

Excess risk of hip fractures attributable to the use of antidepressants in five European countries and the USA

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Abstract

Summary The association between antidepressant use and hip fracture remains unclear. We conducted a systematic review to estimate Population Attributable Risks (PAR) for France, Germany, Italy, Spain, UK, and the USA. We report a heterogeneous prevalence of antidepressant use and related PARs, both lowest for Italy and highest for the USA.

Introduction Antidepressant use has been associated with an increased hip fracture risk in observational studies. However, the potential contribution of antidepressant consumption on the population rate of hip fractures has not been described. Our aim was to estimate the impact of the use of different classes of antidepressants on the rate of hip fracture at a population-level in France, Germany, Italy, Spain, the UK, and the USA.

Methods We conducted a systematic literature review to estimate the pooled relative risk (RR) of hip fracture according to use of antidepressants. Prevalence rates of antidepressant use

(Pe) in 2009 were calculated for each country using the The Intercontinental Medical Statistics database and three public databases from Denmark, the Netherlands, and Norway. Both the RR and Pe were used to calculate PAR of hip fractures associated with antidepressant use.

Results The literature review showed an increased risk of hip fractures in antidepressant users (RR, 1.7; 95 % confidence interval (CI), 1.5–2.0). Rates of antidepressant use showed considerable differences between countries, ranging from 4.4 % (Italy) to 11.2 % (USA) in the year 2009. The estimated PAR of antidepressants on hip fracture rates were 3.0 % (95 % CI, 2.0–4.1; Italy), 3.1 % (95 % CI, 2.1–4.3; Germany), 3.8 % (95 % CI, 2.6–5.3; France), 4.8 % (95 % CI, 3.3–6.5; Spain), 4.9 % (95 % CI, 3.4–6.8; UK), and 7.2 % (95 % CI, 5.0–9.9; USA). PARs differed for different types of antidepressants, with highest attributable risks for selective serotonin reuptake inhibitors.

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Conclusions These findings suggest that the potential contribution of antidepressant use to the population rate of hip fractures in the five large EU countries and the USA varies between 3 and 7 %.

Keywords Antidepressants · Drug utilization · Hip fractures · Pharmacoepidemiology

Introduction

An estimated total of 1.26 million hip fractures occurred worldwide in 1990. This number is expected to increase to 2.6 million in 2025 and 4.5 million in 2050 [1]. Hip fractures affect mainly the elderly, particularly women [2, 3]. They are an important source of morbidity and mortality and are related to high direct management costs [4]. Reports show that 32–80 % of the patients surviving initial hospitalization become permanently disabled [5] and estimated 3-month mortality rates range from 20 to 25 % [6]. In the USA, estimated annual costs for patients with hip fractures were more than seven billion dollars. By the year 2040, these costs are expected to increase to more than 16 billion dollars as a consequence of population aging [4].

In March 2010, the Pharmacovigilance Working Party at the European Medicines Agency recommended that a statement on the epidemiological findings of an increased risk of bone fractures with several selective serotonin reuptake inhibitors (SSRIs) and tricyclic/tetracyclic antidepressants (TCAs), mostly in patients aged 50 years or older, should be included in the product information for these products [7]. Although the underlying mechanism between antidepressant use and fracture risk remains unclear, several explanations have been reported. First, antidepressants may affect bone metabolism by inhibiting the serotonin transporter [8]. Secondly, antidepressants may increase the propensity to fall, particularly in elderly patients [9], possibly through their anticholinergic and cardiovascular adverse effects, which are more accentuated for TCAs [10].

There is a scarcity of data comparing consumption of antidepressants across multiple countries and their possible contribution to population-based hip fracture rates. Drug consumption data at the patient level are generally not publicly available in the largest EU countries and the USA. For this study, we obtained volume sales data from the Intercontinental Medical Statistics (IMS) database, which gathers drug utilization data from many countries [11, 12].

As part of the European IMI PROTECT program [13], we used IMS data to estimate the impact of antidepressants use on hip fracture rates at a national level in five large European countries (France, Germany, Italy, Spain, and the UK) and the USA.

