Considerations re. exposure

Epidemiology:

The neglected half of pharmacoepidemiology

Pharmacology:

The neglected half of pharmacoepidemiology

Epidemiology:
The neglected half of pharmacoepidemiology

Pharmacology:
The neglected half of pharmacoepidemiology

Correctly classifying the subjects of a study in exposed or non-exposed constitutes the foundation of an epidemiologic study.

Since by definition, in a pharmacoepidemiological study, the exposure is a drug, a sound knowledge of drug utilisation, pharmacology and toxicology are essential to the design and critical appraisal of these studies.

Jacques LeLorier

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Jacques LeLorier

Does use of tranexamic acid during HIP SURGERY cause… problems?

Bleeding?

Myocardial infarction?

Ischemic stroke?

Single dose

T1/2 = 3 hours

Coding?

Does use of tranexamic acid during MENORRHAGIA cause… problems?

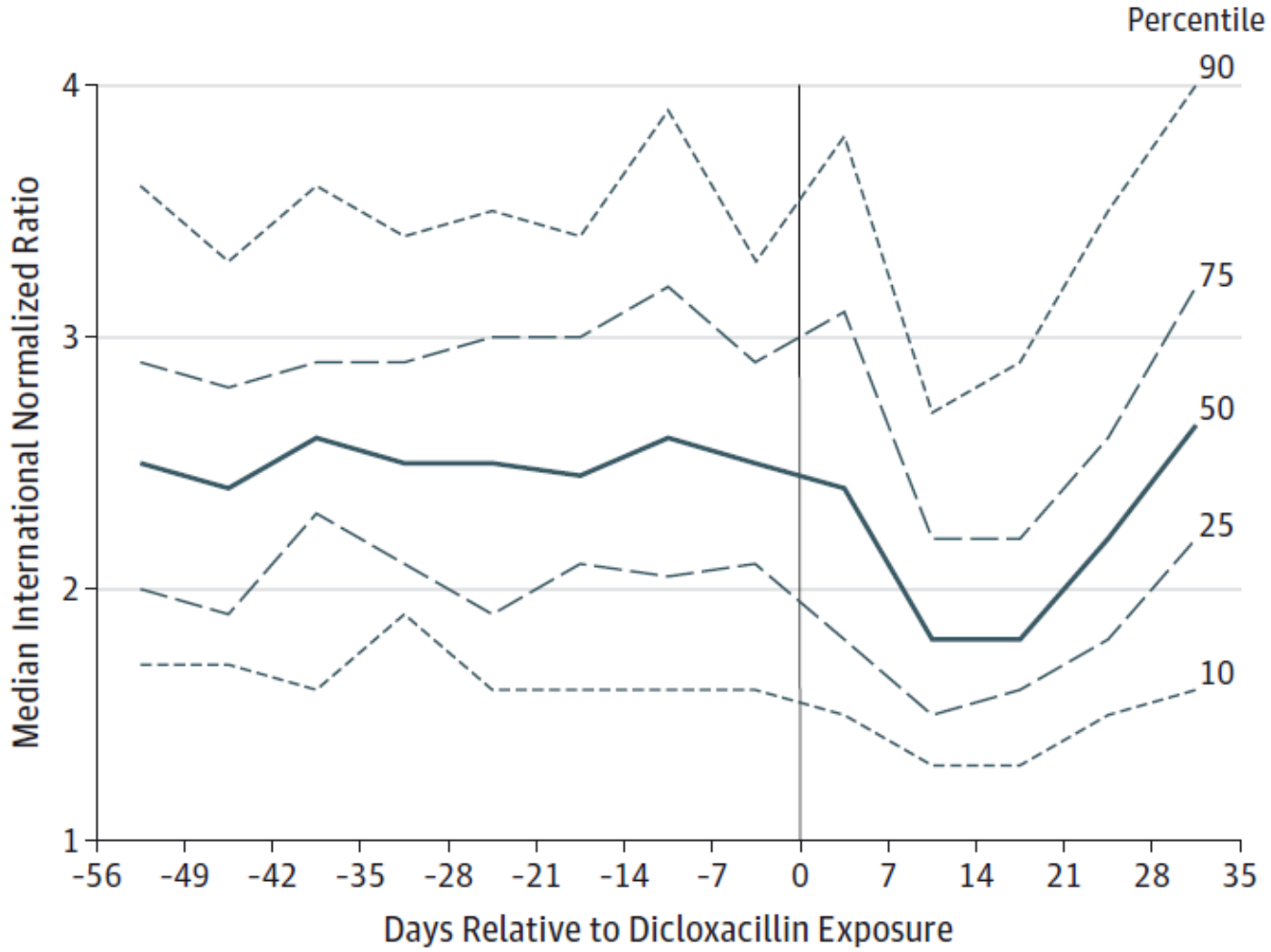
Bleeding?

Myocardial infarction?

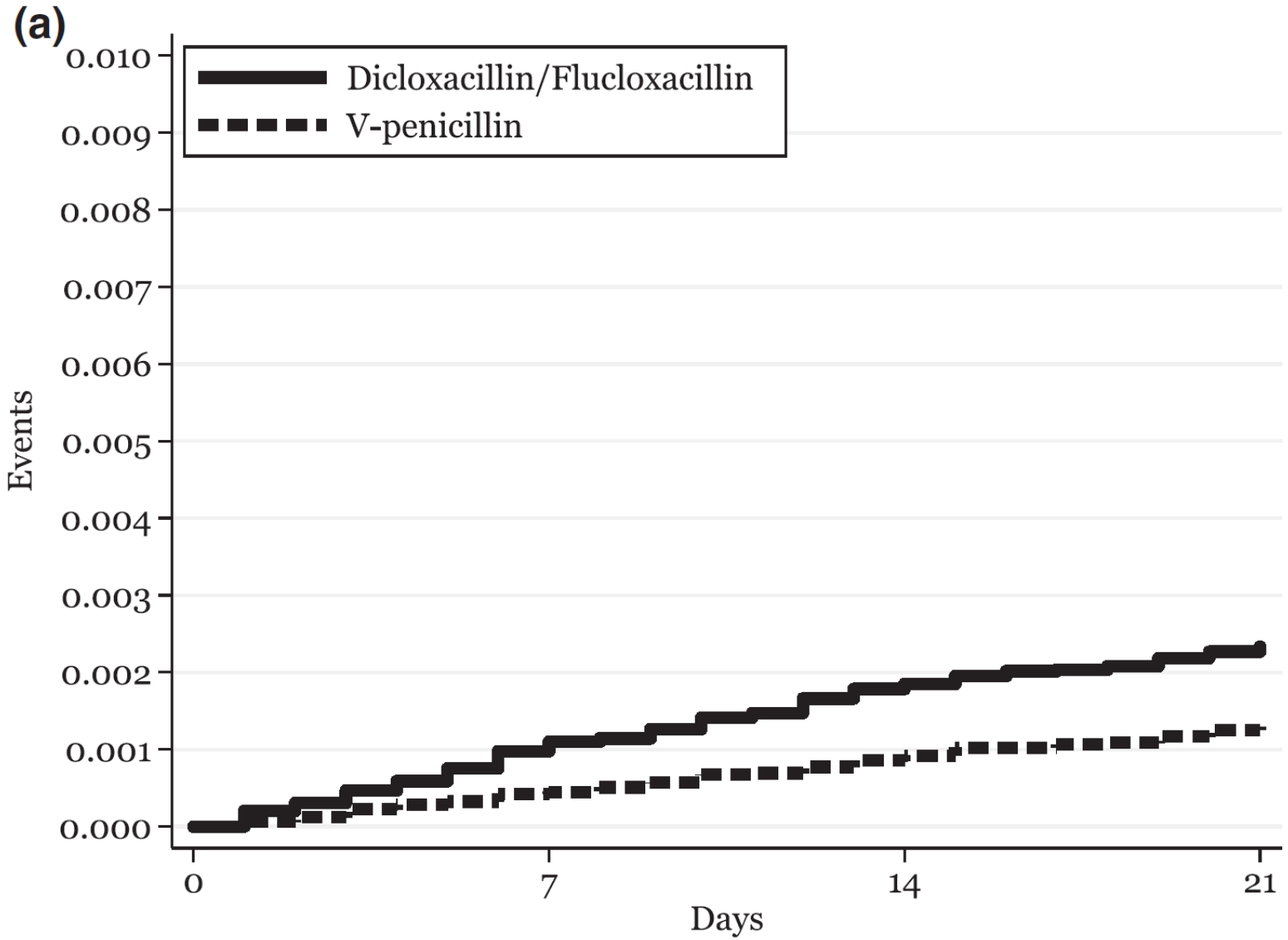
Ischemic stroke?

