Bias

Random variation

Systematic error (Bias)

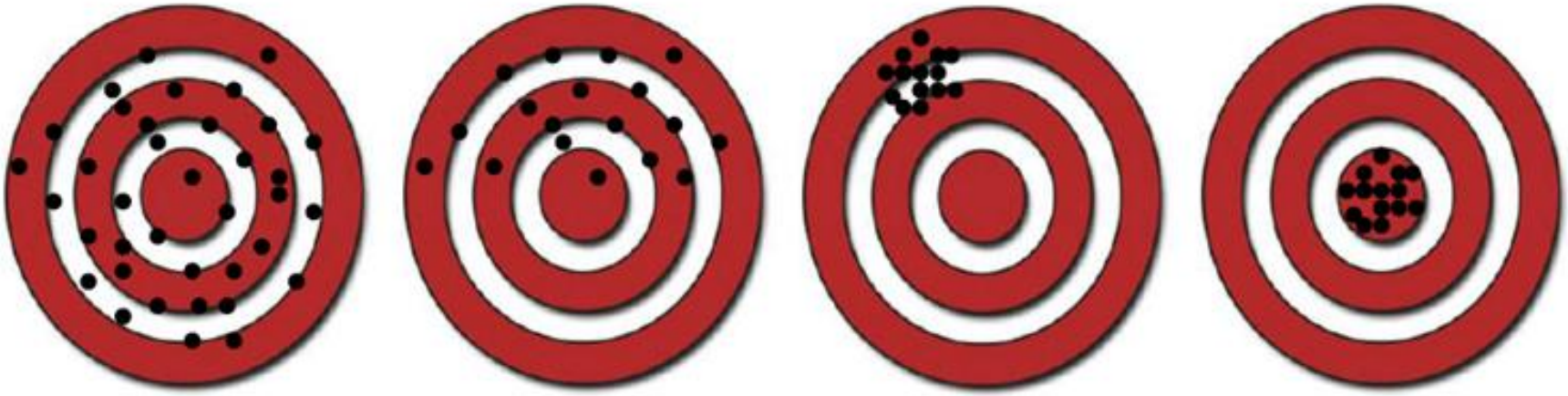
Selection bias

Information bias

Confounding

Statistician's expertise

Epidemiologist's expertise



Types of bias

Selection bias

Information bias
(misclassification bias)

Protopathic bias
(reverse causation bias)

Immortal-time bias

Confounding

Selection bias

Bias comming from **OUTSIDE** the material, due to the selective inclusion of individuals with particular characteristics (related to either exposure or outcome)

Women with vague symptoms of DVT has higher likelihood of getting admitted for tests if using oral contraceptives.

Mothers of children with malformations are more likely to participate in study on use of drugs during pregnancy if they have thought about a given drug they have been using.

Information bias

Bias from **WITHIN** the material
due to incorrect information

Differentiated

Non-differentiated

Information bias (differentiated)

If the classification of exposure depends on whether the patient has an outcome (or vice-versa)

Mothers of children with malformations will be better at recalling information on drug use during pregnancy than women with children without malformations.

Information bias (non-differentiated)

General misclassification of exposure, independent of outcome status or other variables.

Will always infer a bias towards the null (i.e. no difference).

In a study of the risk of brain hemorrhage associated with use of platelet inhibitors, the classification of use/non-use is not 100% correct, as the algorithm does not capture patients stopping before having used a full package of tablets.

