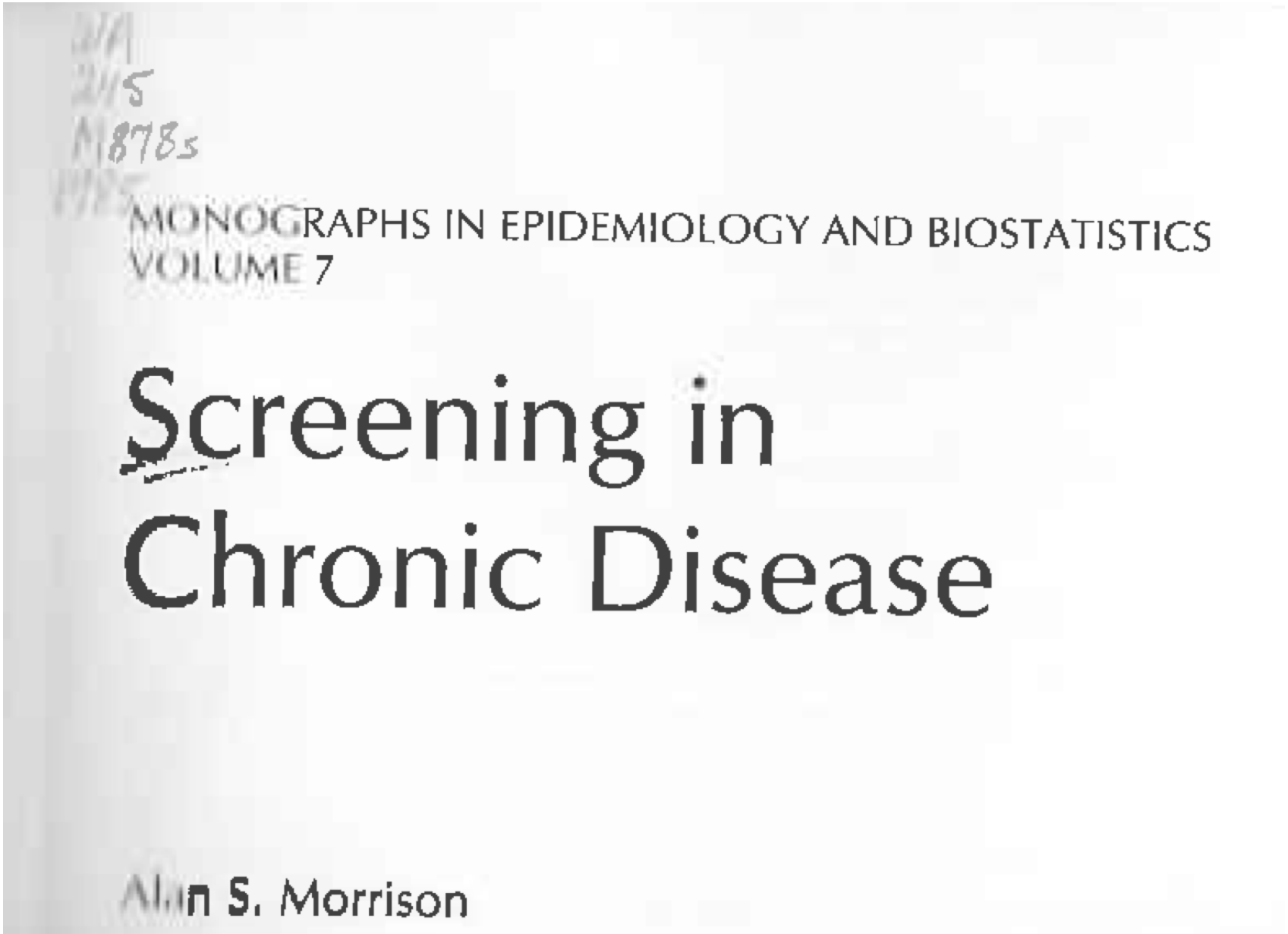
Cumulative Risk of Death from Prostate Cancer.



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. Deaths that were associated with interventions were categorized as being due to prostate cancer. 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). The Nelsen-Aalen method was used for the calculation of cumulative hazard.