Melanoma?

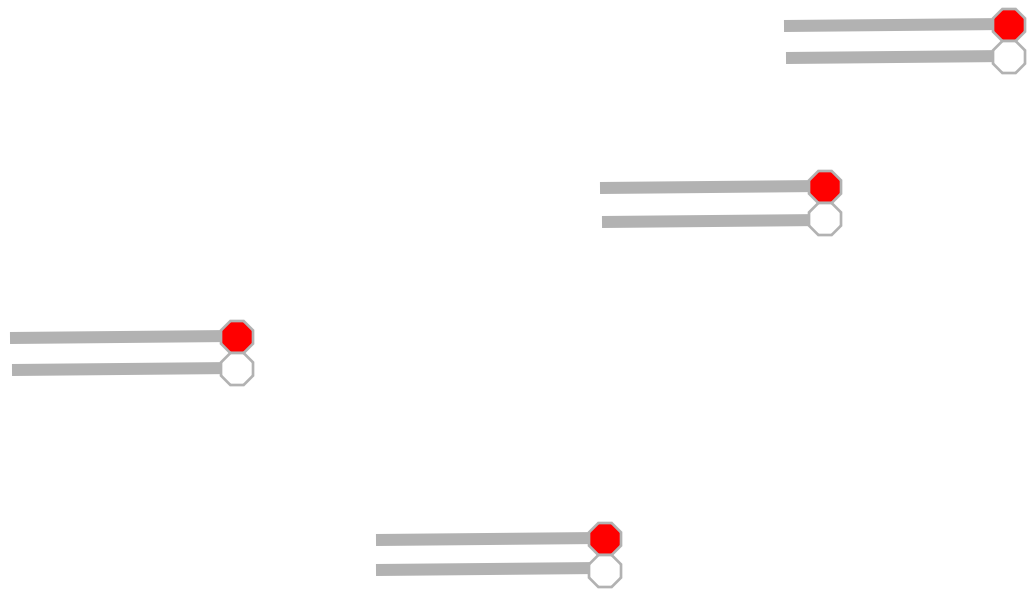
Figure 2. Median International Normalized Ratio Levels Over Time Among Users of Warfarin Exposed to Dicloxacillin

