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ORIGINAL ARTICLE

Fractures in users of antidepressants and anxiolytics and sedatives: effects of age and dose

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Abstract
Summary Antidepressants have been associated with fractures. In a case–control study, increasing age was associated with more fractures in users of selective serotonin reuptake inhibitors and tricyclic antidepressants, whereas for anxiolytics and sedatives, more fractures were seen among the younger users. Depression per se did not seem associated with fractures.
Introduction This study aims to study the effects of age and dose of selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) and anxiolytics/sedatives on fracture risk.
Methods The study was designed as a case–control study. From the Danish National Health Service, we identified 124,655 fracture cases and 373,962 age- and gender-matched controls. Crude odds ratios were estimated, and propensity score adjustment was used to minimise confounding by indication.
Results A higher risk of fractures was associated with an increasing dose of anxiolytics and sedatives; the highest excess risk was present in the age stratum below 40 years of age ($p<0.01$), and thereafter, the excess risk of fractures declined with age. For SSRI, a growing excess risk of fractures was seen with both increasing dose and age. Regarding TCA, no particular trend with age was present. However, an increasing risk of fractures was associated with increasing TCA dose in the age group above 60 years. Finally, for other antidepressants, no particular trend with age or dose was observed. In our data, a hospital diagnosis of depression or manic depression was associated with fewer fractures.
Conclusion Caution should be shown upon prescription of SSRI to older subjects. A hospital diagnosis of depression or manic depression and thus potentially a more severe disease was not a risk factor for fractures.

Keywords Antidepressant · Fracture · Selective serotonin reuptake inhibitors · Tricyclic antidepressants

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Introduction

A recent meta-analysis has pointed at an increased risk of fractures with use of selective serotonin reuptake inhibitors (SSRI) for depression, independent of bone mineral density (BMD) [1]. The increase in risk of fractures raises is seen after starting SSRI therapy [2]; such an increase was, in

particular, demonstrated within the first 2 weeks after the first prescription of SSRI, suggesting an increased risk of falls as the lead cause for this [3]. Similar early effects on fracture have been observed almost immediately after the initiation of tricyclic antidepressants (TCA) [3]. However, these studies have been heterogeneous in their definition of depression as well as in the definition of exposure (drug use) and duration of follow-up [4].

The interaction between a disease being treated (in this case depression) and the drugs used (here antidepressants) is complex. Depression per se may lead to bone loss due to immobilisation and low physical activity stemming from lack of initiative. Low vitamin D levels [5] related to low outdoors activity and, perhaps, dietary issues may also play a role. Conversely, an increase in activity might be induced by treating depressed patients, who may then be more likely to fall due to low muscle strength secondary to previous immobilisation resulting in increased fractures. In addition, bone density may be low, following prolonged immobilisation. Finally, it might also be difficult to disentangle the effect of confounding by indication in observational studies, as the more depressed subjects may be more likely to receive higher doses of antidepressants for longer periods of time.

Previous studies have reported a potential interaction between antidepressant and anxiolytic drugs use and gender on bone metabolism and fractures. The studies on the effects of depression per se on fracture risk and bone density are few, and the methods used for defining depression have varied as well as the length of follow-up and skeletal sites addressed in the studies reporting on the association of drugs against depression, BMD and fracture risk [4]. Frail elderly subjects may be more susceptible to both an increased risk of falls as the effect of a decreased BMD as well as to an interaction from concomitant effects of use of anxiolytics and sedatives. The aims of the current study, thus, were to assess the effects of age and dose of SSRI and TCA as well as anxiolytics and sedatives on the risk of fractures.

Subjects and methods

In Denmark, the extensive nature of registers, covering contacts to the health sector, offers good possibilities for studies on the occurrence of fractures [6]. Using the unique 10-digit civil registry number that is assigned to all Danish citizens shortly after birth, a complete hospital discharge and prescription history can be established for each individual, and valid linkage between population-based registries can be obtained. The unique civil registry number is used in all registers, i.e. if a person buys a drug on prescription, the drug is registered as bought by this individual, and the same applies for admissions to hospitals and contacts to general practitioners for reimbursement purposes. Due to the extensive nature of the registers, only a few values were missing for socioeconomic status such as civil status, working status and income.

This case–control study was performed within the Danish population that constituted approximately 5.3 million individuals during the study period. The study was subject to control by the National Board of Health and the Danish Data Protection Agency.