Methods

In order to estimate the population attributable risk (PAR) of hip fracture associated with use of antidepressants, we followed a two-stage process: (1) first, we carried out a systematic literature review and obtained a pooled estimate of relative risk (RR) of hip fracture according to use of antidepressants and (2) secondly, we calculated country-specific prevalence rates of antidepressant use (Pe) in a 1-year period (2009) using IMS data. Both were then combined to calculate country-specific PARs using the following formula [14]:

$$\text{PAR\%} = \frac{\text{Pe}(\text{RR}-1)}{1 + \text{Pe}(\text{RR}-1)} \times 100 \quad (1)$$

Formula 1 used for the calculation of the population attributable risk; where PAR is the population attributable risk, Pe is the prevalence rate of antidepressant use in 2009, and RR is estimated pooled relative risk

Systematic review

Methods

Three databases (PubMed, Cochrane Library, and Embase) were systematically searched in September and October 2010 with terminologies that related to fracture and antidepressants. Details can be found in the appendix. Unpublished studies were not considered.

Inclusion criteria

Randomized controlled trials, cohort studies and case-control studies, published before September 2010 and in English language, were included. Outcome of interest was either hip fracture in particular or osteoporotic/fragility fractures in general including hip fracture. Exposure/intervention of interest was use of antidepressants, SSRIs, and/or TCAs. Studies had to show RRs or odds ratios (ORs) and 95 % confidence intervals (CIs) to be eligible.

Statistical analysis

Cochrane Review Manager (version 5, <http://www.cochrane.org/>) was used to calculate a pooled RR and its 95 % CI for each drug of interest under the assumption of a random effects model. We assumed that a hip fracture is a rare disease and thus OR is a valid approximation of RR. Pooled RRs were estimated for different exposure categories: any antidepressant, SSRIs only, and TCAs only.

Estimation of prevalence rates of antidepressant use

Source populations

IMS Health database is a commercial database that collects data on a global level. In most countries, sales from both wholesalers to retail or hospital pharmacies and manufacturers to retail or hospital pharmacies are covered by IMS Health. In other countries, dispensing data are collected from pharmacy departments. IMS Health uses a sample size of a number of retail or hospital pharmacies and wholesalers, and projects this to estimate sales for all retail and hospital pharmacies in a country [11]. Sales data are registered in volume measures by IMS using the anatomical classification of Pharmaceutical Products developed and maintained by the European Pharmaceutical Marketing Research Association (EphMRA) [12].

The IMS database contains only sales data in product volume. In order to estimate the number of antidepressant users in IMS, we used three publicly accessible databases that contained both wholesale data and the number of antidepressant users as antidepressant prescription data from Denmark, the Netherlands, and Norway. These non-IMS data sources were the Register of Medicinal of Product Statistics of the Danish Medicines Agency [15], the Dutch GIPdatabank [16], and the Norwegian Prescription Database (NorPD) [17]. The database of the Danish Medicines Agency contains information derived from Danish pharmacies, on prescribed and reimbursed drugs and over-the-counter drugs. The NorPD database is developed by the Norwegian Institute of Public Health, that monthly receives data of all prescribed (reimbursed or not) and dispensed drugs to all individual patients in every Norwegian pharmacy. The GIPdatabank was set up by the Dutch Health Care Insurance Board and contains data on outpatient medication, as dispensed and reimbursed.

Study population

In each IMS country data source, antidepressants were classified into: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), TCAs (amitriptyline, amoxapine, clomipramine, desipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, opipramol, protriptyline, and trimipramine), or other antidepressants.

Estimation of prevalence

The 2009 prevalence year rates (Pes) were defined as the number of antidepressant users divided by the total population number in 2009. In each country, total population numbers of the same calendar year were retrieved from Eurostat and the US Census Bureau [18, 19]. A user was anyone who had one or more prescriptions in that same year. To estimate the number of users, IMS wholesale data were converted into

the World Health Organization defined daily dose (DDD) per 1,000 inhabitants per day (DDD/1,000 persons/day). Expression of drug utilization in DDDs/1,000 persons/day allows aggregation of data that differ in administration form and strength of dose and makes it possible to compare drug use between countries [20].