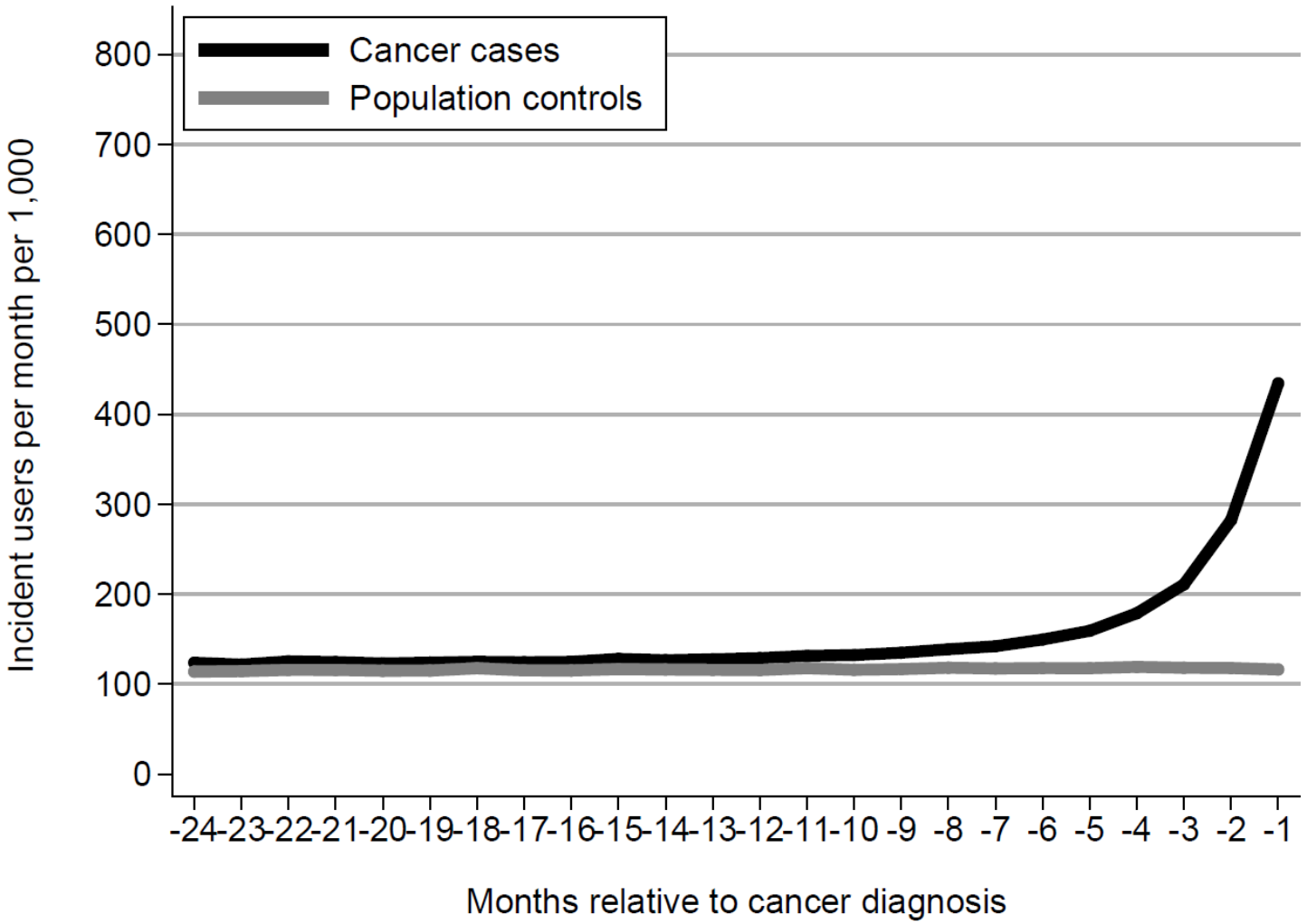


Pottegård et al. JAMA 2015

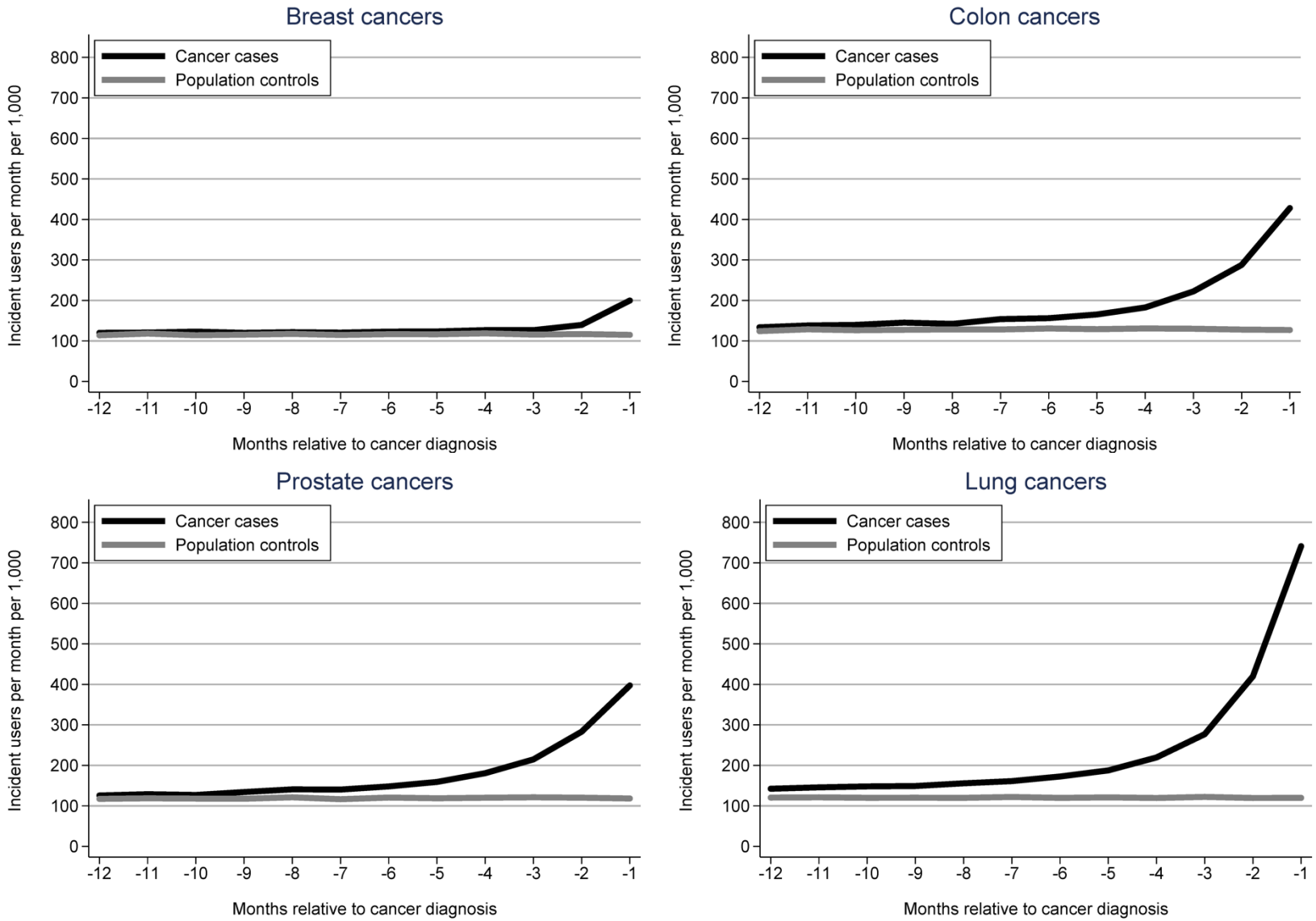


Hellfritzsch et al. Clin Pharmacol Ther 2020





Pottegård & Hallas, Pharmacoepidemiology Drug Saf 2015



Pottegård & Hallas, Pharmacoepidemiology Drug Saf 2015

Received: 19 April 2018 | Accepted: 18 May 2018
DOI: 10.1002/pds.4576

BRIEF REPORT

WILEY

Use of proton pump inhibitors and risk of pancreatic cancer

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Funding information
Cancer Research UK

Abstract

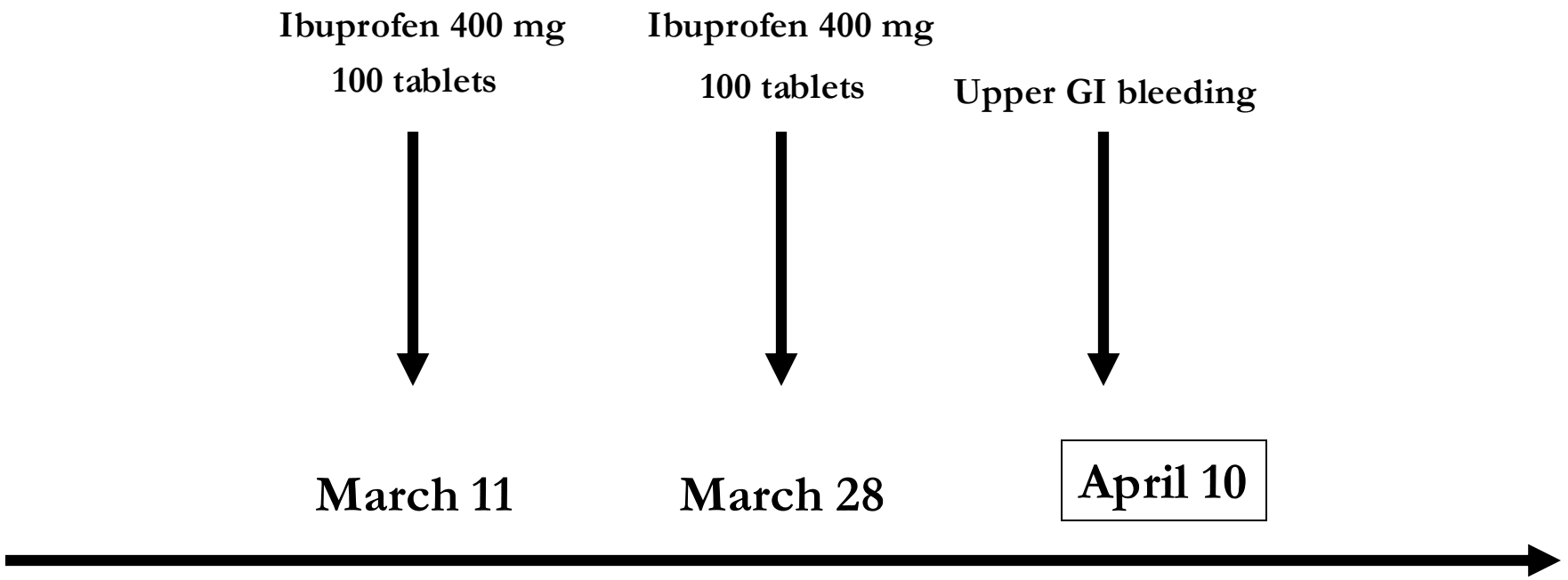
Purpose: Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk; however, epidemiological studies are few, with conflicting results. This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study.

