# Bias

**Random variation**

**Systematic error (Bias)**

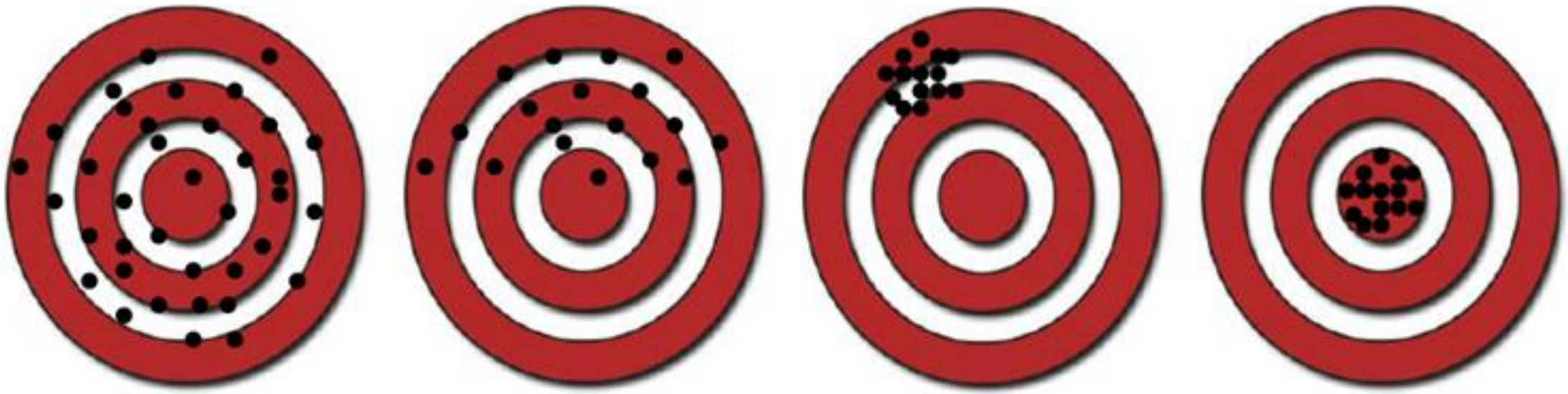
Selection bias

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

# Types of bias

Selection bias

Information bias

(misclassification bias)

Protopathic bias

(reverse causation bias)

Immortal-time bias

Confounding

# Selection bias

Bias coming 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.

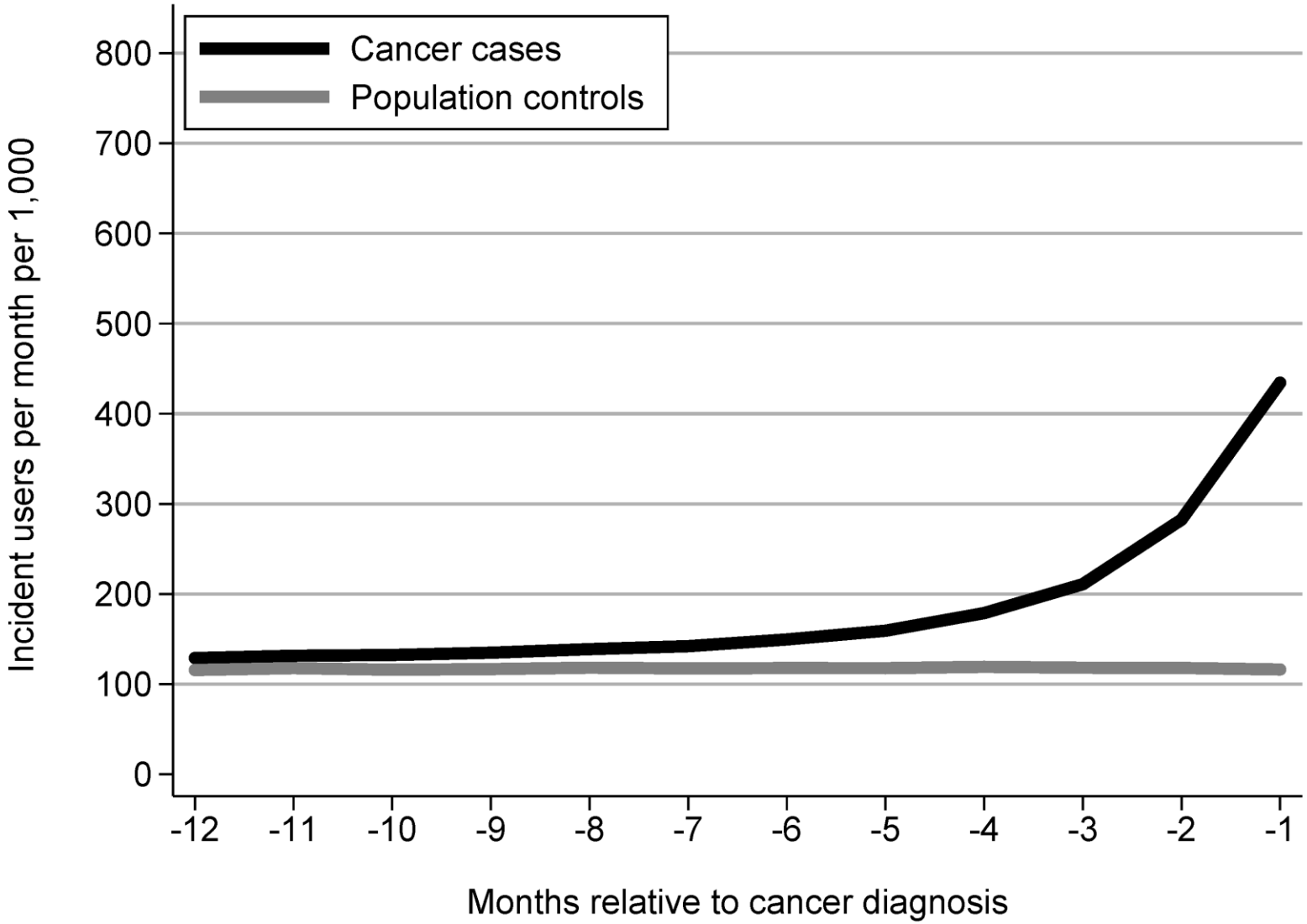
One year's worth of prescription data is corrupt…