Study design

The study was designed as a classical case–control study. Cases were all subjects, both genders and all ages, who sustained a fracture during the year 2000. Controls were matched subjects without a fracture in the same year using the criteria below. Exposure was use of drugs and diseases before the date of fracture or a matched index date in the controls. Information on fractures and diseases prior to the fracture was based on hospital records of in- and outpatients and did not include diagnoses from general practitioners.

Identification of fracture cases

In Denmark, the National Hospital Discharge Register covers all contacts (on in- or outpatient basis) to the hospitals [16]. The register was founded in 1977, but outpatient records were first completely incorporated from 1995. The files of the National Hospital Discharge Register include information on the civil registry number of the patient, date of discharge and discharge diagnoses, assigned exclusively by the physician at discharge according to the Danish version of the International Classification of Diseases, 8th revision until the end of 1993, and to the Danish version of the International Classification of Diseases, 10th revision. The register has nationwide coverage of public hospitals with an almost 100 % completeness of recordings and a high precision of diagnoses [7, 8], particularly for fracture diagnoses [9]. Using the National Hospital Discharge Register, we identified all subjects who had sustained a fracture between January 1, 2000 and December 31, 2000 (n= 124,655). The following end points were assessed: any clinical fracture, hip fracture (neck and pertrochanteric), distal forearm fracture, clinical spine fracture and/or any non-traumatic fracture (any fracture not presenting with an accident mechanism code signalling a trauma of more than a fall at the same level or less as fracture energy). Based on accident codes and admission codes (e.g. hospitalised from home, etc.), incident fractures were identified and separated from say re-admissions.

Selection of population-based controls

Using the Civil Registration System, which has electronic records on all changes in vital status, including change of

address and date of death for the entire Danish population since 1968, we randomly selected three controls for each case, matched by gender, year of birth and region. The controls were selected using the incidence density sampling technique [10].

Data on use of drugs to treat depression

In Denmark, pharmacies are equipped with a computerised accounting system through which data are sent directly to a Register of Medicinal Product Statistics (i.e. a prescription database) at the Danish Medicines Agency with key information on prescriptions for refundable drugs. The prescription database includes information on patient's civil registry number, the type and amount of drug prescribed according to the Anatomical Therapeutic Chemical classification system [11, 12] and the date when the prescription was filled. The database was started on January 1, 1996 and updated hereafter. We explored all drugs bought during the observation period available in the database.

Each time a subject goes to the pharmacy with a prescription filled by a doctor, the pharmacy registers: (1) who bought the drugs, (2) the date of filling the prescription, (3) the type of drugs and (4) the number and the dose of the tablets (e.g. 100 pills of amitriptyline each of 25 mg).

The dose of the drug bought during the observation period was expressed as defined daily doses (DDD). One DDD is the dose that a person on average uses of the drug in 1 day (WHO Collaborating Centre for Drug Statistics Methodology; Internet www.whocc.no/atcddd/; accessed on December 8, 2005). Standard conversion formulas exist for the various drugs. DDD was chosen as the exposure variable to better allow comparison of drug classes. Amount of DDD was calculated from the number of prescriptions, the number of tablets prescribed and the dose of the pills in the actual prescription. Drugs refilled at short and long intervals may thus be compared using DDD. Antidepressants were identified based on their Anatomical Therapeutic Chemical classification system codes: TCA (N06AA09, N06AA04, N06AA16, N06AA12, N06AA02, N06AA10, N06AA06, N06AA21), SSRI (N06AB04, N06AB10, N06AB03, N06AB08, N06AB05, N06AB06) and other antidepressants (N06AX03, N06AX16, N06AX11, N06AX18, N06AF01, N06AG02). DDDs were calculated as the sum of all redeemed prescriptions of the drug group in question from the first date of prescription after January 1, 1996 to the date of fracture or the equivalent dummy date among the controls divided by the time interval from the first date prescription to the date of fracture or dummy date among the controls. In Denmark, the drugs in question are only available by prescription.

Data on potential confounding factors

We analysed for presence of psychiatric comorbidity using occurrence of manic-depressive disorders, schizophrenia, other psychoses, eating disorders and use of anxiolytics and sedatives and neuroleptics [7]. Using the National Hospital Discharge Register, the number of days spent in hospital the year preceding fracture (year 1999) and a history of a prior fracture in the period 1977–2000, as well as data from the National Bureau of Statistics on income in 1999, social status in 1999, working status in 1999, educational status in 1999 and data from the National Health Organisation Register on number of contacts to general practitioners and practising specialists for the period 1996 to 2000.