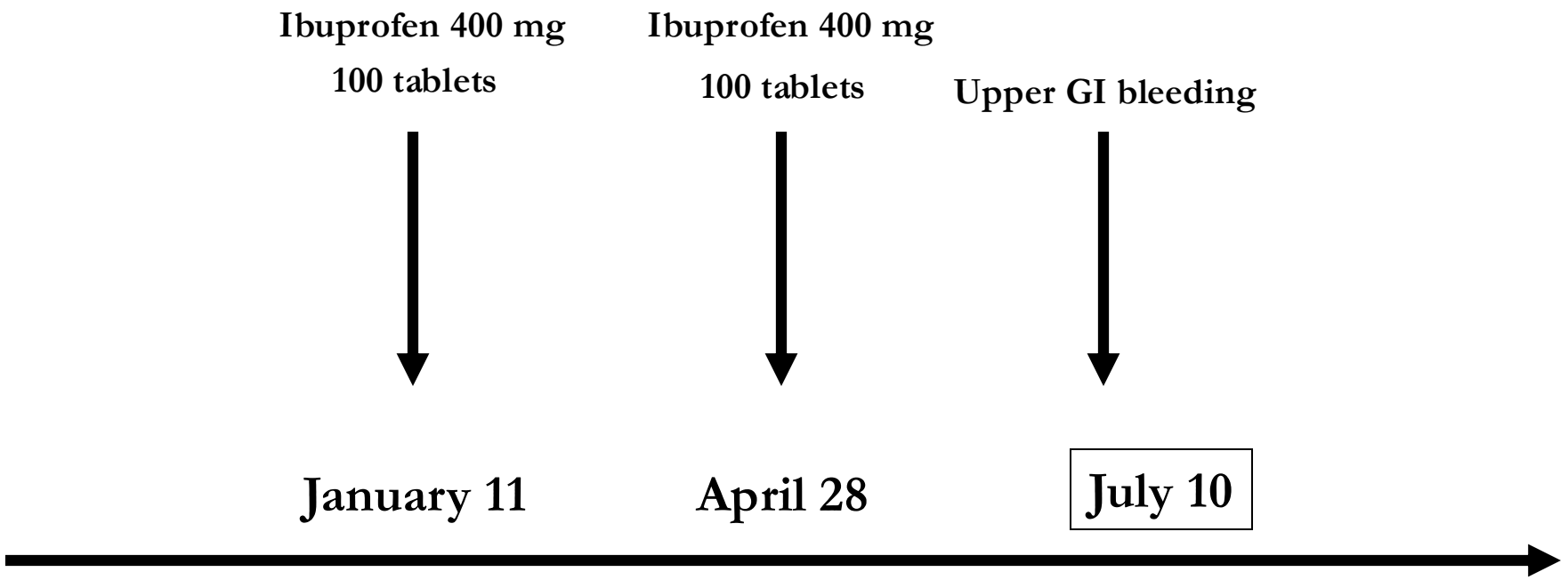
Methods: We conducted a nationwide case-control study using data from Danish demographic and health care registries. All patients with a first cancer diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-matched, sex-matched, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. Secondary analyses examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists.

Results: Ever use of PPIs occurred among 27.8% of 6921 pancreatic cancer cases and 25.4% of 34 695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97-1.11). Odds ratios were also close to unity in analyses of high use of PPIs (≥1000 DDDs; OR, 0.92 95% CI 0.80-1.07). There was no evidence of a dose-response relationship, with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95% CI 0.84-1.26). Analyses of subgroups as well as individual types of PPI and of histamine-2-receptor antagonists use also returned neutral associations.

Lagtime (months)	Adjusted OR
0	1.51 (1.31-1.73)
6	1.02 (0.90-1.17)
12	1.00 (0.87-1.15)
18	0.97 (0.85-1.12)
24	**0.92 (0.79-1.07)**
30	0.92 (0.79-1.07)
36	0.94 (0.80-1.10)
42	0.97 (0.82-1.14)
48	0.95 (0.80-1.12)
54	0.96 (0.81-1.15)
60	0.97 (0.81-1.16)

Hicks et al. Pharmacoepidemiology Drug Saf 2018

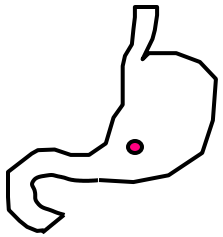

Ibuprofen 400 mg
100 tablets
Ibuprofen 400 mg
100 tablets
Upper GI bleeding
March 11
March 28
April 10


Ibuprofen 400 mg
100 tablets
Ibuprofen 400 mg
100 tablets
Upper GI bleeding
January 11
April 28
July 10

Prescribing

9.1%

Fill



Ingestion

Eur J Clin Pharmacol
DOI 10.1007/s00228-014-1677-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Primary non-adherence in general practice: a Danish register study

Anton Pottegård · Rene dePont Christensen · Alae Houji · Camilla Binderup Christiansen · Maja Skov Paulsen · Janus Laust Thomsen · Jesper Hallas

Received: 5 August 2013 / Accepted: 31 March 2014

Abstract
Purpose The aim of this study was to describe primary non-adherence (PNA) in a Danish general practitioner (GP) setting, i.e. the extent to which patients fail to fill the first prescription for a new drug. We also assessed the length of time between the issuing of a prescription by the GP and the dispensing of the drug by the pharmacist. Lastly, we sought to identify associations between PNA and the characteristics of the patient, the drug and the GP.
Methods By linking data on issued prescriptions compiled in the Danish General Practice Database with data on redeemed prescriptions contained in the Danish National Prescription Registry, we calculated the rate of PNA among Danish patients [illegible]. "Cardiovascular system" (ATC group C). Most of the patients redeemed their prescriptions within the first week. Older age, high income and a diagnosis of chronic obstructive pulmonary disease were found to be significantly associated with lower rates of PNA, while polypharmacy and a diagnosis of ischaemic heart disease were associated with higher rates of PNA.
Conclusions The overall rate of PNA among Danish residents in a GP setting was 9.3 %. Certain drug classes and patient characteristics were associated with PNA.

Keywords Patient adherence · Medication adherence · General practice · Registries · Pharmacology · Pharmacoepidemiology

Exposure Definition	Adjusted OR[b] (95% Confidence Interval)
Fixed window	
30 d	5.17 (2.40-11.11)
60 d	5.13 (2.75-9.55)
90 d	4.73 (2.72-8.23)
120 d	3.64 (2.14-6.18)
Fixed daily intake	
1.5 DDD/d	6.48 (2.88-14.57)
1.0 DDD/d	5.95 (3.02-11.71)
0.5 DDD/d	2.78 (1.77-4.37)
0.2 DDD/d	1.49 (1.16-1.93)

Hallas, Pottegård, and Støvring, PDS 2016

What is the height difference between men and women?

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Hallas, Pottegård, and Støvring, PDS 2016

Incidence rate ratios of GI-hospitalisations of NSAID users

	Current users (0-30 days)	Recent past users (30-60 days)	Old past users (60-150 days)
Diclofenac	3.9	2.2	1.3
Indomethacin	4.0	1.7	1.4
Naproxen	3.8	2.3	1.4
Nonusers		1.0	

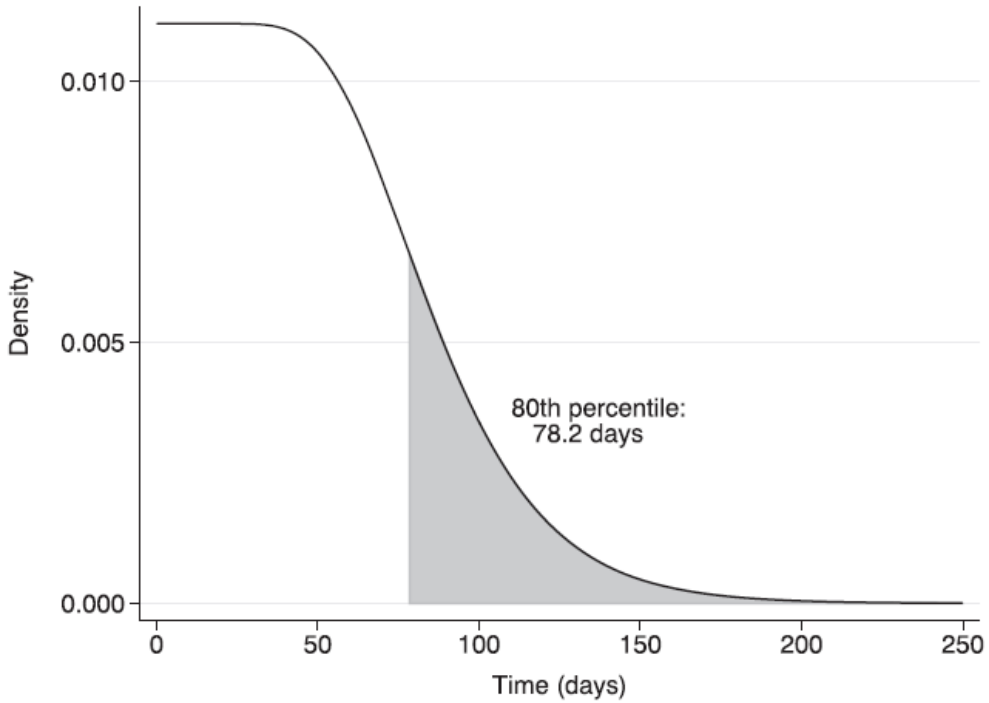
One statin tablet a day?