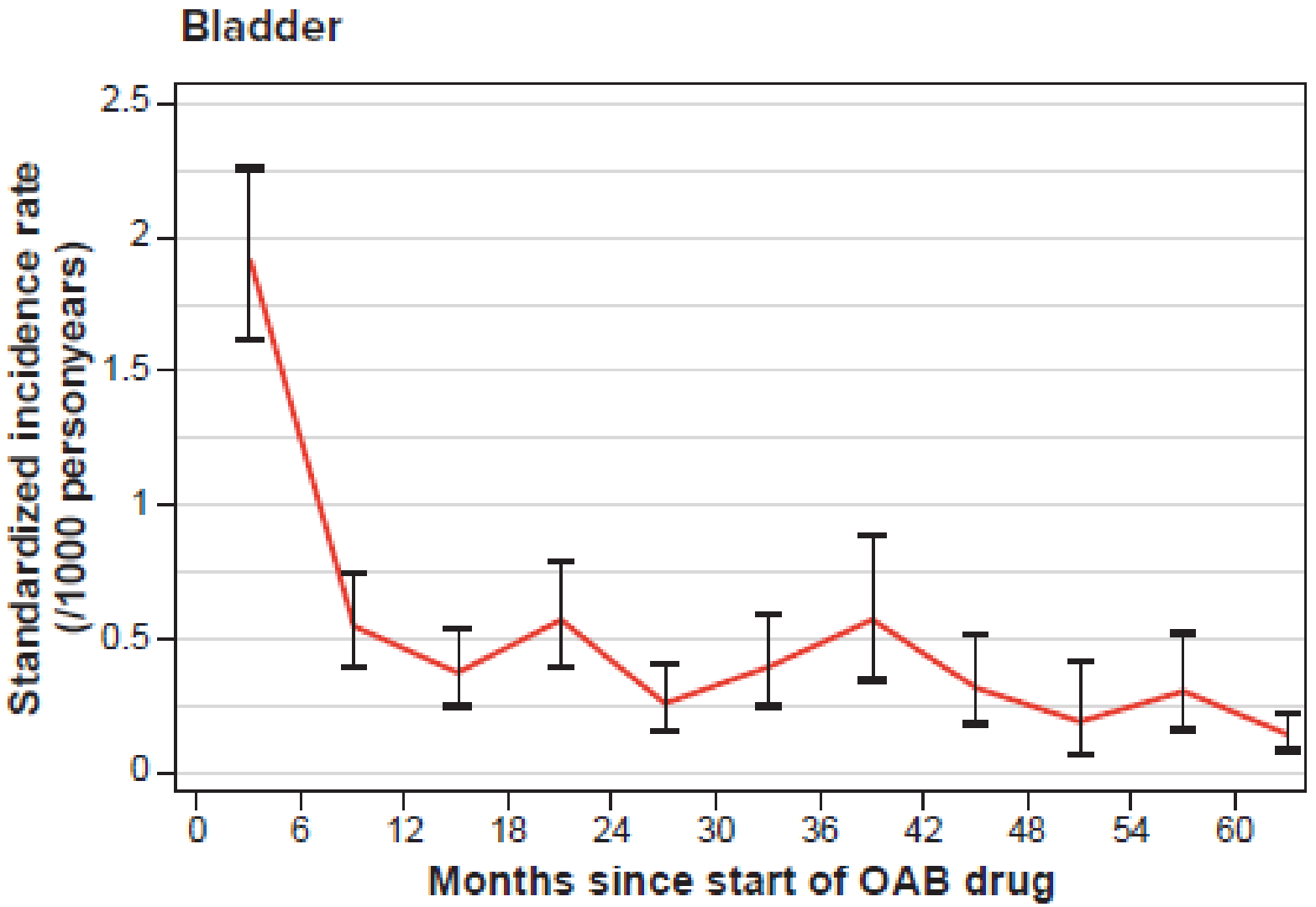
# Protopathic bias

(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.


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


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

# Immortal-time bias

(the epidemiologist messed 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.

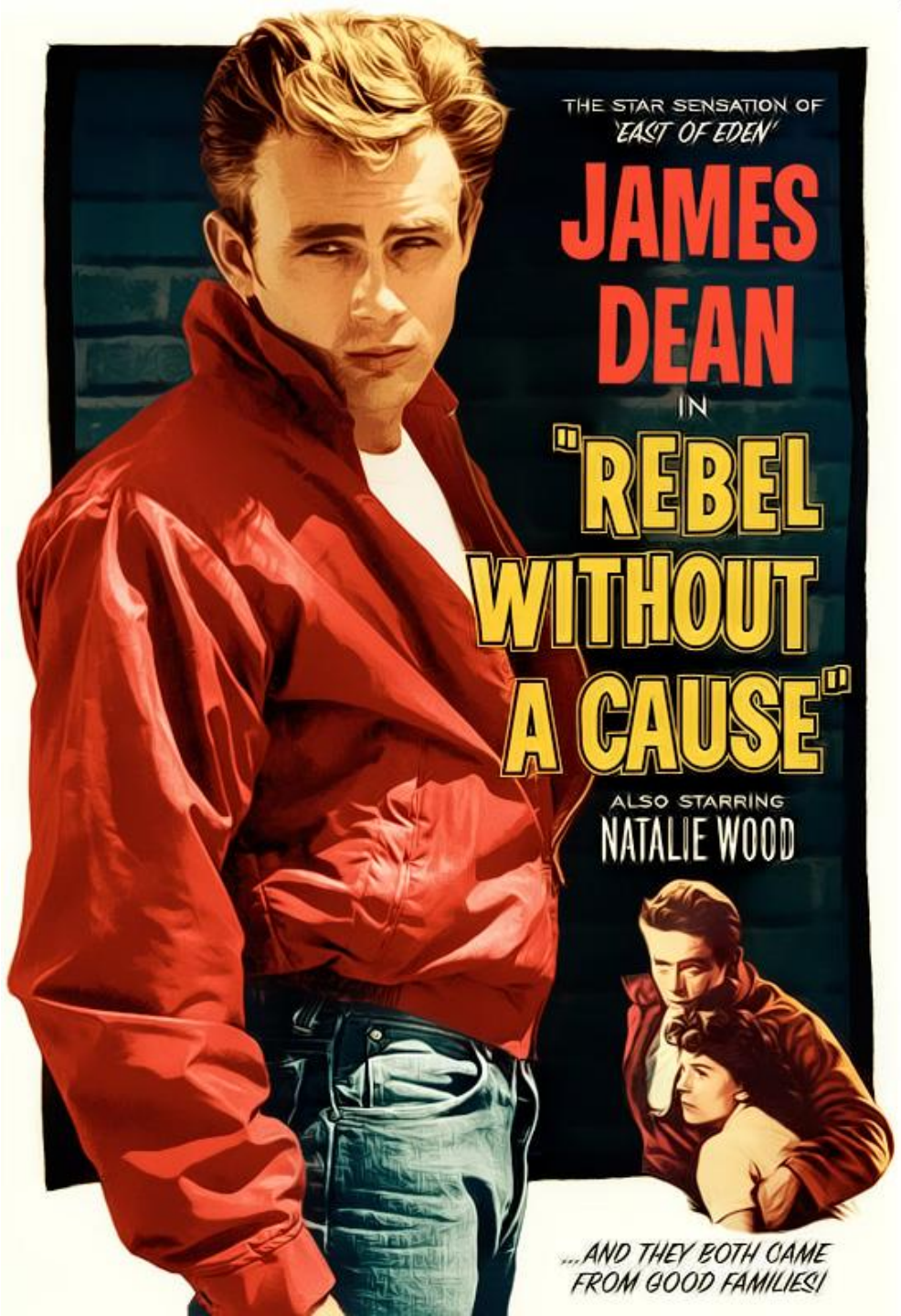
Results: All 1649 performers were analyzed; the median duration of follow-up time from birth was 66 years, and 772 deaths occurred (primarily from ischemic heart disease and malignant disease). Life expectancy was 3.9 years longer for Academy Award winners than for other, less recognized performers (79.7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