Information on alcoholism was collected as appearance of a diagnosis of alcoholism in the National Hospital Discharge Register [7] or in the Psychiatric Central Register [13], or a prescription of disulfiram in the prescription database. Information on prior fractures was based on data from the National Hospital Discharge Register [7].

Statistics

Data from the different registers were merged at the National Bureau of Statistics, and for each subject, the 10-digit civil registry number was substituted by a unique anonymous case number. A different propensity score was calculated for each drug of interest and for each participant using logistic regression. Potential covariables for the propensity score, which were associated with fracture risk and antidepressant prescription, were use of individual antidepressants, psychiatric comorbidity, use of neuroleptics, anxiolytics and sedatives, prior fracture, alcoholism, over use of corticosteroids, income, living alone vs living with someone, working vs not working and Charlson Index. Psychiatric comorbidity was not included in the propensity score.

The analyses of the association between each drug use and fracture (cases vs controls) were carried out using conditional logistic regression. These models were adjusted for the corresponding propensity score in order to minimise confounding for indication [14–18]. As a sensitivity analysis, we carried out a further propensity-matched analysis, where users of the various antidepressants and anxiolytics and sedatives were matched 1:1 to non-users on the propensity score using a 0.2 standard deviation calliper, as recommended by some authors [19]. This propensity-matched analysis was only possible for the end point of any fracture due to reduced power, especially among the younger subjects with hip fractures.

We tested for differences by age and dose using interaction analyses. It was tested if interactions were present between age and dose and potential confounders. Few participants shifted between different antidepressants, and analysis with interaction terms for shifts did not change the results (data not shown).

All these analyses were performed using STATA 12.0 (STATA Corp., College Station, TX) and Statistical Package for the Social Sciences (SPSS) 19.0 (SPSS Inc., Chicago, IL). SPSS was used to generate the datasets from raw data and check the completeness of data, while STATA was used for the actual statistical analyses.

Results

Table 1 shows baseline characteristics of the fracture cases and controls. The cases and controls were well matched on age and gender. The fracture cases were more likely to be single (living without a partner, i.e. both unmarried, divorced or

Table 1 Characteristics of fracture patients (cases, any fracture) and controls

Variable	Cases (n=124,655)	Controls (n=373,962)	p Value
Age (years)	43.44±27.39 (0–100)	43.44±27.39 (0–100)	–
Gender (%)			–
Men	60,107 (48.2)	180,321 (48.2)	
Women	64,548 (51.8)	193,641 (51.8)	
Annual income (DKR)	161,036±138,789	172,322±193,704	<0.01
Marital status (%)			<0.01
Widowed	18,365 (14.8)	52,550 (14.2)	
Divorced	10,423 (8.4)	23,239 (6.3)	
Married	35,859 (28.9)	123,719 (33.3)	
Unmarried	59,335 (47.8)	171,349 (46.2)	
Other[a]	90 (0.1)	264 (0.1)	
Occupational status (%)			<0.01
Independent	3,374 (3.3)	11,816 (3.9)	
Assisting wife	209 (0.2)	951 (0.3)	
Working	37,797 (36.9)	124,984 (40.8)	
Retired	40,201 (39.3)	109,447 (35.7)	
Other[b]	20,752 (20.3)	59,278 (19.3)	
Charlson index* (%)			<0.01
0	97,256 (78.0)	314,099 (84.0)	
1–2	19,634 (16.8)	47,745 (12.8)	
3–4	5,450 (4.4)	9,132 (2.4)	
≥5	2,315 (1.9)	2,986 (0.8)	
Previous fracture (%)	41,315 (33.1)	56,200 (15.0)	<0.01
Alcoholism (%)	8,863 (7.1)	9,473 (2.5)	<0.01
Antiepileptic drugs (%)	7,091 (5.7)	10,974 (2.9)	<0.01
Sedatives, anxiolytics, and hypnotics (%)	35,840 (28.8)	82,766 (22.1)	<0.01
Neuroleptics (%)	9,738 (7.8)	17,243 (4.6)	<0.01
Antidepressants (%)			
Any antidepressant	18,511 (14.8)	34,521 (9.2)	<0.01
Tricyclic antidepressants	4,774 (3.8)	8,948 (2.4)	<0.01
Tetracyclic antidepressants	1,965 (1.6)	3,493 (0.9)	<0.01
SSRIs	14,958 (12.0)	26,793 (7.2)	<0.01
MAO inhibitors	232 (0.2)	464 (0.1)	<0.01
Serotonin or noradrenalin uptake inhibitors	3,329 (2.7)	5,834 (1.6)	<0.01
Ever use of any corticosteroid (%)	67,695 (54.3)	189,636 (50.7)	<0.01
Ever use of lithium (%)	440 (0.4)	963 (0.3)	<0.01
Schizophrenia (%)	765 (0.6	1,580 (0.4)	<0.01
Manic-depressive states (%)	3,702 (3.0)	6,939 (1.9)	<0.01
Other psychoses (%)	2,565 (2.1)	4,594 (1.2)	<0.01
Any eating disorder (%)	116 (0.1)	236 (0.1)	<0.01
Anorexia nervosa	97 (0.1)	195 (0.1)	<0.01

