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ORIGINAL REPORT

Case-only designs for studying the association of antidepressants and hip or femur fracture

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ABSTRACT

Purpose The purpose of this study is to evaluate the performance and validity of the case-crossover (CCO) and self-controlled case-series (SCCS) designs when studying the association between hip/femur fracture (HF) and antidepressant (AD) use in general practitioner databases. In addition, comparability with cohort and case–control designs is discussed.

Methods Adult patients with HF and who received an AD prescription during 2001–2009 were identified from UK's The Health Improvement Network (THIN) and the Dutch Mondriaan databases. AD exposure was classified into current, recent and past/non-use (reference). In the CCO, for each patient, a case moment (date of HF) and four prior control moments at −91, −182, −273 and −365 days were defined. In SCCS, incidence of HF was compared between exposure states. Conditional logistic regression was used in the CCO and Poisson regression in the SCCS to compute odds ratios and incidence rate ratios, respectively. In CCO, we adjusted for time-varying co-medication and in SCCS for age.

Results Adjusted estimates for the effect of current AD exposure on HF were higher in the CCO (co-medication-adjusted odds ratio, THIN: 2.24, 95% confidence interval [CI]: 2.04–2.47; Mondriaan: 2.57, 95%CI [1.50, 4.43]) than in the SCCS (age-adjusted incidence rate ratio, THIN: 1.41, 95%CI [1.32, 1.49]; Mondriaan: 2.14, 95%CI [1.51, 3.03]). The latter were comparable with the traditional designs.

Conclusion Case-only designs confirmed the association between AD and HF. The CCO design violated assumptions in this study with regard to exchangeability and length of exposure, and transient effects on outcome. The SCCS seems to be an appropriate design for assessing AD–HF association. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—case-only design; case-crossover; self-controlled case series; methodology; antidepressant; hip/femur fracture; pharmacoepidemiology

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INTRODUCTION

Assessing the association between hip or femur fracture (HF) and antidepressants (AD) is challenging, and dissimilar results have been reported.[1,2] The risk of HF is influenced by both the strength of the bones

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and the chance of falling. Either of these can be directly or indirectly affected by factors such as patient characteristics and the environment. These include age, sex, physical fitness, neurological status, nutrition habits, hormonal status, drug use and morbidity.[3,4]

Estimation of an association between drug use and HF might be confounded by any of these factors, especially when both the indication for the drug and the risk of the outcome are related to these factors.[5,6] As long as these factors are accurately measured and available in our data, we can adjust for them in traditional designs like the cohort and case–control.[7–9]

Case-only designs, where cases serve as their own controls, are not subject to bias caused by measured and unmeasured time-invariant confounders such as genetics, frailty or underlying disease. In addition, potential selection bias when sampling controls, provided that timing of the control moments is correct, is absent. Application of these case-only designs seems therefore attractive, but suitability of these designs to study a specific association within the same person depends on transience of exposure and outcome and thus requires several assumptions related to exposure over time and the time relation with the outcome.[10] While studying the association between AD use and HF in electronic healthcare databases, we aim to do the following: (1) compare the risk estimates of the case-crossover (CCO)[11,12] with the self-controlled case-series (SCCS) design; (2) assess the effects when the assumptions for each of these designs are violated; and (3) compare the results with traditional cohort and (nested) case–control (NCC) designs.[8]

METHODS

Setting and study population

A common protocol and data specification for both the case-only designs (this manuscript) and the traditional methods (described in more detail in this *Pharmacoepidemiology and Drug Safety* issue[8]) were registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.[13]

The association between AD use and HF was assessed using electronic health records from the UK collected by The Health Improvement Network (THIN). For a subset of the analyses, data from the Mondriaan database were used as a second data source to illustrate feasibility and generalizability on a small database. The Dutch Mondriaan database combines data extracted from the NIVEL Primary Care Research Database and the Almere Health Care Group database. These data sources are described in more detail elsewhere.[9] A blinding procedure was maintained until all results were available at the coordinating centre (at Utrecht University, the Netherlands).

The study period was defined as from 1 January 2001 to 31 December 2009. The study population included all patients who met the following criteria: (i) being ≥18 years old; (ii) having had at least 1 year of enrolment with the general practitioner; (iii) having received at least one AD prescription; (iv) having had a recorded diagnosis of HF during the study period; and (v) having had 12 months free of HF before the observation period started in order to ensure they experienced 'new' events.

Exposure and outcome definition

The exposure of interest was an AD prescription (ATC N06AA [tricyclic AD, TCA] or N06AB [selective serotonin reuptake inhibitors, SSRI]).[13] In THIN, AD prescription duration was estimated based on the amount prescribed and the dosage regimen. Because this information was unavailable in Mondriaan, a fixed duration of 90 days was set for each AD, based on the maximal prescription duration for chronic prescriptions in the Netherlands.