NEJM, March 2009.

Expected 'Response function': Guidance from 1985 textbook



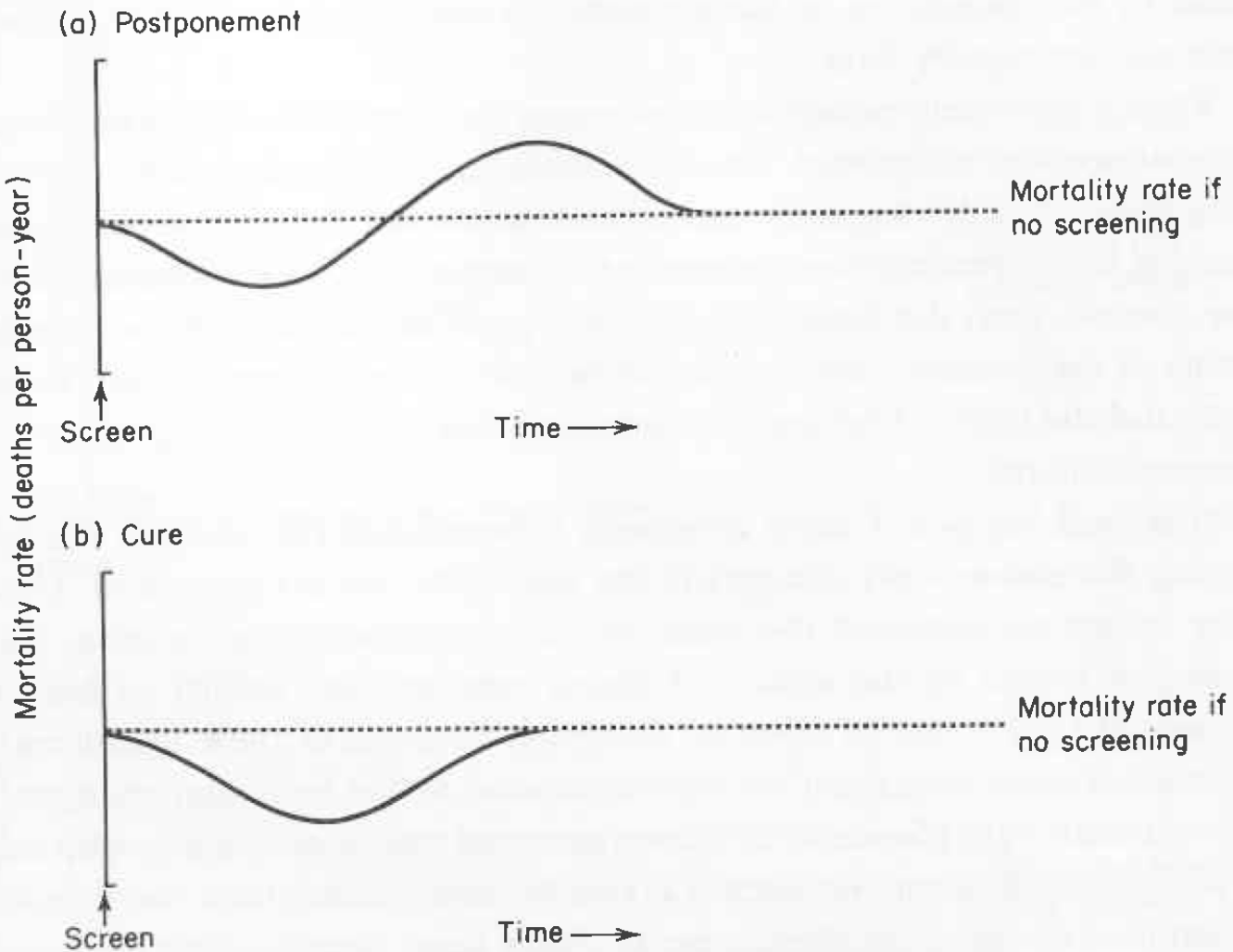


Figure 2-5. Changes in the disease-specific mortality rate brought about by postponement of death and by "cure" of screen-detected cases.