The drugs are ever use from 1996 to 2000 and the diseases prior occurrence of the disease in question between 1977 and 2000

[a]Registered partnership

[b]Not working (students, children, etc.)

[c]A composite index of 19 comorbid conditions (see text)

widowed), have a higher degree of comorbidity and a lower income. The use of almost all antidepressants was more frequent in cases than in controls.

Table 2 shows results for the association between drug use and any clinical fracture risk after adjustment for propensity score. For anxiolytics and sedatives, significant interactions with age and dose were present ($p<0.01$). In general, the increased in fracture risk from these drugs increased with higher doses of these drugs, but declined with age. Although an excess risk was still present in the highest age stratum (>60 years), the detrimental effect of anxiolytics on fracture risk in the highest dose group (≥0.33 DDD/day) was highest in patients aged ≤40 years (odds ratio (OR) 1.76 (1.56–1.98)) and lowest in those aged over 60 years (OR 1.25 (1.21–1.29), p for trend <0.01).

For TCAs, no interaction with age was present, and no excess fracture risk was observed except for the oldest age group (>60 years), OR 1.37 (1.19–1.58) for the highest dose (≥0.75 DDD/day).

Regarding the association between SSRI use and fracture, a trend towards higher excess risk was seen with increasing dose for subjects older than 40 years (but not among those aged <40). Also, an increasing risk of fractures was present with increasing age, but only in medium and high-dose users (≥0.15 DDD/day).

For other antidepressants, no particular trend with dose was present, and no definite excess fracture risk was seen in the oldest age stratum except for the highest doses. The effect of depression or manic depression per se upon fractures changed significantly with age; in the youngest age group (<40 years), a hospital diagnosis was not associated with risk of fractures, whilst among older participants, a hospital diagnosis of depression or manic depression was associated with reduced fracture risk.

The sensitivity propensity-matched analyses for use of antidepressants and anxiolytics and sedatives on any clinical fracture risk gave identical results to the just mentioned propensity-adjusted models (data not shown). An additional sensitivity analysis, excluding traumatic fracture cases (and their matched controls), did not change the results either (data not shown).

Table 3 shows the results for hip fracture outcomes. The low number of TCA users identified among hip fracture cases aged below 40 years led to wide confidence intervals for the risk estimators. For older patients, the results for TCA and SSRI were similar to those seen for overall risk

Table 2 Age stratified analyses—risk of any fracture (OR and 95 % CI)

Daily dose	Age group						
	≤40 years	p Dose	41–60 years	p Dose	>60 years	p Dose	p Age
Anxiolytics							
Never users	Reference	<0.01	Reference	<0.01	Reference	<0.01	
<0.1 DDD/day	1.30 (1.23–1.37)*		1.21 (1.16–1.26)*		1.14 (1.10–1.18)*		<0.01
0.1–0.33 DDD/day	1.54 (1.37–1.72)*		1.29 (1.21–1.38)*		1.21 (1.17–1.26)*		<0.01
≥0.33 DDD/day	1.76 (1.56–1.98)*		1.48 (1.39–1.57)*		1.25 (1.21–1.29)*		<0.01
TCA							
Never users	Reference	0.82	Reference	<0.01	Reference	<0.01	
<0.15 DDD/day	1.00 (0.84–1.18)		1.07 (0.97–1.18)		1.07 (1.01–1.14)*		0.46
0.15–0.74 DDD/day	1.00 (0.76–1.30)		0.97 (0.85–1.11)		1.18 (1.10–1.27)*		0.24
≥0.75 DDD/day	0.95 (0.63–1.43)		0.72 (0.58–0.89)*		1.37 (1.19–1.58)*		0.10
SSRI							
Never users	Reference	0.07	Reference	0.01	Reference	<0.01	
<0.15 DDD/day	1.12 (1.00-1.25)*		1.05 (0.97–1.13)		1.20 (1.14–1.26)*		0.27
0.15–0.74 DDD/day	0.95 (0.85–1.07)		1.08 (1.00–1.17)		1.59 (1.52–1.67)*		<0.01
≥0.75 DDD/day	0.96 (0.85–1.09)		1.22 (1.12–1.33)*		1.69 (1.61–1.77)*		<0.01
Other antidepressants							
Never users	Reference	0.04	Reference	0.03	Reference	0.32	
<0.15 DDD/day	0.88 (0.74–1.05)		1.05 (0.93–1.18)		1.07 (0.99–1.16)		0.05
0.15–0.74 DDD/day	0.74 (0.60–0.91)*		0.84 (0.73–0.96)*		0.97 (0.90–1.05)		0.02
≥0.75 DDD/day	0.63 (0.48–0.83)*		0.83 (0.70–0.98)*		1.14 (1.04–1.26)*		<0.01
Depression, manic depression or not	1.08 (0.97–1.21)	–	0.75 (0.68–0.83)*	–	0.79 (0.74–0.84)*	–	<0.01