Antidepressant treatment episodes were constructed for each patient, and exposure time was divided into periods of non-use, current, recent and past use.[14] Periods of 'current use' were extended with 30 days after the theoretical end date of the last prescription within a treatment episode and followed by 60 days of 'recent use'. After that time and until renewal, exposure was defined as 'past use' that together with 'non-use' served as a reference category (Figure 1).

Hip/femur fracture cases were defined as patients having a code for hip or femur fracture registered in their electronic health records during the study period as described by Requena *et al.*[15] (see European Network of Centres for Pharmacoepidemiology and Pharmacovigilance registered protocol for the full list of codes[13]). Only the first HF was considered as event for the CCO, while for the SCCS, all HFs were considered; however, a new fracture was only considered as such if at least 12 months had elapsed from the previous HF.

Case-crossover design

The date of first diagnosis of HF after the start of the observation period was considered as the index date. For each HF case, up to four control moments were selected, defined at −91, −182, −273 and −365 days (C1 through C4) prior to the index date. The selection of control moments included a control moment at 1 year prior to the index date to consider potential

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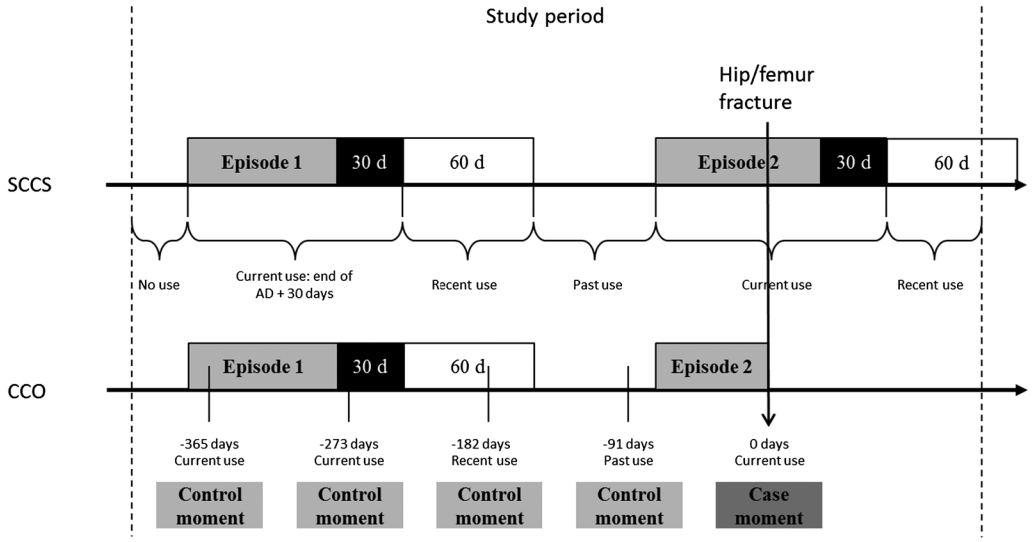

Figure 1. Schematic overview of case-crossover (CCO) and self-controlled case-series (SCCS) design. AD, antidepressant

seasonal variations. Control moments were only included if they met all eligibility criteria. In the CCO, we adjusted for time-varying co-medication use in the 3 months before the index date and each control moment by using the same method and algorithm as we did in the cohort and NCC design.[8] The list of co-medications can be found online in the Supporting Information and in the protocol.[13]

Case-crossover sensitivity analysis

A prerequisite for CCO is discordancy of the exposure of interest; concordant cases, having the same exposure state during all moments, will contribute to the estimate of the treatment effect only through the confounding adjustment for co-medications. When used for the treatment of depression, ADs should be prescribed for at least 6 months following symptom resolution according to both British and Dutch guidelines.[16,17] To study the effect of such expected low discordancy, we included a 1:1 matched analysis of HF-C1, HF-C2, HF-C3 and HF-C4 in addition to the 1:4 matching of case and control moments.

Self-controlled case-series design

The observation time for each individual was divided among the AD exposure categories. In the SCCS, age was the only confounder considered and was included in the adjusted model as categorical (1-year age band for patients from 60 to 95 years old, 5-year age band for other ages) in THIN and as a continuous covariate in Mondriaan (because the age categories were too sparsely populated with events).