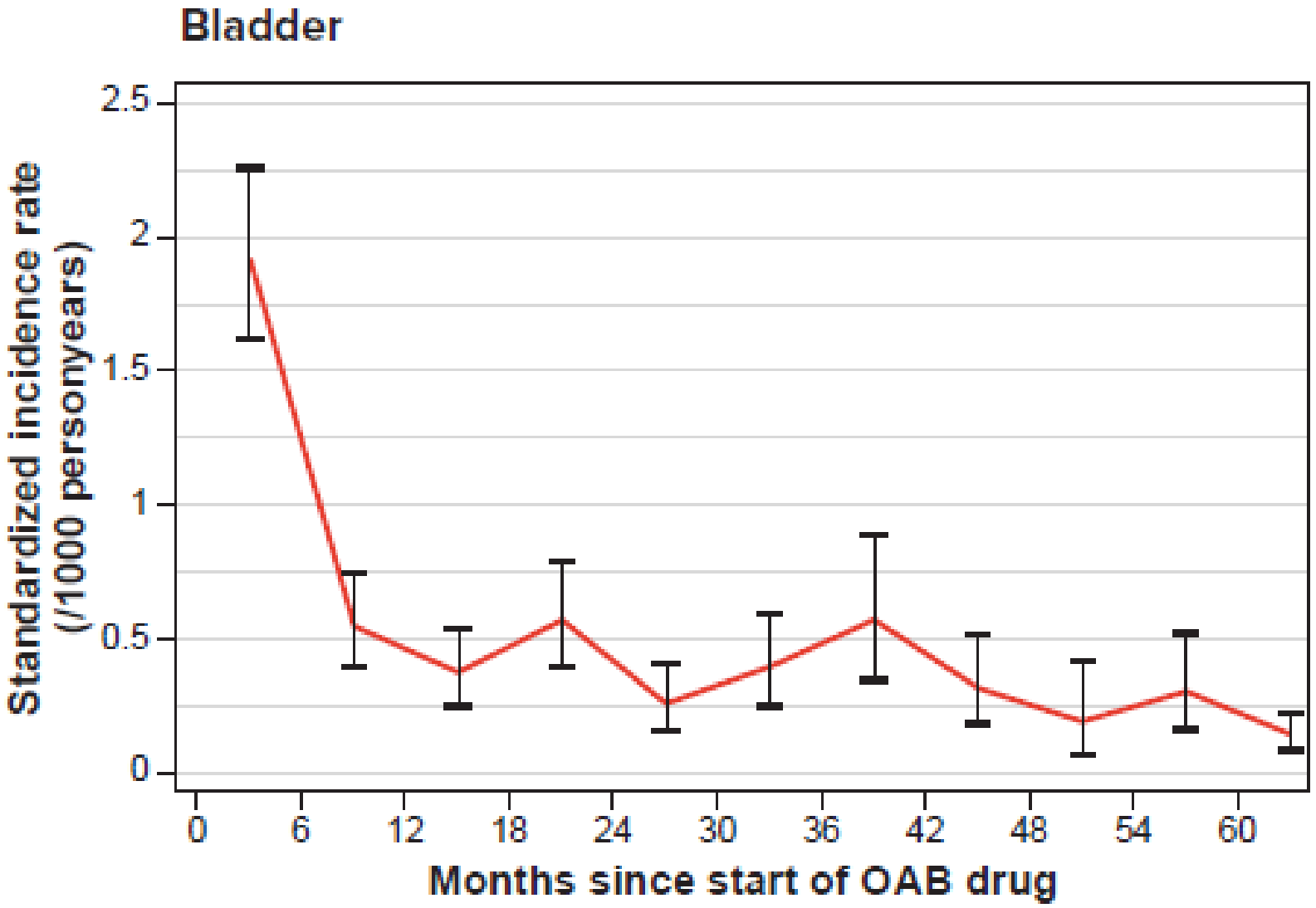
One year's worth of prescription data is corrupt…

