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Persistent User Bias in Case-Crossover Studies in Pharmacoepidemiology

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Studying the effect of chronic medication exposure by means of a case-crossover design may result in an upward-biased odds ratio. In this study, our aim was to assess the occurrence of this bias and to evaluate whether it is remedied by including a control group (the case-time-control design). Using Danish data resources from 1995–2012, we conducted case-crossover and case-time-control analyses for 3 medications (statins, insulin, and thyroxine) in relation to 3 outcomes (retinal detachment, wrist fracture, and ischemic stroke), all with assumed null associations. Controls were matched on age, sex, and index date, and exposure over the preceding 12 months was ascertained. For retinal detachment, the case-crossover odds ratio was 1.60 (95% confidence interval (CI): 1.42, 1.80) for statins, 1.40 (95% CI: 1.02, 1.92) for thyroxine, and 1.53 (95% CI: 1.04, 2.24) for insulin. Estimates for the retinal detachment controls were similar, leading to near-null case-time-control estimates for all 3 medication classes. For wrist fracture and stroke, the odds ratios were higher for cases than for controls, and case-time-control odds ratios were consistently above unity, thus implying significant residual bias. In case-crossover studies of medications, contamination by persistent users confers a moderate bias upward, which is partly remedied by using a control group. The optimal strategy for dealing with this problem is currently unknown.

case-crossover design; drug utilization; epidemiologic methods; pharmacoepidemiology; research design; self-controlled designs

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; ICD-10, *International Classification of Diseases, Tenth Revision*.

The case-crossover design is a within-person, case-only study design whereby a case-patient's exposure at the time of the case-defining event is compared with the same person's exposure at a different time in the past. Owing to its attractive property of eliminating confounders (measured as well as unmeasured) that are constant over time (1), this design has become commonly used in pharmacoepidemiology (2, 3).

For several reasons, the case-crossover design is not suited for investigating medication exposures that do not vary over time. The analytical method is based on contrasting exposure status within individuals at different time points at the time of and prior to the case-defining event. For patients with chronic, long-term medication use, exposure status may remain constant over the compared periods, and such subjects do not contribute to the conditional analysis. This reduces statistical efficiency, but it is not in and of itself a source of bias (4).

Another, potentially more serious, problem is that only certain patterns of contrasting exposure are likely to occur. Consider a hypothetical study of statins as a cause of retinal detachment (an assumed null association), carried out as a case-crossover study. Statins are usually intended to be taken permanently, once the indication for their use has been established. If the retinal detachment occurs soon after statin initiation, then the subject will have the pattern of statin use at the time of the retinal detachment and nonuse at the reference time in the past. The opposite pattern (nonexposed at retinal detachment and exposed at the reference time in the past) cannot occur if the drug is taken as intended. Since only these 2 patterns contribute to the analysis, the resulting odds ratio would in principle be infinite (Figure 1). The problem described here may also arise if the first treatment episodes are right-truncated for some reason—for example, if the subjects leave the country or reach

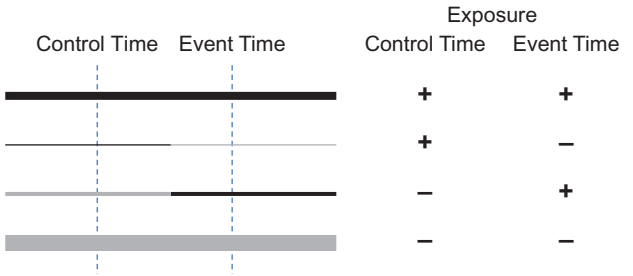

Figure 1. Origin of persistent user bias in pharmacoepidemiologic case-crossover studies. If a medication is intended to be taken permanently once the indication for its use has arisen, only 4 patterns will emerge. These 4 patterns are illustrated using the width of the bars as a symbolic representation of their relative frequency. The black line indicates use of the medication, and the gray line indicates nonuse. Only the middle 2 patterns will contribute to the case-crossover analysis.

the end of the observation period while still being in their first treatment episode. If such a person has a retinal detachment before he emigrates, he cannot possibly show a pattern of being unexposed to statins at the time of retinal detachment and exposed at the reference time in the past. Since the opposite pattern is possible, the resulting odds ratio would also be infinite. We thus chose "persistent user bias" as a unifying term to cover both permanent medication use and right-truncated first treatment episodes as a source of bias. In clinical practice, there will be a mix of patients who take the drug indefinitely and patients who take the drug transiently, due to intolerance or nonadherence or for other reasons. In the absence of other sources of bias, the transient users will produce an unbiased estimate of the statin effect, and the mix of transient- and persistent-user subpopulations will therefore determine the strength of persistent-user bias in the study as a whole.