Self-controlled case-series sensitivity analyses

For the SCCS,[18] the main assumption is that occurrence of the event must not alter the probability of subsequent exposure. This was assessed by defining a 'pre-exposure' period prior to the first prescription of an AD during the study period. Different lengths of the 'pre-exposed' were chosen (15, 30, 45 and 60 days) and removed from past/non-use comparator period to adequately cover the period in which the event might have altered the probability of being prescribed an AD.

Another key assumption is that the event should not censor the observation period[10]; we therefore tested the impact of right censoring at the first event. To simulate what happens in real life in a database, where we cannot know how many patients are censored at the first event, we varied the proportions of subjects to be randomly right censored (0%, 2%, 5%, 10%, 20%, 50% and 100%), and for each proportion, the incidence rate ratio (IRR) was averaged over 1000 replications.

The last planned sensitivity analysis was to facilitate the comparison with the traditional designs studying the impact of 6 months free AD prior to their start of the observation period to create a 'new user' cohort.

Subsequently, as a post hoc analysis to understand the discrepancy between the CCO and SCCS, we investigated the effect of including only patients that had discordant exposure in the CCO design. For this purpose, the SCCS analysis was stratified by subgroups of patients being discordant or concordant in the CCO.

Data analysis

The association between AD use and HF was assessed comparing 'current' and 'recent' use with 'past/non-use'.

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In addition, results were stratified by type of AD into TCA, SSRI and both. For the CCO, conditional logistic regression was used to estimate the OR with 95% confidence intervals (CI). For the SCCS, Poisson regression, with patient identifier and offset for duration included as covariates, was used to estimate the IRR and corresponding 95%CI.

SAS® 9.3 (SAS Institute, Cary, NC, USA) was used for all statistical analyses in THIN and the CCO in Mondriaan, while the SCCS in Mondriaan was analysed using R statistical software package version 2.14.2.

RESULTS

Patient characteristics

During the study period, 9682 patients in THIN were eligible, and characteristics of this population are shown in Table 1. Patients were on average 77.6 years old at the time of HF, and almost 79% was female.

In the CCO, only patients who were discordant for exposure directly contributed to the estimate of the treatment effect, consisting of 2905 patients in THIN. The patient characteristics of this discordant subset had on average 14% more co-morbidities and 15% more co-medications registered per patient than the population from which they were extracted and were treated for a shorter time with ADs in both databases (Table 1 in the Supporting Information for more details). In Mondriaan, 277 patients were eligible, of which 92 were discordant for exposure.

Case-crossover and self-controlled case-series main analyses

In CCO, the OR for current use in THIN, matched by design for age, sex and all time-fixed confounders, was 2.45 (95%CI [2.23, 2.69]), and adjustment for co-medication resulted in a somewhat lower OR of 2.24 (95%CI [2.04, 2.47]) as shown in Table 2. For current use, in the age-adjusted analysis, the SCCS showed an IRR of 1.41 (95%CI [1.32, 1.49]). In Mondriaan CCO, the OR for current use was 2.93 (95%CI [1.75, 4.90]) and adjusted for co-medication 2.57 (95%CI [1.50, 4.43]). Also in SCCS, the age-adjusted IRR was lower: 2.14 (95%CI [1.51, 3.03]). Recent use is also associated with increased risk of HF in both case-only designs.

Figure 2 shows the relative risks of CCO and SCCS for both databases compared with other designs.

Type of antidepressant

In the CCO design, we found higher ORs for HF associated with current SSRI exposure compared with TCA (in THIN SSRI: OR 2.89; 95%CI [2.56, 3.26], TCA: OR 1.75; 95%CI [1.53, 2.02], Table 2 and Figure 3). However, the SCCS resulted in an almost equal risk for both AD types in the age-adjusted

Table 1. Patient characteristics of cases in the CCO and SCCS

	THIN			Mondriaan		
Demographics/characteristics	All cases, *N* (%)	Discordant cases, *N* (%)	Concordant cases, *N* (%)	All cases, *N* (%)	Discordant cases, *N* (%)	Concordant cases, *N* (%)
Patients*	9682	2905	6777	277	92	168
Age						
Mean	77.6	77.6	77.7	79.2	81.4	78.1
Standard deviation	13.4	13.3	13.5	14.6	11.7	15.8
Sex						
Female	7608 (78.6)	2247 (77.3)	5361 (79.1)	217 (78.3)	70 (76.1)	131 (78.0)
Male	2074 (21.4)	658 (22.7)	1416 (20.9)	60 (21.7)	22 (23.9)	37 (22.0)
Co-morbidity						
Average number per patient	1.20	1.38	1.12	0.98	1.22	0.95
Co-medication						
Average number per patient	1.72	2.02	1.59	2.40	2.72	2.48
AD prescriptions						
Average number per patient	29.34	22.89	32.11	31.23	20.90	38.01
Observation period						
Mean (years)	6.6	6.3	6.7	5.5	5.0	5.9
Median (years)	7.4	6.8	7.7	5.9	4.9	6.2
Treatment episode						
Mean (days)	323	202	401	458	332	582
Median (days)	87	70	112	221	191	283

THIN, The Health Improvement Network; AD, antidepressant; CCO, case-crossover; SCCS, self-controlled case series.
*Number of patients eligible and included in the SCCS. For CCO, patients without enough follow-up time before the hip/femur fracture for at least one control moment were excluded (350 patients in THIN and 17 in Mondriaan).

