

# Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry

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## Abstract

**Background:** hip fractures are usually caused by a combination of reduced bone mineral density and falls; using antidepressant drugs may affect both of these.

**Objective:** we aimed to examine associations between exposure to antidepressant drugs and the risk of hip fracture among older people, and, provided associations found, to estimate the attributable risk of hip fracture.

**Design:** we conducted a nationwide prospective cohort study of the 906,422 people in Norway born before 1945.

**Methods:** information on all prescriptions of antidepressants dispensed in 2004–10 and all primary hip fractures in 2005–10 was obtained from the Norwegian Prescription Database, and the Norwegian Hip Fracture Registry, respectively. The incidence rates of hip fracture during the time people were exposed and unexposed to antidepressant drugs were compared by calculating the standardised incidence ratio (SIR).

**Results:** altogether 39,938 people (4.4%) experienced a primary hip fracture. The risk of hip fracture was increased for people exposed to any antidepressant [SIR = 1.7, 95% confidence interval (CI) 1.7–1.8]; tricyclic antidepressants (SIR = 1.4, 95% CI: 1.3–1.5); selective serotonin reuptake inhibitors (SSRIs) (SIR = 1.8, 95% CI: 1.7–1.8) and other antidepressants (SIR = 1.6, 95% CI: 1.5–1.7). The risk of hip fracture attributable to exposure to antidepressant drugs was 4.7%.

**Conclusions:** this study indicated an increased risk of hip fracture among people exposed to antidepressants, especially those with serotonergic properties such as SSRIs. This association needs to be explored further in clinical studies.

**Keywords:** antidepressants, hip fractures, pharmacoepidemiology, population registers, older people

## Introduction

The risk of hip fracture increases with age. The estimated lifetime risk is 25% for women and 7% for men [1]. Hip fractures represent critical events, with great implications for morbidity and mortality [2]. Most hip fractures result from a combination of reduced bone mineral density and a fall [3]; using antidepressants may affect both of these [4, 5].

Antidepressants are prescribed to 10–25% of women and 5–20% of men 60 years and older in Europe and the USA, mostly selective serotonin reuptake inhibitors (SSRIs) [6–9]. Clinical guidelines recommend SSRIs for depression because they have fewer sedative, anticholinergic and cardiovascular side effects than tricyclic antidepressants (TCAs). Observational studies indicate associations between the use of antidepressants and hip fracture, especially

recently initiated drug treatment [9–11]. Some studies suggest that SSRIs may be associated with a greater risk of hip fracture than TCAs [10, 12], postulating a specific serotonergic effect on bone physiology [13].

We aimed to examine associations between exposure to antidepressant drugs and the risk of hip fracture among older people. If we found associations, we aimed to estimate the attributable risk of hip fracture.

## Methods

This was a nationwide prospective study based on merged data from the Norwegian Prescription Database (NorPD) [14], the Norwegian Hip Fracture Registry [15] and the Central Population Registry [16].

### Data sources

The NorPD, starting from January 2004, contains information on all prescription drugs purchased at all pharmacies in Norway [17]. The data extracted for this study comprises all prescriptions of antidepressants, Anatomical Therapeutic Chemical (ATC) system code [18] N06A, dispensed from January 2004 until December 2010, by the items' ATC code, drug volume by defined daily dose (DDD) [18] and date of dispensing. The NorPD lacks individual information on medication dispensed to people living in nursing homes, 40,000 at any time.

The Norwegian Hip Fracture Registry, starting from January 2005, contains national data (i.e. injury, fracture and surgery) on people operated on for hip fracture at all 55 hospitals in Norway performing such surgery [15]. For the purpose of this study, we extracted the date of hip fracture, or the date of surgery in case of missing information, for the period January 2005 until December 2010. Although the registry comprises fractures in nursing home patients, these individuals cannot be identified.

The Central Population Registry contains demographic information on the entire population of Norway. The data extracted for this study comprise birth year, sex and date of death or emigration if applicable.

The variables selected from these three registries were linked, using the unique 11-digit personal identity number assigned to everyone living in Norway after 1960.

### Study population

The study population included everyone born before 1945 and living in Norway on 1 January 2005. They were followed up until the day of any first hip fracture, emigration or death or until the end of the study period on 31 December 2010.