Cumulative & Year-specific results, if screen 0,1,...,4 times, q 4y [HYPOTHETICAL]

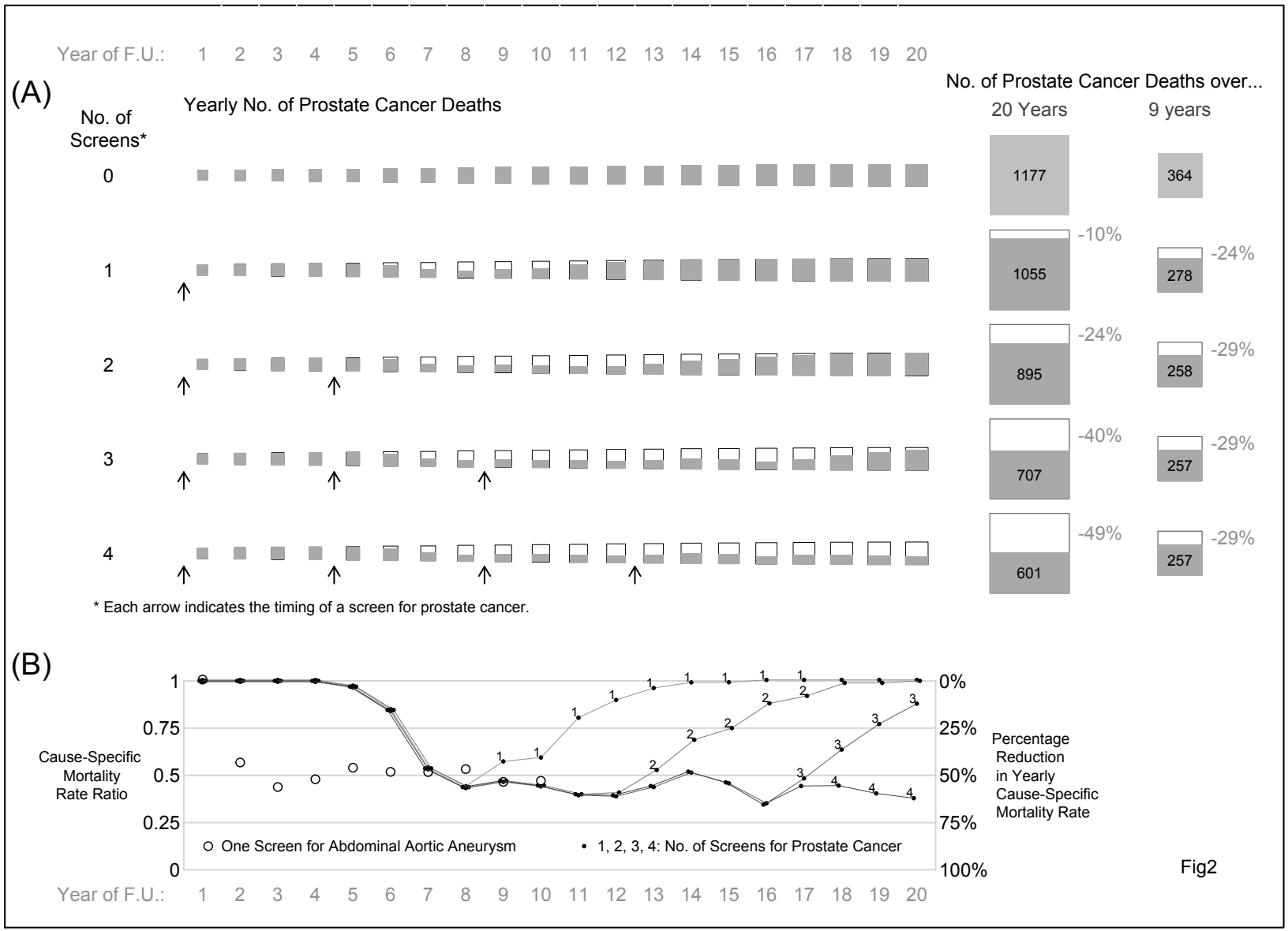
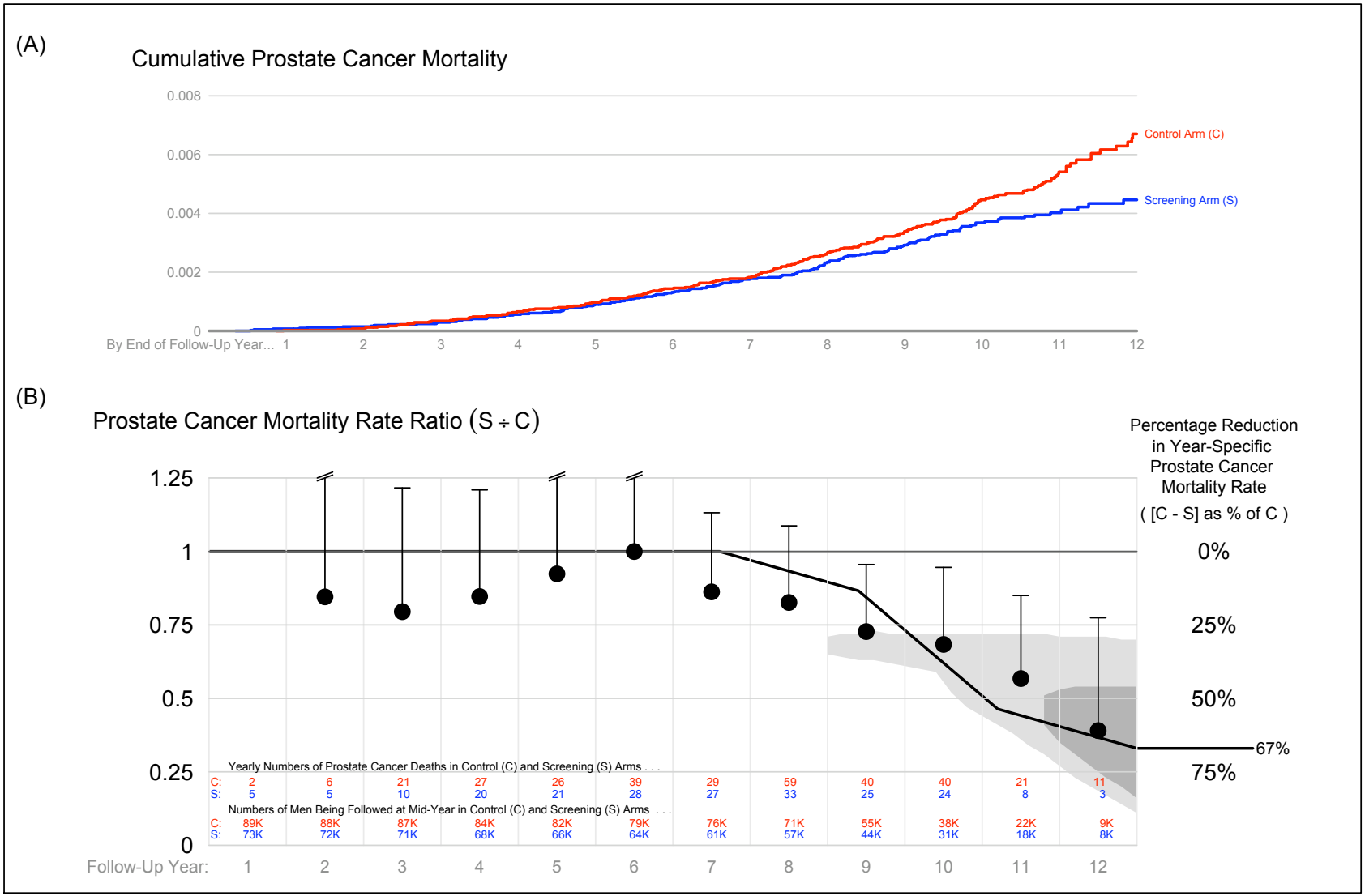