Formula 2 shows a summary of the steps that were taken to convert these DDDs/1,000 persons/day to country-specific prevalence rates. Public (non-IMS) data from Norway, Denmark, and the Netherlands were used as a source of information on the number of users of antidepressants/volume of prescriptions (available to us from these three countries only). These were used to infer number of users in all countries with the IMS data, which cover prescription volume but no data on number of users using Formula 2. For this estimation, we assumed that the prevalence was proportional to DDD/1,000 persons/day and that the ratio of mean (DDD/1,000 persons/day)_{public databases} to mean (DDD/1,000 persons/day)_{IMS databases} was equal in each country. We called this ratio the “conversion factor” and, setting the Danish, Dutch, and Norwegian databases as standard, multiplied all IMS data by this factor.

$$\text{Prevalence rate of antidepressant use in 2009} = \text{Pe} = \frac{A \times B}{C} \quad (2)$$

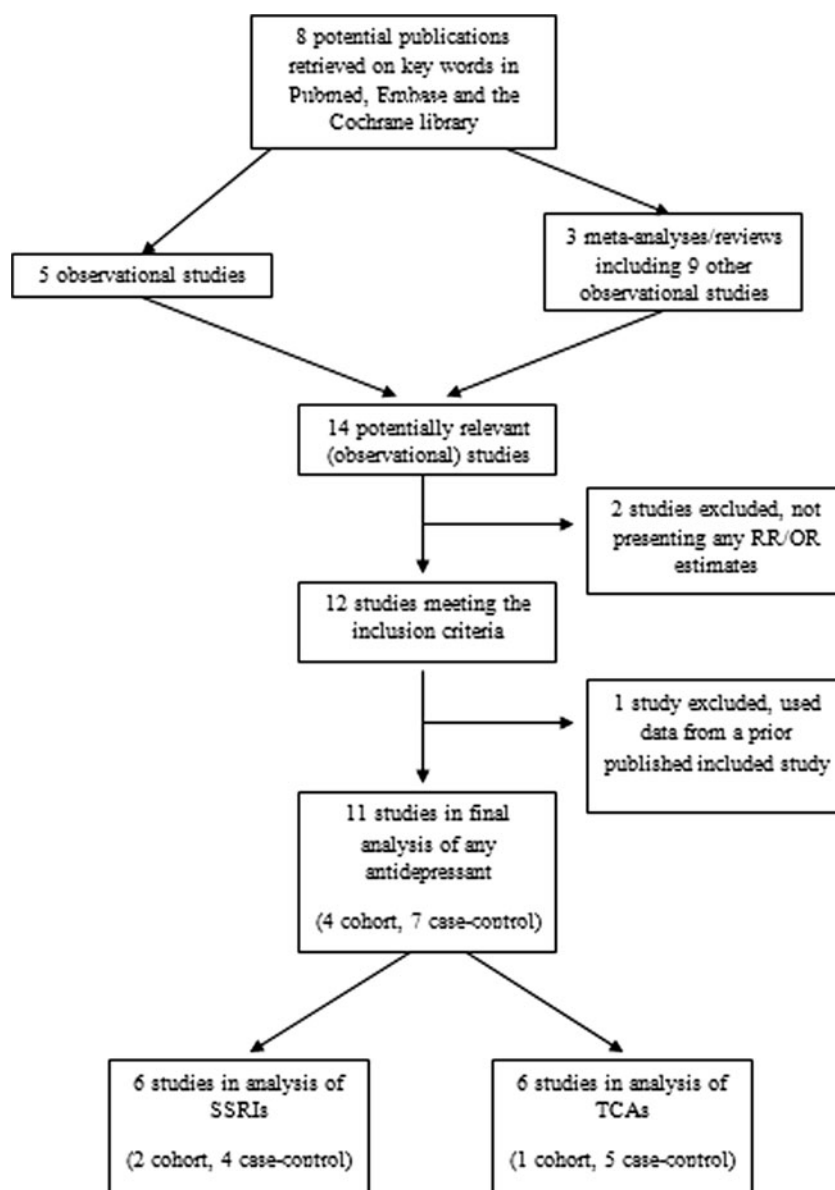
where *A* is country-specific antidepressant consumption in DDD/1,000 persons/day (IMS databases, converted with conversion factor); *B* is mean prevalence of antidepressant use in Denmark, the Netherlands, and Norway (public databases); and *C* is mean antidepressant consumption in DDD/1,000 persons/day in Denmark, the Netherlands, and Norway (public databases).

Statistical analyses

The primary outcome measure of this study was the population-attributable risk. PARs offer an indirect estimate of the proportion of hip fractures that could be prevented if exposure to the risk factor (i.e., antidepressant use) was eliminated [21]. Country-specific PARs were estimated using the previously calculated pooled RR and Pe for each country (see Formula 1). This was done for each class of antidepressants.

As we speculated a priori that the excess risk would be highest in the elderly female subpopulation, we performed a sensitivity analysis to estimate the impact of antidepressant use on PARs within a population of 65 years or older, stratified by sex. For this purpose, data on antidepressant consumption were extracted from the Danish national registries [15] (2007) and the Norwegian NorPD database [17] (2008), and stratified by age and sex.