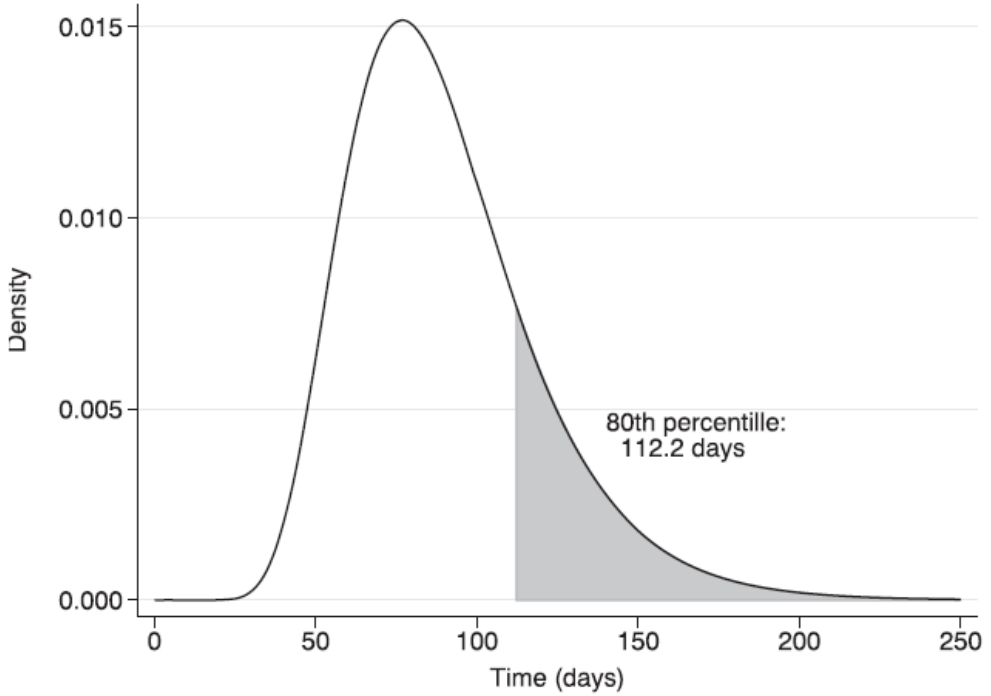
One alendronic acid a week?

An SSRI tablet a day?

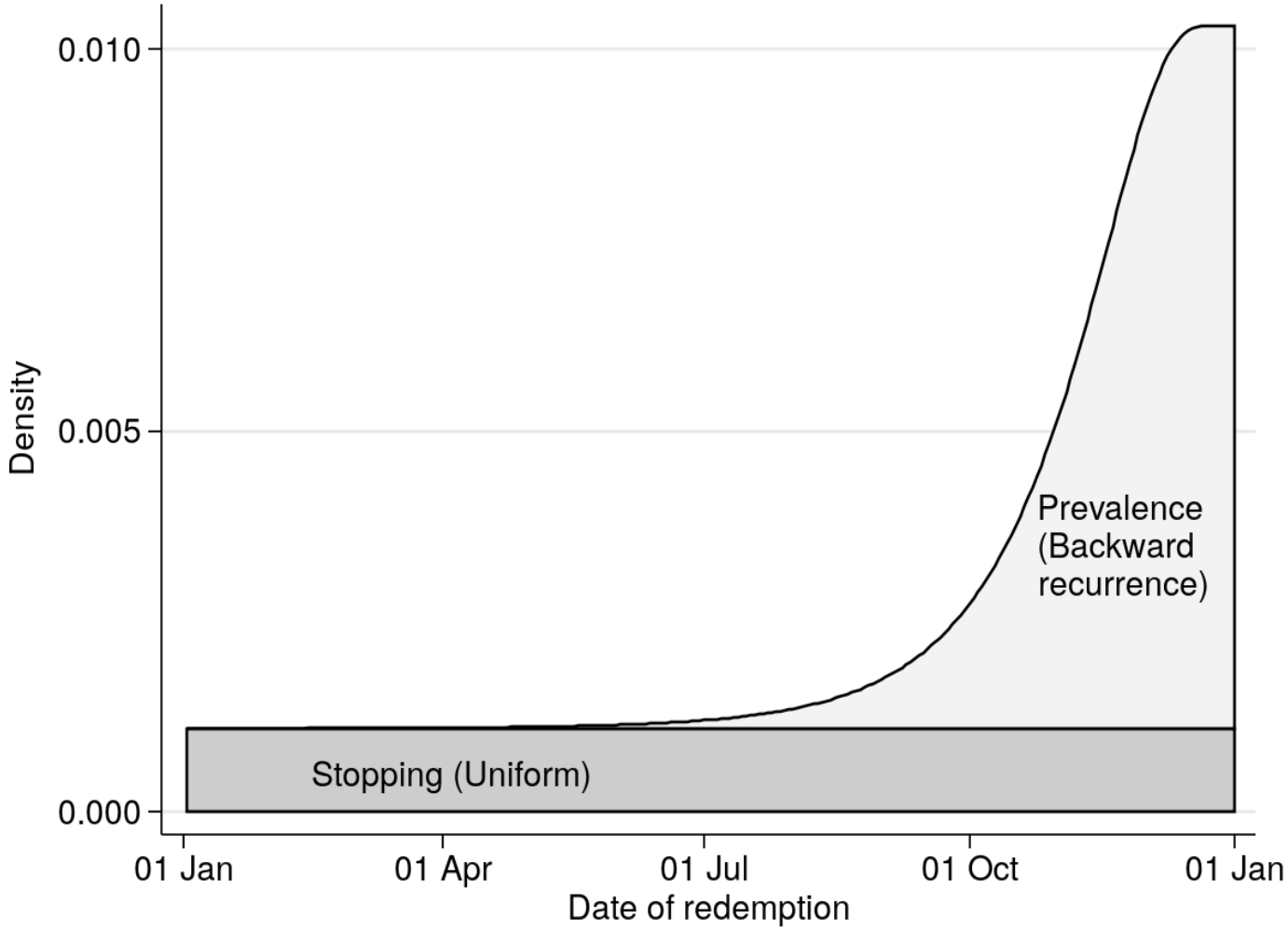
1-2 paracetamol 3-4 times daily?