### Antidepressant medication

Antidepressant medication was divided in two different ways, according to; (i) therapeutic subgroups (ATC group):

TCAs (N06AA), SSRIs (N06AB) and other antidepressants (N06AG, N06AX); (ii) the drugs' serotonergic effects: high or intermediate serotonergic properties, and those with low or no serotonergic properties [10, 19].

### Exposure

Since the NorPD does not include information on whether or when the purchasers consumed the dispensed drugs, we had to make assumptions on drug exposure. Antidepressants are usually prescribed in 30 or 100 day lots, and we assumed people to start using them the day they were purchased. Antidepressants are predominantly used on a regular daily basis. The DDD is the assumed average maintenance dose per day for a drug used for its main indication among adults, as defined by the WHO [18]. Because the actually prescribed dose may diverge from the DDD, we calculated the risk of hip fracture for various assumed total exposure times (3 and 14 days and the number of days corresponding to the number of DDDs prescribed, respectively). The latter was considered the best proxy for the number of person-days exposed.

We defined overall use as any exposure to antidepressants within the study period, including all exposure periods. Recently started treatment was defined as the first 14 days of first-time exposure to antidepressants after a 360-day wash-out period.

### Statistical analysis

We compared the incidence of hip fracture during the person-days exposed and unexposed to antidepressants in the study period by calculating standardised incidence ratios (SIRs) [20]. An SIR >1 indicates an increased risk of hip fracture associated with exposure. We adjusted the SIRs for sex, birth year and time period (in 2-month intervals). Results based on overall use of antidepressants in the entire study population are presented throughout the article. We performed subanalysis for recently started drug use.

For the SIRs, 95% CIs were calculated assuming a Poisson distribution of the observed number of hip fractures among exposed people, estimating the mean by the expected number of hip fractures among the exposed people.

To calculate the attributable risk of exposure to antidepressant drugs on hip fracture, we divided the observed minus the expected number of fractures during the number of person-days exposed to antidepressant drugs by the observed number of fractures in the study population.

## Results

The study population (Appendix 1 in the Supplementary data available at *Age and Ageing* online) comprised 906,422 people with a mean age of 72.8 years [standard deviation (SD) 8.9 years] on 1 January 2005 (56% women) and mean

follow-up 5.2 (SD 1.7) years. Altogether 218,775 persons died (53% women) and 4,949 emigrated (44% women).

A total of 153,301 (17%) people purchased at least one prescription of an antidepressant drug during the study period; 69% were women. Antidepressants with serotonergic properties and SSRIs were most frequently used (Table 1). More women than men used TCAs (31 versus 26% of antidepressant users) and SSRIs (63 versus 58%), with minor sex differences for other subgroups. The use of antidepressants in various subgroups was similar across different birth cohorts, except for TCAs, which decreased with increasing age, from 33% (among those born in 1935–44) to 21% (born before 1915) (not shown).

During the study period, 39,938 individuals experienced a primary hip fracture. Most fractures among the people exposed to antidepressants occurred among those born in 1915–24 (40%) or in 1925–34 (41%). The mean age at the time of fracture was 83 years, and the mean number of days of exposure prior to fracture was 116. Of all hip fractures, 72% occurred in women. Within all birth year cohorts, the prevalence of hip fracture was higher among exposed women than exposed men (Table 2). However, the excess risk of hip fracture was more pronounced among exposed men (SIR = 1.9; 95% CI: 1.8–2.0) than among exposed women (1.7; 1.6–1.7). Sex differences were most prominent in the youngest cohort born in 1935–44 (men 2.9; 2.6–3.4, women 2.5; 2.3–2.7). Generally, for the people

using antidepressants, the excess risk of hip fracture decreased with increasing age (Table 2).

Within all antidepressant subgroups, the SIR increased with increasing numbers of assumed exposed person-days from 3 to 14 days, and remained largely stable when SIR was calculated for DDD (not shown).

