'Immortal Time' Blunders: history, identification, severity

Good morning. Thank you organizers for putting this conference together. Part 1 shows what happens when amateur epidemiologists ignore or don't even seek the advice of professional statisticians and epidemiologists, and why we must be forceful. Part 2 is about fitting smooth-in-time-hazard functions via logistic regression. ↓ 47 / 47

1. 'Immortal Time' Blunders: history, identification, severity

2. Case-base sampling

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Interdisciplinary FRIAS Junior Researcher Conference 2016
Avoiding Bias induced by Design and Analysis in Life History Cohort Studies

September 21-23, 2016
Freiburg Institute for Advanced Studies, Freiburg, Germany

Ten years ago, Queen Elizabeth gave us a key reference for the concept of ‘immortal time’ ↓ 17 / 64

Queen Elizabeth II, at her 80th birthday celebration in 2006

“ As Groucho Marx once said, ‘Getting older is no problem. You just have to live long enough.’ ”

The performer George Burns also understood it. He had never even been nominated until he was 80. Despite, or maybe because of the cigars, he lived till 100. Richard Burton was nominated 6 times, but died sans Oscar at 59. Here is the ARITHMETIC, and here is the QUESTION.

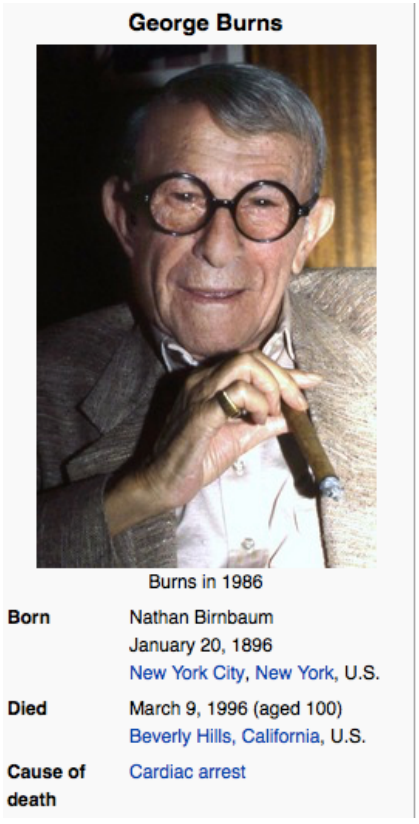
George Burns, on receiving an Oscar, at age 80, in 1976

"This award proves one thing: that if you stay in the business long enough and if you can get to be old enough, you get to be new again."

Died at 59.

Nominated 6 times; never won

Lived to 100



100 - 59 = 41

How many of the 41 should we credit to his winning the Oscar?

This author was studying what makes a good leader, but noticing a pattern in the data, he came up with this hypothesis. 22 / 135

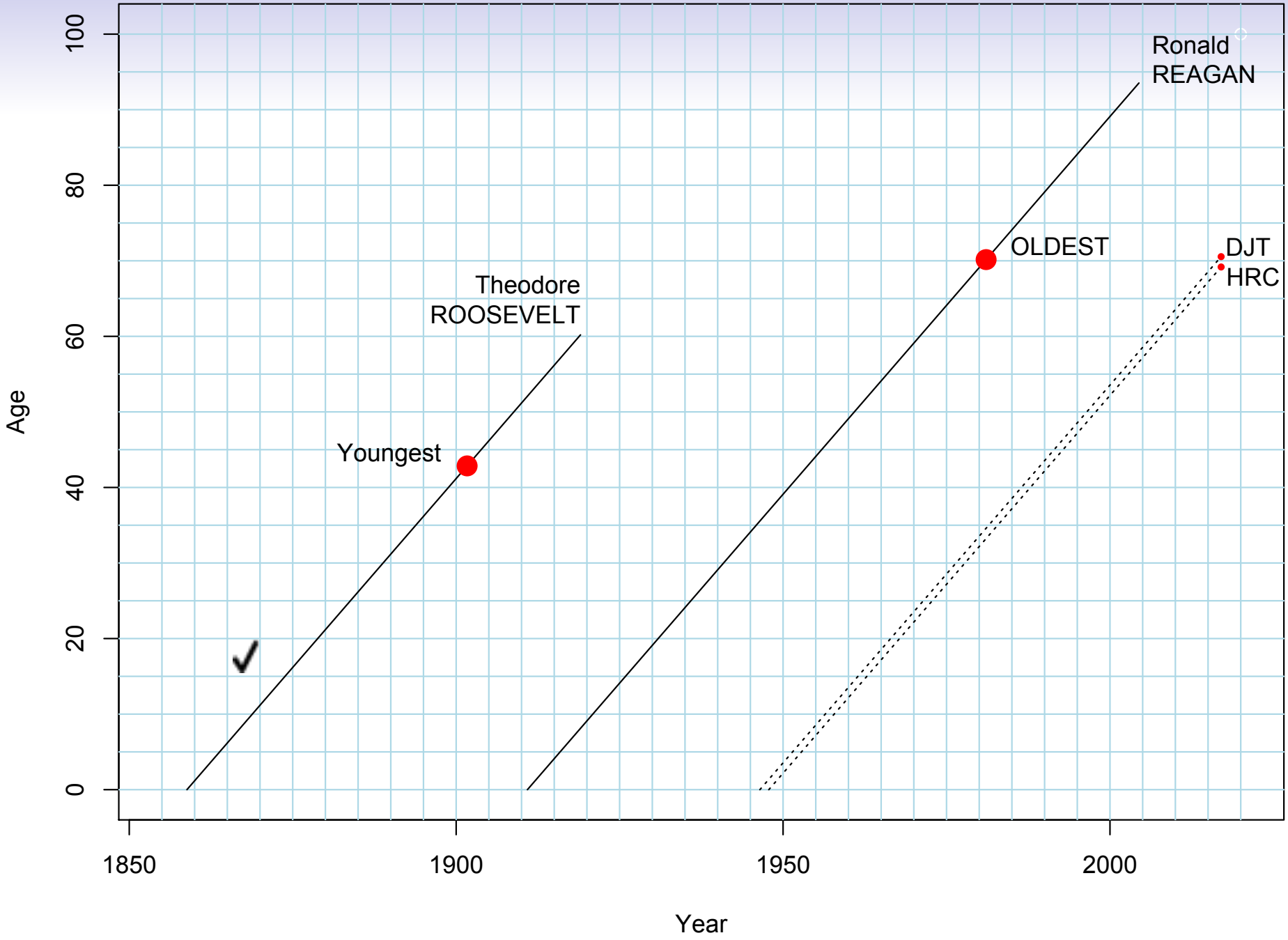
SJH McCann. Personality and Social Psychology Bulletin 2001;27:1429-1439

Some time ago, while conducting research on U.S. presidents, I noticed that those who became president at earlier ages tended to die younger.

This informal observation led me to scattered sources that provided occasional empirical parallels and some possibilities for the theoretical underpinning of what I have come to call the precocity-longevity hypothesis

Simply stated, the hypothesis is that those who reach career peaks earlier tend to have shorter lives.

Here are the lifelines of the youngest and oldest US presidents to serve. Do you see a problem? ↓ 19 / 154


Ronald
REAGAN
OLDEST
DJT
HRC
Theodore
ROOSEVELT
Youngest
Age
Year
0
20
40
60
80
100
1850
1900
1950
2000

Statistical errors in longevity comparisons of actors or presidents don't have serious direct consequences for the public since all they can do is dream about winning. [But social epidemiologists have used them to prop up their theories.] Errors like this one can have more direct consequences. Many people benefit from statins, but the reputation of statins has probably benefitted more from immortal time blunders than any other medication or procedure. ↓

Yee et al. Diabetic Medicine 2004;21:962-67

Statin use in type 2 diabetes mellitus is associated with a delay in starting insulin.

These examples give the essence of the problem, and you can already see ways way to avoid it. So I won't spend the entire talk preaching to the converted. I will just quote the principles put forward by two major contributors to epidemiology and biostatistics. I will say why I think people fall into the immortal time trap, and show 2 examples where we quantified how much distortion it produces. Since POPULATION-TIME is prominent in the story, I will spend the last part on case base sampling and what it has to offer in broader contexts. ↓ 97 / 322

OUTLINE

- Principles; why blunders happen; how big can they be?
- Case-base sampling and population-time plots

As we explain here, teaching on so-called immortal time goes back as far as William Farr, and has to be repeated every generation or so. Walker defined the term immortal TIME, and it is broader than just mortality. My colleague Suissa popularized – maybe even immortalized – the BIAS. Olli Miettinen, another colleague of mine, objected to the term saying it is not the person-TIME that is immortal, but the PERSON. Many statisticians don't like the term either. But Suissa preferred a catchy title over a precise one. I'll come back to Mantel and Breslow. ↓ 96 / 418

Teachers 1843-2014

- William Farr , Fifth Report of the Registrar General 1843, page xxx
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- **WALKER**. IMMORTAL TIME: 'event-free time, by definition or by construction' Observation and Inference: Intro. to Methods of Epi. 1991 – a broader term.
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- **SUISSA** Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. Am J Respir Crit Care Med 2003;168:49?53.
- van Walraven. Time-dependent bias common in survival analyses in leading clinical journals J Clin Epi 2004
- Wolkewitz, Allignol, Harbarth, de Angelis, Schumacher, Beyersmann. Time-dependent study entries and exposures in cohort studies can easily be sources of different and avoidable types of bias. J Clin Epi. 2012
- Giobbie-Hurder, Gelber, Regan. Challenges of guarantee-time bias. J Clin Oncol 2013
- Schumacher, Allignol; Beyersmann, Binder, Wolkewitz Hospital-acquired infections – appropriate statistical treatment is urgently needed! Int J Epi. 2013.
- Hanley & Foster. Avoiding blunders involving 'immortal time.' Int J Epi 2014

But first let me list more longevity comparisons – some better than others, and more teaching. we cover these in our 2014 piece. ↓ 24 / 442

Additional Longevity Comparisons

- ↓ Longevity of jazz musicians: flawed analysis.[Letter] Rothman KJ. Am J Pub H 1992
- ↑ How long did their hearts go on? A Titanic study. Hanley et al. BMJ 2003;327:1457
- ↓ Survival in Academy Award-winning actors and actresses. Redelmeier DA, Singh SM. Ann Intern Med 2001;134:955?62. ↑ Do Oscar winners live longer than less successful peers? A reanalysis of the evidence. Sylvestre, Huszti, Hanley. Annals Int. Med. 2006. ↑ Wolkewitz et al. Am. Statistician 2010 ↑ Han et al. Applied Statistics 2011.
- ↑ Death rates of medical school class presidents. Redelmeier, Soc Sci Med 2004
- ↑ The longevity of Baseball Hall of Famers compared to other players. Abel et al. Death Studies 2005;29:959-63.
- ↓ Longevity of popes and artists between the 13th and the 19th century. Carrieri MP, Serraino D. Int J Epidemiol 2005;34: 1435-36; ↑ Statistical fallibility and the longevity of popes: William Farr meets Wilhelm Lexis. Hanley JA, Carrieri MP, Serraino D. Int J Epidemiol 2006;35:802-05)
- Elvis to Eminem: quantifying the price of fame through early mortality of European and North American rock and pop stars. Bellis, J Epi Comm, Health 2007;
- Mortality and Immortality: The Nobel Prize as an Experiment into the Effect of Status upon Longevity Rablen MD, Oswald AJ, Journal of Health Economics 27 (2008) 1462-1471
- ↑ Aging of US Presidents. Olshansky SJ. JAMA 2011;306:2328-29.
- ↑ Childlessness, parental mortality and psychiatric illness: a natural experiment based on in vitro fertility treatment and adoption. Agerbo et al. J Epi Comm Health 2012)

In 1972 Gail (of the breast cancer risk model) pointed out that the patients in the heart transplant groups in Houston and Stanford were GUARANTEED (by definition) to have survived at least until a donor was available, and this GRACE PERIOD period was implicitly added into the survival time of the transplanted groups. But his fixes were designs involving randomization. Mantel summarized the problem and the earlier proposals for dealing with non-experimental data like these. This is one of the early and still cleanest descriptions of a time-dependent variable. ↓

KEY PRINCIPLES

Evaluation of Response-Time Data Involving Transient States: An Illustration Using Heart-Transplant Data

NATHAN MANTEL and DAVID P. BYAR*
© Journal of the American Statistical Association
March 1974, Volume 69, Number 345

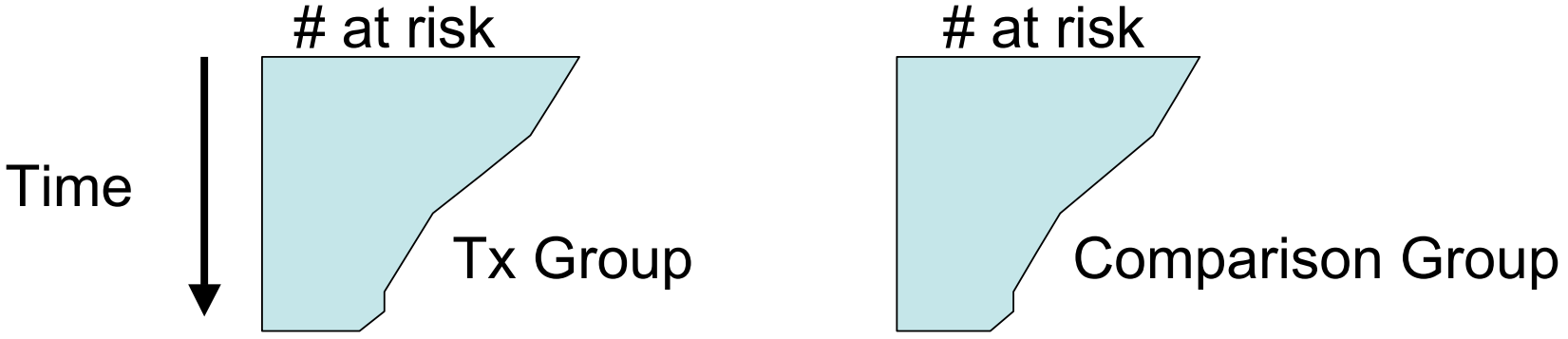
situation. A particularly common bias when the survival of treated patients is compared with that of untreated controls results from a failure to make allowance for the fact that the treated patients must have at least survived from time of diagnosis to time of treatment, while no such requirement obtained for their untreated controls.

Alternative statistical methodologies for avoiding the "time-to-treatment" bias indicated by Gail have been proposed by Turnbull, Brown, and Hu [9]. In these methodologies, a patient selected for heart transplant is nevertheless considered to be a control patient until he actually receives his transplant and to be a treated patient thereafter. This possibility of a patient trans-

Now comes Mantel's own reasoning. In a classical analysis, the sizes of both compared groups go down as time goes on. $\downarrow$ 22 / 554

2. MODIFICATION OF COMPARATIVE LIFE TABLES TO COVER TRANSIENT STATES

In the customary presentation of life-table data, one begins a time interval with a certain number of individuals at risk, observes the number of responses during the interval and the number of losses to observation for the interval (which it would be desirable to arrange to have occur at the end of the interval, see [5, Appendix Discussion 1]). The number at risk at the beginning of the next interval is simply the preceding number less both the preceding interval losses and responses (for responses like death which remove the individuals from further risk.)



But does it have to be like that? No, says Mantel, patients can transfer from the 'waiting' status to the 'transplanted' status. ↓ 23 / 577

In principle there is no reason why the number of individuals at risk may not be *increased* by accessions of survivors from some other comparable study group, a point noted in [5]. In the transient-state problem just such accessions do occur. Thus when a heart-transplant candidate receives his heart transplant, he becomes an accession into the transplanted group, though a loss from the untransplanted group. The usual life-table procedure is adapted simply to cover this case by adding a column for accessions into a group. Losses remain as before, but it may be desirable to distinguish between losses to observation and losses through transfer. With this concept we may actually have any number of different groups, keeping track of responses, accessions, losses to observation, and losses through transfer for each group. We illustrate this later with the heart-transplant data, although in this case only one kind of transfer arises, from untransplanted to transplanted.