Drug	Parametric WTD
NSAID	116
Warfarin	91
Bendroflumethiazide	137
Levothyroxine	118





Hallas, Pottegård, and Støvring, PDS 2016



Sex	Age	100 pills	200 pills	300 pills
Male	**50**	62.7	90.2	125.2
Male	**70**	78.1	112.9	157.1
Female	**50**	65.4	92.2	126.5
Female	**70**	81.2	117.3	163.1


MYSTERY
BOX
?

Breast Cancer Res Treat (2011) 129:541–548
DOI 10.1007/s10549-011-1506-2

EPIDEMIOLOGY

The use of atypical antipsychotics and the risk of breast cancer

Laurent Azoulay · Hui Yin · Christel Renoux · Samy Suissa

Received: 1 April 2011 / Accepted: 4 April 2011 / Published online: 9 April 2011

Abstract To determine whether atypical antipsychotics, when compared to typical antipsychotics, increase the risk of breast cancer. We conducted a retrospective cohort study using a nested case–control analysis within the United Kingdom General Practice Research Database population. We identified all female patients prescribed at least one antipsychotic (either typical or atypical), between 1 January 1988 and 31 December 2007, with follow-up until 31 December 2010. All incident cases of breast cancer were identified and matched up to 10 controls. Adjusted rate ratios (RR) of breast cancer associated with ever use of atypical antipsychotics was compared to ever use of typical antipsychotics. The cohort included 106,362 patients prescribed antipsychotics during the study period. During a mean follow-up of 5.3 years, 1237 patients were diagnosed with breast cancer (overall rate: 2.7 per 1000/year). Compared to patients who only used typical antipsychotics, exclusive users of atypical antipsychotics were not an observed in terms of cumulative duration of use and cumulative dose in olanzapine equivalents. The results of this study should provide reassurance that compared to typical antipsychotics, atypical antipsychotics do not increase the risk of breast cancer.

Keywords Antipsychotics · Breast cancer · Population-based

Introduction

Antipsychotics are now playing important role in the treatment of several psychiatric disorders. In fact, there has been a significant increase in their use, particularly for off-label indications [1, 2]. Despite their effectiveness, antipsychotics frequently cause side effects, including hyperprolactinemia [3–5]. High serum prolactin levels

	Cases (n = 1237)	Controls (n = 11,625)	Adjusted RR (95% CI)[a]
Typical antipsychotics only, n (%)	976 (78.9)	9090 (78.2)	1.00 (Reference)
Atypical antipsychotics only			
Cumulative duration of use, n (%)[b]			
≤224 days	36 (2.9)	355 (3.1)	0.95 (0.65, 1.39)
224–687 days	30 (2.4)	366 (3.1)	0.73 (0.48, 1.11)
≥687 days	30 (2.4)	357 (3.1)	0.75 (0.50, 1.13)
Cumulative dose (in olanzapine equivalents), n (%)[b]			
≤910 mg	32 (2.6)	354 (3.0)	0.85 (0.57, 1.26)
910–3965 mg	31 (2.5)	369 (3.2)	0.76 (0.51, 1.13)
≥3965 mg	33 (2.7)	355 (3.1)	0.82 (0.56, 1.20)

[a] Adjusted for the variables listed in Table 1

[b] Based on tertile categories

British Journal of Clinical Pharmacology

ORIGINAL ARTICLE

Use of antipsychotics and risk of breast cancer: a Danish nationwide case–control study

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Received 10 February 2018; **Revised** 29 May 2018; **Accepted** 30 May 2018

Anton Pottegård[1], Timothy L. Lash[2,3], Deirdre Cronin-Fenton[2], Thomas P. Ahern[4] and Per Damkier[5,6]

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Keywords antipsychotics, breast cancer, pharmacoepidemiology

AIMS

Some antipsychotics increase prolactin levels, which might increase the risk of breast cancer. Existing evidence is conflicting and based on sparse data, especially for the increasingly used second-generation antipsychotics. We conducted a nationwide case–control study of the association between antipsychotic use and incident breast cancer.

METHODS

From the Danish Cancer Registry, we identified women with a first-time diagnosis of breast cancer 2000–2015 (n = 60 360). For each case, we age-matched 10 female population controls. Using conditional logistic regression, we calculated odds ratios (ORs) for breast cancer associated with use of antipsychotics. We stratified antipsychotics by first- and second-generation status and by ability to induce elevation of prolactin.

RESULTS

In total, 4951 cases (8.1%) and 47 643 controls (7.9%) had ever used antipsychotics. Long-term use (≥10 000 mg olanzapine equivalents) was associated with breast cancer, with an adjusted OR of 1.18 [95% confidence interval (CI), 1.06, 1.32]. A weak dose–response pattern was seen, with ORs increasing to 1.27 (95% CI 1.01, 1.59) for ≥50 000 mg olanzapine equivalents. Associations were similar for first- and second-generation antipsychotics (ORs 1.17 *vs*. 1.11), but also for nonprolactin inducing-antipsychotics (OR 1.17). Stratifying by oestrogen receptor status, positive associations were seen for oestrogen receptor-positive cancers (long-term use: OR 1.29; 95% CI 1.13, 1.47) while no associations were observed for oestrogen receptor-negative cancers.

CONCLUSIONS

Overall, our results do not suggest a clinically important association between antipsychotic use and risk of breast cancer. The importance of drug-induced prolactin elevation is unclear but may lead to a slightly increased risk of oestrogen receptor-positive breast cancer.

Main exposure variables and covariates

Exposure to different antipsychotics was standardized using olanzapine equivalents [38]. For drugs not assigned a conversion factor, one defined daily dose (DDD), per WHO definitions, was considered equivalent to 10 mg olanzapine [39]. We applied a pre-specified main exposure measure corresponding to a cumulative exposure of 10 000 mg olanzapine, while restricting to antipsychotics with prolactin inducing properties (Appendix S2). We included all exposure from 1995 (the opening of the Prescription Registry) until 1 year before an individual's index date. The largely arbitrary cut-off of 10 000 mg olanzapine equivalents was selected based on pharmacological consideration that if antipsychotic use inferred a risk of breast cancer, a substantial use was likely to be necessary to detect an increased risk. For dose–response analyses, we used the following prespecified categories: 0–4999 mg, 5000–9999 mg, 10 000–19 999 mg, 20 000–49 999 mg and ≥50 000 mg. These strata were selected to ensure that we did not overlook risk associated with either very short or very high use of antipsychotics. In all exposure calculations, we disregarded prescriptions redeemed within 1 year before the index date to reduce the possibility of reverse causation [40], and because such recent exposure is unlikely to affect cancer development.

Exposure group	Cases	Controls	Adjusted OR[b]
Nonuse			
Ever use			
Long-term use[c]			
Cumulative use[c]			
0–4999 mg			
5000–9999 mg			
10 000–19 999 mg			
20 000–49 999 mg			
≥50 000 mg			

Exposure group	Cases	Controls	Adjusted OR[b]
Nonuse	55 409	555 957	1.0 (ref.)
Ever use	4798	46 156	1.00 (0.97–1.04)
Long-term use[c]	693	5659	1.18 (1.06–1.32)
Cumulative use[c]			
0–4999 mg	3756	37 619	0.97 (0.94–1.01)
5000–9999 mg	349	2878	1.19 (1.05–1.34)
10 000–19 999 mg	243	2131	1.11 (0.95–1.29)
20 000–49 999 mg	246	1993	1.27 (1.07
≥50 000 mg	204	1535	1.27 (1.01