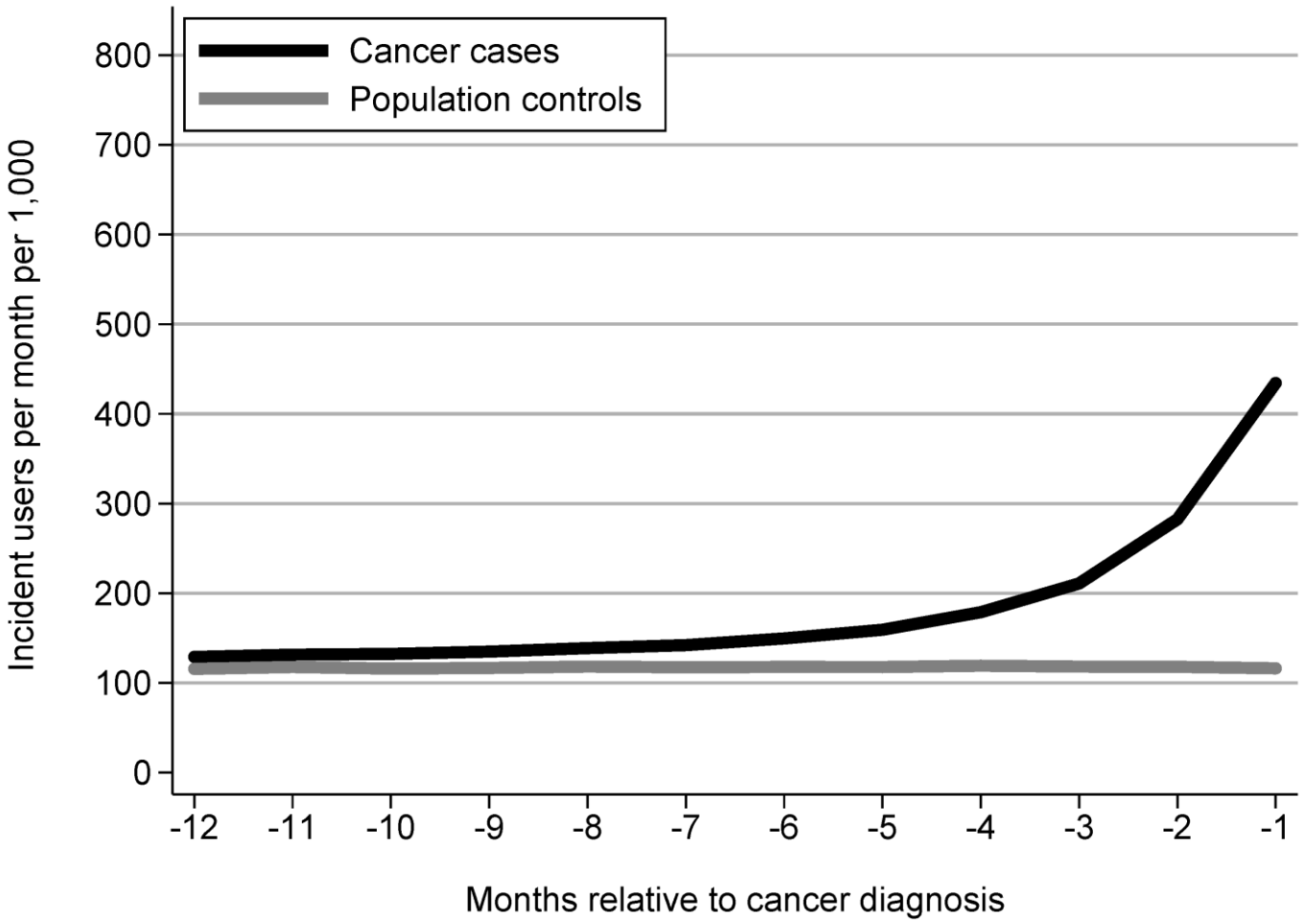
Protopathic bias

(reverse-causation bias)

A mixture (reversal) of the cause and effect, e.g. if the drug is given for an early (not yet recognized or recorded) disease.

In a study of the association between use of valproic acid (antiepileptic) and risk of cancer, you find an increased risk of brain cancer. This is caused by valproic acid prescribed due to epilepsi as an early marker of brain cancer.


Bladder
Standardized incidence rate (/1000 personyears)
2.5
2
1.5
1
0.5
0
0
6
12
18
24
30
36
42
48
54
60
Months since start of OAB drug


Cancer cases
Population controls
Incident users per month per 1,000
800
700
600
500
400
300
200
100
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
-3
-2
-1
Months relative to cancer diagnosis

Immortal-time bias
(the epidemiologist fucked up-bias)

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.