Day of death	Transplants						
	N_1	Deaths (A)	Accessions	Losses		N_2	Deaths (C)
				From observation	By transfer		
0	0		II			68	I
1	2		II			65	II
2	4		IIII			61	III
5	8	I		I		54	II
7	6		I			52	I
8	7		I			50	I
11	8		III			48	I
15	11	I	III			44	I
17	13		~~IIII~~ IIII			40	I
27	22	I	III			28	

CALCULATION OF CHI SQUARE

$$\sum A = 26; \quad \sum \text{Exp}(A) = \sum \frac{N_1 M_1}{T} = \sum \frac{N_1(A+C)}{N_1+N_2} = 26.575$$

$$\sum \text{Var}(A) = \sum \frac{N_1 N_2 M_1 M_2}{T^2(T-1)} = \sum \frac{N_1 N_2 (A+C)(N_1+N_2-A-C)}{(N_1+N_2)^2(N_1+N_2-1)} = 7.349$$

$$\text{Chi Square} = \frac{(|\Sigma A - \Sigma \text{Exp}(A)| - 0.5)^2}{\Sigma \text{Var}(A)} = \frac{(0.075)^2}{7.349} = 0.001$$

CALCULATION OF RELATIVE ODDS

$$\sum \frac{AD}{T} = \sum \frac{A(N_2 - C)}{N_1 + N_2} = 7.263$$

$$\sum \frac{BC}{T} = \sum \frac{(N_1 - A)C}{N_1 + N_2} = 7.838$$

$$R = \left(\sum \frac{AD}{T}\right) \Big/ \left(\sum \frac{BC}{T}\right) = \frac{7.263}{7.838} = 0.927$$

Norm Breslow with Nick Day enunciated the principle even more broadly and also more precisely by telling us how to allocate person-time to time-dependent exposure categories. [Their teaching example was another classic blunder, by British Petroleum epidemiologists who claimed lower liver cancer mortality rates in workers exposed to vinyl-chloride for a longer period (SMR = 112 if less than10 years, SMR = 60 if greater than 15).] The correct assignment of each increment in person-time-years of follow-up is to... THAT SAME EXPOSURE CATEGORY TO WHICH

A DEATH WOULD BE ASSIGNED SHOULD IT OCCUR AT THAT TIME. The way they saw it, is easy enough to know which category to assign the death to: the mistakes are in assigning the TIME. ↓ 122 / 727

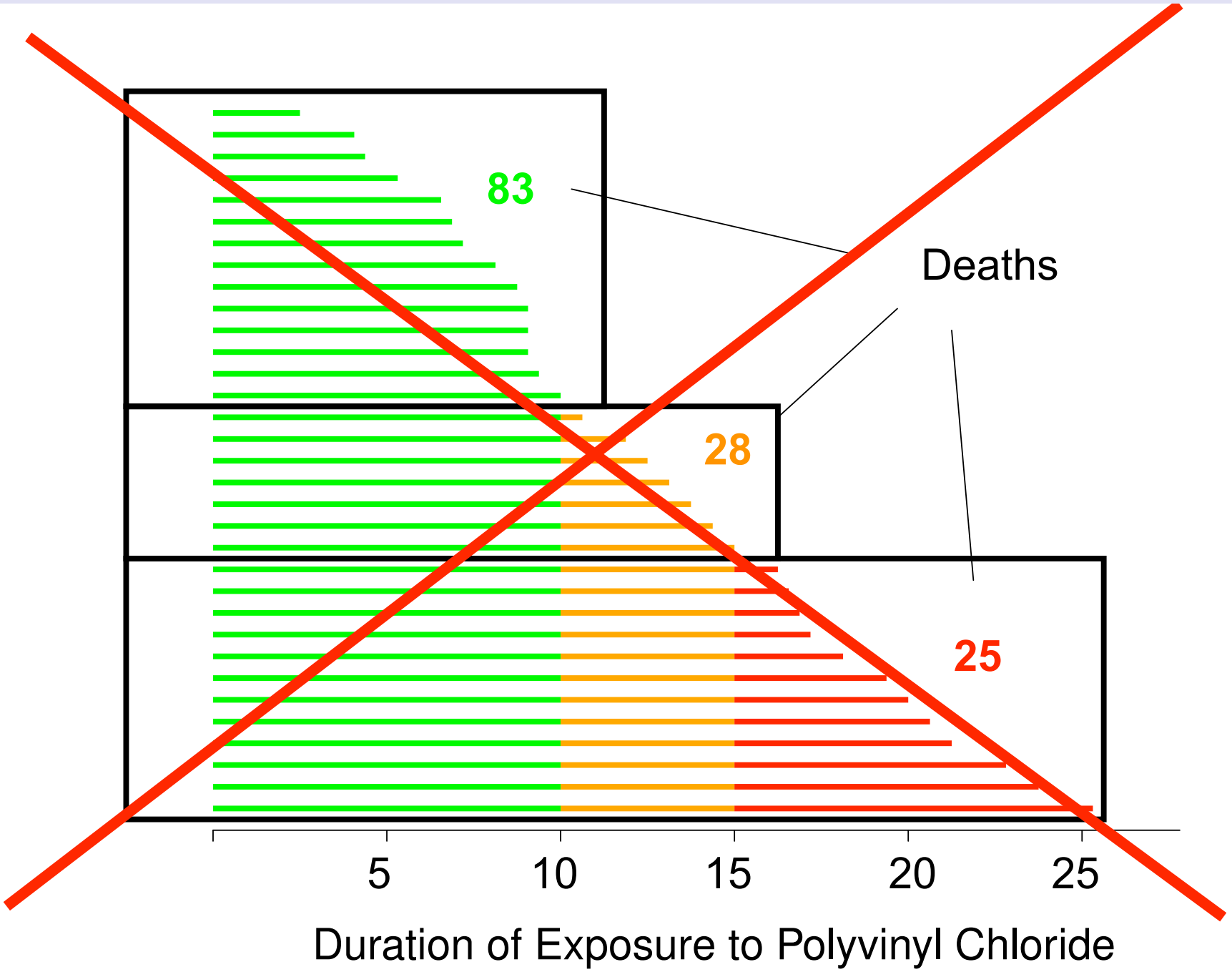
Allocation of person-time to time-dependent exposure categories

The correct assignment of each increment in person-time-years of follow-up is to…

THAT SAME EXPOSURE CATEGORY TO WHICH A DEATH WOULD BE ASSIGNED SHOULD IT OCCUR AT THAT TIME

Breslow & Day, Vol II, page 83

For the BP data, here is the incorrect way to allocate person time, AFTER THE FACT. $\downarrow$ 17 / 744


83
28
25
Deaths
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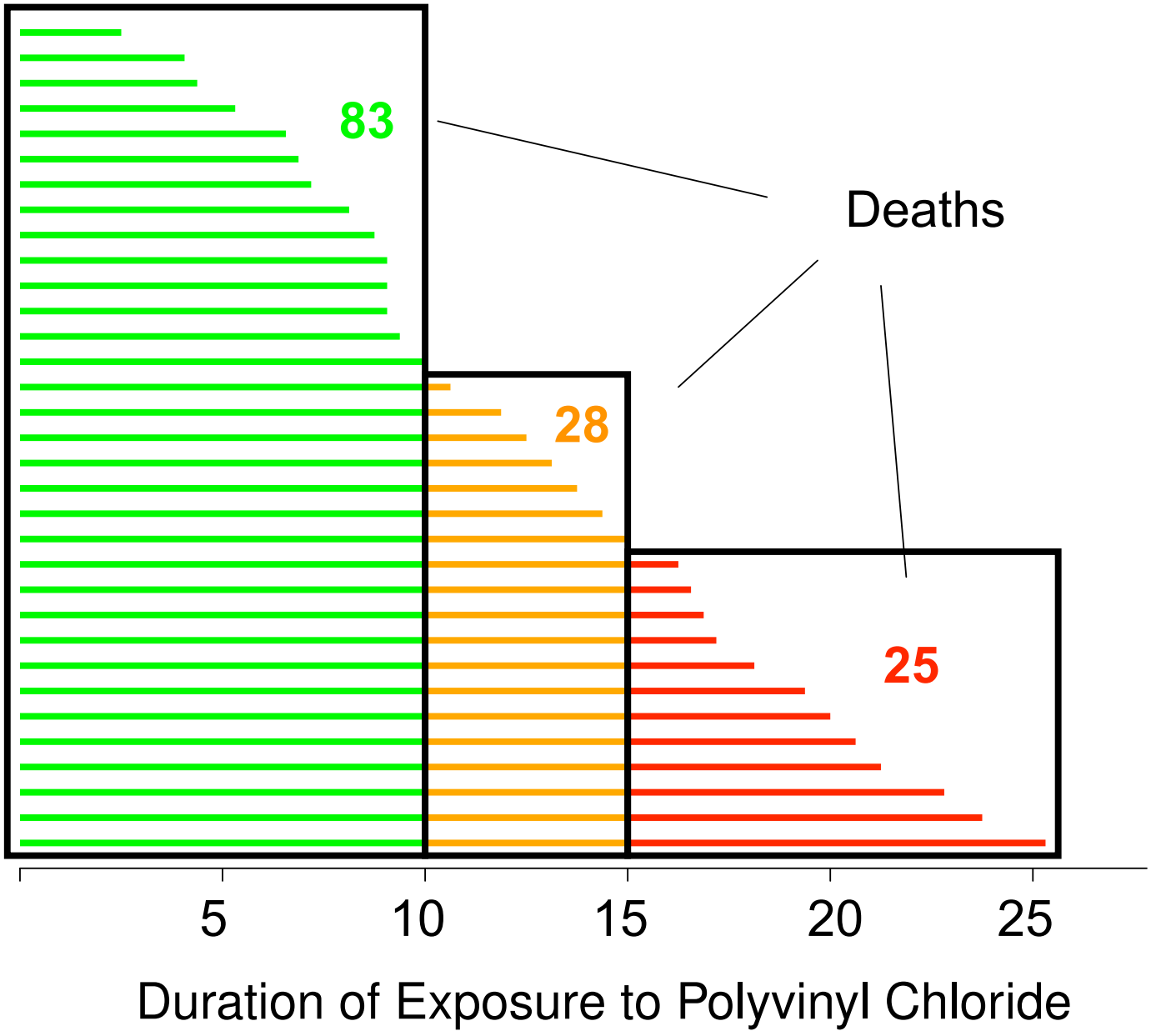
Duration of Exposure to Polyvinyl Chloride

and here is the correct way, AS YOU GO ALONG IN TIME. I will come back to this Population-Time plot at the end. ↓ 24 / 768


83
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Deaths
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Duration of Exposure to Polyvinyl Chloride

Why do these mistakes continue to happen? If we have any chance to talk to the amateur (pretend) epidemiologists, what should we tell them? In our IJE article we tried to list some advice ↓ 35 / 803

WHAT NEEDS TO CHANGE?

Table 1. Ways to recognize immortal time

Suggestion	Remarks/tests
Distinguish state from trait	A trait (e.g. blood group) is usually forever; people and objects move between states (on/off phone; intoxicated/not; on/off medication; failed allograft in place/removed)
Distinguish dynamic from closed population	Membership in a closed population (cohort) is initiated by an event (transition from a state) and is forever; in a dynamic population, it is for the duration of a state. Dynamic populations are the only option for studying transient exposures with rapid effects (e.g. cellphone/alcohol use vs the rate of motor vehicle accidents)
Focus on person-time in index and reference categories, rather than on people in exposed and unexposed 'groups'	These refer to exposure categories, not to people per se; a person's time may be divided between exposure categories; unless people remain in one category, it is misleading to refer to them as a 'group'
If authors used the term 'group', ask …	When and how did persons enter a 'group'? Does being in or moving to a group have a time-related requirement? Is the classification a fixed one based on the status at time zero, or later? Is it sufficient to classify a person just once, or do we need to classify the 'person-moments,' that is the person at different times?
Sketch individual timelines	If there are two time scales, a Lexis diagram can help; use different notation for the time portion of the timeline where the event-rate of interest might be affected, and the portion where it cannot (see Figures)
Measure the apparent longevity- or time-extending benefits of inert agents/interventions	After the fact, use a lottery to assign virtual (and never actually delivered) interventions, but with same timing as the one under study. Or use actually-received agents with same timing
Imagine this agent/intervention were being tested within a randomized trial	How, and when after entry, would the agent be assigned? Administered? How would event rates be computed? How would Farr have tested his 'early-promotion' suggestion?
Think short intervals and hazard rates, even if the hazard rates do not change abruptly	In addressing the present, conditional on the past, the hazard approachhas already correctly documented the experience in each small past interval; the natural left to right time-ordering of the short intervals allows for correct recognition of transitions between exposure states. By computing a mortality rate over a longer time-span defined after the fact, one may forget that in order to contribute time to the index category, people had to survive the period spent in the (initial) reference category

Lets zoom in. The first advice is to start with the most fundamental concepts in all of epidemiology, TRAIT and STATE. State/status is a familiar concept for students of the Facebook era. And EVENTS are transitions from one state to another. [One enters a closed population or cohort by way of an event, AND one never leaves, even at death. Koch, Einstein and Zur Hausen will always be in the cohort of Nobel Laureates. One is in an open or dynamic population for the duration of a state, e.g., while driving (and this can be subdivided into on-the-phone or off-the-

phone time).] Epidemiologists should stop talking about rates in groups and instead should compute the rates at which events occur in person-time spent in the different exposure categories. In the bible story, Solomon took advantage of the human instinct that PEOPLE are INDIVISIBLE. BUT THEIR TIME IS DIVISIBLE. ↓ 148 / 951

Suggestion	Remarks/tests
State *versus* Trait	Trait (e.g. blood group) usually forever; people & objects move between states (on/off phone; intoxicated/not; on/off medication; failed allograft in place/removed)
Dynamic *versus* closed	Membership in closed population (cohort) is initiated by an event (transition from a state) and is forever; in a dynamic population, it is for duration of a state. Dynamic populations are the only option for studying transient exposures with rapid effects (e.g. cellphone/ alcohol use vis-a-vis rate of motor vehicle accidents)
Focus on person-time in index & reference exposure categories, rather than people in exposed and unexposed 'groups'	These refer to exposure categories, not to people per se; a person's time may be divided between exposure categories; unless people remain in one category, it is misleading to refer to them as a 'group'.
If authors used the term 'group', ask ...	When and how did persons enter a 'group'? Does being in or moving to a group have a time-related requirement? Is classification a fixed one based on the status at time zero, or later? Is it sufficient to classify a person just once, or do we need to classify the 'person-moments,' that is the person at different times?

And just as in lab sciences, we should use negative controls and inert agents as a way to check for artifacts or faulty theories or methods. And get used to dividing up time into small slices. ↓ 37 / 988

Suggestion	Remarks/tests
Draw individual timelines	If there are two time scales, a Lexis diagram can help; use different notation for the time portion of the timeline where the event-rate of interest might be affected, and the portion where it cannot (see Figures)
Measure the apparent longevity- or time-extending benefits of inert agents/ interventions	After the fact, use a lottery to assign virtual (and never actually delivered) interventions, but with same timing as the one under study. Or use actually-received agents with same timing.
Imagine this agent / intervention being tested within a randomized trial	How, and when after entry, would the agent be assigned? Administered? How would event rates be computed? How would Farr have tested 'early-promotion' suggestion?
Think short intervals and hazard rates, even if the hazard rates do not change abruptly	In addressing the present, conditional on the past, the hazard approach has already correctly documented the experience in each small past interval; the natural left to right time-ordering of the short intervals allows for correct recognition of transitions between exposure states. By computing a mortality rate over a longer time-span defined after the fact, one may forget that in order to contribute time to the index category, people had to survive the period spent in the (initial) reference category

HOW BIG CAN TIME-BLUNDERS BE? There are two dimensions (1) how big is the error, and (2) how long can the mis-information persist?, and how big an audience can it affect? I can tell you that this one, started 16 years ago

HOW BIG CAN TIME-BLUNDERS BE?

Survival in Academy Award–Winning Actors and Actresses

Donald A. Redelmeier, MD, and Sheldon M. Singh, BSc

Background: Social status is an important predictor of poor health. Most studies of this issue have focused on the lower echelons of society.

Objective: To determine whether the increase in status from winning an academy award is associated with long-term mortality among actors and actresses.