The comparator was never use of the drugs in question

*2p<0.05; adjusted for propensity score

Table 3 Age stratified analyses—risk of hip fracture (OR and 95 % CI)

Daily dose	Age group						
	≤40 years	*p* Dose	41–60 years	*p* Dose	>60 years	*p* Dose	*p* Age
Anxiolytics							
Never user	Reference	0.02	Reference	<0.01	Reference	<0.01	
<0.1 DDD/day	1.32 (0.52–3.33)		1.37 (1.07–1.76)*		1.11 (1.03–1.19)*		0.72
0.1–0.33 DDD/day	2.68 (0.64–11.2)		1.70 (1.18–2.45)*		1.26 (1.17–1.36)*		0.30
≥0.33 DDD/day	9.04 (2.16–37.8)*		2.82 (2.04–3.89)*		1.30 (1.22–1.38)*		<0.01
TCA							
Never user	Reference	–	Reference	0.35	Reference	0.03	
<0.15 DDD/day	–		0.65 (0.38–1.14)		0.93 (0.82–1.07)		0.21
0.15–0.74 DDD/day	–		2.07 (1.04–4.11)*		1.35 (1.17–1.57)*		0.23
≥0.75 DDD/day	–		1.24 (0.36–4.28)		1.35 (0.99–1.84)		0.90
SSRI							
Never user	Reference	0.76	Reference	0.02	Reference	<0.01	
<0.15 DDD/day	2.06 (0.37–11.3)		1.08 (0.66–1.75)		1.32 (1.19–1.45)*		0.61
0.15–0.74 DDD/day	1.26 (0.18–8.78)		1.36 (0.84–2.19)		2.07 (1.89–2.26)*		0.62
≥0.75 DDD/day	3.35 (0.25–45.0)		2.35 (1.47–3.78)*		2.19 (2.01–2.39)*		0.75
Other antidepressants							
Never user	Reference	0.80	Reference	<0.01	Reference	0.57	
<0.15 DDD/day	0.23 (0.02–2.24)		1.23 (0.64–2.35)		1.22 (1.05–1.43)*		0.17
0.15–0.74 DDD/day	–		0.79 (0.37–1.69)		0.94 (0.82–1.09)		–
≥0.75 DDD/day	0.04 (0.00–5.38)		0.19 (0.07–0.55)*		1.14 (0.96–1.36)		0.46
Depression, manic depression or not	2.39 (0.28–20.2)	–	0.39 (0.20–0.78)*	–	0.73 (0.65–0.83)*	–	0.28

The comparator was never use of the drugs in question

*2p<0.05; adjusted for propensity score

of fractures, with an increasing excess risk with higher doses of SSRI. However, no dose response was seen for TCAs in the age group 40–60 years, while a clear dose–response effect was observed among those aged 60 years and older. For other antidepressants, no particular trends were observed. Also, for hip fractures, a hospital diagnosis of depression or manic depression was associated with fewer fractures in those aged 40 and older.

Data on the analyses of the association between drug use and forearm fractures are shown in Table 4. No particular age trends were observed except for a declining trend with age at the highest dose for anxiolytics and sedatives. Conversely, an increasing excess risk with age was observed for the highest doses of SSRI (p<0.01) and TCA (p=0.02). Further, a dose-dependent trend was also present in the oldest age group for TCA and SSRI and in those aged 40 to 60 years for SSRI. In contrast, an increasing trend with dose of anxiolytics and sedatives was only present among those younger than 40 years (p=0.03). For a hospital diagnosis of depression or manic depression, no age trend was present, but in the age group 40–60 years, for whom a hospital depression or manic depression diagnosis was associated with fewer forearm fractures.