The risk of hip fracture was elevated among people exposed to any antidepressant drug (SIR = 1.7, 95% CI: 1.7–1.8). The excess risk of hip fracture was higher among people exposed to SSRIs (1.8, 1.7–1.8) than among those exposed to TCAs (1.4, 1.3–1.5) and other antidepressants (1.6, 1.5–1.7). The risk of hip fracture was higher for drugs with high or intermediate serotonergic properties (1.7, 1.7–1.8) than for drugs with no or low serotonergic properties (1.2, 1.1–1.5).

The sex differences in SIR were greatest for SSRIs and drugs with high or intermediate serotonergic effects (Table 3).

**Subanalysis**

The risk of hip fracture was higher during recently started treatment with any antidepressant drug (SIR, all 2.0, 1.5–2.4; women 1.8, 1.3–2.3; men 2.7, 1.7–4.0) and SSRIs (all 2.7, 2.1–3.4; women 2.5, 1.9–3.3; men 3.3, 2.0–5.2) than during overall use (not shown in table). The total number of hip fractures during recently started

**Table 1.** Number of people in Norway born before 1945 who purchased antidepressant drugs during 2005–10 and proportions by various antidepressant subgroups

Study population	Any antidepressant (%)	Antidepressant subgroups (% of people who purchased)				
		Therapeutic subgroup			Serotonergic properties	
		TCA	SSRI	Others	Low	High
All (n = 906,422)	153,301 (16.9)	29.2	62.1	39.6	14.1	92.2
Women (n = 506,568)	105,830 (20.9)	30.8	63.2	38.8	14.0	92.6
Men (n = 399,854)	47,471 (11.9)	25.8	57.7	41.5	14.4	91.1

The totals in each of the subgroups do not add up to 100%, because individuals may have purchased more than one antidepressant.

TCA (ATC N06AA): tricyclic antidepressants (clomipramine, trimipramine, amitriptyline, nortriptyline and doxepin).

SSRI (N06AB): selective serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram).

Others (N06AG, N06AX): moclobemide, mianserin, mirtazapine, bupropion, venlafaxine, reboxetine and duloxetine.

High or intermediate serotonergic properties: All SSRIs, TCAs (clomipramine and amitriptyline) and others (mianserin, mirtazapine, venlafaxine and duloxetine).

Low or no serotonergic properties: TCAs (nortriptyline, doxepin and trimipramine), moclobemide, bupropion and reboxetine.

**Table 2.** Number of hip fractures (n) and excess risk of hip fracture (SIR, 95% CI) in Norway’s population born before 1945 exposed to antidepressant drugs in 2005–10, by birth cohort and sex

Hip fractures observed during exposed person-days	Birth cohort (years)									
	All		1935–44		1925–34		1915–24		<1915	
	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)	n	SIR (95% CI)
All	4,465	1.7 (1.7–1.8)	756	2.6 (2.4–2.8)	1,814	1.9 (1.8–2.0)	1,774	1.4 (1.3–1.5)	121	1.2 (1.0–1.4)
Women	3,594	1.7 (1.6–1.7)	561	2.5 (2.3–2.7)	1,431	1.9 (1.8–2.0)	1,493	1.4 (1.3–1.5)	109	1.2 (1.0–1.4)
Men	871	1.9 (1.8–2.0)	195	2.9 (2.6–3.4)	383	2.2 (2.0–2.4)	281	1.4 (1.2–1.6)	12	1.0 (0.5–1.7)

SIR, standardised incidence ratio. CI, confidence interval.

**Table 3.** Observed number of hip fractures (*n*) and excess risk of hip fracture (SIR, 95% CI) in Norway's population born before 1945 exposed to various antidepressant drug subgroups in 2005–10 (Exposed person days, DDD)

	Antidepressant subgroups											
	Any antidepressant		Therapeutic subgroup						Serotonergic properties			
	<i>n</i>	SIR (95% CI)	TCA		SSRI		Others		Low		High	
		<i>n</i>	SIR (95% CI)	<i>n</i>	SIR (95% CI)	<i>n</i>	SIR (95% CI)	<i>n</i>	SIR (95% CI)	<i>n</i>	SIR (95% CI)	
All	4,465	1.7 (1.7–1.8)	364	1.4 (1.3–1.5)	3,272	1.8 (1.7–1.8)	1,119	1.6 (1.5–1.7)	147	1.2 (1.1–1.5)	4,345	1.7 (1.7–1.8)
Women	3,594	1.7 (1.6–1.7)	305	1.4 (1.3–1.6)	2,632	1.7 (1.7–1.8)	898	1.6 (1.5–1.7)	120	1.2 (1.0–1.5)	3,499	1.7 (1.6–1.8)
Men	871	1.9 (1.8–2.0)	59	1.4 (1.1–1.8)	640	2.1 (1.9–2.2)	221	1.6 (1.4–1.8)	27	1.3 (0.8–1.9)	846	1.9 (1.8–2.1)
Attributable risk (% of hip fractures during DDD exposure throughout the study period)												
All	4.7		0.3		3.6		1.0		0.1		4.6	