Design: Retrospective cohort analysis.

Setting: Academy of Motion Picture Arts and Sciences.

Participants: All actors and actresses ever nominated for an academy award in a leading or a supporting role were identified ($n = 762$). For each, another cast member of the same sex who was in the same film and was born in the same era was identified ($n = 887$).

Measurements: Life expectancy and all-cause mortality rates.

Results: All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7 vs. 75.8 years; $P = 0.003$). This difference was equal to a 28% relative reduction in death rates (95% CI, 10% to 42%). Adjustment for birth year, sex, and ethnicity yielded similar results, as did adjustments for birth country, possible name change, age at release of first film, and total films in career. Additional wins were associated with a 22% relative reduction in death rates (CI, 5% to 35%), whereas additional films and additional nominations were not associated with a significant reduction in death rates.

Conclusion: The association of high status with increased longevity that prevails in the public also extends to celebrities, contributes to a large survival advantage, and is partially explained by factors related to success.

Ann Intern Med. 2001;134:955-962. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 1001-1003.

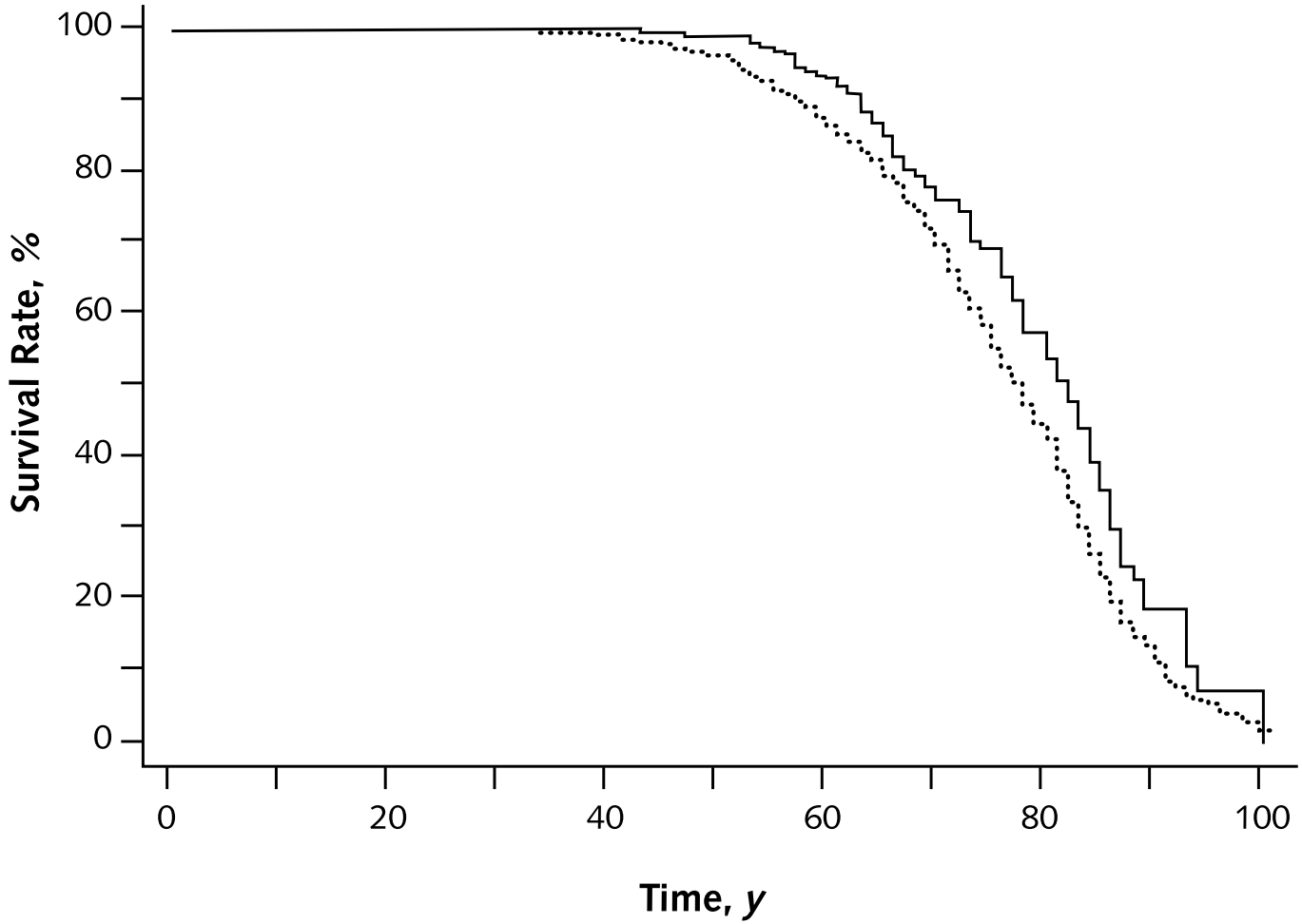
is still going strong. Harvard continues to sell the story, and has not revised it. ↓ 16 / 1047

In Brief: ...and I'd like to thank the Academy for a longer life

A doctor's research suggests that Oscar-winning actors and directors may live longer partly as a result of their honors.

Pairs of Kaplan-Meier plots like this strongly suggest a problem. $\downarrow 11$ / 1058

Survival in Academy Award-winning actors and actresses (solid line) and controls (performers who were never nominated) (dotted line), plotted by using the Kaplan-Meier technique.



Analysis is based on log-rank test comparing 235 winners (99 deaths) with 887 controls (452 deaths). The total numbers of performers available for analysis were 1122 at 0 years, 1056 at 40 years, 762 at 60 years, and 240 at 80 years. P=0.003 for winners vs. controls.

By how much did their 28% overestimate the mortality rate difference? $\downarrow$ 12 / 1070

Annals of Internal Medicine | Academia and Clinic

Do Oscar Winners Live Longer than Less Successful Peers? A Reanalysis of the Evidence

Marie-Pierre Sylvestre, MSc; Ella Huszti, MSc; and James A. Hanley, PhD

In an article published in *Annals of Internal Medicine* in 2001, Redelmeier and Singh reported that Academy Award–winning actors and actresses lived almost 4 years longer than their less successful peers. However, the statistical method used to derive this statistically significant difference gave winners an unfair advantage because it credited an Oscar winner's years of life before winning toward survival subsequent to winning. When the authors of the current article reanalyzed the data using methods that avoided this "immortal time" bias, the survival advantage was closer to 1 year and was not statistically significant. The type of bias in Redelmeier and Singh's study is not limited to longevity comparisons of persons who reach different ranks within their profession; it can, and often does, occur in nonexperimental studies of life- or time-extending benefits of medical interventions. The current authors suggest ways in which researchers and readers may avoid and recognize this bias.

Ann Intern Med. 2006;145:361-363. **www.annals.org**

For author affiliations, see end of text.

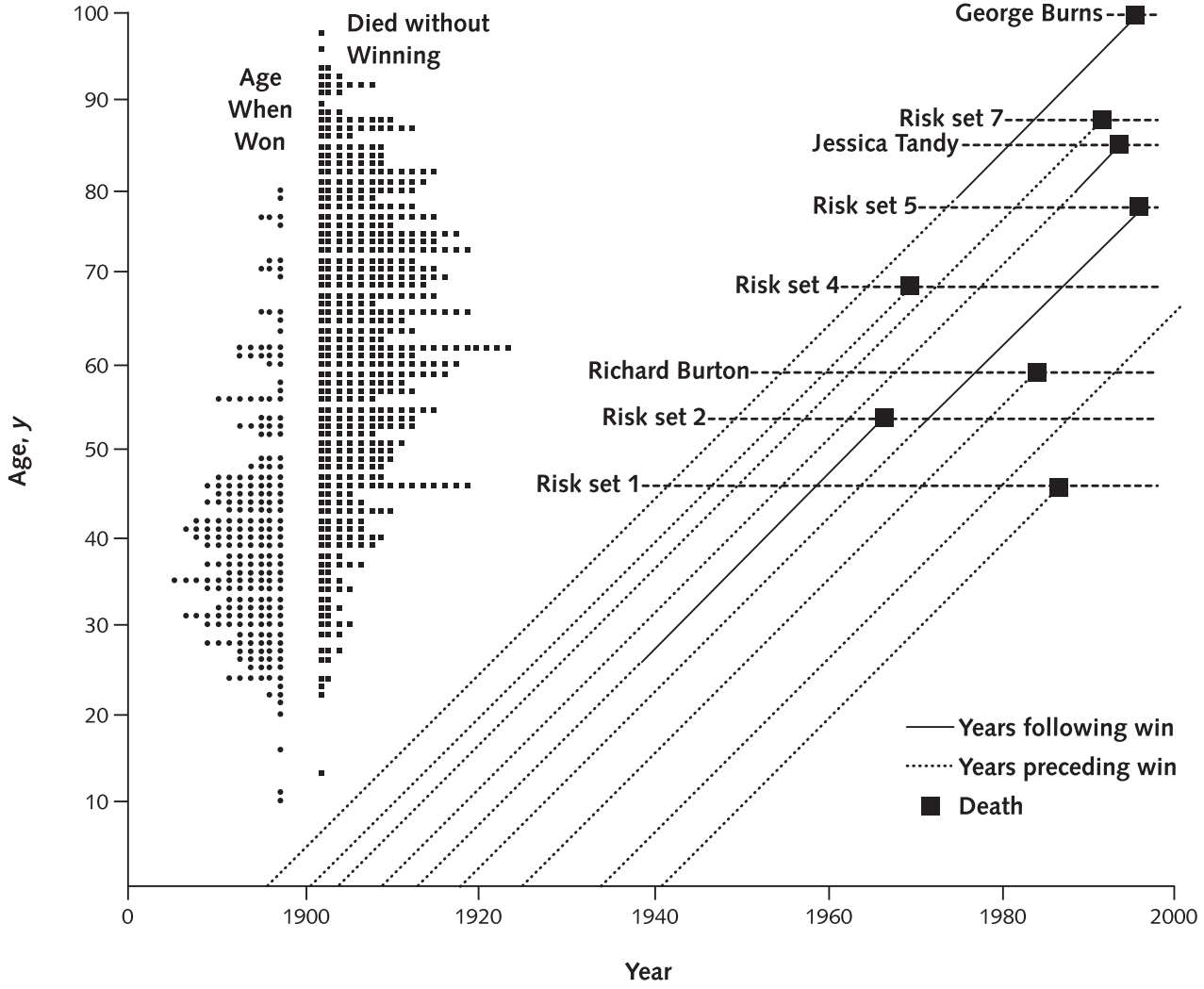
We re-calculated it as 18%, i.e. a HR = 0.82. [I avoid the word 'reduction', which has a causal connotation.] ↓ 21 / 1091

Re-analysis of mortality rates in as.winner.time vs. as.nominee.time. 1

- Time-dependent Cox proportional hazards model, with age in years as the time axis (risk sets constructed at each unique age at death), sex and year of birth as covariates, and each performer's status updated at each successive risk set. Those not yet been nominated by that age at death were excluded from that risk set.
    - Already a winner, 1 or not 0. The estimated difference in mortality rates was 18% (CI, -4% to 35%).
    - Number of years since winning, 0 non-winners, 1, 2, 3, ... again not statistically significant, whether represented by just a linear term or by linear and quadratic terms.

Here is the Lexis diagram we used to explain the problem and depict the data. We recommend the Lexis diagram to everyone, including professional epidemiologists and statisticians. ↓ 28 / 1119

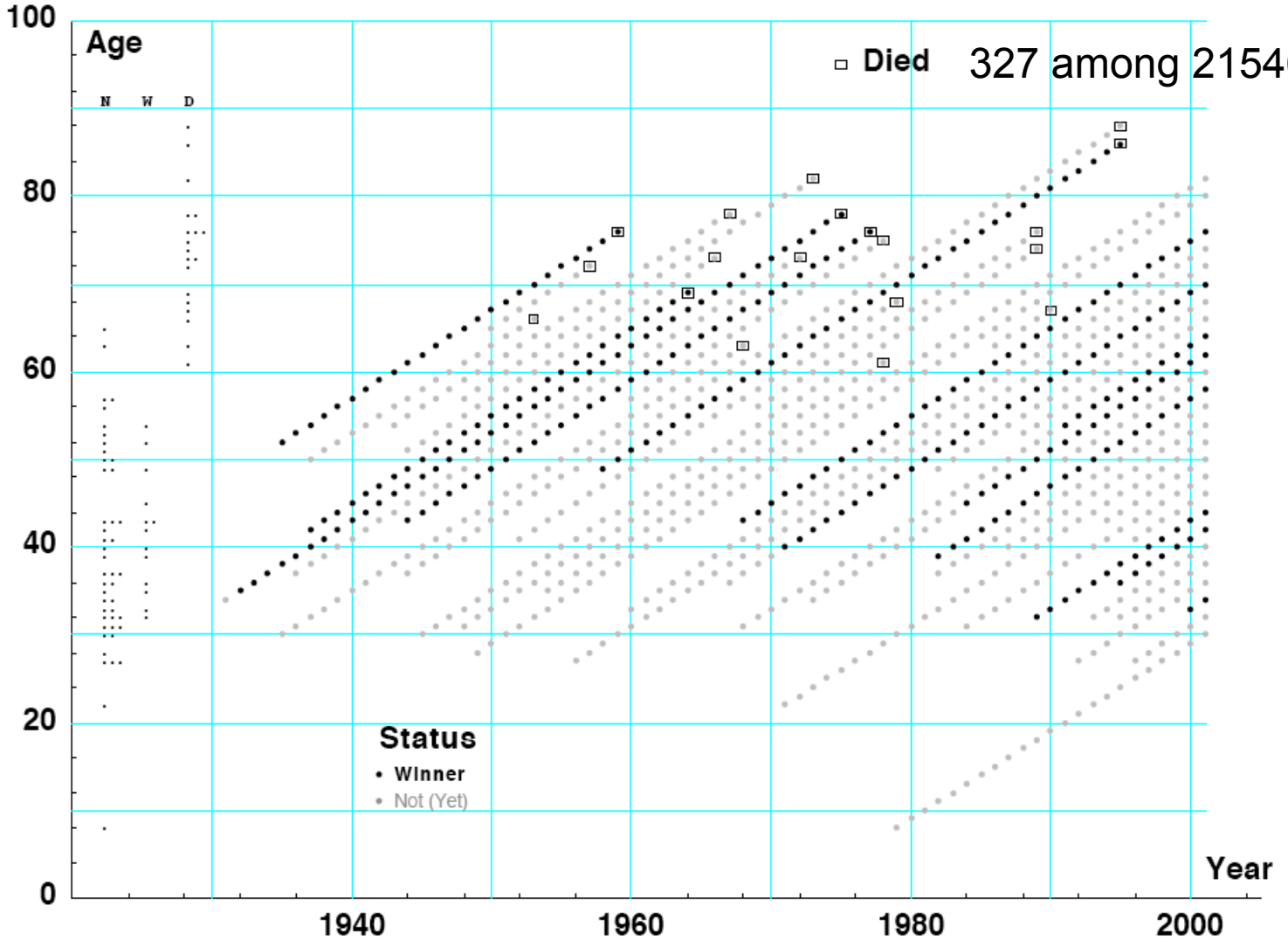
Figure. **Lexis diagram showing life course for 9 selected performers (all nominated), along with their status at the time of the 8 risk sets (1 at each death).**



A Lexis diagram (4) represents each performer's time course as a diagonal line, with advancing age on the vertical axis and advancing calendar time on the horizontal axis. Winners, by virtue of their having lived long enough to win, were, in hindsight, "immortal" in the years that preceded their win. Circles and squares at the left of the figure indicate ages at which winners won and ages at death of those who died without winning.