Table 5 shows the age and dose trends for clinical spine fractures. For anxiolytics and sedatives, an increasing trend towards more fractures was present in all age groups, although this trend was only borderline significant in the youngest ages. For TCA and SSRI, a dose trend towards higher fracture risk was seen only in the oldest age group (>60 years). For other antidepressants, no particular age or dose trends were seen. As previously, a hospital diagnosis of depression or manic depression was associated with fewer spine fractures only among the oldest participants. Analyses by matching for propensity score did not change these results either.

Most users of antidepressants had started use long before the fracture (mean time since first prescription 4.44± 1.77 years for anxiolytics and sedatives, 5.24±0.63 years for SSRI, 3.98±1.95 years for TCA and 2.78±1.86 years for other antidepressants). Consistent with this, analyses by duration of exposure (<2, 2–4 and >4 years) did not change the results (data not shown). High adherers (>0.75 DDD/day) thus had been exposed for a prolonged time period. It did not change the results to stratify for cumulative exposure. An analysis using multivariable covariate adjustment for the fracture risk factors included in the propensity score did not change the results (data not shown).

Table 4 Age stratified analyses—risk of forearm fracture (OR and 95 % CI)

Daily dose	Age group						
	≤40 years	*p* Dose	41–60 years	*p* Dose	>60 years	*p* Dose	*p* Age
Anxiolytics							
Never user	Reference	0.03	Reference	0.72	Reference	0.20	
<0.1 DDD/day	1.19 (0.98–1.45)		1.06 (0.95–1.19)		1.08 (1.00–1.17)*		0.37
0.1–0.33 DDD/day	1.30 (0.82–2.08)		1.05 (0.87–1.26)		1.07 (0.97–1.18)		0.42
≥0.33 DDD/day	1.98 (1.29–3.02)*		1.10 (0.93–1.31)		1.16 (1.07–1.25)*		0.02
TCA							
Never user	Reference	0.08	Reference	0.82	Reference	0.02	
<0.15 DDD/day	1.02 (0.55–1.90)		0.66 (0.49–0.89)*		1.06 (0.91–1.24)		0.91
0.15–0.74 DDD/day	0.27 (0.06–1.22)		0.87 (0.59–1.26)		1.19 (0.99–1.42)		0.06
≥0.75 DDD/day	0.15 (0.02–1.22)		0.61 (0.34–1.12)		1.67 (1.18–2.34)*		0.02
SSRI							
Never user	Reference	0.97	Reference	0.03	Reference	<0.01	
<0.15 DDD/day	0.99 (0.65–1.51)		1.05 (0.84–1.30)		1.13 (1.00–1.28)		0.55
0.15–0.74 DDD/day	0.93 (0.59–1.45)		1.43 (1.16–1.76)*		1.41 (1.25–1.59)*		0.08
≥0.75 DDD/day	0.98 (0.62–1.57)		1.48 (1.18–1.86)*		1.85 (1.64–2.08)*		<0.01
Other antidepressants							
Never user	Reference	0.80	Reference	0.45	Reference	0.08	
<0.15 DDD/day	0.94 (0.51–1.74)		1.24 (0.90–1.70)		0.89 (0.73–1.09)		0.87
0.15–0.74 DDD/day	1.46 (0.69–3.08)		0.63 (0.42–0.96)*		0.86 (0.70–1.04)		0.18
≥0.75 DDD/day	1.10 (0.37–3.25)		1.00 (0.63–1.59)		1.18 (0.93–1.50)		0.90
Depression, manic depression or not	1.14 (0.76–1.69)	–	0.73 (0.55–0.97)*	–	0.89 (0.77–1.04)	–	0.26

The comparator was never use of the drugs in question

*2p<0.05; adjusted for propensity score

Discussion

In this large-scale population-based case–control study, we have shown significant age and dose interactions for the effect of a number of antidepressant and sedative drugs on fracture outcomes. For most fracture types, an increasing risk of fractures was seen with increasing doses of anxiolytics and sedatives, TCA and SSRI, especially among older participants. Excess risk of fractures related to SSRI use increased with age, whereas this was not the case for TCA and other antidepressants. In contrast, anxiolytics and sedatives were associated with highest risk among the youngest participants.