Fig2

RE-ANALYSIS, with emphasis on time-specificity

- Year-by-year mortality rate ratios
  - pdf file containing Fig 2 $\longrightarrow$ encapsulated postscript (eps) file format;
  - eps file $\longrightarrow$ exact information (co-ordinates of line segments and dots) that statistical program, Stata, had used to draw two Nelson- Aalen cumulative hazard curves. eps file contained exact co-ordinates of each of 89,308 and 72,837 line segments or dots, one per man.
  - horizontal/vertical co-ordinates of each segment/dot $\longrightarrow$ exact numbers of men being followed at each point in follow-up time, and thus at exact times of the vertical steps in curves (pr ca deaths).
  - size of step $\times$ number being followed $\longrightarrow$ number of prostate cancer deaths at each time point
  - Numbers aggregated by year (each of 1st 12) and study arm $\longrightarrow$ counts listed in new Figure.
- Moving averages to reduce the statistical noise (deaths in moving 3-year intervals)
- Smooth curve for rate ratio function (data bins 0.2 y wide).

Year-specific prostate cancer mortality ratios



Interpretation

- After an expected delay (data indicate $\approx$ 7 years), the prostate mortality reductions that become evident in years 9 and beyond are statistically significant and considerably greater than the reported 20% reduction in the rate of prostate cancer deaths.
- The best (ML) estimate is that, although the rate ratio became non-null starting at $\approx$ 7 years, the steady state reduction has not yet been reached: the point estimate so far is a sustained 67% reduction (80%CI 30% to 89%) beginning at year 12.
- Numbers of deaths are not sufficient to establish its timing and magnitude more precisely. (Data cutoff: Dec 2006)

Implications - substantive

- '**Downsides**' of PSA-based prostate cancer screening: well documented and long since agreed upon.
- Even if screening could achieve a sustained reduction of 67%, (or even 77 or 87%!) the very low prostate mortality rates in the control group means that the **small absolute reductions** would be achieved at what some people would consider to be an unacceptable cost. (So far, only 326 or 0.36% of the 89,353 men in control group have died of prostate cancer; the number will approximately triple by follow-up year 20.)
- 'Upsides': 5 RCTs; 23 years; 321,000 men; 10 countries average f.-u. ranging from 7-15 years.
  - 4 have virtually no resolving power.
  - **ERSPC**: much larger Δ in screening activity b/w 2 arms $\longrightarrow$ considerably greater **resolving power**.
  - Must measure signal in f.-u. window where probably strongest $\longrightarrow$ collect **additional data**.
- Casual reader of ERSPC report **should not conclude** that best we can expect from PSA screening is a reduction in prostate cancer mortality of **20%**.
- Re-analysis: if screening is carried out for several years, and **if f.-u. pursued into window where reduction in mortality becomes manifest**, reduction to be seen there will be **50-60%**.
- ERSPC report published March 2009, but **f.-u. ended in Dec 2006**, just when pattern had begun to emerge. **Not possible to put precise statistical bounds** on this reduction.
- Prostate cancer deaths from **2007 onwards crucial to more precisely measure** the reduction achieved.

Implications - Methodologic

Time-specificity...

- Avoids dilution caused by averaging
  - 7 years of (expected) non-reductions with
  - 5 years of progressively larger reductions
- With current data, imprecise estimates: fixable.
- Follows intention to treat principle
- With objective curve-fitting...
  - avoid need to "pre-specify" **when** reduction reaches steady state
  - data themselves inform us about two critical parameters that determine 'response curve' (i.e., **timing** & **extent** of prostate cancer mortality reduction caused by screening).