Suissa (5) proposed an extension of the case-crossover design, the case-time-control approach, whereby the exposure contrast is analyzed in a nondiseased control group and then used as a reference for the case-crossover estimate for the cases. It was originally intended to adjust for temporal trends in exposure that might otherwise bias a case-crossover estimate based on cases alone. However, if one can identify a control group with the same mix of persistent and transient users as those who eventually become cases, then the case-time-control approach might remove the persistent user bias as well.

The objective of this study was to assess the presence and significance of persistent user bias in case-crossover studies of medication effects and to evaluate whether the bias can be remedied with the case-time-control approach. We will also describe the extent of permanent use for a variety of medication classes.

METHODS

Using data from nationwide Danish health registries, we identified subjects with retinal detachment, wrist fracture, or ischemic stroke and analyzed them with respect to statin, thyroxine, or insulin exposure. We analyzed the data using both the case-crossover design and the case-time-control design. Drug persistence over a 16-year period was analyzed using a modified Kaplan-Meier technique for a variety of medication classes.

Data sources

Three nationwide Danish data sources were employed: the National Patient Register (6), the National Prescription Registry (7), and the Civil Registration System (8). In brief, the National Patient Register contains data on all admissions to public hospitals in Denmark since 1977. Diagnoses have been coded according to the *International Classification of Diseases, Tenth Revision* (ICD-10) since 1994. The prescription database of the Danish Medicines Agency contains data on all prescriptions redeemed by Danish citizens since 1995 (7). Drugs are categorized according to Anatomical Therapeutic Chemical (ATC) classification code, and the quantity of medication in each prescription is expressed in terms of the defined daily dose measure developed by the World Health Organization (www.whocc.no). The Danish Person Registry contains data on vital status (date of death) and migrations into and out of the country for all residents of Denmark, which allowed us to extract controls and to keep track of all subjects.

Virtually all medical care in Denmark is furnished by the national health authorities. These data resources allow true population-based studies covering all 5.6 million inhabitants of Denmark. Data were linked by means of the Personal Identification Number, a unique identifier that is assigned to all residents of Denmark (8). All linkages were performed within Statistics Denmark, a governmental institution that collects and processes information for a variety of statistical and scientific purposes (9).

Cases and controls

We included all subjects born in or before 1950 who experienced a first occurrence of one of the following conditions during the period January 1, 2002–December 31, 2012: retinal detachment (ICD-10 code H33), wrist fracture (ICD-10 code S525), and ischemic stroke (ICD-10 code I63). These were chosen as representing conditions characterized by abrupt onset, unpredictable timing, and the requirement for a hospitalization or emergency room visit.

For the purpose of the case-time-control analysis, we used risk-set sampling to identify controls from the entire Danish source population, individually matched to the index cases with respect to birth year and sex and assigned an index date identical to the date of diagnosis for the corresponding case. Controls were required to have no prior history of the outcome of interest on the index date; however, because of the risk-set sampling, controls could subsequently become cases. Controls were selected at a ratio of up to 4 per case. Because some of the cases were very old, not all cases had 4 eligible controls, and the resulting average control:case ratio became slightly less than 4:1.

Drug exposure

Three medication classes were chosen: statins (ATC code C10AA), thyroxine (ATC code H03AA01), and insulin (ATC code A10A). These were chosen to represent commonly used medications with long or intermediate intended durations of use.