This age interaction suggests that SSRI users become more susceptible to their detrimental effects with age. This may be due to both an effect on BMD and on falls, as both worsen with age. Alternatively, this could be secondary to increased activity in previously sedentary depressed elderly patients who tend to be frail and prone to both falls and fractures. Our results suggest that older patients should be cautiously assessed for fracture risk before starting them on SSRI therapy.

In our data, a hospital diagnosis of depression or manic depression from a psychiatric ward, presumably the more severe case of depression or manic depression, was associated with fewer fractures in the elderly. This may signal that it was not the depression and its severity, but rather the drug therapy used that induced the excess risk of fractures, at least among the older participants of this study. The decreasing risk of hip fracture for other antidepressants in the age group 40–60 years was probably a spurious finding and needs further replication in future studies.

A study from Norway reported an increased risk of non-vertebral fractures with self-reported depression [20], but only among men using nerve medications and not among women (independent of whether they were using or not using nerve medications; the authors did not define the term nerve medication in detail) or among men not using nerve medications. In this study, only forearm BMD was assessed, and no decrease was seen among those with self-reported depression [20]. In a cross-sectional study from Hong Kong using depression diagnosed by interview, applying a depression scale, the proportion with T-score of<−2.5 did not differ among those depressed (1.8 vs 1.9 %), whereas a much higher proportion of those diagnosed as being depressed had osteopenia (41 vs 29 % with T-score of>−2.5 and<−1) [21]. Use of antidepressants was sparse in this

Table 5 Age stratified analyses—risk of spine fracture (OR and 95 % CI)

Daily dose	Age group						
	≤40 years	*p* Dose	41–60 years	*p* Dose	>60 years	*p* Dose	*p* Age
Anxiolytics							
Never user	Reference	0.06	Reference	0.03	Reference	0.01	
<0.1 DDD/day	1.82 (1.32–2.50)*		1.16 (0.91–1.48)		1.19 (1.01–1.40)*		0.02
0.1–0.33 DDD/day	2.84 (1.42–5.70)*		1.41 (0.97–2.04)		1.59 (1.33–1.89)*		0.11
≥0.33 DDD/day	3.93 (1.90–8.13)*		1.90 (1.33–2.73)*		1.58 (1.36–1.82)*		0.02
TCA							
Never user	Reference	0.37	Reference	0.49	Reference	0.02	
<0.15 DDD/day	1.30 (0.53–3.19)		1.71 (1.03–2.84)*		0.92 (0.69–1.23)		0.47
0.15–0.74 DDD/day	13.2 (2.85–61.4)*		2.70 (1.32–5.52)*		1.27 (0.91–1.78)		<0.01
≥0.75 DDD/day	4.12 (0.39–44.2)		1.15 (0.42–3.19)		1.97 (1.13–3.45)*		0.55
SSRI							
Never user	Reference	0.45	Reference	0.92	Reference	0.02	
<0.15 DDD/day	1.57 (0.82–2.99)		1.32 (0.83–2.07)		1.27 (1.01–1.59)*		0.54
0.15–0.74 DDD/day	1.56 (0.80–3.04)		1.57 (0.96–2.58)		1.76 (1.42–2.18)*		0.74
≥0.75 DDD/day	1.07 (0.50–2.29)		1.37 (0.81–2.32)		1.84 (1.49–2.26)*		0.18
Other antidepressants							
Never user	Reference	0.70	Reference	0.68	Reference	0.76	
<0.15 DDD/day	1.30 (0.49–3.41)		0.90 (0.46–1.78)		1.27 (0.89–1.81)		0.96
0.15–0.74 DDD/day	0.14 (0.02–0.94)*		1.05 (0.40–2.76)		1.38 (1.00–1.90)*		0.02
≥0.75 DDD/day	1.88 (0.39–8.99)		1.13 (0.48–2.71)		1.38 (0.92–2.07)		0.71
Depression, manic depression or not	1.50 (0.78–2.90)	–	0.84 (0.47–1.49)	–	0.55 (0.41–0.73)*	–	<0.01

The comparator was never use of the drugs in question

*2p<0.05; adjusted for propensity score

population (1.8 % of depressed were users vs 0.4 % among non-depressed) [21]. In young adults (aged 20–39 years) from the NHANES III survey, a diagnosis of major depressive episode made from an interview schedule was associated with a decrease in hip BMD in men, but not in women [22].

