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

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Key-points (max5):

- 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 SSRI and TCA in contrast to case-crossover, nested case-control and cohort.

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Conflicts of interest

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Abstract (max 250) 246

Purpose: 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 to 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 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 (OR) and incidence rate ratios (IRR), 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 OR, THIN: 2.24, 95%CI: 2.04 – 2.47; Mondriaan: 2.57, 95%CI: 1.50 - 4.43) than in the SCCS (age-adjusted IRR, THIN: 1.41, 95%CI:1.32– 1.49; Mondriaan: 2.14, 95%CI:1.51 – 3.03). The latter were comparable to 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.

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 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 health care databases, we aim 1) to compare the risk estimates of the case-crossover (CCO)[11, 12] to the self-controlled case-series (SCCS) design, 2) assess the effects when the assumptions for each of these designs are violated, and 3) to compare the results with traditional cohort and (nested) case-control (NCC) designs. [13]

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 PDS

issue [13]) were registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). [14]
The association between AD use and HF was assessed using electronic health records from the United Kingdom collected by The Health Improvement Network (THIN). For a subset of the analyses data from the Mondriaan database was 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 details 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 1st January 2001 to 31st December 2009. The study population included all patients who met the following criteria: i) ≥ 18 years old; ii) having had at least one year of enrolment with the GP; iii) received at least one AD prescription; iv) had a recorded diagnosis of HF during the study period and v) had to have 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 [TCA] or N06AB [SSRI]).[14] 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.
AD treatment episodes were constructed for each patient and exposure time was divided into periods of non use, current, recent and past use. [15] 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 reference category (see Figure 1).

HF 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.[16] (see ENCEPP registered protocol for the full list of codes[14]). Only the first HF was considered as event for the CCO while for the SCCS all HF fractures were considered; however a new fracture was only considered as such if at least 12 months had elapsed from the previous HF.

CCO design

The date of *first* diagnosis of HF after 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 index date. The selection of control moments included a control moment at one year prior to index date to consider potential 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 three 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 Appendix 1 and in the protocol.[14]

CCO 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 resolvement according to both British and Dutch guidelines[17, 18]. 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 to 4 matching of case and control moments.

SCCS 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 (one year age band for patients from 60 to 95 years old, five years age band for other ages) in THIN and as a

continuous covariate in Mondriaan (because the age categories were too sparsely populated with events).

SCCS sensitivity analyses

For the SCCS [19] 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 antidepressant 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, 100%) and for each proportion the 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'. 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 incidence rate ratio (IRR) and corresponding 95% CI. SAS® 9.3 (SAS Institute, Cary, North Carolina, 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 9,682 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 2,905 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 shorter time with ADs in both databases (table 1, Appendix 1). In Mondriaan 277 patients were eligible of which 92 were discordant for exposure.

CCO & SCCS 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 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 comedication 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 to other designs.

Type of AD

In the CCO design we found higher ORs for HF associated with current SSRI exposure compared to 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 & Figure 3). However, the SCCS resulted in an almost equal risk for both AD types in the age-adjusted 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 since conclusions are similar, sensitivity analyses results are presented only for THIN.

Sensitivity analysis CCO

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 appendix).

Sensitivity analysis SCCS

Figure 5 and table 3 of the appendix show the results of possible event-exposure dependency. Risk of HF during the pre-exposure period was statistically significant for pre-exposure period of at least 30 days and increased with the length of the pre-exposure period. For instance, for the 30 days pre-exposure period IRR was 1.16 and increased to 1.45 for the 60 days 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, starting diverging when 50% or more of the patients were censored (Figure 5, appendix Table 4). When all patients were censored at the first event, IRR was considerably higher compared to 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 SCCS

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 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 realise that all the SCCS results stratified for concordancy in CCO are not valid and are presented for illustration only.

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.[13]

1. Comparison of CCO and SCCS

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 to 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 supported by the results of the SCCS sensitivity analysis where patients with discordant exposure

in the CCO showed IRRs much higher than 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. [20-22] 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 to a SCCS design on CPRD data (UK) and showed that the higher risk of HF in SSRI use over TCA use disappeared in the SCCS design.[23] 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.