	Cases (n = 1237)	Controls (n = 11,625)	Adjusted RR (95% CI)[a]
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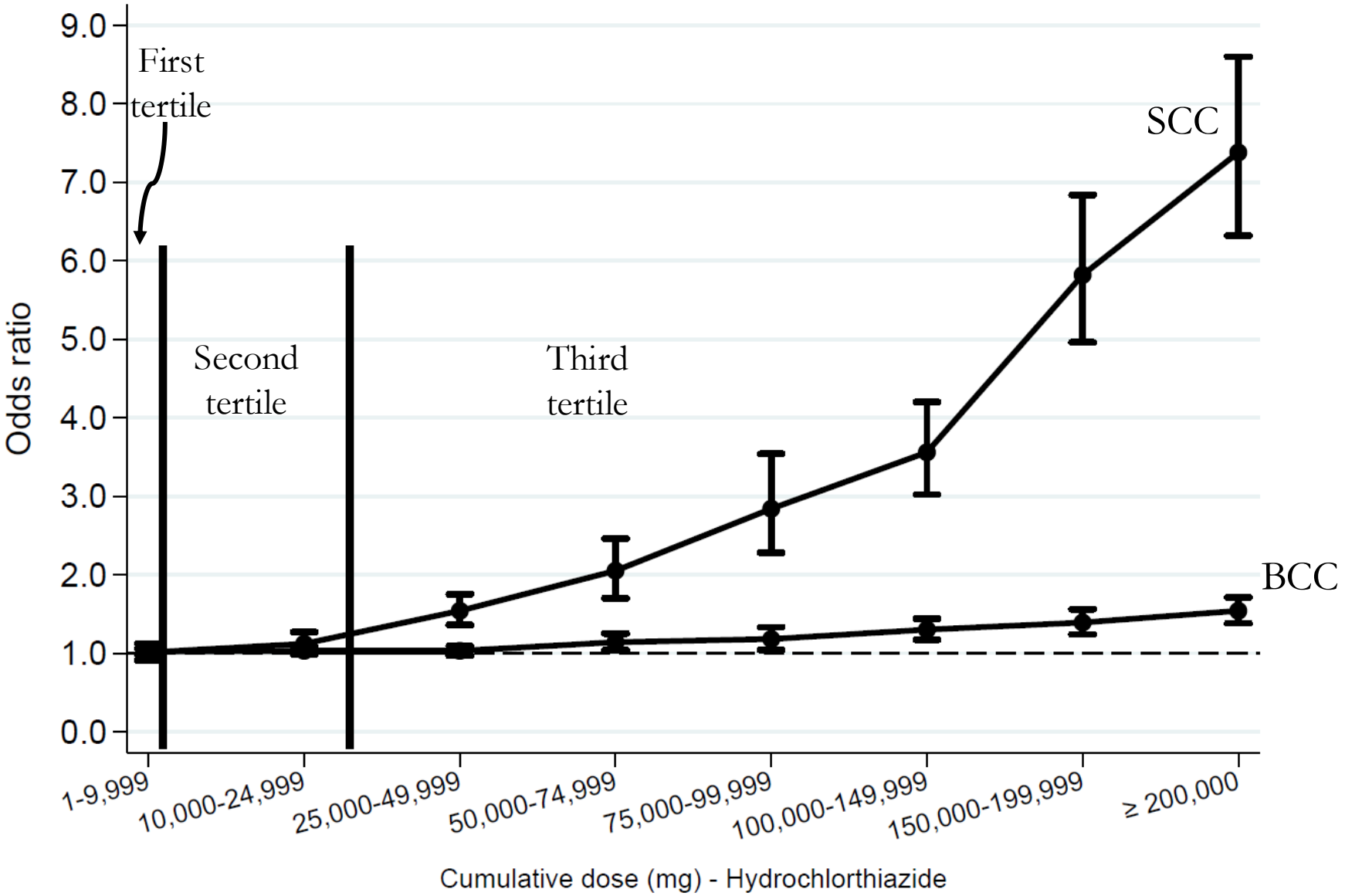
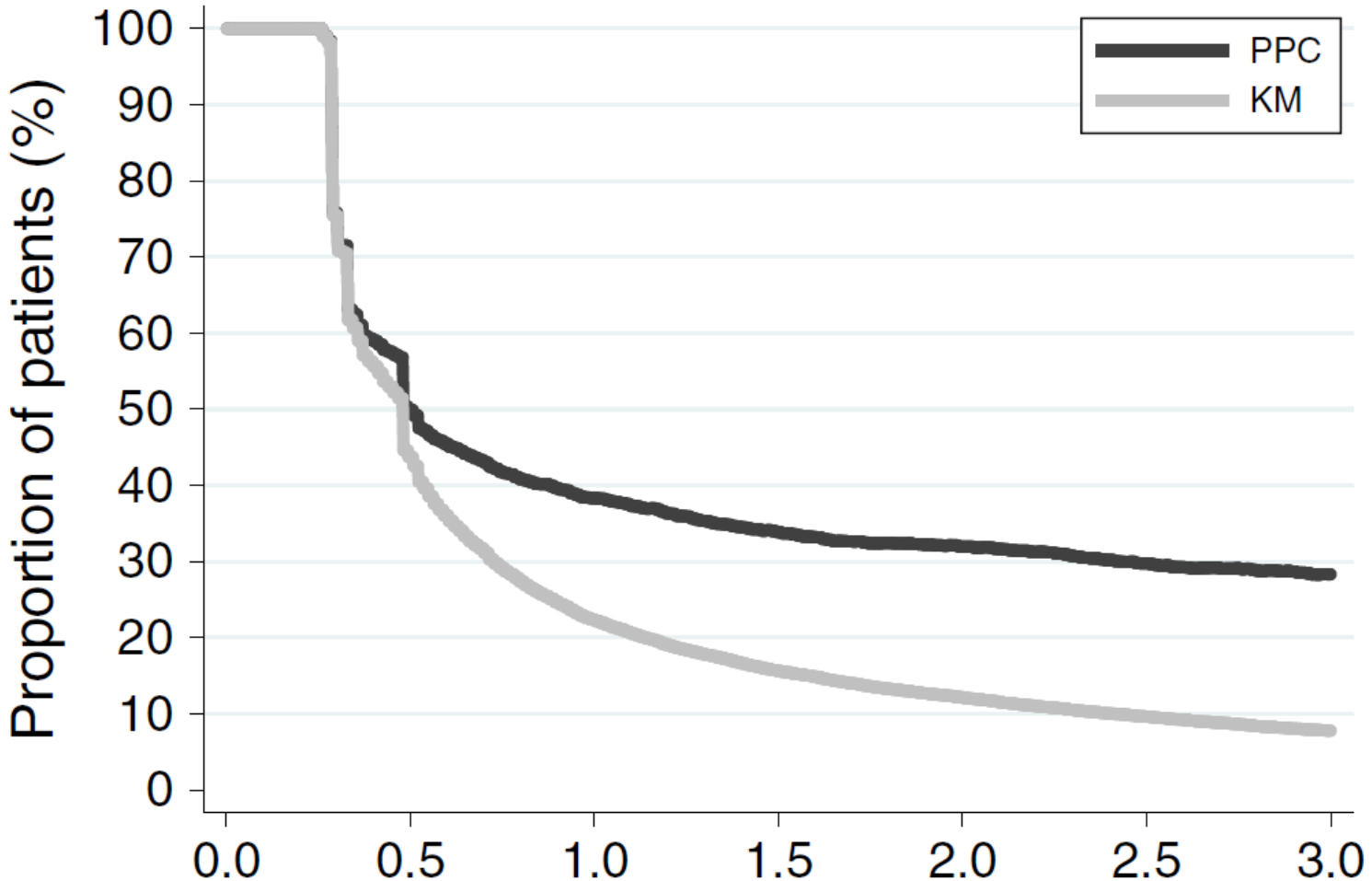
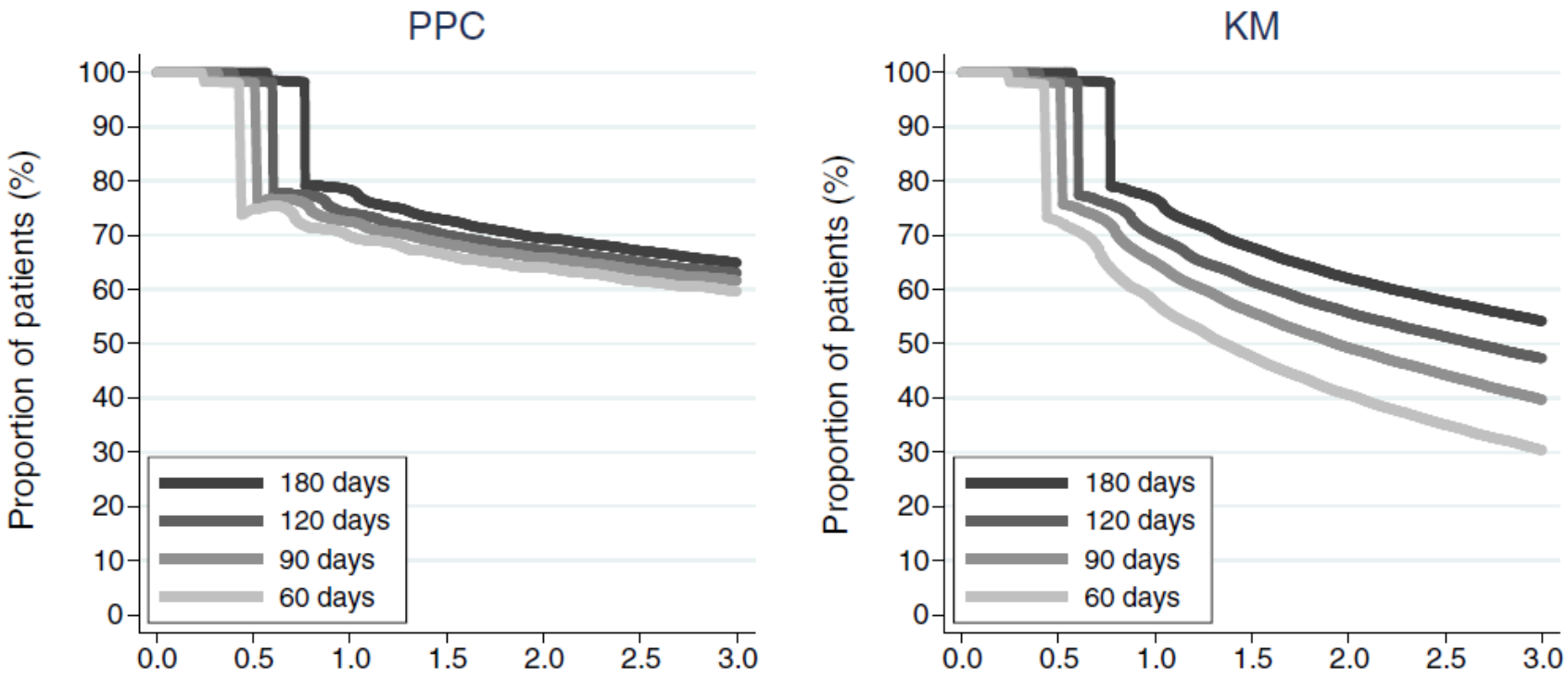