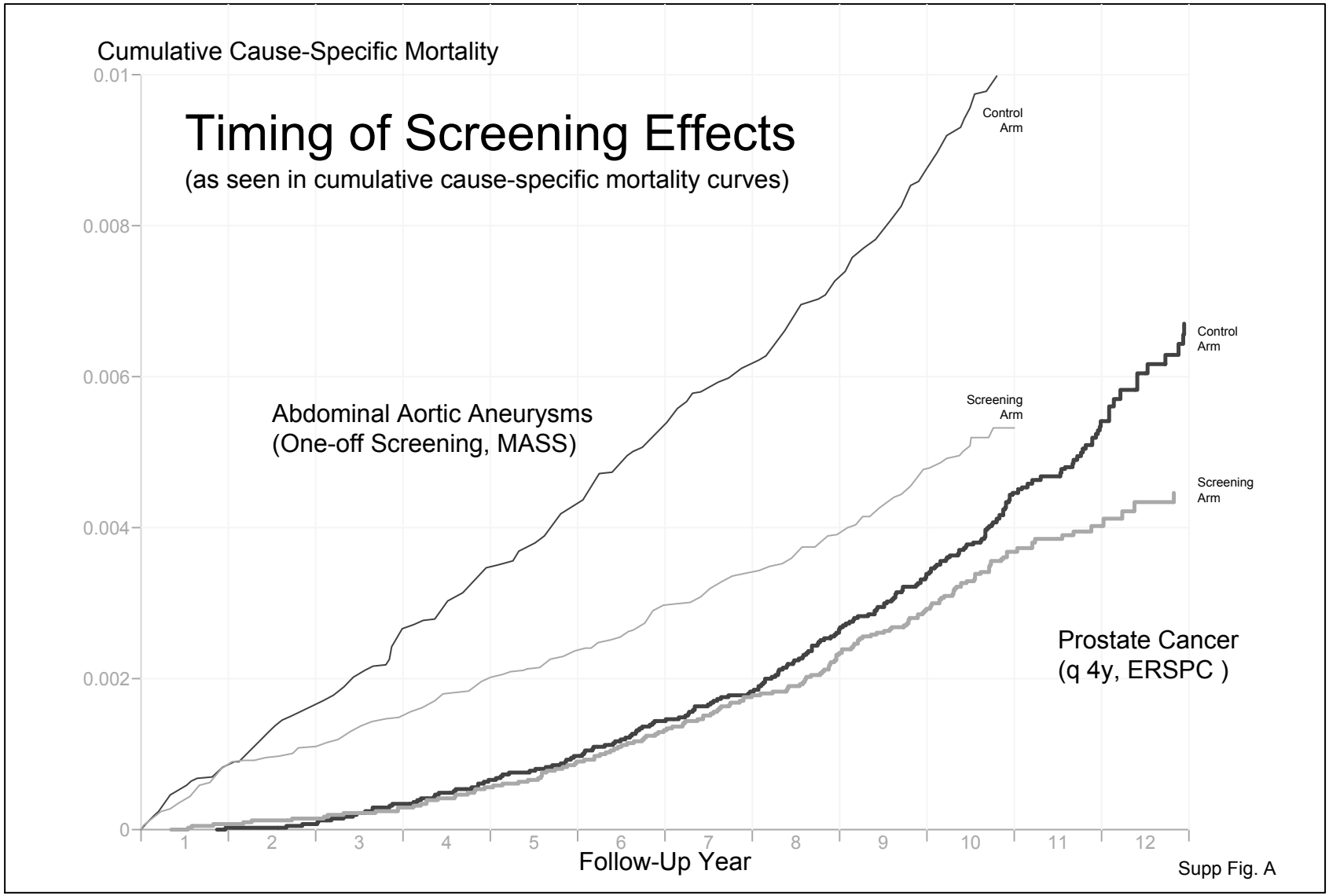
Only an ineffective cancer screening program can yield proportional hazards!

- Time-specific analysis only necessary when effect of intervention is delayed, as in case of Pr Ca screening.
- Screening for abdominal aneurysms produces an immediate and sustained reduction in mortality from ruptured aneurysms; cumulative mortality, in this case, fully captures benefit of screening.
- Recognition of difference between interventions with immediate and delayed effects should prompt similar re-analyses of data from trials of screening in other cancers, and similar analyses in yet-to-be reported cancer screening trials.