Keywords: chronic obstructive pulmonary disease; inhaled corticoste

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 hospitalization and mortality in elderly patients with COPD re-

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)

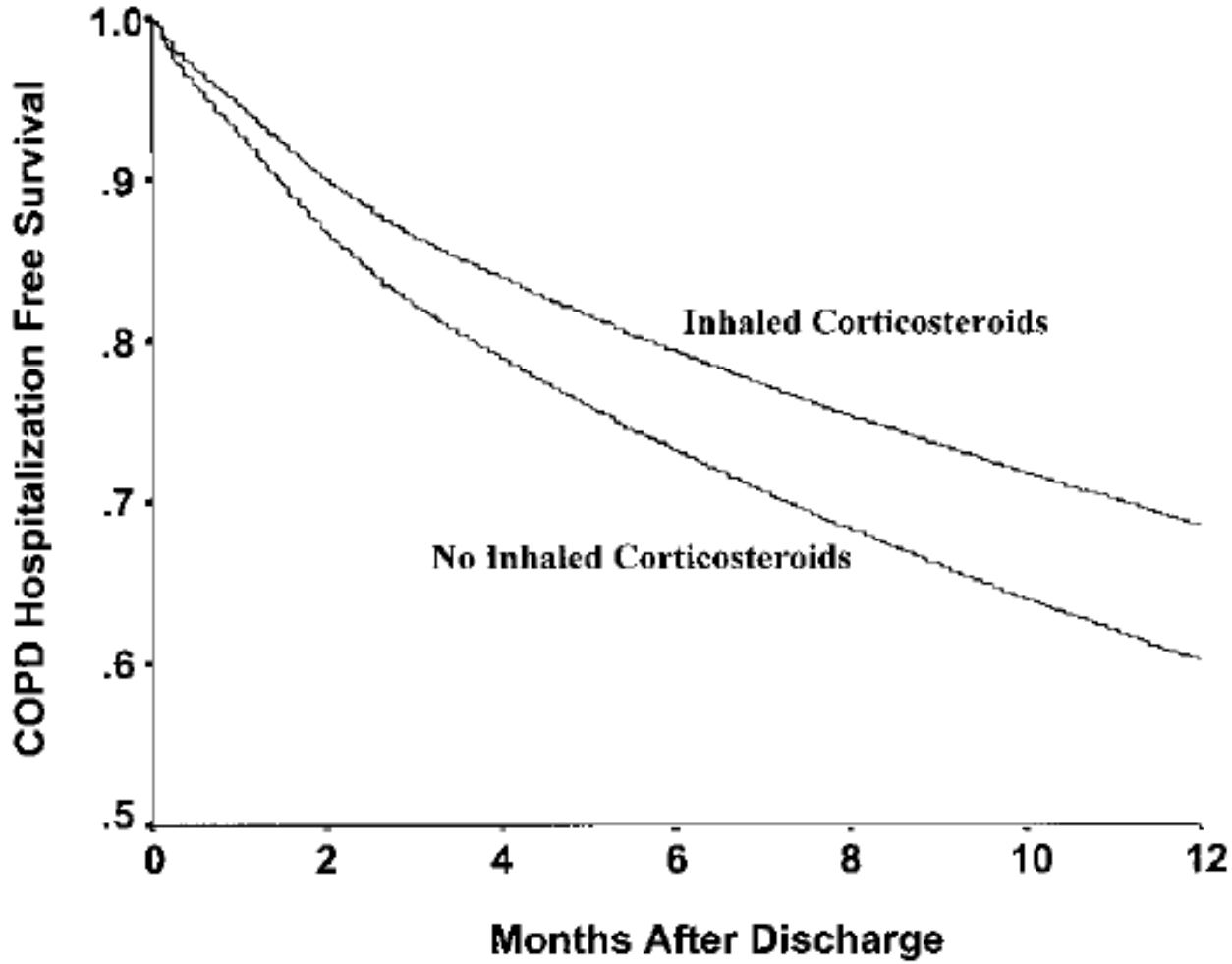



*Figure 1.* Adjusted probability of hospitalization-free survival in patients with chronic obstructive pulmonary disease who did and did not receive inhaled corticosteroids postdischarge (within 90 d of discharge).