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Table 2. lMain analysis case-only estimates of the association for AD–HF

CCO	THIN				Mondriaan			
	Cases	Control moments	Crude*	Co-medication adjusted	Cases	Control moments	Crude*	Co-medication adjusted
	N	*N*	*OR (95% CI)*	*OR (95% CI)*	*N*	*N*	*OR (95% CI)*	*OR (95% CI)*
Past non-use (baseline)	4,868	20,660	-	-	127	567	-	-
Current	4,040	13,506	2.45 (2.23 - 2.69)	2.24 (2.04 - 2.47)	121	368	2.93 (1.75 - 4.90)	2.57 (1.50 - 4.43)
Recent	424	1,250	2.08 (1.83 - 2.36)	1.95 (1.72 - 2.22)	12	28	3.24 (1.49 - 7.04)	3.22 (1.40 - 7.39)
SSRI Current	2,155	6,689	3.13 (2.77 - 3.52)	2.89 (2.56 - 3.26)	91	255	4.40 (2.37 - 8.17)	3.80 (1.99 - 7.27)
TCA Current	1,469	5,120	1.93 (1.68 - 2.21)	1.75 (1.53 - 2.02)	28	101	1.42 (0.62 - 3.22)	1.16 (0.47 - 2.87)
SSRI and TCA	416	1,697	0.97 (0.70 - 1.33)	0.85 (0.62 - 1.17)	2	12	-	-
SCCS	**THIN**				**Mondriaan**			
	Cases		**Crude***	**Age adjusted**	**Cases**		**Crude***	**Age adjusted**
	N	*PY*	*IRR (95% CI)*	*IRR (95% CI)*	*N*	*PY*	*IRR (95% CI)*	*IRR (95% CI)*
Past/non-use (baseline)	5,278	39,709	-	-	132	895		
Current	4,379	21,934	1.72 (1.62 - 1.82)	1.41 (1.32 - 1.49)	134	590	2.00 (1.43 - 2.79)	2.14 (1.51 - 3.03)
Recent	436	2,150	1.52 (1.38 - 1.69)	1.36 (1.22 - 1.50)	11	51	1.50 (0.80 - 2.82)	1.58 (0.84 - 2.96)
SSRI Current	2,319	10,380	1.91 (1.78 - 2.06)	1.46 (1.35 - 1.57)	94	388	2.57 (1.68 - 3.92)	2.76 (1.75 - 4.35)
TCA Current	1,505	8,204	1.50 (1.37 - 1.64)	1.36 (1.24 - 1.50)	35	191	1.26 (0.76 - 2.09)	1.35 (0.81 - 2.26)
SSRI and TCA	555	3,350	1.53 (1.78 - 1.32)	1.25 (1.07 - 1.47)	5	11	-	-

The total numbers of cases in CCO and SCCS differ because in the CCO only the first fracture is considered and some subjects do not have control moments. OR: odds ratio, CI: confidence interval, PY: person years, IRR: incidence rate ratio, THIN, The Health Improvement Network; CCO, case-crossover; SCCS, self-controlled case series.

**Crude risk estimates in CCO are matched by design for sex and age, in SCCS for sex.*

analysis (in THIN SSRI: IRR 1.46; 95%CI [1.35, 1.57], TCA: IRR 1.36; 95%CI [1.24, 1.50]).

To preserve readability of this manuscript and because conclusions are similar, sensitivity analyses results are presented only for THIN.

Sensitivity analysis of case-crossover

The 1:1 comparison of HF to different individual control moments (HF-C1 → HF-C4) resulted in ORs that were similar and did not differ from the 1:4 analysis including all control moments in THIN (Figure 4).

In the HF-C1 comparison, exposure states were largely unchanged between the case and control moments, and discordancy was 15%, whereas in the HF-C4 comparison, discordancy increased to 24% (Table 2 in the Supporting Information).