The increase in fracture risk associated with the use of antidepressants seems to be related to their effect on the serotonin system [23, 24]. This may affect BMD [25, 26] and thus long-term fracture risk.

Regarding falls, a number of studies have indicated an increased body sway and thus a decreased postural balance with TCAs [27], probably due to either their anticholinergic effects [27] or to their cardiovascular side effects [28, 29]. Scarce data coming from cross-sectional studies have failed to show an effect of TCAs on BMD and rate of BMD loss [25, 26], thus indicating that TCAs may not affect bone metabolism. The mentioned effect on the risk of falls is particularly interesting as the risk of falls increases with age, potentially exposing older subjects to a larger risk than younger subjects [30, 31]. Also, BMD decreases with age making the bone more prone to fracture upon a fall [32]. However, it is not known if SSRIs per se affect the central nervous system leading to a raise in falls incidence with age.

Similarly, little is known on the effects of age on the risk of fractures induced by SSRI use. Two cohort studies have reported on fractures in older adults using SSRI [33, 34]. The first study reported that, compared with secondary amine tricyclics, SSRIs showed the highest association with composite fracture rate (hazard ratio (HR) 1.30; 95 % confidence interval (CI) 1.12–1.52), followed by atypical antidepressants (HR=1.12; 95 % CI 0.96–1.31) and tertiary amine tricyclics (HR=1.01; 95 % CI 0.87–1.18) [33]. A second study only assessed fracture risk in older women, reporting that, compared to non-users of antidepressant medications, women using SSRIs experienced a higher risk of non-spine fracture in (HR=1.30, 95 % CI 1.04–1.62) [34]. SSRI use was not associated with an increased risk of first hip fracture (HR=1.01, 95 % CI 0.71–1.44), but appeared associated with an increased risk of wrist fracture (HR=1.54, 95 % CI 1.01–2.36) [34]. TCA use was associated with an increased risk of non-spine fracture in age-adjusted models, but in multivariable models, this risk was attenuated [34]. However, no specific analysis of the effects of age per se was performed in these studies. It may thus be that age per se significantly interacts with the risk of falls and thus fractures with use of antidepressants. Not only

antidepressants, but also concomitant use of anxiolytics and sedatives may affect the risk of falls and thus fractures [35].

In a recent study, treatment with SSRI (escitalopram 10 mg/day) was associated with decreased concentrations of parathyroid hormone and CTX and increased osteocalcin [36], which may actually suggest a positive effect on bone metabolism. An increased physical activity may perhaps explain why prior studies have indicated an increased fracture risk early after initiation of SSRI [3]—the patients may become physically active at a point where their muscles and bone are still weak, and falls may thus lead to fractures.

Strengths and weaknesses of the study

The major strengths of the study are the large study sample and the uniform nature of the registrations with nationwide coverage with a high precision of most data. The main limitation of this study is the non-validation of fractures at an individual level. Notwithstanding, this fracture coding has been demonstrated to be highly valid within the Danish National Hospital Discharge Register [9]. A further major limitation is that most patients with psychiatric disorders are treated outside hospital, and the diagnoses thus not being included in the hospital discharge register. However, SSRI, TCA and other antidepressants are almost exclusively used to treat depression. Furthermore, only the most severe cases are treated in hospital, making the findings for the diagnoses true for the most severe cases. Due to the observational nature of these data, causality cannot be ensured; although we adjusted for several potential confounding factors in the analyses and used propensity scores to minimise confounding for indication, our results may still be influenced by potential confounders not included in the analyses, e.g. smoking, physical activity, differences in body weight, use of calcium/vitamin D supplements or by residual confounding due to the use of crude measures (risk of fractures). A special problem arises for vertebral fractures, where many may be asymptomatic. Many fractures are thus probably overlooked. Finally, we did not have access to drugs used in hospitalised patients. However, the number of days spent in hospital, in general, was limited, thus not suggesting a severe bias. Nevertheless, all these factors are likely to be balanced among cases and controls, driving the observed estimates of risk towards the unity.

In conclusion, SSRI was associated with an increased risk of fractures with age above 60 years, an effect that was not present among younger subjects. Therefore, caution should be shown upon prescription of SSRI to older subjects. For TCA, no particular age interaction was present. However, a dose-dependent increase in fracture risk was still seen in subjects 60 years or older. Besides, a hospital diagnosis of depression or manic depression and thus potentially more severe disease was not a risk factor for fractures, suggesting that it was not the disease, but rather the drugs that were responsible for the increase in risk of fractures.

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Conflicts of interest None.

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