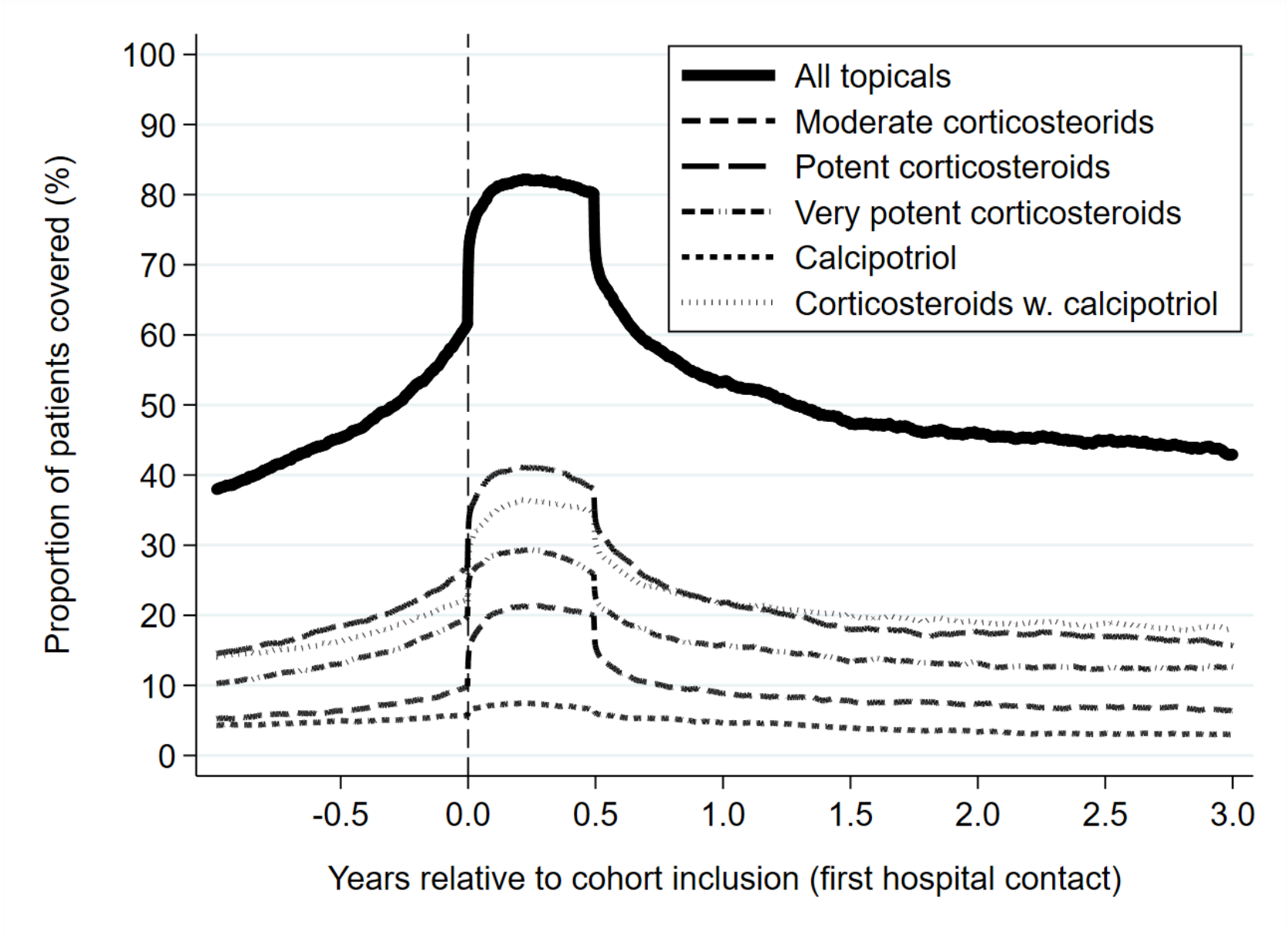
Pedersen et al. J Am Acad Dermatol. 2018



Rasmussen et al. Pharmacoepidemiol Drug Saf 2018



Rasmussen et al. Pharmacoepidemiol Drug Saf 2018



Svendsen et al. Br J Dermatol 2019

Pharmacology:

The neglected half of pharmacoepidemiology!