It also leads naturally to the 2-time-scales approach described by Efron. Each person-time increment (here a person-year) is one dot or observation. And with a resolution of 1 year x 1 year, a logit model is perfectly fine and yields estimates hazard ratios. I am curious what you think the coefficients should be for age year and being.male ↓ 59 / 1178

2. Efron's 2-way proportional hazards model (JRSS-B 2002)



$$\text{logit}\,[\text{Prob}[\square] = B_0 + B_1\text{Age} + B_2\text{Year} + B_3\text{Male} + B_4\text{Winner}$$

here are more details. And by the way, a third old-fashioned way, via the Mantel-Haenszel summmary rate raio, gave exactly the same. No surprize, given what David Clayton showed us about it being the first iteration on the way to the ML estimate from Poisson regression. ↓ 47 / 1225

Re-analysis of mortality rates in as.winner.time vs. as.nominee.time

- We treated the 21,546 post-nomination performer-years as 21,546 separate observations.
  - Winning status was at the time of the observation
  - death in the performer-year was treated as a Bernoulli random variable, with logit link.
  - With sex, age, and calendar year as covariates, the mortality rate reduction was 18% (CI, -4% to 36%).

In measuring reductions in mortality produced by cancer screening, we tend to match on age and year. We could here too, but modelling the rates as a parametric function of time and age means we can make smooth estimates of additional performer-years. The best estimate that rates are18% lower translates into an advantage, over the follow-up time studied, of 1 year, with these 95% limits. The difference in areas under the Kaplan-Meier curves was 3.9 years. So, did ignoring the immortal years while the winners waited for their Oscar create a longevity artifact of 2.9

years? Our 1y estimate is an observed:expected type calculation that doesn't have a direct analog for K-M based calculations. $\downarrow$ 115 / 1340

Extended life-years – via Efron model

From the actuarial life table constructed from the fitted regression coefficients we calculated the expected total number of years alive for a hypothetical group of 238 performers of the same age, sex, and birth year as the 238 winners:

Change in Mortality Rate:	0%	[$\uparrow$ 4%	$\downarrow$ 18%	$\downarrow$ 36%]
Total years alive, win $\rightarrow$ 2001:	5967.6 y	[5922.9	6194.2 y	6451.3 y]
Mean longevity advantage:	———	[-0.2 y	1.0 y	2.0 y]

SEVERITY of the immortal time bias: Oscar study

Inspiration: Turnbull, Brown & Hu. Survivorship analysis of heart-transplant data. JASA 1974

- Used dataset to calculate conditional probabilities[first win]: e.g., 21% of actresses won the year they were first nominated; 3% of those who did not win immediately won the next year, etc...]
- Regardless of whether performer ever won an Oscar, we used these, and the number of post-nomination years [s]he lived, to generate a random (hypothetical) age at performer's first 'win'.
- Majority of performers in each data set died before they could win; those who did win these 'awards' were not aware that they had won.
- Methods that treated group membership as dynamic recovered the null mortality rate ratio.
- Not accounting for immortal time produced an artifactual longevity advantage of 0.8 year (reduction in mortality rates, 6%) for those who won the randomly generated awards over those who did not survive long enough to win them.

That's why we adopted the Turnbull approach, which allows us to measure the bias directly. The nominee cohort is eligible for lotteries; anyone who is alive at the time can win and cross to the status of winner. But willing doesn't do anything. And yet, the wait to win creates an artifactual advantage of about 1 year. With the smallish numbers of deaths, the various components do not add perfectly to 3.9y. We will come soon to to the Big-Data blunder by the amateur epidemiologists who studied the population of an entire country. 93 / 1433

Before I show you the Google translation, what were they studying? Sun worshippers. They worship so much that they got skin cancer. But they lived 6 years longer than other Danes, or so the article said. The article did say that there was some controversy, but that the authors insisted that 'the numbers as such do not lie'. 58 / 1491

FORBRUG & LIV

Bolig Sundhed Digitalt Forbrug Biler Livsstil Guider Test

SYGDOM 15. OKT. 2013 KL. 23.00

Soldyrkere lever meget længere

Ny forskning blandt 4,4 millioner danskere viser, at soldyrkere i gennemsnit lever seks år længere. Kræftens Bekæmpelse finder tallene spændende.

SOLDYRKERE. Måske er solens stråler ikke så farlige, som vi tror - i hvert fald viser ny dansk forskning, at mennesker, som har været ivrige soldyrkere, i gennemsnit lever længere. Foto: Gorm Branderup(Arkiv)

Sun worshipers live much longer

New research among 4.4 million Danes shows that sun worshipers **on average live six years longer**

POLITIKEN. 15. OKT. 2013

Sun worshipers . Perhaps the sun's rays are not as dangerous as we think - at least according to new Danish research that people who have been eager sun worshipers, on average, live longer.

I will come in a minute to the intervention by the Copenhagen biostatisticians, but first, here is an important commentary the next day from another Copenhagen newspaper. I think this cartoon is very telling, and it should be a warning to publicity-seeking investigators that the public does not trust them. High energy electric lines be harmful to health, but if you live near them, you can take advantage of the sun. 71 / 1562

The Copenhagen Post's daily round-up of the front pages and other major Danish news stories

Don't laugh, he's going to live longer than you do (Photo: Coloubox)

October 16, 2013 08:00

by KM

0

Sunbathers live longer

Spending time in the sun can add years to your life, a 20-year study following the health of 4.4 million Danes finds. The team of Danish scientists, whose research results will be published in the Journal of Epidemiology, found that people who were regular sunbathers and who had developed benign forms of skin cancer lived up to six years longer than the average for the population as a whole. The study also found that sunbathers had lower rates of heart attacks and osteoporosis. While the team said its evidence was conclusive, they said they had not been unable to determine what made sunbathers live longer. – *Politiken*

SEE RELATED: More Danes dying of cancer

State could open its gates to foreign entrepreneurs

Non-western immigrants live longer

Diner fined for whining, but did café cross the line?

Latest Comments

Also I believe a lot of these immigrants are trying to imitate the Danes by...
(Hamish Carey on April 7, 2014 17:51)

He expects 50 permits be issued under the scheme during the first year, with...
(Jon Paris King on April 7, 2014 16:42)

What do you expect from a system that supports wrong in all it's form because...
(Alæn-Roger Mbah on April 7, 2014 14:28)

?You need to go to a ghetto in the USA or a Brazilian favela to see something...
(Leo Carona on April 7, 2014 08:52)

Since there has never been a world wide flood who cares how they portray a myth.
(Lewis Thomason on April 7, 2014 00:20)

About the fork and knife, I think means an "open" sandwich?
(Jens Rost on April 6, 2014 17:19)

One of my favorite Danish immigrants to the USA was George "Dutch" Anderson...
(Bill Jones on April 6, 2014 16:20)

Yeah, this is truly a valid reason for hoisting the flag. For once, I'd not...
(Abhijeet Mishra on April 6, 2014 15:41)

This was the IJE article that the newspaper report was based on. ‘Associates with’ is the new journal-speak. 18 / 1580

Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2013;**42**:1486–1496
doi:10.1093/ije/dyt168

Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause

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The 130,000 Danes who stayed in the direct sun so much that they got skin cancer are the 'exposed' group. ['Exposure' is another over-used term in epidemiology, but it would not be so bad a term here.] The controls are all the other 4.x million Danes. These are 2 large groups so the 2 Kaplan-Meier curves are VERY SMOOTH. Note the new spelling of Paul Meier's name. [I think epidemiologists should form a professional order, and I invite you think up questions that would keep detect imposters.] The 6 year advantage is never mentioned in the article, but the journalist

was able to somehow extract it, maybe from this figure? or maybe from the authors. 115 / 1695

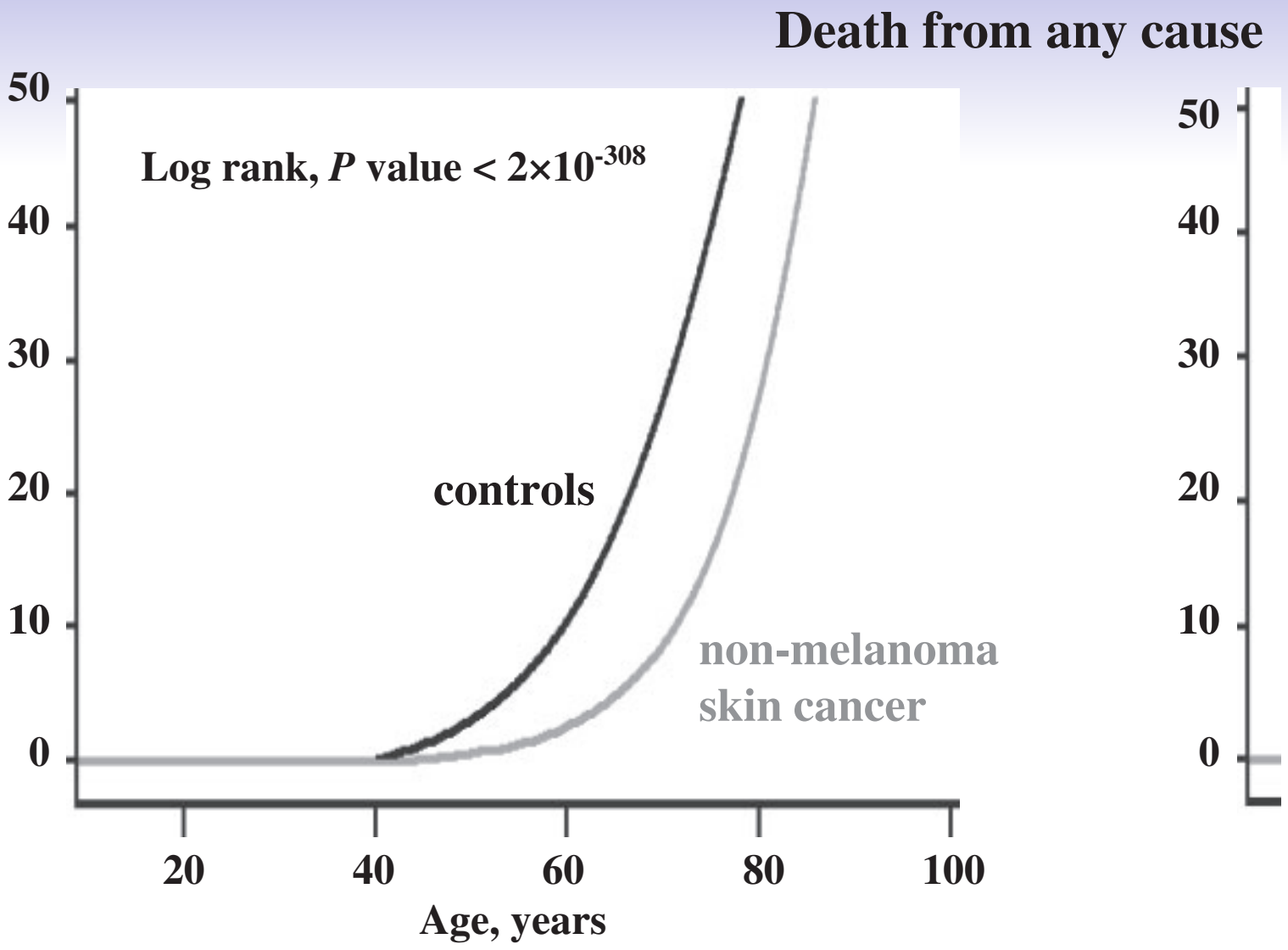

Figure 1 The cumulative incidence of myocardial infarction, hip frac above age 40 years ever diagnosed with non-melanoma skin cancer a incidence curves were generated from Kaplan–Meyer estimates, compa cutaneous malignant melanoma vs individuals free of both diseases. rank tests

This graph, the big-Data P-value, and the 6 years, and the overall HR of 0.52 were too much for these two biostatisticians. 22 / 1717

Skin cancer as a marker of sun exposure: a case of serious immortality bias

From Theis Lange* and Niels Keiding

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Brøndum-Jacobsen *et al.* recently published in this journal[1] analyses of Danish register data concerning myocardial infarction, hip fracture and death from any cause, using incidence of skin cancer as indicator of high exposure to sunlight. The basic idea in the paper is that those who get a skin cancer diagnosis at any age are supposed to have been more exposed to the sun during their life than those who do not, and apparently the authors find it relevant to use ordinary prospective survival analysis to compare incidence of myocardial infarction, hip fracture and death from any cause between the two groups: those who (at some point) get a skin cancer diagnosis and those who do not.

Unfortunately, such an analysis is seriously flawed, because the definition of one of the two groups to be compared conditions on the future: in order to get a skin cancer diagnosis, and thus become a member of the skin cancer group, it is at least necessary to survive until age of diagnosis, but the authors' analysis does not take this conditioning into account. Put another way: for those in the skin cancer group it is impossible to die until the age of diagnosis of the cancer, the so-called immortal person-time.[2]

For ease of exposition we focus on the endpoint 'death from any cause'. It is seen in the lower left panel of Figure 2[1] that those who get non-melanoma skin cancer at some age have a hazard ratio of dying from any cause in the age interval 40–49 years of about 0.2 vs those who never get a non-melanoma skin cancer diagnosis. A main reason for this is probably that very few of those with non-melanoma skin cancer are at all at risk for dying—most of the members of this group get their skin cancer diagnosis at ages >50 years and are therefore by design immortal in the age interval 40–49.

Methodology aside, we find it very surprising that neither the authors nor the editorial process have questioned the strange results at many places in the paper. For example: the upper right corner of Table 2[1] shows that persons who sooner or later get a diagnosis of malignant melanoma have a significantly reduced risk of dying from any cause: a hazard ratio of 0.89. Did no alarm bells sound? That the authors cautiously write 'causal conclusions cannot be made' in the abstract does not justify publishing a methodologically flawed analysis.

As a more comic point, we noted that *IJE* now quotes *P*-values with 308-digit precision—we hope that the chi-square approximation to the distribution of the log-rank statistic is justified!

References

1. Brøndum-Jacobsen P, Nordestgaard BG, Nielsen SF, Benn M. Skin cancer as a marker of sun exposure associates with myocardial infarction, hip fracture and death from any cause. *Int J Epidemiol* 2013;**42**:1486–96.
2. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology.* 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.

They focused on the HR of 0.2 in this age-band. Can you see why it is so close to zero? 20 / 1737

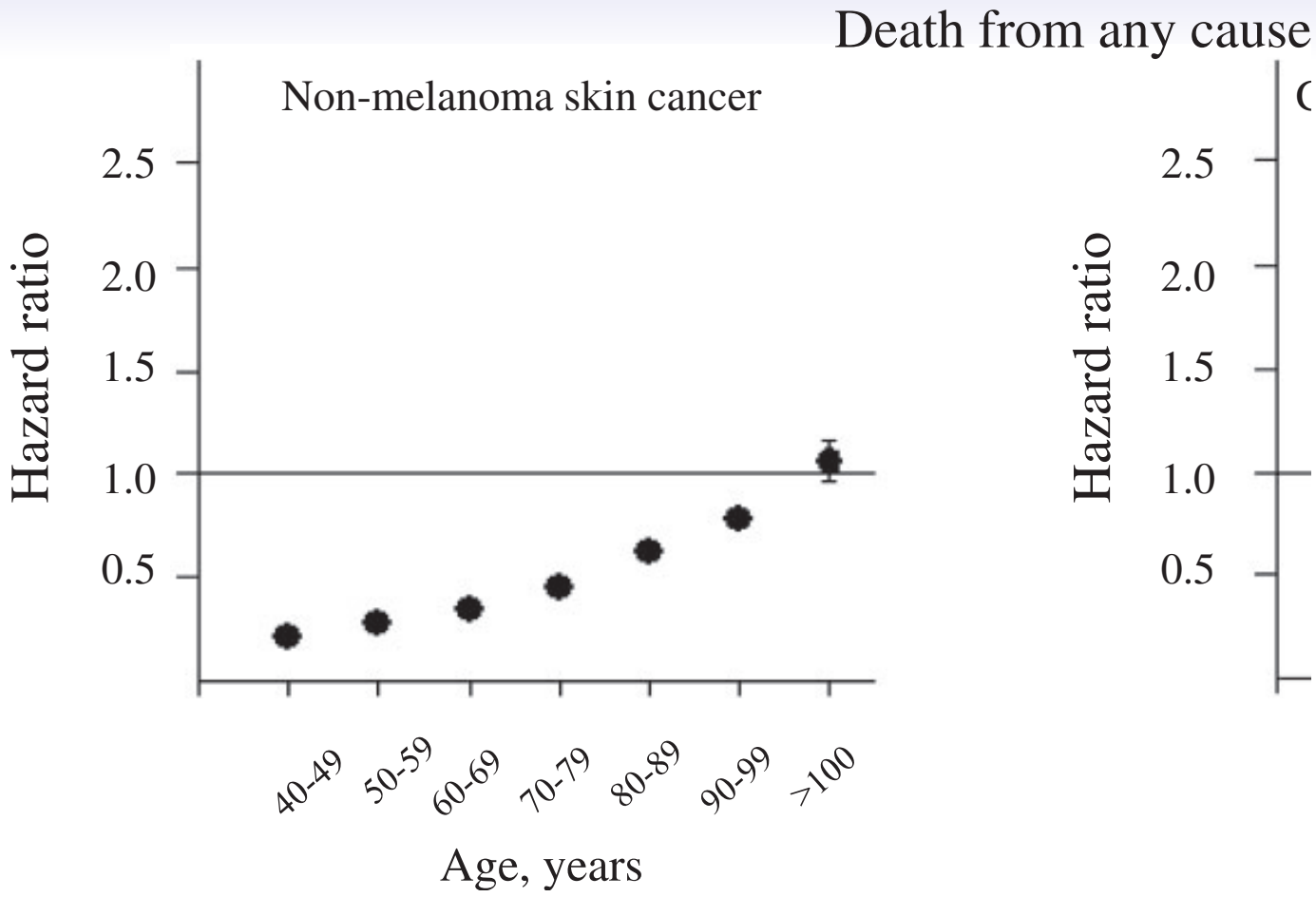

Figure 2 In the entire Danish population above age 40 years, odds ratios hazard ratios for death from any cause within 10-years age-strata. N.E., nc