Sensitivity analysis of self-controlled case series

Figure 5 (and Table 3 of the Supporting Information) show the results of possible event-exposure dependence. Risk of HF during the pre-exposure period was statistically significant for the pre-exposure period of at least 30 days and increased with the length of the pre-exposure period. For instance, for the 30-day pre-exposure period, IRR was 1.16 and increased to 1.45 for the 60-day pre-exposure period. However, the IRR for current users did not seem to be altered by the removal of the pre-exposure period from the past/non-use period (varying between 1.40 and 1.43 in all four scenarios).

When up to 20% of the patients were randomly censored at first event, the IRR was still in line with the main analysis and started to diverge when 50% or more of the patients were censored (Figure 5, Table 4 in the Supporting Information). When all patients were censored at the first event, IRR was considerably higher compared with the main analysis.

Finally, excluding subjects with an AD prescription in the 6 months before study entry did not significantly change the estimates (results not shown).

Post hoc analysis of self-controlled case series

Including in the SCCS only patients that were discordant in the CCO resulted in higher age-adjusted estimates of 4.27 (95%CI [3.87, 4.70]) in THIN. In the analysis per AD drug class, the higher risk for SSRI over TCA already observed in the other

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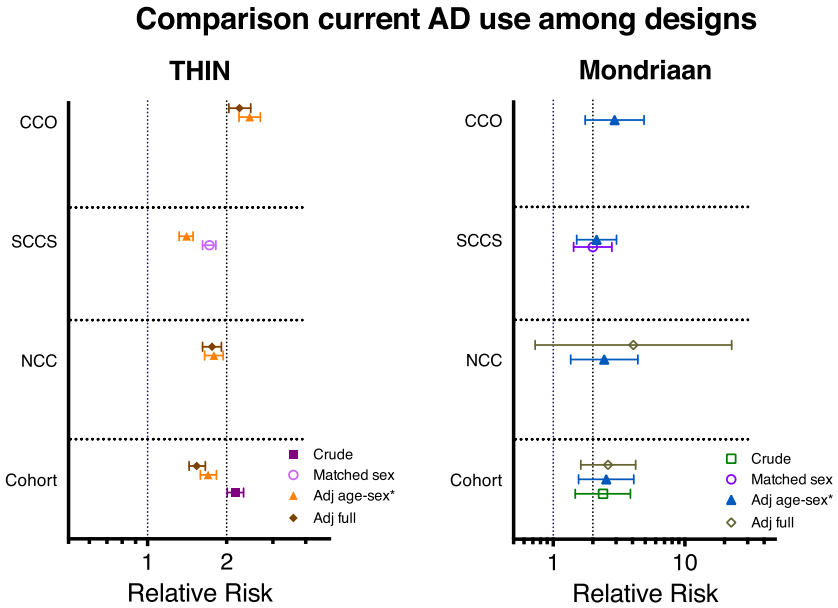

Figure 2. Risk estimates from case-crossover (CCO) and self-controlled case-series (SCCS) versus traditional designs. Symbols indicate relative risk estimates, odds ratios for nested case control (NCC) and CCO, and incidence rate ratios for cohort and SCCS, all with 95% confidence interval.
*Comparable models share the same symbols; thus, adjustment for age and sex in cohort is compared with age adjusted in SCCS as this is already matched on sex by design and with the crude CCO as this is already adjusted on sex and age by design. THIN, The Health Improvement Network

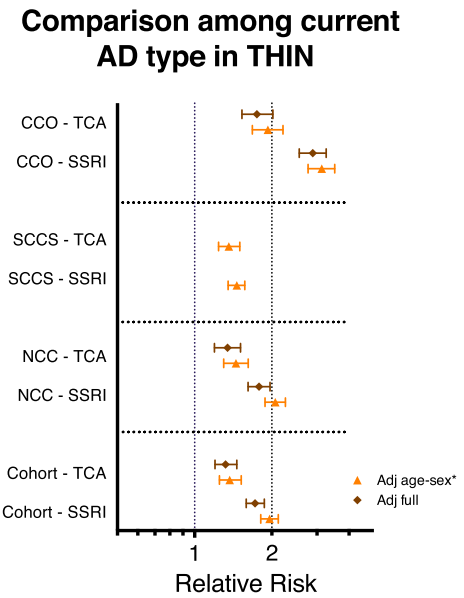

Figure 3. Risk estimates by type of antidepressant (AD) use. Symbols indicate relative risk estimates, odds ratios for case-crossover (CCO) and incidence rate ratios for self-controlled case series (SCCS), all with 95% confidence interval.
*Comparable models share the same symbols; thus, adjustment for age and sex in cohort is compared with age adjusted in SCCS as this is already matched on sex by design. NCC, nested case control; THIN, The Health Improvement Network