The dosing instructions and duration of use for each prescription are not recorded in the data source we used. Instead, we calculated the duration assigned to each prescription using the waiting-time method described by Pottegård and Hallas (10). In brief, with this method one analyzes a fixed time window (e.g., a calendar year) and tabulates the distribution of first occurrences of the drug within that window. The typical waiting-time distribution will have a high plateau in the first months and then level off at a lower rate of first-time prescriptions. Medications that are dispensed with short intervals tend to have their first occurrence early in the time window and reach their low equilibrium level early. This can be formalized to an actual estimate of the period of usage for a prescription. We used the period 2003–2004 as the time window and set the waiting-time parameter to 0.90 (10).

Analyses

The analysis conformed to a conventional case-crossover study with the case-time-control extension. The association between exposure and case status was analyzed by conditional logistic regression, with the individual as the unit of analysis. Because each of the exposure-outcome combinations was thought to represent a null association, we assumed no induction period and set a "risk period" identical to current medication exposure according to the definitions above. For each subject, case or control, we selected 6 reference dates at 2-month intervals prior to the index date (i.e., 2, 4, 6, etc., months before the index date), thus spanning a period between 2 months before the index date and 1 year before the index date. A subject was considered exposed on a given event date or reference date if there was a prescription whose assigned period of usage covered that date. We did not attempt to adjust for time-varying confounders, and no covariates other than the main exposure were included in the analysis.

In addition to statins, thyroxine, and insulin, we analyzed the case-crossover and case-time-control estimates for retinal detachment in relation to all of the medication classes mentioned below in the drug utilization study. We focused on retinal detachment because we expected that time-varying confounding with any of the medications would be less likely for this outcome than for the others, given its unpredictable nature. The analytical choices (e.g., the time windows and definitions of exposure) were similar to those of the main analysis.

For the case-time-control approach, the main result emerged as an interaction term for interaction between case status and exposure discordance, as described by Suissa (5).

Drug utilization analysis

We performed an analysis of the extent of persistent use for the most commonly prescribed medication categories in Denmark, estimating the proportion of new medication users who, at various follow-up points, were either still being treated or had died, emigrated, or reached the end of the study period during their first treatment episode. The latter included all patients who had not terminated their first treatment episode before being censored.

We identified all subjects who started a first prescription for one of 22 different medication classes within the period January 1, 1997–December 31, 2002, after not having redeemed any prescription for the drug during the preceding 2 years. For these subjects, only the first treatment episode for each medication class was analyzed. We thus had up to 16 years of potential follow-up. For each medication, we assessed time-to-discontinuation while accounting for censoring due to emigration, death, or the end of the study period. We used Kaplan-Meier methods to plot the cumulative proportion of patients who discontinued use, before being censored for other reasons, over time.

The study was approved by the National Health Board's Medicines Division. According to Danish law, purely register-based studies do not require approval from an ethics review board (9).

RESULTS

We identified 12,788 subjects with retinal detachment, 66,004 with wrist fracture, and 63,353 with ischemic stroke (Table 1). As expected, the stroke patients were the oldest and had the greatest burden of comorbidity when compared with their controls or the other case categories. Of the wrist fracture patients, 84.3% were women. Patients with retinal detachment were the youngest and had the least comorbidity, in general.

For retinal detachment, the case-crossover estimate for cases was 1.60 (95% confidence interval (CI): 1.42, 1.80) for statins, 1.40 (95% CI: 1.02, 1.92) for thyroxine, and 1.53 (95% CI: 1.04, 2.24) for insulin (Table 2). Case-crossover estimates for the control group were similar, leading to near-null case-time-control estimates for the 3 medication classes: Odds ratios were 1.03 (95% CI: 0.90, 1.18), 1.24 (95% CI: 0.86, 1.78), and 1.09 (95% CI: 0.70, 1.69), respectively.

The corresponding analyses for wrist fracture and ischemic stroke are shown in Table 2. All point estimates for cases, controls, and the combined case-time-control analyses were consistently above unity. In contrast to the analyses of retinal detachment, all control estimates were smaller than their corresponding case estimates, thus resulting in case-time-control estimates that were above unity. The most striking example was for statins and stroke, where the odds ratios for cases and controls and for the case-time-control analysis were 3.16 (95% CI: 3.01, 3.32), 1.39 (95% CI: 1.35, 1.43), and 2.27 (95% CI: 2.15, 2.41), respectively. Case-time-control estimates varied between 1.12 and 1.55 for wrist fracture and between 1.70 and 2.27 for stroke.