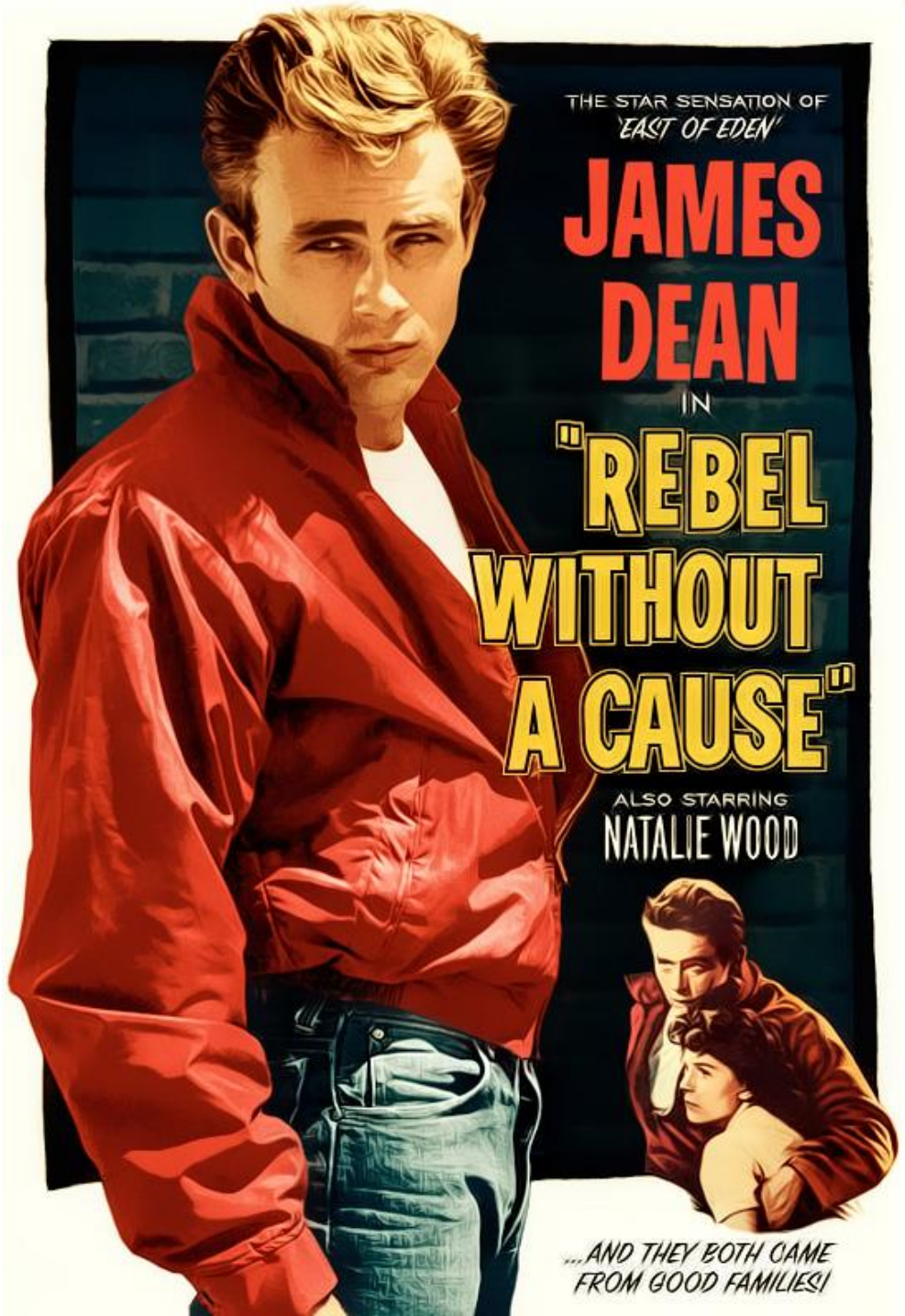
Results: All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7 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.



Starring

James Dean
Natalie Wood
Sal Mineo

All three very talented
All three died at a young age
All three nominated for an Oscar
Neither of them got an Oscar

Christopher Plummer, born 1929,
Won his first Oscar in 2012
(nominated for the first time in 2010)

Time already survived
is per definition ”immortal”!

Inhaled Corticosteroids and the Risk of Mortality and Readmission In Elderly Patients with Chronic Obstructive Pulmonary Disease

DON D. SIN and JACK V. TU

The Institute for Clinical Evaluative Sciences (ICES) and The Department of Medicine, Sunnybrook and Women's College Health Science Center, University of Toronto, Toronto, Ontario; and Department of Medicine, University of Alberta, Alberta, Canada