SIR, standardised incidence ratio. CI, confidence interval. DDD, defined daily dose.

TCA (ATC N06AA): tricyclic antidepressants (clomipramine, trimipramine, amitriptyline, nortriptyline and doxepin).

SSRI (N06AB): selective serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram).

Others (ATC N06AG, N06AX): moclobemide, mianserin, mirtazapine, bupropion, venlafaxine, reboxetine and duloxetine.

High or intermediate serotonergic properties: all SSRIs, TCAs (clomipramine and amitriptyline) and others (mianserin, mirtazapine, venlafaxine and duloxetine).

Low or no serotonergic properties: TCAs (nortriptyline, doxepin and trimipramine), moclobemide, bupropion and reboxetine.

antidepressant drug use (<100) was too small for analysis regarding TCAs and antidepressants with low or no serotonergic properties to yield representative results.

### Attributable risk

The percentage of hip fractures attributable to exposure to any antidepressant drug was estimated at 4.7%, with TCAs comprising 0.3%, SSRIs 3.6% and other antidepressants 1.0%. Antidepressants with high or intermediate serotonergic properties comprised 4.6% (Table 3).

## Discussion

### Excess risk of hip fracture among exposed people

Our results showing excess risk of hip fracture in persons using antidepressants, especially SSRIs and other antidepressants with high or intermediate serotonergic properties (e.g. venlafaxine or mirtazapine), are in accordance with previous studies [10, 12, 13, 21, 22]. About 5% of the hip fractures in the study period were attributable to antidepressant drug use.

We found a higher excess risk of hip fracture among persons on recently started treatment with antidepressants when compared with all users of SSRIs and other antidepressants with high or intermediate serotonergic effects. The numbers of hip fractures are small and these findings must be interpreted with caution, but they support previous research [10, 12]. The relationships between the dose [21, 22] and duration [10, 13] of SSRI use and the risk of hip fracture have been shown earlier.

Other studies suggest that tolerance for TCAs evolves after a few weeks of use, while the risk of hip fracture remains elevated over time among older people using SSRIs [10, 11].

It is reasonable to suspect that SSRIs adversely affect bone strength. A meta-analysis of epidemiological studies indicates that using SSRIs is associated with an increased risk of fracture, although when SSRI use was adjusted for depression and bone mineral density at baseline, it was non-significantly associated with bone loss [23]. A recent case-control study demonstrated associations between using SSRIs and osteoporosis, independent of depression and concomitant use of medication affecting bone metabolism, while using TCAs was associated with higher bone mineral density [24]. Although functional 5-hydroxytryptamine (5-HT) receptors and 5-HT transporters have been localised to osteoblasts and osteocytes, and 5-HT seems to modulate the skeletal effects of parathyroid hormone and mechanical stimulation [13], the detailed effects of serotonin on bone metabolism remain unknown [25]. SSRIs and other drugs with serotonergic properties may possibly contribute to an increased risk of hip fracture through falls in recently initiated treatment, due to hyponatraemia and haemodynamic disturbances [26], and through effects on bone physiology, assumedly impairing bone architecture and bone strength, in longer-lasting treatment.

The excess risk of hip fracture in our study was higher among exposed men than exposed women, supporting the findings of a previous study [27]. As hip fracture and antidepressant drug use are less prevalent among men than among women, exposure to antidepressants will affect the hip fracture risk among men relatively more. Attenuation of the impact of antidepressant drug use with advancing age is possibly due to 'dilution' of the effect by other factors giving rise to an increased risk of hip fracture, such as comorbidities, frailty and concomitant drug use.