The results of the case-crossover and case-time-control analyses of retinal detachment in relation to 18 other medication classes are shown in Table 3. Odds ratios for the case-crossover estimates varied between 1.00 (neuroleptics) and

Table 1. Characteristics of Case-Patients With Retinal Detachment, Wrist Fracture, or Ischemic Stroke and Their Corresponding Controls at the Index Date, Denmark, 2002–2012

	Retinal Detachment				Wrist Fracture				Ischemic Stroke			
	Cases (n = 12,788)		Controls (n = 51,152)		Cases (n = 66,004)		Controls (n = 264,001)		Cases (n = 63,353)		Controls (n = 253,400)	
	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%	No. of Persons	%
Age, years[a]	66 (62–72)		66 (62–72)		71 (64–80)		71 (64–80)		75 (67–83)		75 (67–83)	
Male sex	6,600	51.6	26,400	51.6	10,363	15.7	41,448	15.7	32,932	52.0	131,718	52.0
History of medication use												
Antidiabetic agents	1,160	9.1	4,975	9.7	4,700	7.1	24,024	9.1	8,529	13.5	27,138	10.7
Thiazides	3,870	30.3	15,062	29.4	23,921	36.2	100,148	37.9	28,086	44.3	92,795	36.6
Inhaled anticholinergics	496	3.9	2,668	5.2	3,493	5.3	14,592	5.5	3,709	5.9	15,532	6.1
Osteoporosis drugs	665	5.2	2,842	5.6	7,425	11.2	21,839	8.3	5,005	7.9	18,523	7.3
Antihypertensive agents	6,753	52.8	26,614	52.0	37,704	57.1	155,253	58.8	45,724	72.2	153,487	60.6
Urate-lowering drugs	624	4.9	2,783	5.4	2,496	3.8	11,800	4.5	4,153	6.6	15,849	6.3
Antiplatelets	3,712	29.0	14,716	28.8	21,884	33.2	88,688	33.6	34,506	54.5	99,082	39.1
Anticoagulants	983	7.7	3,859	7.5	4,561	6.9	20,324	7.7	8,267	13.0	25,049	9.9
Ulcer drugs	4,335	33.9	17,681	34.6	24,547	37.2	97,680	37.0	25,548	40.3	95,624	37.7
DMARDs	382	3.0	1,819	3.6	2,078	3.1	9,067	3.4	1,973	3.1	8,129	3.2
Drugs for nicotine addiction	239	1.9	1,469	2.9	1,300	2.0	5,878	2.2	1,401	2.2	5,523	2.2
Drugs for alcohol addiction	356	2.8	2,405	4.7	2,562	3.9	7,403	2.8	2,435	3.8	8,296	3.3
Prescribed weight-loss products	1,258	9.8	4,940	9.7	6,492	9.8	27,443	10.4	4,326	6.8	16,929	6.7
Medical history (prior diagnosis)												
Myocardial infarction	957	7.5	5,166	10.1	4,451	6.7	23,642	9.0	6,480	10.2	27,511	10.9
Ischemic heart disease	1,791	14.0	8,103	15.8	8,234	12.5	38,289	14.5	12,210	19.3	45,534	18.0
Diabetes	1,140	8.9	5,255	10.3	4,619	7.0	23,741	9.0	5,908	9.3	24,130	9.5
Peripheral artery disease	754	5.9	4,303	8.4	3,730	5.7	20,507	7.8	5,031	7.9	21,057	8.3
Hypertension	1,160	9.1	5,500	10.8	5,640	8.5	25,889	9.8	7,023	11.1	24,638	9.7
COPD	500	3.9	3,027	5.9	2,324	3.5	12,822	4.9	1,634	2.6	12,075	4.8
Osteoporosis	817	6.4	4,238	8.3	6,058	9.2	22,840	8.7	3,834	6.1	19,722	7.8
Osteoporotic fracture	901	7.0	5,087	9.9	8,260	12.5	31,848	12.1	6,777	10.7	32,428	12.8
Obesity	555	4.3	3,276	6.4	2,587	3.9	14,110	5.3	1,884	3.0	12,954	5.1

Abbrevations: COPD, chronic obstructive pulmonary disease; DMARDs, disease-modifying antirheumatic drugs.
[a] Values are presented as median (interquartile range).