There is considerable controversy concerning the utility of inhaled corticosteroids for the long-term treatment of patients with COPD. Recent studies have suggested that although inhaled corticosteroids do not alter the rate of decline in lung function, they may reduce airway hyperresponsiveness, decrease the frequency of exacerbations, and slow the rate of decline in the patients' health status. The relationship between inhaled corticosteroids and subsequent risk of hospitalization or mortality remains unknown. We therefore conducted a population-based cohort study using administrative databases in Ontario, Canada (n = 22,620) to determine the association between inhaled corticosteroid therapy and the combined risk of repeat hospitalization and all-cause mortality in elderly patients with COPD. Patients who received inhaled corticosteroid therapy postdischarge (within 90 d) had 24% fewer repeat hospitalizations for COPD (95% confidence interval [CI], 22 to 35%) and were 29% less likely to experience mortality (95% CI, 22 to 35%) during 1 yr of follow-up after adjustment for various confounding factors. This cohort study has suggested that inhaled corticosteroid therapy is associated with reduced COPD-related morbidity and mortality in elderly patients. Although not definitive, because of the observational nature of these findings, these data provide a compelling rationale for a large randomized trial to determine the effect of inhaled corticosteroids on COPD-related morbidity and mortality.

is generally precluded on the basis of significant systemic toxicity (6). In contrast, inhaled corticosteroids appear to have a more favorable toxicity profile, making it an attractive alternative to oral preparations (7). However, there remains considerable controversy concerning their utility for the chronic management of COPD (8, 9).

Previous studies have shown that inhaled corticosteroids do not decelerate the rate of decline in expiratory flow volumes over time in patients with mild to moderate COPD (10, 11). However, a recent study has suggested that inhaled corticosteroids may slow the rate of decline in (disease-specific) health status of patients and reduce the risk of clinical exacerbations (12). Another study has suggested that inhaled corticosteroids may attenuate airway hyperresponsiveness and also reduce clinical symptoms of COPD, including dyspnea and cough (13). Because these clinical and physiologic markers are also associated with COPD outcomes, inhaled corticosteroids might be expected to decrease COPD-related hospitalizations and mortality.

One approach to ascertaining these outcomes is to use a large population-based cohort focusing in on patients at a very high risk of such events (14, 15). We therefore conducted a large observational study to determine the relationship between use of inhaled corticosteroids and rate of repeat hospi-

22,260 patients are followed for a year after discharge following a COPD exacerbation.

Divided into users and non-users of inhaled steroid based on whether they fill an prescription within 90 days after discharge.

Main finding

Mortality reduced by 29% (HR 0.71, 0.65-0.78)

Readmission reduced by 24% (HR 0.76, 0.71-0.80)