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; 16: 241–249
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ORIGINAL REPORT

# Immortal time bias in observational studies of drug effects†

Samy Suissa PhD[1,2]*

[1] *From the McGill Pharmacoepidemiology Research Unit, McGill University Health Centre, Montreal, Canada*
[2] *Departments of Epidemiology and Biostatistics and of Medicine, McGill University, Montreal, Canada*

## 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

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## Practice of Epidemiology

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

**Zheng Zhou[1,2], Elham Rahme[1,2], Michal Abrahamowicz[1,2], and Louise Pilote[1,2]**

[1] Department of Epidemiology and Biostatistics, McGill University, Montréal, Quebec, Canada.
[2] Division of Clinical Epidemiology, Montréal General Hospital, Montréal, Quebec, Canada.

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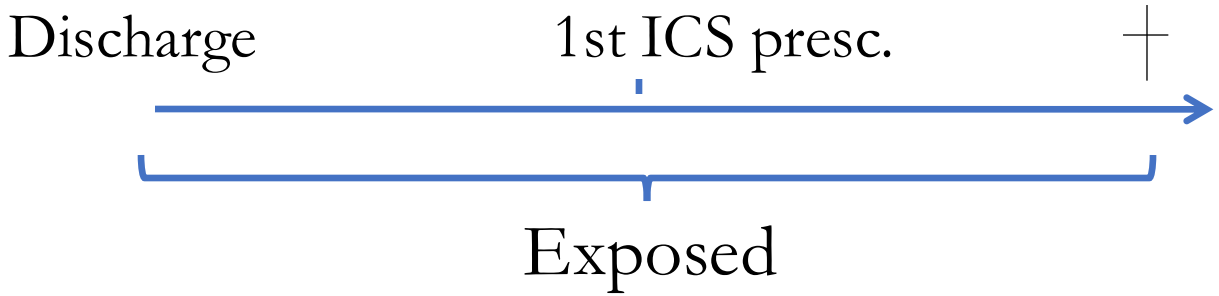
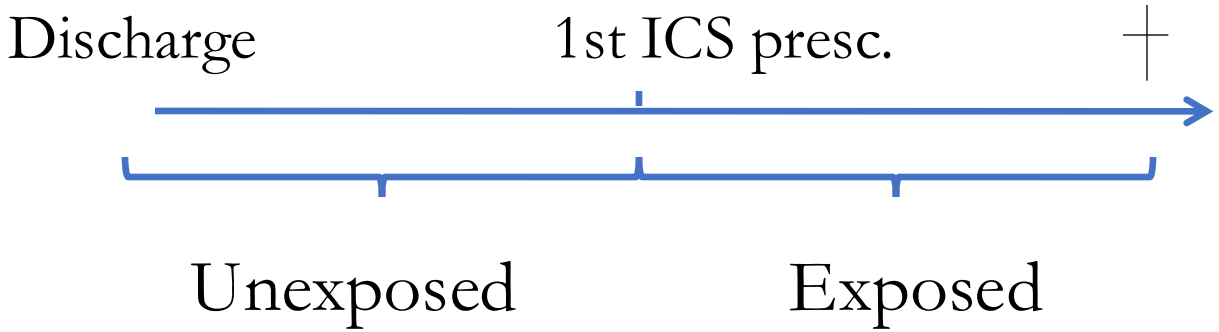
The authors compared five methods of studying survival bias associated with time-to-treatment initiation in a drug effectiveness study using medical administrative databases (1996–2002) from Quebec, Canada. The first two methods illustrated how survival bias could be introduced. Three additional methods 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.

# 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

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

[1]Department of Clinical Biochemistry, Herlev Hospital, Herlev, Denmark, [2]Department of Clinical Biochemistry, Gentofte Hospital, Copenhagen, Denmark and [3]Copenhagen University Hospital and Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

*Corresponding author. Department of Clinical Biochemistry, Gentofte Hospital, Niels Andersensvej 65, DK-2900 Hellerup, Copenhagen, Denmark. E-mail: Marianne.Benn@regionh.dk

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**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

# 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