2.50 (oral antidiabetics), while the case-time-control estimates varied between 0.87 (antithyroid drugs) and 1.61 (oral antidiabetics). For the case-crossover estimates of cases, 17 out of 18 point estimates (94%) were above unity. Sixteen of 18 estimates (89%) were adjusted downward by using the control group; that is, case-time-control estimates were lower than case-crossover estimates for cases. Of the 18 case-time-control point estimates, 15 (83%) were above unity, 9 of them (50%) reaching statistical significance.

The results of the drug utilization analysis are shown in Table 4. The values show the proportion of new users who at any given time since initiation of their medication were either still being treated or had their first treatment episode truncated by death, emigration, or the end of the study period. For insulin, statins, and thyroxine, these proportions at 1 year were 56.9%, 34.4%, and 45.9%, respectively. Corresponding values at 15 years were 34.3%, 11.4%, and 19.8%.

DISCUSSION

Our analyses confirmed the existence of a bias by persistent-user contamination in the execution of case-crossover designs and analyses applied to medication exposures. This should be viewed not as a flaw in the case-crossover design but rather as a flaw in its execution. The original description of the

Table 2. Case-Crossover Estimates of the Association Between Use of Statins, Thyroxine, or Insulin and the Risks of Retinal Detachment, Wrist Fracture, and Ischemic Stroke, Denmark, 2002–2012[a]

Variable	Statins				Thyroxine				Insulin			
	No. of Persons	%	OR	95% CI	No. of Persons	%	OR	95% CI	No. of Persons	%	OR	95% CI
Retinal Detachment												
Cases												
Total	12,788		1.60	1.42, 1.80	12,788		1.40	1.02, 1.92	12,788		1.53	1.04, 2.24
Exposed index dates	2,343	18.3			432	3.4			344	2.7		
Exposed reference dates	13,107	17.1			2,499	3.3			1,982	2.6		
Fully concordant, exposed	1,123	8.8			266	2.1			239	1.9		
Fully concordant, unexposed	9,940	77.7			12,288	96.1			12,394	96.9		
Controls												
Total	51,152		1.56	1.46, 1.66	51,152		1.13	0.95, 1.34	51,152		1.41	1.13, 1.76
Exposed index dates	7,951	15.5			1,383	2.7			865	1.7		
Exposed reference dates	44,568	14.5			8,186	2.7			5,000	1.6		
Fully concordant, exposed	3,907	7.6			937	1.8			545	1.1		
Fully concordant, unexposed	41,407	80.9			49,479	96.7			50,116	98.0		
Cases and controls (CTC estimate)			1.03	0.90, 1.18			1.24	0.86, 1.78			1.09	0.70, 1.69
Wrist Fracture												
Cases												
Total	66,004		1.66	1.57, 1.76	66,004		1.72	1.51, 1.95	66,004		1.30	1.07, 1.58
Exposed index dates	10,412	15.8			3,180	4.8			1,260	1.9		
Exposed reference dates	58,020	14.7			18,102	4.6			7,364	1.9		
Fully concordant, exposed	5,515	8.7			1,637	2.6			1,375	2.2		
Fully concordant, unexposed	46,944	74.1			60,436	95.4			60,766	95.9		
Controls												
Total	264,001		1.48	1.44, 1.53	264,001		1.11	1.04, 1.18	264,001		1.12	1.01, 1.24
Exposed index dates	35,396	13.4			10,714	4.1			3,835	1.5		
Exposed reference dates	200,038	12.6			63,535	4.0			22,716	1.4		
Fully concordant, exposed	16,717	6.6			4,417	1.7			2,603	1.0		
Fully concordant, unexposed	211,894	83.6			245,164	96.7			248,445	98.0		
Cases and controls (CTC estimate)			1.12	1.05, 1.19			1.55	1.34, 1.79			1.16	0.94, 1.45
Ischemic Stroke												
Cases												
Total	63,353		3.16	3.01, 3.32	63,353		2.00	1.73, 2.31	63,353		1.72	1.50, 1.98
Exposed index dates	13,403	21.2			2,596	4.1			2,216	3.5		
Exposed reference dates	66,013	17.4			14,579	3.8			12,494	3.3		
Fully concordant, exposed	5,157	7.8			1,974	3.0			840	1.3		
Fully concordant, unexposed	53,384	80.9			62,437	94.6			64,548	97.8		