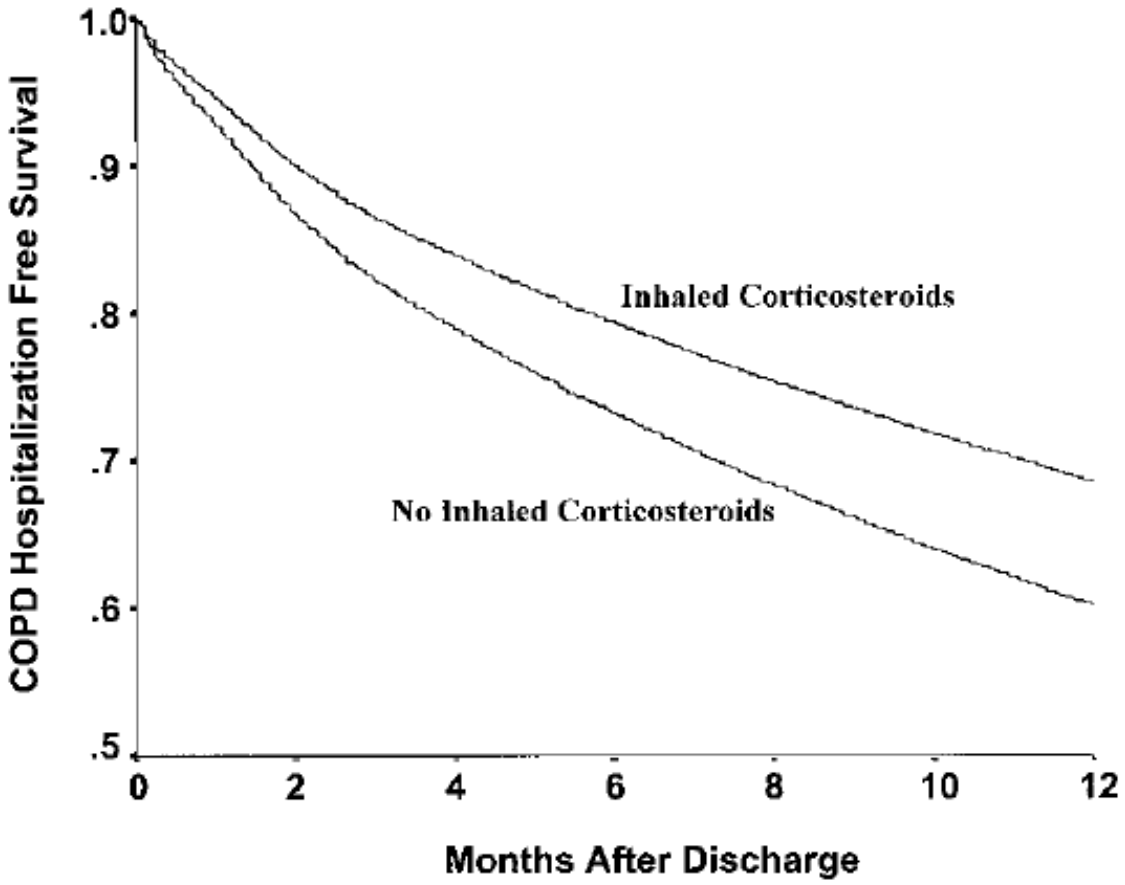


Figure 1. Adjusted probability of hospitalization-free survival in patients with chronic obstructive pulmonary disease who did and did not receive inhaled corticosteroids postdischarge (within 90 d of discharge).

American Journal of Epidemiology

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Practice of Epidemiology

Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods

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The authors compared five methods of studying survival bias associated with time-to-treatment initiation in a drug effectiveness study using medical administrative databases (1996–2002) from Quebec, Canada. The first two methods illustrated how survival bias could be introduced. Three additional methods were considered to control for this bias. Methods were compared in the context of evaluating statins for secondary prevention in elderly patients post-acute myocardial infarction who initiated statins within 90 days after discharge and those who did not. Method 1 that classified patients into users and nonusers at discharge resulted in an overestimation of the benefit (38% relative risk reduction at 1 year). In method 2, following users from the time of the first prescription and nonusers from a randomly selected time between 0 and 90 days attenuated the effect toward the null (10% relative risk reduction). Method 3 controlled for survival bias by following patients from the end of the 90-day time window; however, it suffered a major loss of statistical efficiency and precision. Method 4 matched prescription time distribution between users and nonusers at cohort entry. Method 5 used a time-dependent variable for treatment initiation. Methods 4 and 5 better controlled for survival bias and yielded similar results, suggesting a 20% risk reduction of recurrent myocardial infarction or death events.

bias (epidemiology); databases; epidemiologic methods; survival; treatment outcome

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Published online 25 January 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/pds.1357

ORIGINAL REPORT

Immortal time bias in observational studies of drug effects†

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SUMMARY

Purpose Recent observational studies suggest that various drugs are remarkably effective at reducing morbidity and mortality. These cohort studies used a flawed approach to design and data analysis which can lead to immortal time bias. We describe the bias from 20 of these studies and illustrate it by showing that unrelated drugs can be made to appear effective at treating cardiovascular disease (CVD).

Methods The illustration used a cohort of 3315 patients, with chronic obstructive pulmonary disease (COPD), identified from the Saskatchewan Health databases, hospitalised for CVD and followed for up to a year. We used the biased approach to assess the effect of two medications, namely gastrointestinal drugs (GID) and inhaled beta-agonists (IBA), both unknown to be effective in CVD, on the risk of all-cause mortality. We also estimated these effects using the proper person-time approach.

Results Using the inappropriate approach, the rates ratios of all-cause death were 0.73 (95%CI: 0.57–0.93), with IBA and 0.78 (95%CI: 0.61–0.99), with GID. These rate ratios became 0.98 (95%CI: 0.77–1.25) and 0.94 (95%CI: 0.73–1.20), respectively, with the proper person-time analysis.