### Methodological considerations

The national health registries provided us a unique opportunity to link complete data on antidepressant drugs

purchased by a nationwide unselected community-dwelling older population with all primary hip fractures registered in Norway. The 6-year follow-up period revealed high numbers of cases, and the nationwide prospective study design prevented selection and information bias. In addition, the conservative definition of exposed person-days, not allowing for such factors as non-adherence, yields conservative risk estimates.

The databases have some limitations. The NorPD lacks individual information on medication dispensed to nursing home residents, leading to systematic misclassification of 40,000 people at any time as drug non-users. The prevalence of both antidepressant use [28] and hip fracture is high among nursing home residents, and the excess risk of hip fracture has been underestimated in exposed people. The Norwegian Hip Fracture Registry comprises >80% of all hip fracture operations in Norway [15], with somewhat lower completeness during the first years.

The most important limitation of our study is the lack of clinical information such as depression, comorbidities, frailty, concomitant drug use and life style. Thus, we do not know whether people purchasing prescriptions for antidepressants were actually diagnosed with depression or not. Low-dosage TCAs are also prescribed for chronic pain and SSRIs for neuropsychiatric symptoms among people with dementia. Confounding by indication must be taken into account when interpreting the results. Most importantly, both depression itself and antidepressants may influence muscle strength, psychomotor function, activity level and bone mineral density and thus interfere with the risk of falls and fractures. However, previous studies have shown that associations between an increased risk of hip fracture among individuals using antidepressants remain even when adjusted for depression [24, 29]. Further, a large population-based cohort study among older people diagnosed with depression in the UK adjusted for patient characteristics revealed no evidence that using SSRIs is safer than using TCAs regarding all-cause mortality [12].

Since antidepressants are predominantly used on a daily basis, we considered the number of days corresponding to the number of DDDs dispensed the best proxy for the number of drug-exposed person-days. Studies of psychotropic drug prescribing for older people in Sweden in 2006 [30] and the UK 1996–2007 [12] showed that the actually prescribed mean daily dose of SSRI was nearly 1.0 DDD; the latter study also demonstrated that the mean prescribed daily dose of TCAs was <0.5 DDD [12]. Thus, our study may have underestimated the assumed number of person-days exposed to TCAs and the effect on the risk of hip fracture. However, the risk of hip fracture remained largely stable when the SIR was calculated for different assumed exposure times.

### Implications for practice

Since the risk of hip fracture increases with age, demographic changes will contribute to an increasing number of

hip fractures. SSRIs are the most widely prescribed antidepressants for older people. We found a marked overrepresentation of hip fractures among people using SSRIs and other antidepressants with serotonergic properties compared both with people not using antidepressants and with people using TCAs. At the population level, the excess risk of hip fracture corresponds to 1,900 fractures during the study period. These associations need to be explored further in clinical studies. The growing evidence of SSRIs and other antidepressants not being necessarily safer than TCAs requires conscientious evaluation of the potential risks and benefits when prescribing antidepressants for older people and careful follow-up.

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### Key points

- The risk of hip fracture was markedly increased among older people exposed to antidepressant drugs.
  - Individuals exposed to SSRIs and other drugs with serotonergic properties were at greatest excess risk.
  - About 5% of hip fractures were attributable to antidepressant drug exposure.
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### Authors' contributions

S.R., L.B.E., A.E. and M.S.B.: study concept and design. A.E., L.B.E. and S.R.: acquiring the data. M.S.B., A.E., S.R., A.H.R., S.H. and L.B.E.: analysing and interpreting the data. M.S.B.: drafting the manuscript. S.R., A.E., A.H.R., L.B.E. and S.H.: critically revising the manuscript for important intellectual content. A.E. and M.S.B.: statistical analysis. A.E. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S.R.: administrative, technical or material support and study supervision.

### Conflicts of interest

None declared.

### Ethics and approval

The Regional Committee for Medical and Health Research Ethics (138/07) and the Norwegian Data Inspectorate (08/00133) approved the study. The Norwegian Directorate of Health granted an exemption from the duty of confidentiality (08/1843).

### Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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Received 28 August 2012; accepted in revised form 16 January 2013