Table continues

Table 2. Continued

Variable	Statins				Thyroxine				Insulin			
	No. of Persons	%	OR	95% CI	No. of Persons	%	OR	95% CI	No. of Persons	%	OR	95% CI
Controls												
Total	253,400		1.39	1.35, 1.43	253,400		1.01	0.93, 1.09	253,400		1.01	0.92, 1.11
Exposed index dates	33,284	13.1			6,749	2.7			3,939	1.6		
Exposed reference dates	189,810	12.5			40,455	2.7			23,596	1.6		
Fully concordant, exposed	17,772	6.7			6,841	2.6			2,631	1.0		
Fully concordant, unexposed	220,039	83.3			251,382	95.2			259,102	98.1		
Cases and controls (CTC estimate)			2.27	2.15, 2.41			1.99	1.69, 2.34			1.70	1.43, 2.01

Abbrevations: CI, confidence interval; CTC, case-time-control; OR, odds ratio.
[a] Data were obtained from the National Prescription Registry and the National Patient Register.

case-crossover design (1) and the first published papers on the design (11–13) emphasized its utility with strictly transient exposures such as sexual activity, anger, and strenuous exercise. Bias due to persistent user contamination would not occur in these settings. However, as indicated by the results of our utilization analyses, the presence of persistent users may be common with drug exposures and likely varies across medication classes.

The use of a control group reduced this bias substantially in the main analysis of retinal detachment, while the other outcomes, wrist fracture and ischemic stroke, demonstrated significant residual bias even after we used an age-, sex-, and

Table 3. Crossover Estimates for Cases and Controls and Case-Time-Control Estimates for the Association Between 18 Different Medication Exposures and Retinal Detachment, Denmark, 2002–2012[a]

Medication Class	ATC Code	Crossover Estimate				Case-Time-Control Estimate	
		Cases		Controls			
		OR	95% CI	OR	95% CI	OR	95% CI
Ulcer drugs	A02B	1.34	1.19, 1.51	1.17	1.10, 1.25	1.14	0.99, 1.31
Oral antidiabetic agents	A10B	2.50	1.93, 3.25	1.55	1.36, 1.77	1.61	1.20, 2.16
Anticoagulants	B01AA	1.36	1.06, 1.74	1.26	1.08, 1.45	1.08	0.81, 1.45
Antiplatelets	B01AC	1.76	1.56, 2.00	1.35	1.27, 1.45	1.30	1.13, 1.50
Cardiac glycosides	C01A	1.64	1.18, 2.28	1.12	0.95, 1.33	1.46	1.00, 2.12
Diuretics	C03	1.38	1.23, 1.55	1.10	1.04, 1.17	1.25	1.10, 1.42
β-blockers	C07	1.56	1.35, 1.80	1.16	1.08, 1.25	1.34	1.14, 1.58
Calcium channel blockers	C08	1.35	1.19, 1.53	1.23	1.15 1.32	1.10	0.95, 1.27
Renin-angiotensin inhibitors	C09	1.48	1.33, 1.66	1.39	1.31, 1.48	1.06	0.94, 1.21
Antithyroid drugs	H03B	1.34	0.76, 2.38	1.54	1.15, 2.06	0.87	0.46, 1.66
Opiod analgesics	N02A	1.27	1.13, 1.43	1.02	0.96, 1.08	1.25	1.09, 1.43
Antiepileptic agents	N03A	1.23	0.90, 1.70	1.37	1.17, 1.60	0.90	0.63, 1.29
Neuroleptic agents	N05A	1.00	0.69, 1.44	1.00	0.85, 1.17	1.00	0.67, 1.50
Hypnotic agents	N05C	1.09	0.96, 1.24	0.87	0.81, 0.93	1.25	1.08, 1.45
Antidepressants	N06A	1.55	1.32, 1.82	1.09	1.00, 1.19	1.42	1.19, 1.71
SSRIs	N06AB	1.48	1.23, 1.78	1.07	0.97, 1.18	1.39	1.12, 1.71
Inhaled adrenergic agents	R03A	1.26	1.06, 1.49	1.09	1.00, 1.19	1.15	0.95, 1.39
Inhaled corticosteroids	R03B	1.11	0.89, 1.37	1.07	0.95, 1.19	1.04	0.82, 1.32