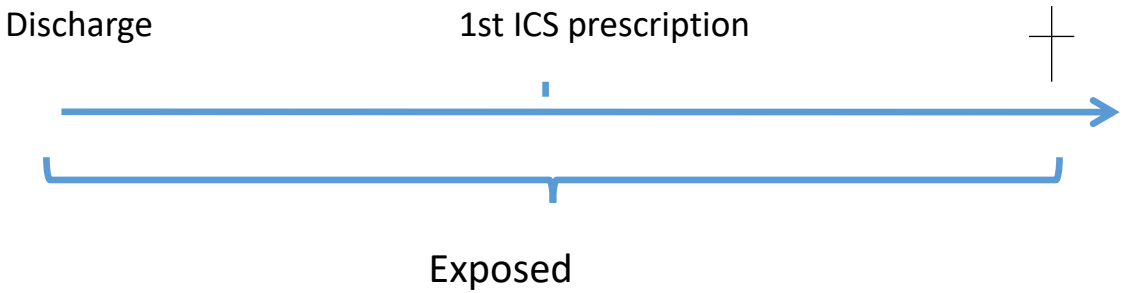
Conclusions Several recent observational studies used a flawed approach to design and data analysis, leading to immortal time bias, which can generate an illusion of treatment effectiveness. Observational studies, with surprising beneficial drug effects should be re-assessed to account for this source of bias.

KEY WORDS — biases; cohort studies; drug effectiveness; databases; epidemiology

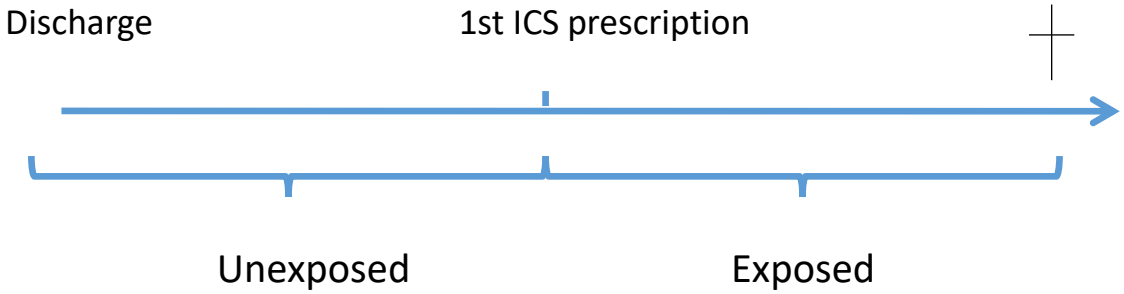
Received 17 October 2006; Revised 15 November 2006; Accepted 22 November 2006

Immortal time

Wrong:



Correct:



Never use a crystal ball!

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

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Accepted 22 July 2013

Background Sun exposure is the single most important risk factor for skin cancer, but sun exposure may also have beneficial effects on health. We tested the hypothesis that individuals with skin cancer (non-melanoma skin cancer and cutaneous malignant melanoma) have less myocardial infarction, hip fracture and death from any cause, compared with general population controls.

Methods We examined the entire Danish population above age 40 years from 1980 through 2006, comprising 4.4 million individuals. Diagnoses of non-melanoma skin cancer ($n = 129\,206$), cutaneous malignant melanoma ($n = 22107$), myocardial infarction ($n = 327\,856$), hip fracture ($n = 129\,419$), and deaths from any cause ($n = 1\,629\,519$) were drawn from national registries.

Results In individuals with vs without non-melanoma skin cancer, multifactorially adjusted odds ratios were 0.96 (95% confidence interval: 0.94–0.98) for myocardial infarction and 1.15 (1.12–1.18) for hip fracture, and the multifactorially adjusted hazard ratio was 0.52 (0.52–0.53) for death from any cause. Risk of hip fracture was reduced (odds ratios were below 1.0) in individuals below age 90 years. In individuals with vs without cutaneous malignant melanoma, corresponding odds ratios were 0.79 (0.74–0.84) for myocardial infarction and 0.84 (0.76–0.93) for hip fracture, and the corresponding hazard ratio for death from any cause was 0.89 (0.87–0.91); however, cutaneous malignant melanoma was associated positively with death from any cause in some individuals.

Immortal-time bias

Always in cohort studies

Signal too good (strong) to be true

When the effect manifests too soon

You will have used a crystal ball

When ”groups” and not ”status” are analysed

The Story of Dr. Kripke and the horrible benzodiazepines!

BMJ open
accessible medical research

PRESS RELEASE

Hypnotics' association with mortality or cancer: a matched cohort study

Daniel F Kripke,[1] Robert D Langer,[2] Lawrence E Kline[1]

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► Prepublication history and additional materials for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-000850).

DFK and RDL contributed equally to the research. Author responsibility: all authors had access to all the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

ABSTRACT

Objectives: An estimated 6%—10% of US adults took a hypnotic drug for poor sleep in 2010. This study extends previous reports associating hypnotics with excess mortality.