In their response, the authors stuck to their claims, 9 /

Authors' Response to: Skin cancer as a marker of sun exposure—a case of serious immortality bias

International Journal of Epidemiology, 2014, 972–973
doi: 10.1093/ije/dyu102
Advance Access Publication Date:

From Peter Brøndum-Jacobsen,[1,2] Børge G Nordestgaard,[1,2] Sune F Nielsen[1] and Marianne Benn[2,3]*

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and added a new figure derived from a modified approach that they thought would exclude immortality bias. I will let you try to get your head around this phrase for a while and come back to it. 37 / 1783

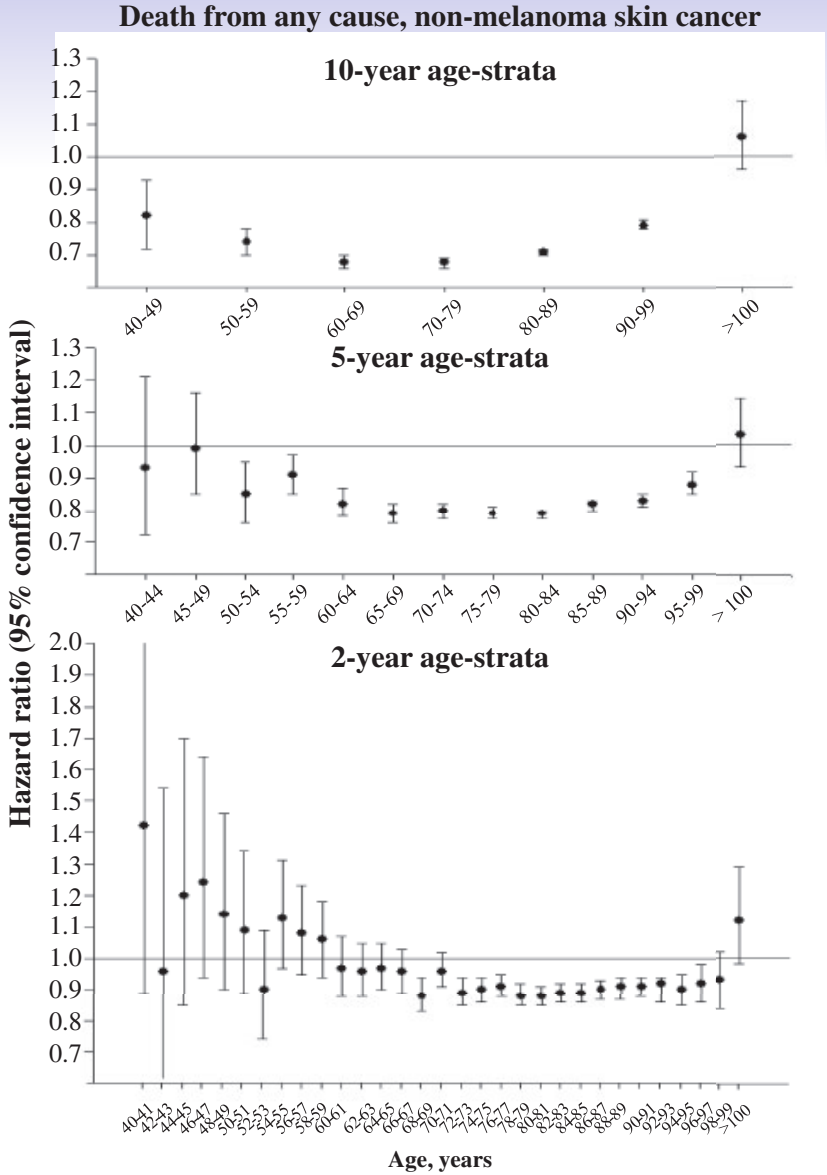

Figure 1. In the entire Danish population above 40 years of age, hazard ratios for death from any cause are shown within 10-year, 5-year and 2-year age-strata in individuals with vs without non-melanoma skin cancer. An individual with a non-melanoma skin cancer diagnosis occurring after the defined age-stratum was coded as an individual without a diagnosis of non-melanoma skin cancer.

and added a new figure derived from a modified approach that they thought would exclude immortality bias. I will let you try to get your head around this phrase for a while and come back to it. 37 / 1783

Avoiding blunders involving 'immortal time'

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Accepted 2 April 2014

As Groucho Marx once said 'Getting older is no problem. You just have to live long enough'.
(Queen Elizabeth II, at her 80th birthday celebration in 2006)

This award proves one thing: that if you stay in the business long enough and if you can get to be old enough, you get to be new again.
(George Burns, on receiving an Oscar, at age 80, in 1996)
(Richard Burton died, a nominee 6 times, but sans Oscar, at 59. Burns lived to 100, so how much of the 41 years' longevity difference should we credit to Burns' winning the Oscar?)

Some time ago, while conducting research on U.S. presidents, I noticed that those who became president at earlier ages tended to die younger. This informal observation led me to scattered sources that provided occasional empirical parallels and some possibilities for the theoretical underpinning of what I have come to call the precocity-longevity hypothesis. Simply stated, the hypothesis is that those who reach career peaks earlier tend to have shorter lives.
(Stewart JH McCann. *Personality and Social Psychology Bulletin* 2001;**27**:1429–39)

Statin use in type 2 diabetes mellitus is associated with a delay in starting insulin.
(Yee *et al. Diabet Med* 2004;**21**:962–67)

Introduction

For almost two centuries, teachers have warned against errors involving what is now called 'immortal time.' Despite the warnings, and many examples of how to proceed correctly, this type of blunder continues to be made in a widening range of investigations. In some instances, the consequences of the error are less serious, but in others the false evidence has been used to support theories for social inequalities; to promote greater use of pharmaceuticals, medical procedures and medical practices; and to minimize occupational hazards.

We use a recent example to introduce this error. We then discuss: (i) other names for it, how old it is and who tried to warn against it; (ii) how to recognize it, and why it continues to trap researchers; and (iii) some statistical ways of dealing with denominators measured in units of time rather than in numbers of persons.

Example and commentary

Example

Patients whose kidney transplants (allografts) have failed must return to long-term dialysis. But should the failed allograft be removed or left in? To learn whether its removal 'affects survival', researchers[1] used the US Renal Data System to study 'a large, representative cohort of [10 951] patients returning to dialysis after failed kidney transplant'. Some 1106, i.e. 32% of the 3451 in the allograft nephrectomy group, and 2679, i.e. 36% of the 7500 in the non-nephrectomy group, were identified as having died by the end of follow-up.

Patients in the two groups differed in many characteristics: to take into account a 'possible treatment selection bias', the authors constructed a propensity score for the

But just as we were expecting the galleys, the Editor invited us to add a postscript commenting on the sun exposure correspondence, where the amateur epidemiologists had had the last word. Our first comment was that this was a lot more serious than telling the public what would happen to them in the unlikely event that they won an Oscar.

Postscript

When writing this piece, we wondered whether we were preaching to the converted. We did not add Rodolfo Saracci's suggested subtitle, 'The fallacy that refuses to die'. Surely such blunders do not occur in epidemiology journals, where the review is more rigorous than in some of the clinical ones? The article that is the subject of the correspondence in this IJE issue[19] indicates otherwise. The flaw in the comparison that led to a multifactorially adjusted, but too good to be true, hazard ratio of 0.52 (and even the other, more finely stratified ratios) was missed not just by the authors themselves, but also by their colleagues, granting agencies, journal referees and editors, and newspaper journalists and editors.

The Editor asked us to 'explain how immortal time bias plays a role in their findings' and to provide 'any comment [we] care to make about their re-analysis in response[20] to the criticisms raised by Lange and Keiding'.[21] We do so, but only after we first make some broader comments.

It will not be easy to put the toothpaste back in the tube, but we hope that those in the academic portion of this chain will each do their part. Might the *IJE* ask its media contacts to carry a follow-up story that might help undo the damage? In addition, instead of reporting additional analyses that still have flaws (or faulting the media for the over-interpretation and for their focus on the longevity 'effect') an *IJE mea (nostra?) culpa* might do more good: it might just add to (rather than subtract from) the limited amount of credibility biomedical scientists currently have remaining with the public.

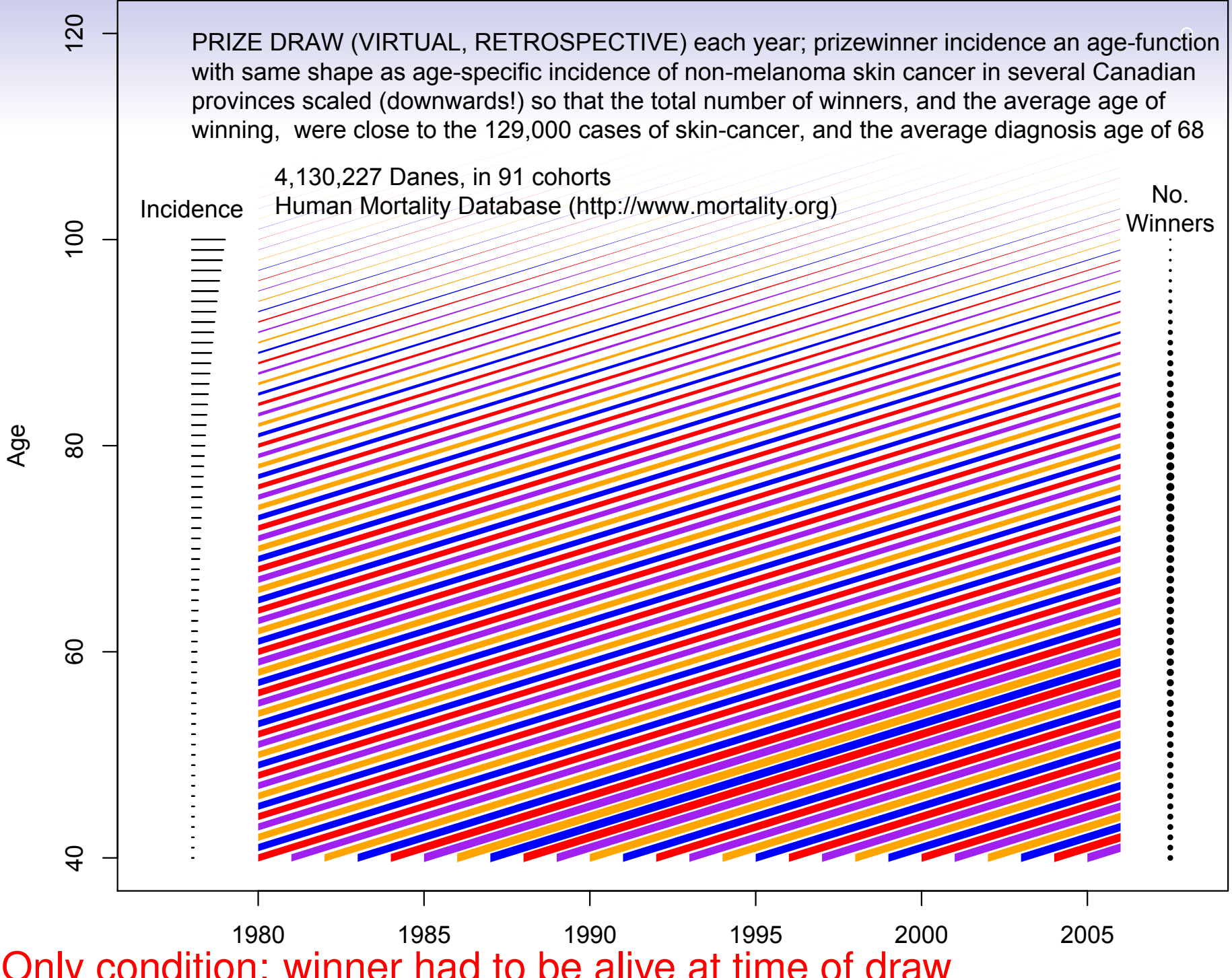
It is one thing to give the public a reason to merely daydream about winning an Oscar and adding four years to one's life; it is quite another to imply—even cautiously—on the basis of the difference in median longevity of six years in the bottom left panel of Figure 1 of the 'sun exposure' article, that an even larger longevity bonus is readily accessible to all. Curiously, the 'extra' six years do not appear anywhere in the article, but figured prominently in the newspaper story. In it, one of the authors emphasized that they could not identify the direct causal link, but added that 'the numbers as such do not lie'. This statement illustrates what one might call a type III error, where an inappropriately set up statistical contrast, not chance, is the culprit.

We then fell back on some of the negative controls I spoke of earlier. Remember these. 16 / 1898

Ways to check for immortal time bias

- Study an event (outcome) that should have no causal relationship with the exposure of interest
- Study the association between an unrelated exposure and the outcome of interest
- Be wary if the hazard ratios are $\ll 1$ or $\gg 1$.

We studied the effect on an unrelated exposure. In this Lexis diagram, you see the 91 Danish cohorts the authors has followed. We gave prizes to a randomly selected 130,000 of them, but did not tell them about their prizes. Indeed we only selected them in 2014. The ages at which they won has the same distribution as the ages at which the 130,000 got their skin cancers. This was the only condition: the winner had to be alive at time of the draw. 84 / 1982



Only condition: winner had to be alive at time of draw

If we used the same analysis as the authors initially used, what effect did this prize have? If we did it wrong, we that our prize was as beneficial as getting lots of sun. And when we sliced time more finely, we got the same pattern they got. If the authors went to the limit with their time-slicing, they would have been effectively using time-dependent exposures the way the rest of the world does. 74 / 2056

Effects of our Virtual Prize

- Using same analysis as in Figure 1 in IJE article, we obtained a difference in median longevity of 8.5 years (and a hazard ratio of 0.57 with a P-value somewhere below the `R pchisq` function limit of 5×10^{-324}).
- Hazard ratios in the 10-year 'strata' looked very similar to those in the lower left panel in the IJE Figure 2.
- When (as the authors did in their response) we narrowed the age slices further and insisted that 'those who [won our prize] beyond the age- strata enter into the analysis as not having [won]', we again get patterns similar to those in the figure in the response to Lange and Keiding. Even using age-slices just two years wide, our hazard ratios were not null: they ranged from 0.93 at age 65 to 0.95 at age 85.

Even with 2-year slices, their approach leaves opportunity for enough immortal time to create HR's of 0.95 or so. that is because persons who receive the prize at age 77.9 are 'immortal' for 1.9 years of the 2-year age slice 76-78. 41 / 2097

Reason for the residual bias

- By definition, a person who receives the prize at age 77.9 is 'immortal' for 1.9 years of the 2-year age slice 76-78.
- To avoid this induced immortality entirely, one needs to shrink the age-slice to an instant.
- Doing so is equivalent to using a time-dependent covariate ('exposure') in the Cox model, with risk sets defined at the moments the events occur. This is the most common way to deal with exposure *states* rather than *traits*.