Abbrevations: ATC, anatomical therapeutic chemical; CI, confidence interval; OR, odds ratio; SSRIs, selective serotonin reuptake inhibitors.
[a] Data were obtained from nationwide Danish data sources.

Table 4. Analysis of First Treatment Episodes for New Users of 20 Different Classes of Medication During 15 Years of Follow-up,[a] Denmark, 1997–2012

Medication Class	ATC Code	No. of New Users	Duration of Follow-up, years[b]				
			1	2	5	10	15
Ulcer drugs	A02B	680,940	37.4	31.6	28.5	27.5	27.3
Insulin	A10A	59,592	56.9	46.7	38.0	34.7	34.3
Oral antidiabetic agents	A10B	173,981	42.2	32.4	24.7	22.5	22.2
Anticoagulants	B01AA	180,239	50.0	39.1	30.6	28.0	27.8
Antiplatelets	B01AC	662,978	47.8	32.7	23.1	21.0	20.8
Cardiac glycosides	C01A	142,041	43.9	35.3	28.9	27.4	27.3
Diuretics	C03	725,784	50.4	39.4	29.1	25.6	25.2
β-blockers	C07	494,691	39.6	24.9	17.8	16.4	16.3
Calcium channel blockers	C08	489,657	20.5	14.0	11.5	11.0	10.9
Renin-angiotensin inhibitors	C09	680,643	29.0	18.9	13.7	12.3	12.2
Statins	C10AA	601,035	34.4	18.3	12.3	11.4	11.4
Thryroxine	H03A	73,982	45.9	31.8	22.4	20.2	19.8
Antithyroid drugs	H03B	44,514	48.2	30.6	20.7	18.8	18.6
NSAIDs	M01A	912,264	26.7	15.0	11.3	10.1	10.0
Opioid analgesics	N02A	866,693	32.0	27.3	25.6	25.1	25.0
Antiepileptic agents	N03A	170,635	40.7	35.0	31.2	30.2	30.1
Neuroleptic agents	N05A	181,481	41.3	35.8	32.7	32.1	32.1
Hypnotic agents	N05C	426,931	33.1	27.2	23.9	22.7	22.5
Antidepressants	N06A	492,448	38.5	28.1	22.7	21.6	21.5
SSRIs	N06AB	385,168	41.3	28.7	22.3	21.0	20.9
Inhaled adrenergic agents	R03A	328,928	31.7	26.7	23.9	23.0	22.8
Inhaled corticosteroids	R03B	216,197	39.4	31.7	26.3	24.6	24.4

Abbrevations: ATC, anatomical therapeutic chemical; NSAIDs, nonsteroidal antiinflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

[a] All Danish subjects born before 1950 and followed from 1997 through 2012.

[b] For any given duration of follow-up, the table shows the percentage of patients who were either still being treated or had died, emigrated, or reached the end of the study period during the first treatment episode.

time-matched control group. The drug utilization substudy showed that, depending on the amount of follow-up, a considerable proportion of new medication users would have their first treatment episodes right-truncated, thus potentially generating bias due to contamination by persistent users.