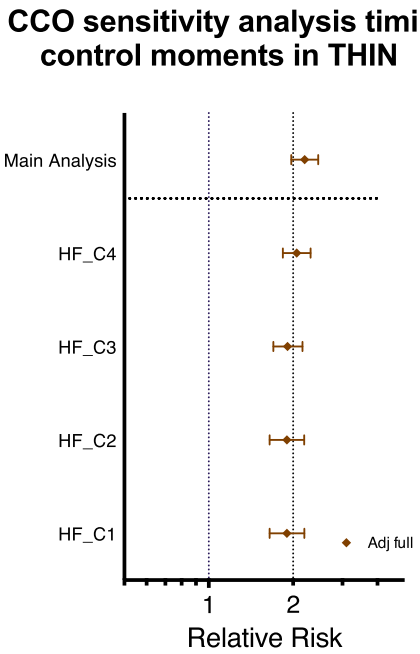

Figure 4. Sensitivity analysis in case-crossover (CCO): timing control moments. Symbols indicate relative risk estimates, odds ratios with 95% confidence interval. THIN, The Health Improvement Network

designs seems to exist for discordant patients only (age-adjusted SSRI: IRR 4.87; 95%CI [4.33, 5.48] versus TCA: IRR 3.88; 95%CI [3.37, 4.47]). In the subgroup of concordant patients, the opposite trends were observed (Table 3). However, it is important to realize that all the SCCS results stratified for concordance in CCO are not valid and are presented for illustration only.

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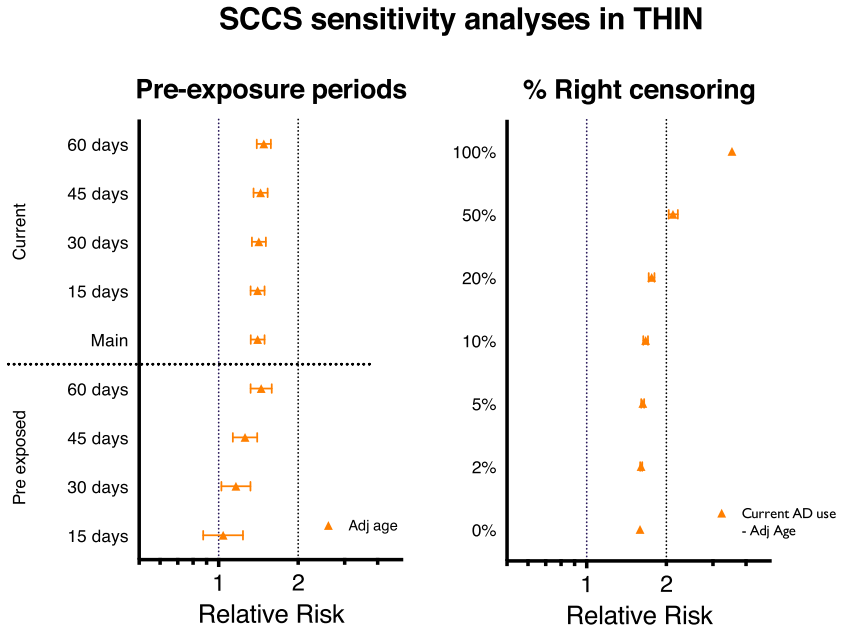

Figure 5. Sensitivity analysis in self-controlled case series (SCCS): pre-exposure periods and right censoring. The left panel shows the relative risk of analysis of a pre-exposure period of different lengths and the influence of this pre-exposure period on the relative risk of current use in that analysis. The right panel shows relative risks for current use when different proportions of patients are randomly right censored at the event. THIN, The Health Improvement Network; AD, antidepressant

Table 3. Sensitivity analyses SCCS in THIN: discordant and concordant patients

	THIN					
	Cases		Age adjusted	Cases		Age adjusted
	N	PY	IRR [95%CI]	*N*	PY	IRR [95%CI]
	Discordant in CCO			Concordant in CCO		
Past/non-use (baseline)	1054	11 844	—	4224	27 865	—
Current	1554	5609	4.27 [3.87, 4.70]	2825	16 325	0.68 [0.63, 0.74]
Recent	422	933	5.62 [4.99, 6.34]	14	1217	0.05 [0.03, 0.09]
SSRI current	932	2899	4.87 [4.33, 5.48]	1387	7481	0.64 [0.58, 0.71]
TCA current	517	2062	3.88 [3.37, 4.47]	988	6142	0.70 [0.62, 0.80]
SSRI and TCA current	105	648	2.13 [1.60, 2.84]	450	2702	0.88 [0.72, 1.07]

IRR, incidence rate ratio; THIN, The Health Improvement Network; CCO, case-crossover.