CASE BASE SAMPLING

Miettinen came up with this idea, but it took him a while to convince me of its usefulness in modelling smooth hazard functions that translate into smooth in time risk functions or prognostic probabilities. 34 / 2132

The International Journal of Biostatistics

Volume 5, *Issue* 1 2009 *Article* 3

Fitting Smooth-in-Time Prognostic Risk Functions via Logistic Regression

James A. Hanley* Olli S. Miettinen†

Consider a person whose only risk factor was hypertension. Given their profile what is the person's 5-year risk of stroke if the hypertension was or was not treated? In this RCT, 263 strokes had occurred in 20,894 person-years of follow-up of 4701 individuals. Given that there was censoring before 5 years, how would you fit such risks? To see how we fitted the HAZARD functions using logistic regression, consider this small example dataset derived from this population-time plot. The time-plot is simply the number at risk vs. time, so these were the first ones recruited, and

DATA TO EXPLAIN OUR APPROACH

Systolic Hypertension in Elderly Program (SHEP)

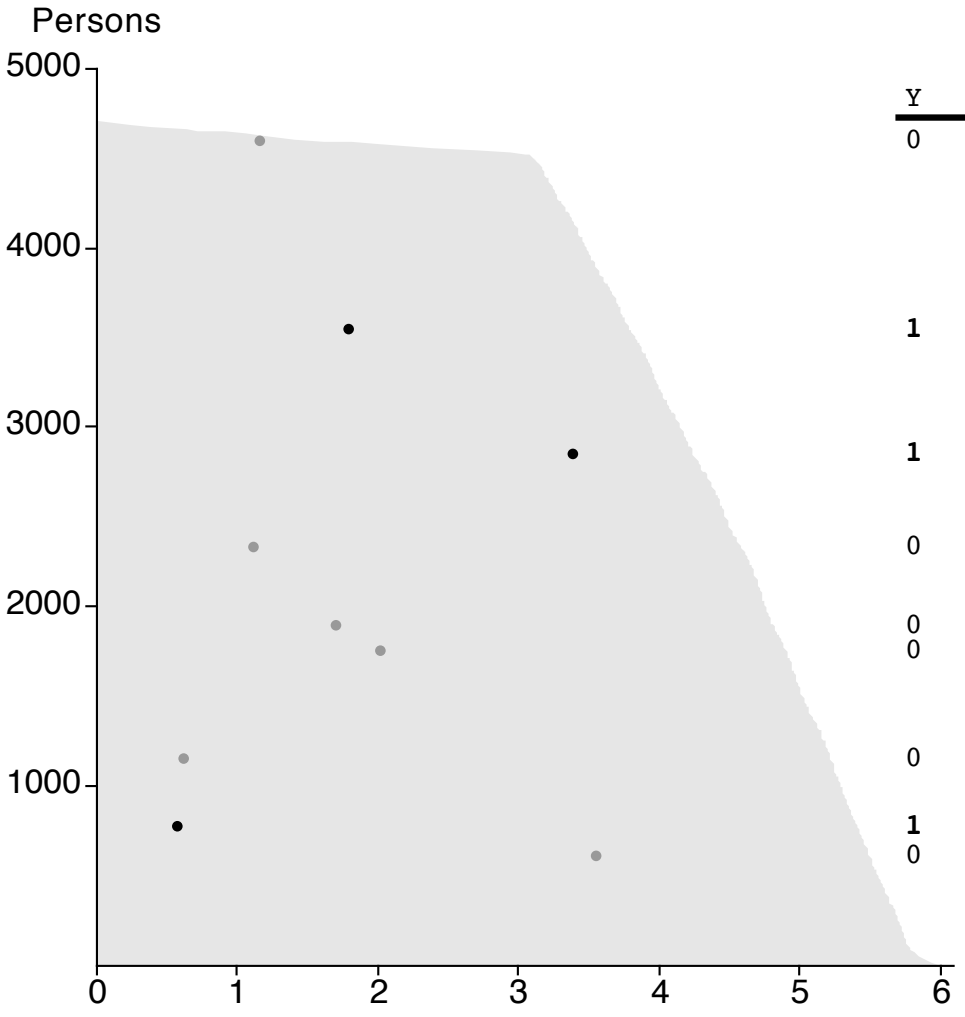
..... SHEP Cooperative Research Group (1991).

..... Journal of American Medical Association 265, 3255-3264.

- 4,701 persons with complete data on $P = \{$age, sex, race, and systolic blood pressure$\}$ and $I = \{$active/placebo$\}$.
- Study base of $B = 20,894$ person-years of follow-up; $c = 263$ events ("cases") of stroke identified.

this is the attrition due to strokes and deaths. The 3 back dots and lines with Y=1 in bold are the 3 deaths, and the grey dots and grey lines with Y=0 are 6 randomly selected person moments. t is time since randomization. 139 / 2271

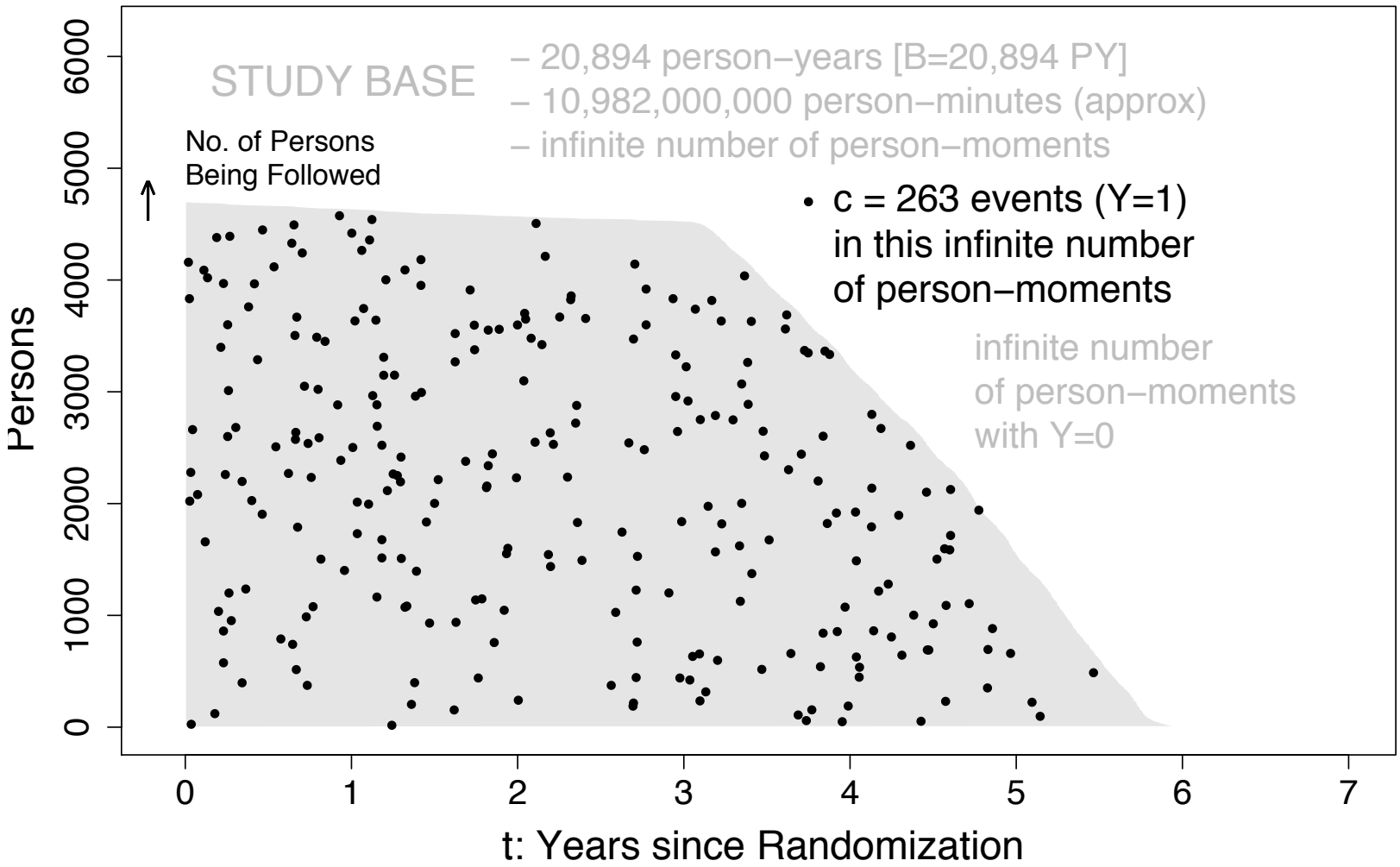
DATASET FOR LOGISTIC REGRESSION (SCHEMATIC)



Y	Age	B	M	SBP	I	t
0	81	1	0	161	0	1.16
1	**69**	**0**	**1**	**161**	**0**	**1.79**
1	**85**	**0**	**1**	**184**	**0**	**3.39**
0	70	0	1	185	0	1.11
0	69	0	0	182	0	1.70
0	73	0	1	167	1	2.02
0	73	1	0	199	0	0.62
1	**69**	**1**	**0**	**166**	**1**	**0.57**
0	72	0	0	172	1	3.56

This is the full case series arising from the base of almost 21,000 patient years. 15 / 2286

STUDY BASE, and the 263 cases



Our base series is a representative (unstratified, i.e., not time matched) sample of b patient moments from the BASE of 21,000 patient years. We model the log of the profile-specific case:base ratio at each time location. It is the product of a hazard function at that x,t and the ratio of the size of the Base to the size of the base sample of person moments. When we treat the log of this as an offset , we can directly model the log of the hazard function – and t is just another regressor variable. 95 / 2381

OUR APPROACH

- Base series: representative (unstratified) sample of base.
- b: size of base series
- B: amount of population-time constituting study base.
- $B(x,t)$: population-time element in study base

$$\frac{\Pr(Y=1|x,t)}{\Pr(Y=0|x,t)} = \frac{h(x,t) \times B(x,t)}{b \times [B(x,t)/B]} = h(x,t) \times (B/b),$$

- $\log(B/b)$ is an offset [a regression term with *known* coefficient of 1].

$\rightarrow$ logistic model, with t having same status as x, and offset,

directly yields $\widehat{h(x,t)} = \widehat{ID}_{x,t} = \exp\{\widehat{g(x,t)}\}$.

OUR HAZARD MODEL FOR SHEP DATA

$\log[h] = \Sigma \beta_k X_k$, where

X_1 = Age (in yrs) - 60
X_2 = Indicator of male gender
X_3 = Indicator of Black race
X_4 = Systolic BP (in mmHg) - 140

.....

X_5 = Indicator of active treatment

.....

$X_6 = T$

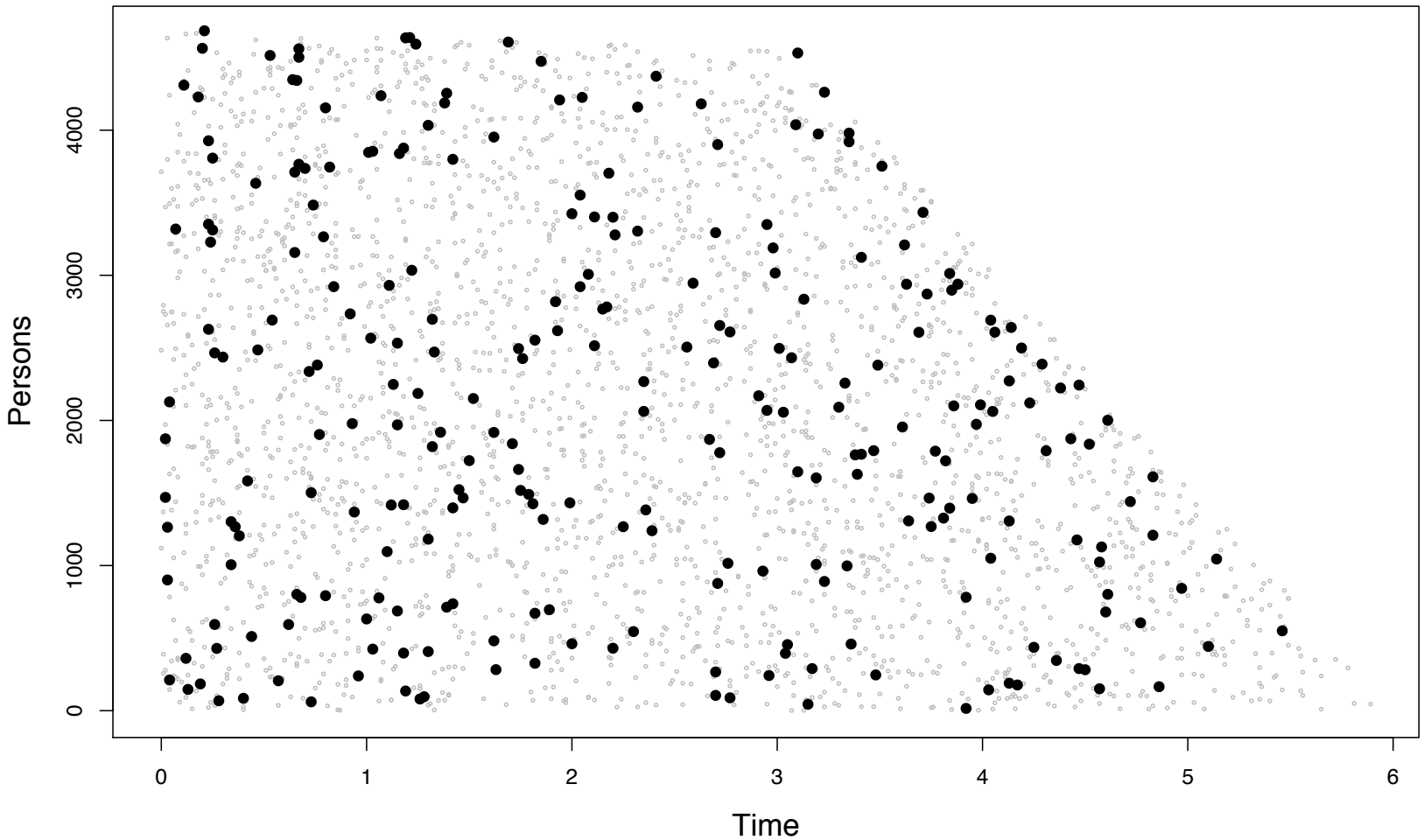
.....

$X_7 = X_5 \times X_6$. (non-proportional hazards)

PARAMETER ESTIMATION

- Formed person-moments dataset pertaining to:
  - case series of size $c = 263$ ($Y = 1$)
    and
  - (randomly-selected) base series of size $b = 26,300$ ($Y = 0$).
- Each of 26,563 rows contained realizations of
  - $X_1, \ldots, X_7$
  - Y
  - offset = $\log(20,894/26,300)$.
- Logistic model fitted to data in the two series.

DATASET: $c = 263; b = 10 \times 263$



and here are the fitted coefficients, side by side with the Cox version. Notice the smooth in time hazard function. The degree of modification of the treatment effect was small, so it is easy to see how close the parametric and non-parametric ones are. And it is very easy to go from a smooth hazard function to the integrated hazard and from there to the 5-year risk or cumulative incidence.

FITTED VALUES

	Proposed logistic regression		Cox regression
β_{age-60}	0.041	0.041	0.041
$\beta_{I_{male}}$	0.257	0.258	0.259
$\beta_{I_{black}}$	0.302	0.301	0.303
$\beta_{SBP-140}$	0.017	0.017	0.017
.....			
$\beta_{I_{Active\ treatment}}$	-0.200	-0.435	-0.435
.....			
β_0	*-5.390*	*-5.295*	
β_t	-0.014	-0.057	
$\beta_{t \times I_{Active\ treatment}}$	-0.107		

- Fitted logistic function represents $\log[h_x(t)]$
- $\rightarrow$ cumulative hazard $H_X(t)$, and, thus, X-specific risk.