IMPLICATIONS: data-analysis, meta-analyses, public health

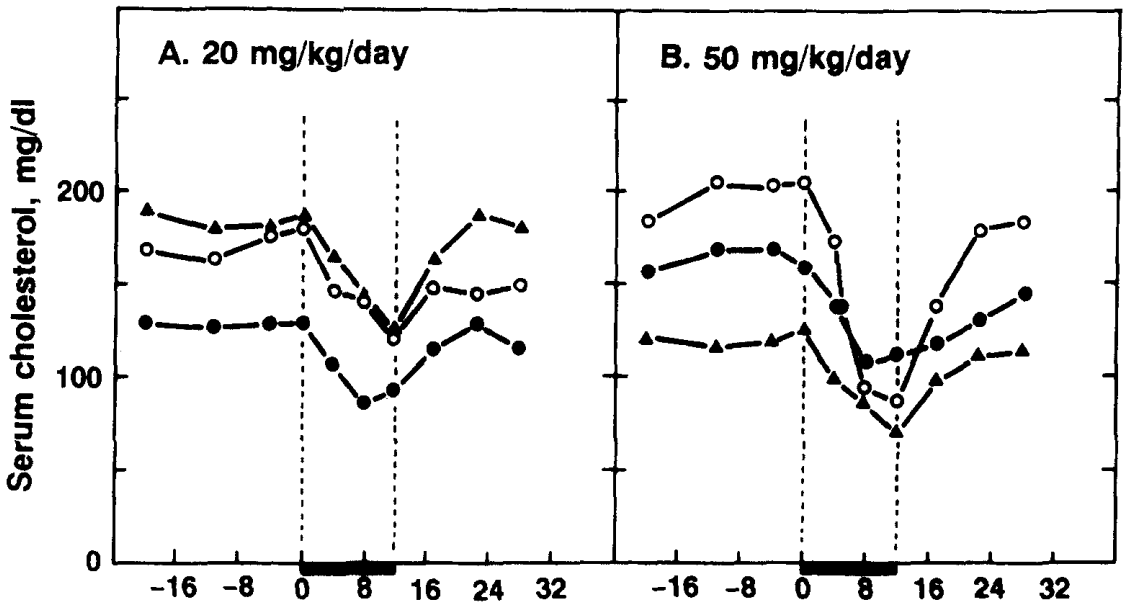
- 'Response Curve' in any one RCT is a function of the number and timing of screens [& compliance]
- Time-specificity in data-analysis is paramount
- No common parameter (response curve) to meta-analyze: trials not uniform w.r.t. number and timing of screens
- REAL Q: reduction with SUSTAINED SCREENING ?
- How about using nadir of response curve ?