DISCUSSION

Overall observations

This study shows that application of case-only designs results in risk estimates that consistently show an association between both current and recent AD use and HF. An elevated risk of HF associated with AD use is in accordance with results from other designs that were studied within our PROTECT consortium using the same databases.[8]

Comparison of case-crossover and self-controlled case series. The CCO risk estimates for current use, matched by design by sex and age, were higher in both THIN (74%) and Mondriaan (37%) when compared with the age-adjusted results from the SCCS study.

The higher ORs in the CCO could be explained by induction of selection bias because in conditional analysis, of all eligible patients in the study, only those patients with discordant exposure for AD directly contributed to the estimate of the association. In fact, the concordant patients contributed only through the effect of the co-medications, and this seems quite modest looking at the difference between the crude results and the fully adjusted one in the CCO (Table 2). This explanation for the higher ORs in the CCO analysis is

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supported by the results of the SCCS sensitivity analysis where patients with discordant exposure in the CCO showed IRRs much higher than those in patients with concordant exposure. In the latter group, exposure had a protective effect (Table 3).

In the literature, higher risks of HF are reported for SSRI over TCA use when cohort and case–control designs are used.[19–21] In this study, the SCCS design resulted in similar IRR for SSRI and TCA in the THIN database. This is in line with the study by Hubbard *et al*. who compared a case–control design with an SCCS design on Clinical Practice Research Datalink data (UK) and showed that the higher risk of HF in SSRI use over TCA use disappeared in the SCCS design.[22] Part of their explanation was that preferential prescribing of SSRI to frail elderly people to avoid adverse drug reactions caused by TCA would induce confounding. By design, these biases are eliminated in the case-only designs. However, the CCO in THIN did not show such cancellation of the difference between SSRI and TCA in our study. The explanation for this is that the selection of only discordant patients in the CCO biases the estimates as we observed a higher risk of SSRI over TCA when selecting only discordant patients in the SCCS. In fact, estimates in concordant patients showed similar risk across SSRI and TCA.

Validity of case-only designs: analysis of violations of assumptions. The concept of case-only studies to control by design for time-invariant measured and unmeasured confounding sounds attractive. In this discussion, we will consider the added value of the CCO and SCCS designs in studying AD–HF by assessing validity, applicability and resulting estimates.

Validity of case-crossover design

The CCO design is susceptible to bias caused by trends in exposure over time.[11] From our descriptive study on AD use in the same databases and study period, we know that prevalence of AD use increased by less than 4% (THIN) and 0.9% (Mondriaan) per year during the study period.[6] For THIN, this could have resulted in an overestimation of the OR by 2% (4%/2) at most as the probability of having a prescription during the four control moments, on average half a year before, was slightly lower.

A prerequisite of the CCO design is that effects of exposure are transient over time and that reference periods or control moments are sufficiently remote in time to prevent the long-lasting effects of exposure to be present after end of exposure ('carry-over effect'). The association between AD and HF is related to the increased risk of falling in AD users that is reported to peak about 2 days after dose changes[23] and on physiological cumulative and long-lasting effects of AD use on bone strength via a decrease in bone mineral density.[24] The latter might be the reason that in our studies, 'recent use' was also associated with increased risk for HF. These results, therefore, seem to violate the prerequisite on transient effect of exposure.

Exposure needs to be transient to allow discordancy between the case and control moments for each patient to contribute to the analysis.[25] In addition, to prevent non-exchangeability due to selection bias in CCO designs, the chance of each exposure state should be independent during the entire observation period.[26,27] These assumptions are most likely violated in our study because the median treatment duration in our study was 115 days in THIN and 221 in Mondriaan, and as a result, discordancy was low. In the sensitivity analysis where the timing of selection of control moments was varied, we observed that discordancy of exposure dropped in both databases when case and control moments were spaced only 3 months in time.

Finally, not fulfilling the prerequisite of transient exposure by both prescription patterns and methodological choices resulted in the selection of discordant patients that seem to be at higher risk compared with 'stable' long-term users of AD as we observed in the post hoc sensitivity analysis when patients being discordant in the CCO were studied in the SCCS design. These patients also showed higher co-morbidity and used more co-medication than concordant patients.

Therefore, the selection bias we described as a possible explanation of the higher ORs in the CCO is likely the result of the violation of the assumption of transient exposure; if the latter was not (or at least less) violated, the proportion of cases with discordant exposure would be greater, and the selection bias and its effect on the estimate less problematic.