2. 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 design in studying AD-HF by assessing validity, applicability, and resulting estimates.

Validity of CCO 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 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 the most as the probability of having a prescription during the four control moments, on average a half 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 two days after dose changes[24] and on physiological cumulative and long-lasting effects of AD use on bone strength via a decrease in bone mineral density.[25] The latter might be the reason why 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.[26] 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.[27, 28] These assumptions are most likely violated in our study since 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 pre-requisite 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 to '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 selction bias we described as 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 SCCS design

SCCS can be considered as cohort logic applied to a case-only design, therefore, it can be used with non-acute effects of exposure.[10] Since 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.[29] 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 seem to be a tendency for people who have experienced a HF to be prescribed an AD within a relatively short time period and, what is maybe surprising, that the effect estimate for the pre-exposure period gets 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. [30] and Farrington et al. [31] 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. Morevoer, 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, though the number of percentage of censoring may vary between studies.

3. Comparison of results to cohort and NCC designs

Case only designs differ from more traditional designs by considering different operational hypothesis that are tested within each design. Whereas cohort and case control studies answer the questions wheter users have a higher risk

compared to 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?'. [32]

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 GP 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.

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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**	*9,682*	*2,905*	*6,777*	*277*	*92*	*168*
Age						
Mean	77.6	77.6	77.7	79.2	81.4	78.1
Std. Dev.	13.4	13.3	13.5	14.6	11.7	15.8
Sex						
Female	7,608 (78.6)	2,247 (77.3)	5,361 (79.1)	217 (78.3)	70 (76.1)	131 (78.0)
Male	2,074 (21.4)	658 (22.7)	1,416 (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

** Number of patients eligible and included in the SCCS. For CCO patients without enough follow-up time before the HF for at least one control moment were excluded (350 patients in THIN and 17 in Mondriaan).*

Table 2. Main analysis Case-Only estimates of the association for AD-HF

CCO	THIN				Mondriaan			
	Cases	Control moments	Crude*	Comedication adjusted	Cases	Control moments	Crude*	Comedication 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	-	-

**Crude risk estimates in CCO are matched by design for sex and age, in SCCS for sex.*
OR: odds ratio, CI: confidence interval, PY: person years, IRR: incidence rate ratio.
The sum of cases in CCO and SCCS does not equal because in the CCO only the first fracture is considered and some subjects do not have control moments.

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)	1,054	11,844	-	4,224	27,865	-
Current	1,554	5,609	4.27 (3.87 - 4.70)	2,825	16,325	0.68 (0.63 - 0.74)
Recent	422	933	5.62 (4.99 - 6.34)	14	1,217	0.05 (0.03 - 0.09)
SSRI Current	932	2,899	4.87 (4.33 - 5.48)	1,387	7,481	0.64 (0.58 - 0.71)
TCA Current	517	2,062	3.88 (3.37 - 4.47)	988	6,142	0.70 (0.62 - 0.80)
SSRI and TCA Current	105	648	2.13 (1.60 - 2.84)	450	2,702	0.88 (0.72 - 1.07)

Figure captions

Figure 1. Schematic overview of CCO and SCCS design

Figure 2. Risk estimates from CCO and SCCS versus traditional designs

Symbols indicate relative risk estimates, ORs for NCC and CCO, and IRRs for cohort and SCCS, all with 95% CI.

* Comparable models share the same symbols, thus adjustment for age and sex in cohort is compared to age adjusted in SCCS as this is already matched on sex by design and to the crude CCO as this is already adjusted on sex and age by design.

Figure 3. Risk estimates by type of AD use

Symbols indicate relative risk estimates, ORs for CCO, and IRRs for SCCS, all with 95% CI.

* Comparable models share the same symbols, thus adjustment for age and sex in cohort is compared to age adjusted in SCCS as this is already matched on sex by design.

Figure 4. Sensitivity analysis in CCO: timing control moments

Symbols indicate relative risk estimates, ORs with 95% CI.

Figure 5. Sensitivity analysis in 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.

* Adjusted model in SCCS is matched on sex by design and adjusted by age.