The loneliness of the long-distance trialist

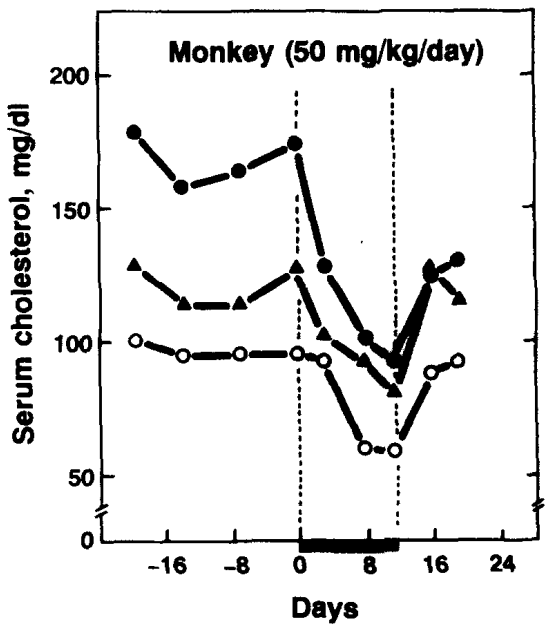


Timing of cholesterol reductions produced by statins

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

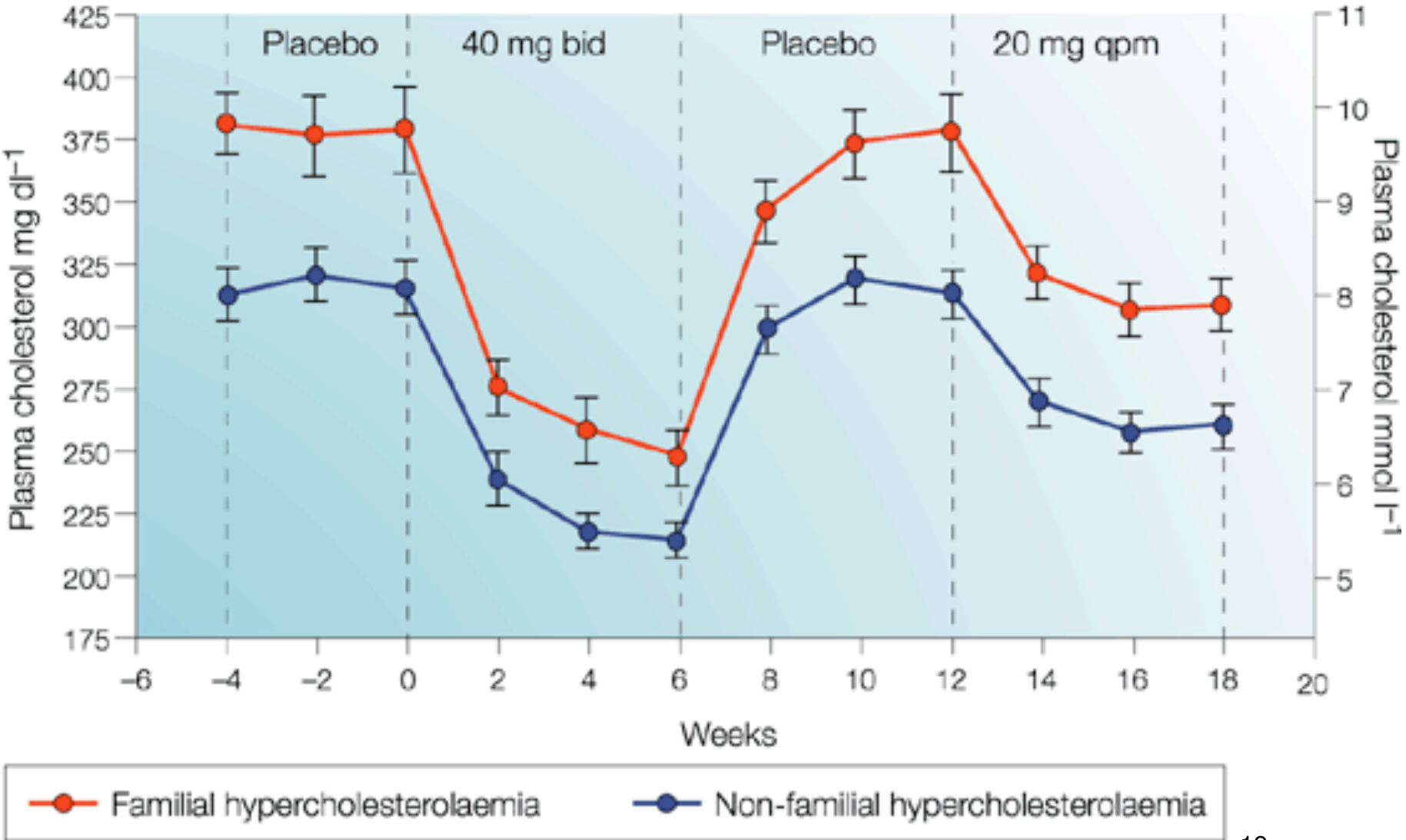


3 monkeys at 50



Timing of cholesterol reductions produced by statins

Humans



Acknowledgments

Mammographic screening: no reliable supporting evidence?

Olli S Miettinen, Claudia I Henschke, Mark W Pasmantier, James P Smith, Daniel M Libby, David F Yankelevitz

Much confusion is being generated by the conclusion of a recent review that "there is no reliable evidence that screening for breast cancer reduces mortality." In that review, however, there was no appreciation of the appropriate mortality-related measure of screening's usefulness; and correspondingly, there was no estimation of the magnitude of this measure. We take this measure to be the proportional reduction in case-fatality rate, and studied its magnitude on the basis of the only valid and otherwise suitable trial. We found reliable evidence of fatality reduction, apparently substantial in magnitude.

Lancet 2002; **359:** 404–06

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