Validity of self-controlled case-series design

Self-controlled case series can be considered as cohort logic applied to a case-only design; therefore, it can be used with non-acute effects of exposure.[10] Because this design accounted for exposure before and after the HF, it is less susceptible to changes in exposure trends over time, and it does not require that the exposure is intermittent, therefore limiting some of the assumptions violation discussed in the CCO.[28]

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However, SCCS assumes that the event of HF in itself does not alter the probability of using AD nor affects censoring of the observation period. We assessed the former by including a pre-exposure period in the model; this removal of time from past/non-use to the pre-exposure period had little impact on the main exposure estimate for current use. Moreover, results show that there seems to be a tendency for people who have experienced an HF to be prescribed an AD within a relatively short time period and, what maybe surprising, that the effect estimate for the pre-exposure period becomes stronger as this period expands.

When subjects are censored at their first HF, the assumption underlying the SCCS design that events can be recurrent is violated. Weldeselassie *et al.*[29] and Farrington *et al.*[30] stated that censoring at the event produces a biased estimate that is unpredictable in direction. In our study, the bias was upward because the observation time removed from the analysis was mainly time during which subjects were exposed. Moreover, when censoring at the event, patients with no exposure before the event did not contribute to the result other than for the age adjustment as they had no contrast in exposure. Results indicated that the bias due to censoring at the event was dependent on the magnitude of censoring; if less than 20% of patients left or died after the event, the SCCS design still produced robust results, although the number of percentage of censoring may vary between studies.

Comparison of results with cohort and nested case–control designs. Case-only designs differ from more traditional designs by considering different operational hypotheses that are tested within each design, whereas cohort and case–control studies answer the question of whether users have a higher risk compared with non-users independent of duration of use; case-only studies compare changes in exposure within the cases. In the words of Maclure, the difference can be expressed in answering different questions: 'Why me?' versus 'Why now?'.[31]

In spite of these methodological differences, the SCCS estimates were, except for the difference between TCA and SSRI, very similar to the cohort and NCC results in both databases.[13]

The higher estimates observed in CCO can be understood by considering that chronic users do not directly contribute to the analysis as they are concordant. The NCC shares the exclusion of concordant patients from the analysis with the CCO; however, for the latter, concordance was based on exposure of the same patient; for the former, concordance was based on concordant pairs (pairs in which the case and control are either both exposed or both not exposed). In our analysis, CCO concordance could be considered as a proxy for 'stable patients having no need to start or stop their AD medication'; these patients were potentially different as we showed in the post hoc sensitivity analyses; therefore, excluding them created a selection bias.

For the NCC, concordance does not have a specific meaning; the likelihood of a pair being concordant is unrelated to the clinical exposure pattern of the case and therefore less likely to be associated with any important confounder. Consequently, concordant patients should not be different, and excluding them did not bias the NCC results.

CONCLUSIONS

In summary, in accordance with results from the cohort and NCC studies, our case-only studies confirmed a positive association between AD and HF when, by design, all time-invariant confounding was adjusted for.

However, the CCO design is not suited to study this association. The main reason seems to be that in both general practitioner databases, typical AD exposures were too long. This resulted in considerable lack of discordancy, which both (i) reduced power by exclusion of 65–70% of the eligible cases for analysis and (ii) introduced selection bias by selecting patients that needed to change their medication for some reason. Moreover, objective decisions should be made about the timing of control moments, and these should fit typical exposure of the drug under study and the physiological effects of exposure on outcome underlying any association studied.

The SCCS design seems more robust to assumptions about exposure and better suited to assess the association between AD and HF. Moreover, similar IRR for SSRI and TCA in THIN might show how the SCCS is likely to deal better with the problem of confounding by frailty present in the traditional designs.

CONFLICTS OF INTEREST

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KEY POINTS

- Case-only designs support the association between antidepressant use and hip fracture in electronic healthcare databases in accordance with results from traditional designs (cohort and nested case–control).
- In this study, assumptions of the case-crossover design are violated with regard to exchangeability and length of exposure and transient effects on outcome.
- The self-controlled case series seems to be an appropriate design for assessing the association between antidepressant use and hip fracture. Moreover, it shows a similar risk estimate for selective serotonin reuptake inhibitors and tricyclic antidepressants in contrast to case-crossover, nested case–control and cohort.

ETHICS STATEMENT

The THIN scheme for obtaining and providing anonymous patient data to researchers was approved by the National Health Service South-East Multicentre Research Ethics Committee (MREC) in 2002. Approval for this study was obtained from the Scientific Review Committee. For Mondriaan, approval was obtained from the institutional review boards of each of the GP databases (Almere Health Care group, Netherlands Institute for Health Services Research and Julius General Practitioners Network). All data are anonymized, and no explicit informed consent is needed according to Dutch law and regulations.

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The views expressed are those of the authors only and not of their respective institution or company.

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