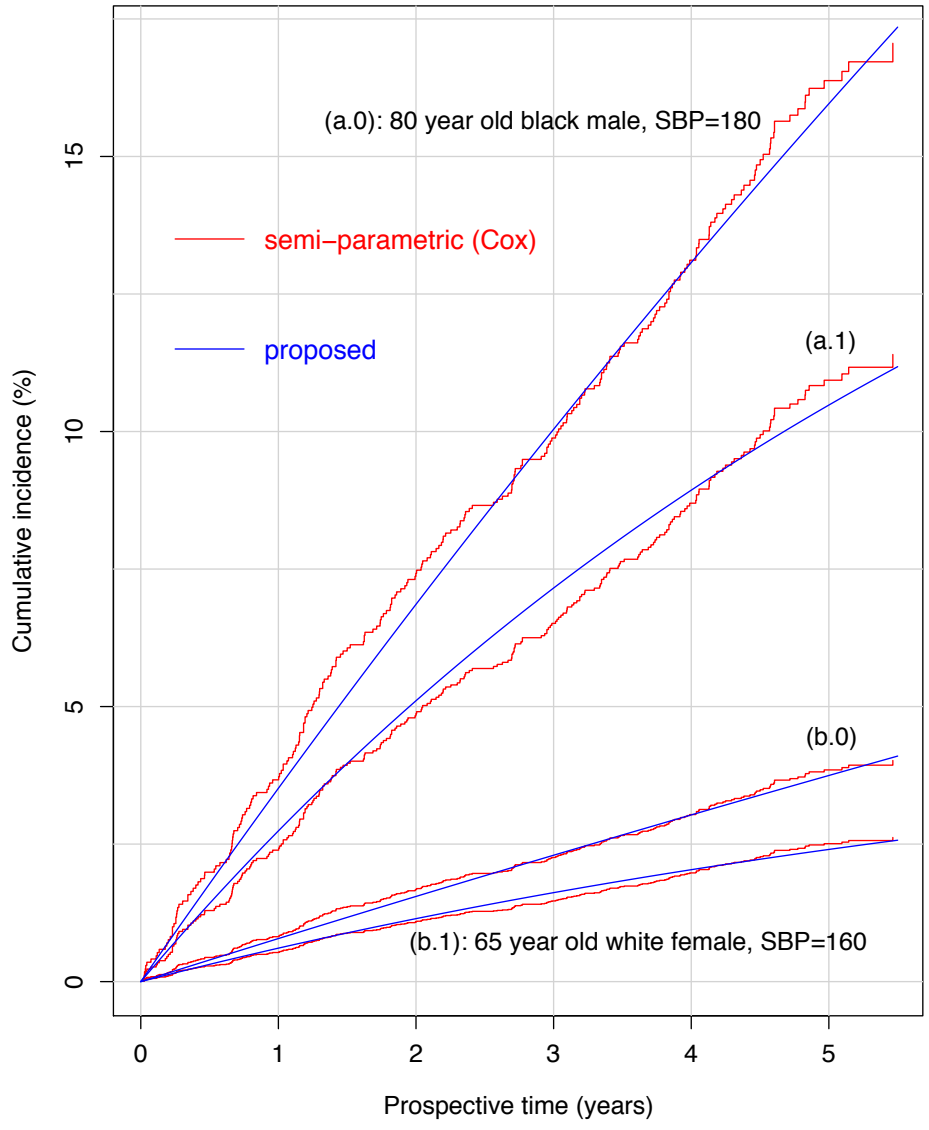
Here are the fitted 5 y risks if treated and if not, and the risk difference. The difference is much bigger if the risk is high to begin with. 29 / 2525

ESTIMATED 5-YEAR RISK OF STROKE

Risk	I	$h(t)$ [ID(t)]	$H(5)$ [$\int_0^5 h_x(t)dt$]	$CI(5)$ [$1 - e^{-H(5)}$]	Δ
Low	0	$e^{-4.86-0.014t}$	0.037	0.036	
	1	$e^{-5.06-0.124t}$	0.024	0.024	1.2%
High	0			0.16	
	1			0.10	6%
Overall	0			0.076	
	1			0.049	2.7%

Low: 65 year old white female with a SBP of 160 mmHg.
High: 80 year old black male with a SBP of 180 mmHg

And here they are graphically. 5 / 2530

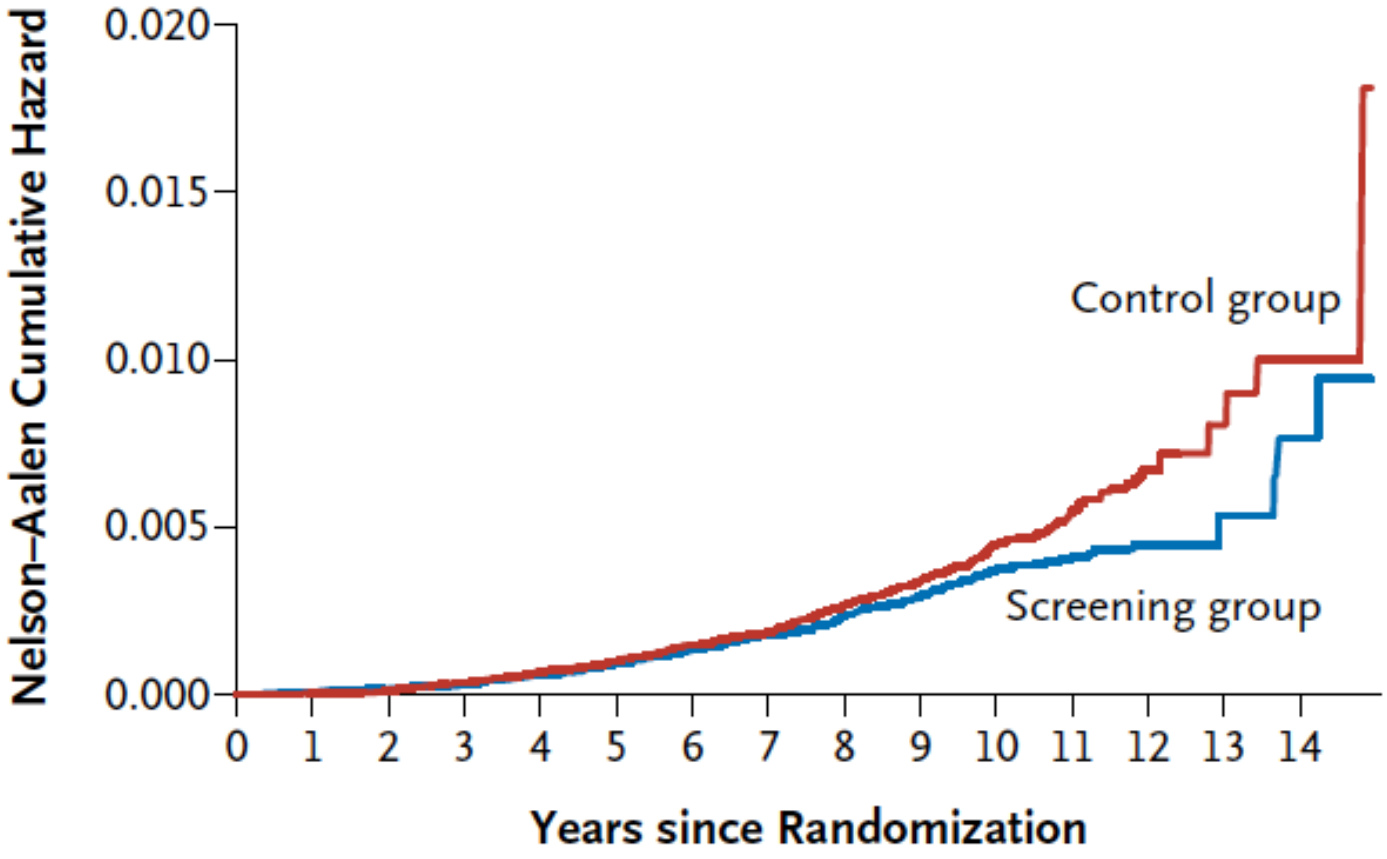

(a.0): 80 year old black male, SBP=180
semi−parametric (Cox)
proposed
(a.1)
(b.0)
(b.1): 65 year old white female, SBP=160
Cumulative incidence (%)
0
5
10
15
0
1
2
3
4
5
Prospective time (years)

another POPULATION-TIME plot 3 / 2533

Screening and Prostate-Cancer Mortality in a Randomized European Study

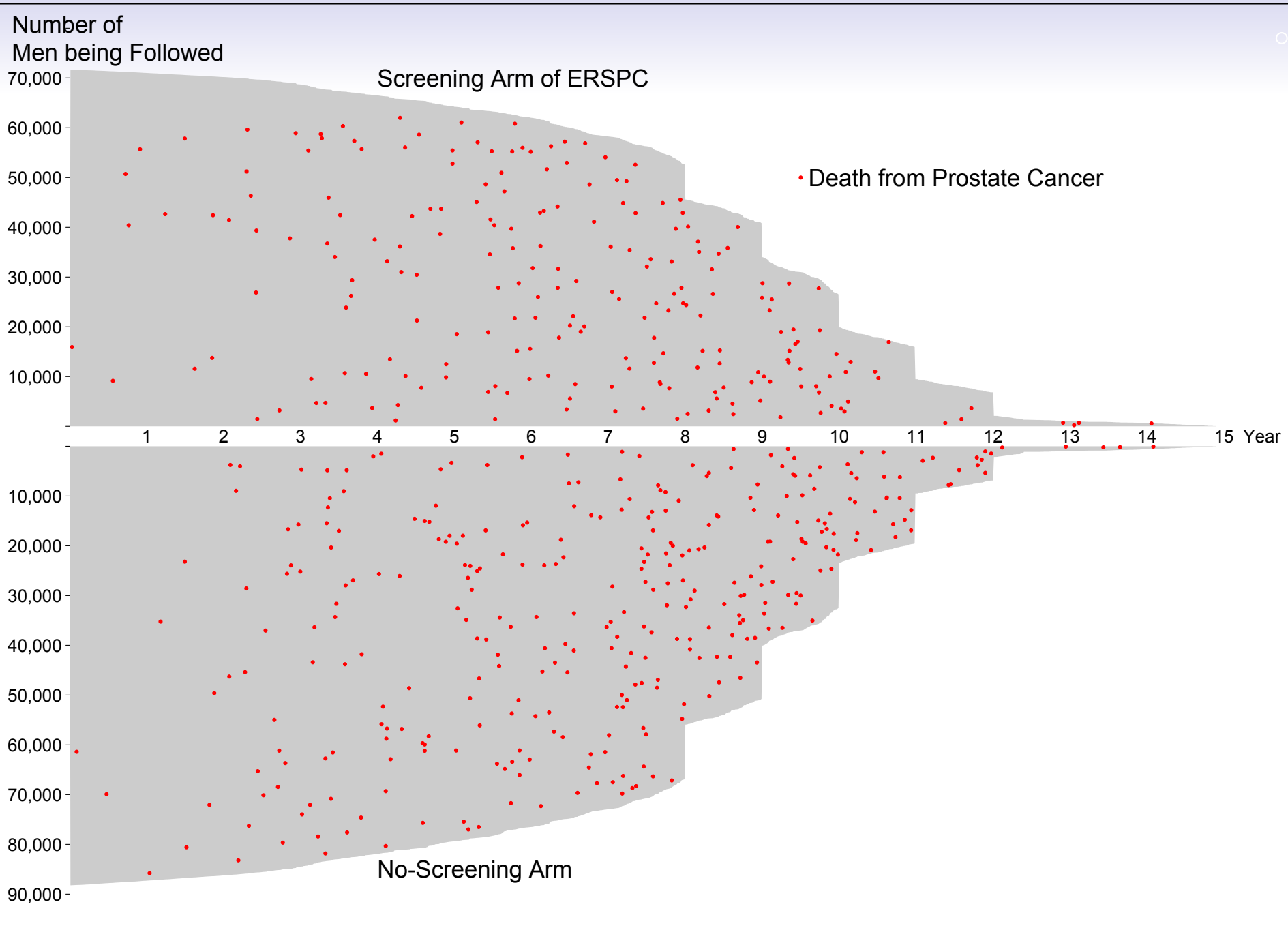
Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,

NEJM 2008



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758


Number of
Men being Followed
Screening Arm of ERSPC
Death from Prostate Cancer
70,000
60,000
50,000
40,000
30,000
20,000
10,000
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Year
10,000
20,000
30,000
40,000
50,000
60,000
70,000
80,000
90,000
No-Screening Arm

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

or Google "James Hanley McGill"

Canadian Institutes of Health Research

EXTRA

William Farr , Fifth Report of the Registrar General 1843, page xxx

Certain professions, stations, and ranks are only attained by persons advanced in years; ... hence it requires no great amount of sagacity to perceive that ‘the mean age at death’, or the age at which the greatest number of deaths occurs, cannot be depended upon in investigating the influence of occupation, rank, and profession upon health and longevity.

William Farr , Fifth Report of the Registrar General 1843, page xxx

If it were found, upon an inquiry into their health, that

Rank	Mean age at death
Cornets, Ensigns, and Second-Lieutenants	22 years;
Lieutenants	29 years
Captains	37 years
Majors	44 years
Lieutenant-Colonels	48 years
General Officers	ages still further-advanced
Curates	. .
Rectors	. . ditto
Bishops	. .
Barristers of seven years' standing	..
leading Counsel	. . ditto
venerable Judges	. .

a strong case may no doubt be made out on behalf of those young, but early-dying Cornets, Curates, and Juvenile Barristers, whose mean age at death was under 30! It would be almost necessary to make them Generals, Bishops, and Judges — for the sake of their health.

Bradford Hill. Principles of medical statistics.

XIV: Further fallacies and difficulties. Lancet 1937;229:825-827.

‘Few men become bishops before they have passed middle life, while curates may die at any age from their twenties upwards.’

‘The average age at death is not often a particularly useful measure. Between one occupational group and another it may be grossly misleading ... the average age at death in an occupation must, of course, depend in part upon the age of entry to that occupation and the age of exit from it — if exit takes place for other reasons than death.’

Hill AB. Principles of medical statistics,

XII: Common fallacies and difficulties. Lancet 1937;229:706-708.

‘Neglect of the period of exposure to risk:

A further fallacy in the comparison of the experiences of inoculated and uninoculated persons lies in neglect of the time during which the individuals are exposed first in one group and then in the other. Suppose that in the area considered there were on Jan. 1st, 1936, 300 inoculated persons and 1000 uninoculated persons. The number of attacks are observed within these two groups over the calendar year and the annual attack-rates are compared. This is a valid comparison so long as the two groups were subject during the calendar year to no additions or withdrawals. But if, as often occurs in practice, persons are being inoculated during the year of observation, the comparison becomes invalid unless the point of time at which they enter the inoculated group is taken into account.’

The adjective ‘immortal’ time is not broad enough

Hill: ‘neglect of the durations of exposure to risk must lead to fallacious results and must favour the inoculated’.

‘event-free time, by definition or by construction’

Walker AM. Observation and Inference: An Introduction to the Methods of Epidemiology. Chestnut Hill, MA: Epidemiology Resources, 1991.

is a more general and thus a more appropriate term.

Hill AB. Hill AB. Cricket and its relation to the duration of life. Lancet 1927;949-950.

‘period of exposure to risk’ when comparing, ‘from age 25 to age 80’, the longevity of cricketers with that of the general male population.

‘The comparisons show that cricketers form by no means a short-lived population, but on the contrary hold a substantial advantage at every age ... this advantage is undoubtedly somewhat exaggerated since it is assumed that all cricketers are ‘exposed’ from age 25, while in actual fact probably some do not ‘enter exposure’ in first-class cricket till a later age.’

SURVIVAL-TIMES AFTER CARDIAC ALLOGRAFTS

BRUNO J. MESSMER JAMES J. NORA
ROBERT D. LEACHMAN DENTON A. COOLEY

FROM THE CORA AND WEBB MADING DEPARTMENT OF SURGERY, BAYLOR COLLEGE OF MEDICINE, AND THE TEXAS HEART INSTITUTE OF ST. LUKE'S AND TEXAS CHILDREN'S HOSPITALS, HOUSTON, TEXAS

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Summary During the period May 2, 1968, to March 1, 1969, fifteen patients underwent cardiac transplantation for end-stage heart-disease. Their survival-time is compared with that of forty-two potential recipients who did not receive allografts. Mean survival of the potential recipients was 74 days. The average for the transplant patients was 111 days (including 22 days waiting-time before operation). This difference does not justify wide clinical application of cardiac transplantation, but is an indication for its use in suitable cases where it may prolong life and relieve symptoms.