Setting: A large integrated health system in the USA.

Design: Longitudinal electronic medical records were extracted for a one-to-two matched cohort survival analysis.

Subjects: Subjects (mean age 54 years) were 10 529 patients who received hypnotic prescriptions and 23 676 matched controls with no hypnotic prescriptions, followed for an average of 2.5 years between January 2002 and January 2007.

Main outcome measures: Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer. Hazard ratios (HRs) for death were computed from Cox proportional hazards models controlled for risk factors and using up to 116 strata, which exactly matched cases and controls by 12 classes of comorbidity.

ARTICLE SUMMARY

Article focus

- Estimate the mortality risks associated with specific currently popular hypnotics in a matched cohort design, using proportional hazards regression models.
- Estimate the cancer risks associated with specific currently popular hypnotics.
- Explore what risk associated with hypnotics can be attributed to confounders and comorbidity.

Key messages

- Patients receiving prescriptions for zolpidem, temazepam and other hypnotics suffered over four times the mortality as the matched hypnotic-free control patients.
- Even patients prescribed fewer than 18 hypnotic doses per year experienced increased mortality, with greater mortality associated with greater dosage prescribed.
- Among patients prescribed hypnotics, cancer

Comorbidity	Non-users	Any hypnotic
Asthma***	6.6	11.3
Cerebrovascular disease***	3.8	6.2
Coronary heart disease***	9.4	14.5
Chronic kidney disease***	0.9	1.7
COPD***	5.5	9.1
Cardiovascular disease, all***	14.1	21.4
Dementia	0.6	0.6
Diabetes***	14.6	17.9
Heart failure***	3.2	6.6
Hypertension***	37.5	42.8
Obesity***	6.7	10.5
Reflux and peptic disease***	15.0	27.9
Peripheral vascular disease***	2.1	3.9

For each hypnotic user, we attempted to identify two controls with no record of a hypnotic prescription in the [database] at any time from among the 212 292 remaining non-users

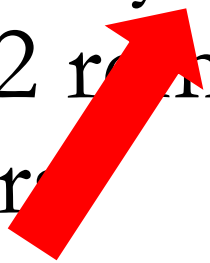

Table 3 HRs for deaths and for cancers with dose–response analyses

Hypnotic	Cancers	
	p Value	HR (95% CI)
Any hypnotic: doses/year	<0.001	
No hypnotics, N=23 676	Reference	
0.4–18 pills/year, mean 8, N=3491	0.086	0.86 (0.72 to 1.02)
18–132 pills/year, mean 57, N=3548	0.022	1.20 (1.03 to 1.40)
>132 pills/year, mean 469, N=3490	<0.001	1.35 (1.18 to 1.55)
Zolpidem only: mg/year	0.035	
No zolpidem or other hypnotics, N=23 671	Reference	
Zolpidem 5–130 mg/year, mean 60, N=1453	0.095	0.79 (0.60 to 1.04)
Zolpidem 130–800 mg/year, mean 360, N=1456	0.585	1.07 (0.83 to 1.39)
Zolpidem >800 mg/year, mean 3600, N=1427	0.023	1.28 (1.03 to 1.59)
Temazepam only: mg/year	<0.001	
NO temazepam or other hypnotics, N=23 674	Reference	
Temazepam 1–240 mg/year, mean 98, N=798	0.003	0.48 (0.30 to 0.77)
Temazepam 240–1640 mg/year, mean 683, N=613	0.024	1.44 (1.05 to 1.98)
Temazepam >1640 mg/year, mean 7777, N=665	<0.001	1.99 (1.57 to 2.52)

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12001

Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study

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Keywords
benzodiazepines, cancer, case–control study, pharmacoepidemiology, population based

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••

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The association between benzodiazepines and benzodiazepine related drugs (BZRD) and cancer risk is disputed.

AIM

Studies of the carcinogenic potential of benzodiazepines and related drugs (BZRD) have been equivocal. A recent study reported a 35% excess cancer risk among users of hypnotics, including

Main result

Crude OR:	1.14 [1.09 - 1.19]
Adjusted OR:	1.09 [1.04 - 1.14]

We did not find an association between long term use of BZRD and risk of cancer, except for what is likely explained by residual confounding.