There might be several explanations for the observed residual bias despite the use of control groups. One possibility is time-dependent confounding—that is, that patients change their behavior immediately before they experience an outcome. Another possibility is differences in persistence between case and control groups—for example, that patients who are at risk for a stroke are more persistent than an age- and sex-matched control group recruited from the general population. Apart from some late prodromal symptoms, the timing of a retinal detachment episode is unpredictable, which renders time-variant confounding less likely to occur for this outcome. In addition, we found that the characteristics of retinal detachment patients were very similar to those of their age- and sex-matched controls. It thus seems plausible that these case and control groups would have the same level of drug persistence, which would favor a null result of the main case-time-control analysis. We did find some indication of residual bias for the retinal detachment cases; 15 out of 18 case-crossover estimates were above the null (Table 3). However, the residual bias found for the retinal detachment outcome was generally small. The cases of fracture and stroke were very dissimilar to their respective controls and may have had a different mix of transient and permanent medication-using subpopulations. It is possible that the residual bias found for the stroke and fracture outcomes—and to some extent the retinal detachments—could have been eliminated by using a different strategy for selecting controls, such as by recruiting controls that were more similar to the cases.

Our study had several important strengths. We had access to data from a large, stable population with full coverage of prescriptions and hospital contacts, independent of income or employment (7). The validity of the prescription data is generally high (7, 14), and with the given government reimbursement, there would be little incentive to redeem prescriptions outside of the system. All prescriptions have been recorded since 1995, which enabled us to perform a long-term

drug persistence study. The positive predictive value of a stroke diagnosis in the Danish Patient Registry is on the order of 80% (15, 16), and approximately 93% for a fracture diagnosis (17). Sixty percent of patients with a diagnosis of retinal detachment in Denmark also have a record of a retinal reattachment procedure (18).

One limitation of our study is that the case-time-control approach adjusts for other problems in addition to persistent user bias—for example, a temporal trend in utilization (5) or a trend by age (19). If these trends were strongly present in our material, the adjustments conferred by using a control group might have been explained by the removal of bias by temporal trend in use or by aging, rather than persistent users. During the study period, the annual growth of the count of statin users was 17% (20), which would correspond to a trend bias of 8% in the case-crossover odds ratio. Neither insulin nor thyroxine showed any important trend. With a crossover time frame as short as 12 months, aging of the subjects is unlikely to have played a substantial role.

Another limitation is that some of the studied drug-outcome pairs might not represent null associations. Statins do protect against ischemic stroke (21). However, the effect is not particularly strong (21), and within a time frame of 12 months as used in our study, the effect is minute (22–24). On the basis of observational data, it has been postulated that statins also protect against fractures (25), but this contention has largely been refuted by data from randomized clinical trials (26–28). We thus believe that genuine modification of risk by the studied medications was not a problem in our study.

Finally, an important limitation of our study is the fact that duration of usage for prescriptions is not recorded in our data source (7) and that we had to model this parameter, at the risk of causing exposure misclassification. Case-crossover studies are particularly vulnerable to misclassification of exposure (29). If the true exposure changes infrequently—as is the case with chronic medication use—exposure misclassification at either the case date or the reference date may very well become the dominant cause of apparently discordant exposure, which can potentially cause a strong bias towards the null (4). It may explain why the magnitude of the persistent user bias was so moderate in our study, even for medications that practically always should be taken permanently. Possibly, a different data source with better information on prescription durations could have demonstrated a stronger bias due to contamination by persistent users.

Our findings have several implications. First, at least some of the literature using the case-crossover design to study medication effects should be reinterpreted. Second, if a self-controlled design is warranted to address a drug-related research question, one may consider either the self-controlled case-series method (30) or the symmetry analysis (31). Neither of these is biased by the presence of persistent users, although each may have other important limitations. Finally, new research is needed on how to deal with the problem of persistent user contamination. We have shown that using population controls is not entirely satisfactory, but other strategies for control selection might work (32). Another solution could be to remove the persistent users from the data. Although this may seem to be a fairly intuitive approach, it is presently not clear how one could do this without the risk of affecting a potential causal signal. Yet another possibility could be to model and adjust the persistent user bias on the basis of drug utilization analyses. Additional research is needed on the extent and magnitude of the persistent user problem and on alternative solutions, whether applied by design or in the analysis.

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