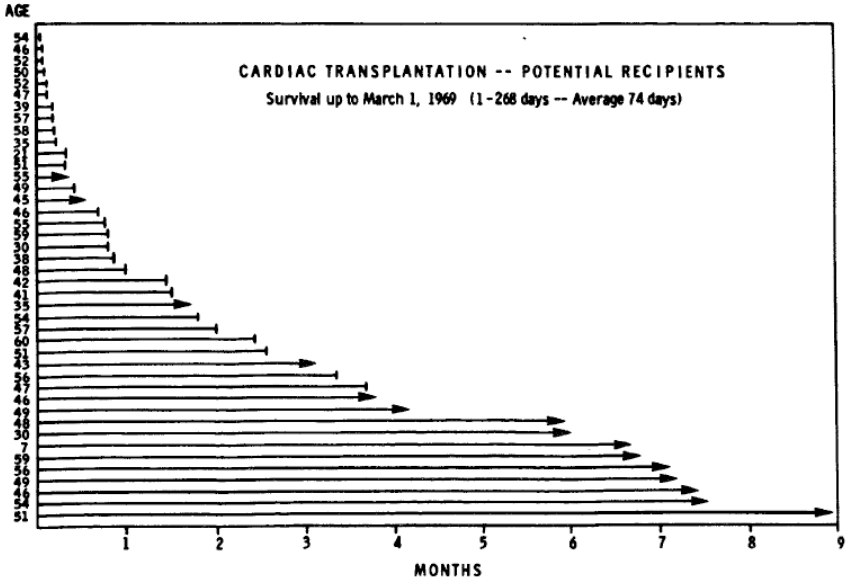


Fig. 1—Survival of forty-two potential recipients for heart transplant.
Arrow indicates patients still alive on March 1, 1969.

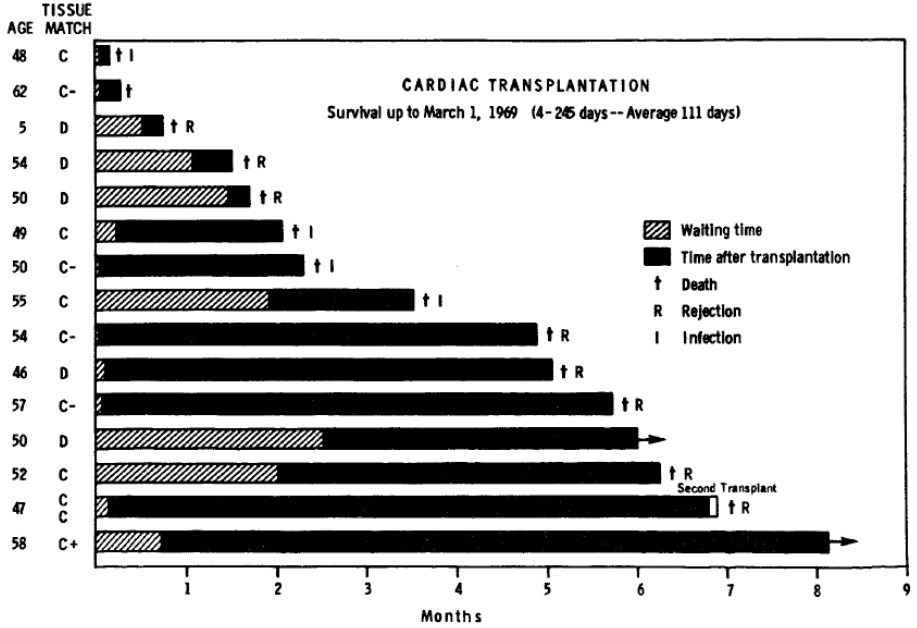


Fig. 2—Survival of fifteen patients given a cardiac allograft.
Arrow indicates patients still alive on March 1, 1969.

To compare the survival-times of the potential recipients with those of the transplant patients, we added the waiting-time of the transplant patients from the moment they were considered as recipients to the postoperative survival-time (fig. 2). Therefore only three (20%) transplant patients died within the first month in contrast to nineteen (45%) of the potential unoperated recipients. Eight (53%) of the transplant patients and fourteen (33%) of the unoperated potential recipients survived 3 months. Surviving 6 months were four (27%) of the transplant patients and eight (19%) of the potential recipients. The mean survival-time for the fifteen transplanted patients up to March 1, 1969, was 111 days (range 4–245 days) compared with a mean survival-time of 74 days (range 1–268 days) for the forty-two potential recipients. In the transplant patients, the mean survival-time of 111 days included 22 days waiting-time before transplantation.

Evaluation of Response-Time Data Involving Transient States: An Illustration Using Heart-Transplant Data

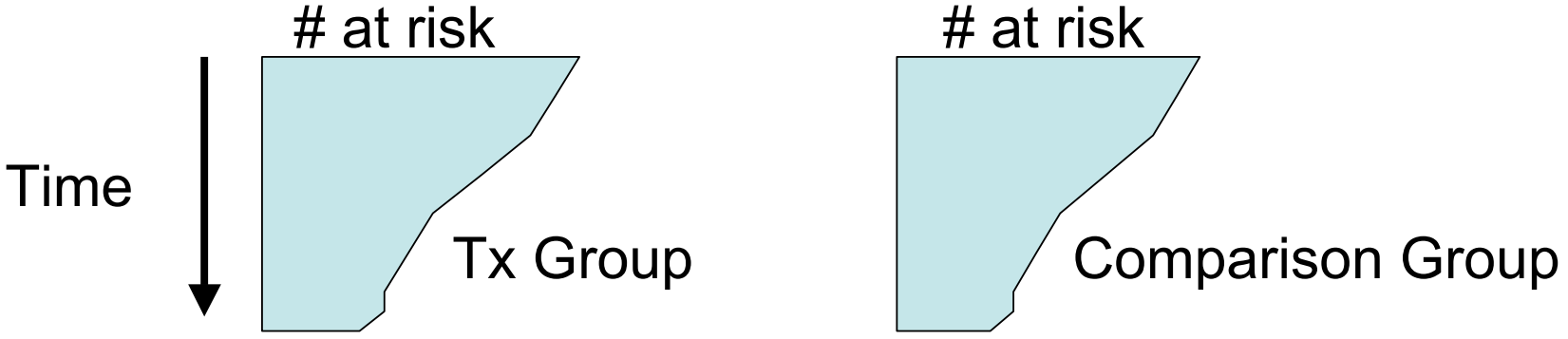
NATHAN MANTEL and DAVID P. BYAR*
© Journal of the American Statistical Association
March 1974, Volume 69, Number 345

situation. A particularly common bias when the survival of treated patients is compared with that of untreated controls results from a failure to make allowance for the fact that the treated patients must have at least survived from time of diagnosis to time of treatment, while no such requirement obtained for their untreated controls.

Alternative statistical methodologies for avoiding the "time-to-treatment" bias indicated by Gail have been proposed by Turnbull, Brown, and Hu [9]. In these methodologies, a patient selected for heart transplant is nevertheless considered to be a control patient until he actually receives his transplant and to be a treated patient thereafter. This possibility of a patient trans-

2. MODIFICATION OF COMPARATIVE LIFE TABLES TO COVER TRANSIENT STATES

In the customary presentation of life-table data, one begins a time interval with a certain number of individuals at risk, observes the number of responses during the interval and the number of losses to observation for the interval (which it would be desirable to arrange to have occur at the end of the interval, see [5, Appendix Discussion 1]). The number at risk at the beginning of the next interval is simply the preceding number less both the preceding interval losses and responses (for responses like death which remove the individuals from further risk.)



In principle there is no reason why the number of individuals at risk may not be *increased* by accessions of survivors from some other comparable study group, a point noted in [5]. In the transient-state problem just such accessions do occur. Thus when a heart-transplant candidate receives his heart transplant, he becomes an accession into the transplanted group, though a loss from the untransplanted group. The usual life-table procedure is adapted simply to cover this case by adding a column for accessions into a group. Losses remain as before, but it may be desirable to distinguish between losses to observation and losses through transfer. With this concept we may actually have any number of different groups, keeping track of responses, accessions, losses to observation, and losses through transfer for each group. We illustrate this later with the heart-transplant data, although in this case only one kind of transfer arises, from untransplanted to transplanted.

Day of death	Transplants						
	N_1	Deaths (A)	Accessions	Losses		N_2	Deaths (C)
				From observation	By transfer		
0	0		II			68	I
1	2		II			65	II
2	4		IIII			61	III
5	8	I		I		54	II
7	6		I			52	I
8	7		I			50	I
11	8		III			48	I
15	11	I	III			44	I
17	13		~~IIII~~ IIII			40	I
27	22	I	III			28	

CALCULATION OF CHI SQUARE

$$\sum A = 26; \quad \sum \text{Exp}(A) = \sum \frac{N_1 M_1}{T} = \sum \frac{N_1(A+C)}{N_1+N_2} = 26.575$$

$$\sum \text{Var}(A) = \sum \frac{N_1 N_2 M_1 M_2}{T^2(T-1)} = \sum \frac{N_1 N_2 (A+C)(N_1+N_2-A-C)}{(N_1+N_2)^2(N_1+N_2-1)} = 7.349$$

$$\text{Chi Square} = \frac{(|\Sigma A - \Sigma \text{Exp}(A)| - 0.5)^2}{\Sigma \text{Var}(A)} = \frac{(0.075)^2}{7.349} = 0.001$$

CALCULATION OF RELATIVE ODDS

$$\sum \frac{AD}{T} = \sum \frac{A(N_2 - C)}{N_1 + N_2} = 7.263$$

$$\sum \frac{BC}{T} = \sum \frac{(N_1 - A)C}{N_1 + N_2} = 7.838$$

$$R = \left(\sum \frac{AD}{T}\right) \Big/ \left(\sum \frac{BC}{T}\right) = \frac{7.263}{7.838} = 0.927$$

THE LANCET, DECEMBER 13, 1975

MORTALITY STUDY OF WORKERS IN A POLYVINYL-CHLORIDE PRODUCTION PLANT

B. W. DUCK J. T. CARTER
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E. J. COOMBES
B.P. Chemicals International Ltd, Penarth, Glamorgan

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Summary Age-standardised mortality-rates for a population of 2100 male workers exposed to vinyl chloride for periods of up to 27 years do not show any excess of total or cause-specific mortality. 1 case of angiosarcoma of the liver was identified just outside the study period. There was no suggestion of an increased frequency of deaths from the more common malignant diseases.

TABLE II—TOTAL MORTALITY

Group	O	E	S.M.R.	No.	Man-years at risk
All exposed workers	136	142·22	96	2122	23 052
Occupation					
Autoclave operators	13	13·79	94	338	3745
Polymer plant	4	6·54	61	110	1282
Monomer plant	7	8·21	85	66	919
Other workers	112	113·68	98	1606	17 106
Duration of exposure					
< 10 yr	83	74·01	112	1538	13 697
10–14 yr	28	26·91	107	246	3271
15 + yr	25	41·30	61	336	6084
Time of first exposure					
Before 1956	99	93·60	106	571	10 022
1956–65	31	41·04	76	757	9661
1966 +	6	7·58	79	792	3368

O=Observed. E=Expected. No.=Number of men.

THE LANCET, JULY 24, 1976

Letters to the Editor

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R. SARACCI

VINYL CHLORIDE AND MORTALITY?

SIR,—Excess cancer after exposure to vinyl chloride (V.C.) was demonstrated in animals by Viola et al.[6] and Maltoni and Lefemine[7] in Italy, and subsequently suggested by Monson et al.[8] and later definitively demonstrated by several investigations in man in the United States.[9–11] However, Duck et al.[12] of British Petroleum in the U.K. found no excess of cancer mortality—indeed, the longer workers were exposed to V.C., the healthier they seemed to be, as suggested by table II of their report, which shows a decreasing risk of death with an increasing duration of exposure.

In those exposed for less than 10 years, the standardised mortality from all causes was 112, but it fell to 107 for those exposed between 10 and 14 years and to 61 for those exposed for more than 15 years. Several interpretations of these find-

for more than 15 years. Several interpretations of these findings are possible: (1) the formulated V.C. as received by B.P. is uniquely non-toxic, (2) V.C. as polymerised or processed at B.P. is uniquely safe, (3) workers at B.P. have a particular genetic endowment which decreases their likelihood for V.C.-induced cancer, or conversely, other working populations[3–6] have a unique susceptibility to V.C., or (4) certain dietary factors unique to the workers at B.P. may scavenge free-radical V.C. (e.g., some have advocated eating lots of onions or garlic containing free sulphydryl groups.[13]) Before venturing any interpretation in biological, occupational, or technological terms, however, a closer consideration of the B.P. data seems wise, especially in view of studies[14 15] which demonstrated that the S.M.R. for total mortality increases with an increased duration of employment, due to elimination of the "healthy worker" effect. If in a follow-up study one selects, for example,

worker'' effect. If in a follow-up study one selects, for example, a subgroup of workers by the fact that they have achieved at least 15 years' exposure, then none of these workers could have died before the 15th anniversary, so information on risk of dying can only come from the number of man-years at risk and the number of deaths after 15 years. Of course these same men, provided they are properly regrouped together with those dying or coming to the end of the follow-up between, for example, 10 and 14 years can provide similar information for this time-interval—and so on for all previous time-intervals. This

REANALYSIS OF DATA BY DUCK ET AL. SHOWING PREVIOUSLY REPORTED VERSUS ESTIMATED NUMBERS OF EXPECTED DEATHS AND S.M.R.'S BY DURATION OF EXPOSURE AND CAUSE OF DEATH

Duration of exposure yr	Cause of death									
	All causes					Total cancers				
	O	E		S.M.R.		O	E		S.M.R.	
		Duck et al.	RE	Duck et al.	RE		Duck et al	RE	Duck et al.	RE
<10	83	74·01	105·46	112	79	23	18·68	26·62	123	86
10–14	28	26·91	20·49	107	137	4	6·87	5·23	58	76
15+	25	41·30	7·09	61	353	8	10·89	1·87	73	428
	Digestive system cancer					Lung cancer				
<10	6	5·64	3·04	106	75	10	7·76	11·06	129	90
10–14	1	2·13	1·62	47	62	3	2·97	2·26	101	133
15+	4	3·31	0·57	121	702	3	4·80	0·82	62	366

O=Observed E=Expected. RE=Recalculated estimates.

A MORE Recent Professional Longevity Comparison

Rothman KJ. Longevity of jazz musicians: flawed analysis. [Letter]. Am J Public Health 1992;82:761.

A letter in response to a retired professor of management, and jazz amateur (but sadly also a statistical amateur), whose data analysis suggested that jazz musicians, despite their rough lifestyle, live at least as long as their peers. In 'Premature death in jazz musicians: fact or fiction? (Spencer FJ. Am J Public Health 1991;81:804?05)', the longevity of their peers was measured by the life expectancy of those born the same year as they, although the musicians are, by definition, immortal until they became musicians and eminent enough to be included in the sample.

Tone of letter provides an interesting contrast with Farr's teaching style.

"Time-dependent bias common in survival analyses in leading clinical journals"

van Walraven C, Davis D, Forster AJ, Wells GA. J Clin Epidemiol 2004; 57:672-82.

They gave immortal time bias a slightly different name because they covered a slightly broader spectrum of situations. Their review surveyed articles containing survival analysis that may have incorrectly handled what they define as a 'baseline immeasurable' time-dependent variable, i.e. one that could not be measured at baseline. They focused not just on the exposure of interest, but also other time-dependent covariates. They describe an interesting study on whether patients having a follow- up visit with a physician who had received the discharge summary would have a lower rate of re-hospitalization. When analysed as a fixed-in-time variable (i.e. as two 'groups', we found a large difference in readmission rates. However, this is a biased association, because patients who are readmitted to the hospital early after discharge do not have a chance to see such physicians and are placed in the 'no-summary' group. When a (correct) time-dependent analysis is used, we found a much smaller rate difference.