Fig. 1 Study selection from the literature search. *OR* odds ratio, *RR* relative risk, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant



Results

Systematic review: excess risk of hip fracture amongst antidepressant users (pooled RR)

A total of 11 studies [22–32] that met the selection criteria were reviewed. This included four cohort [22–25] and seven case-control studies [26–32]. Figure 1 presents a flow chart reporting on the selection process.

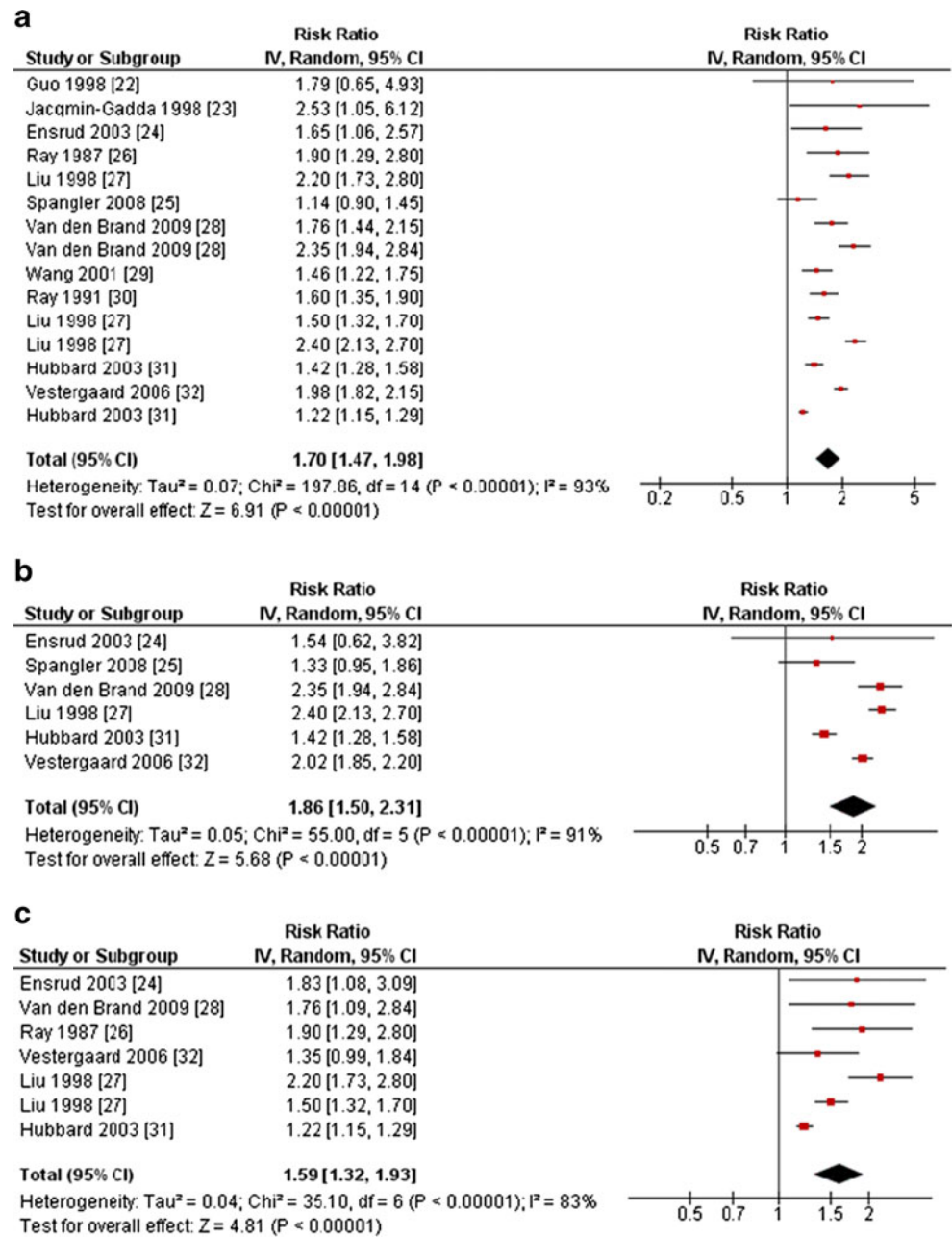
According to these data, the overall pooled RR of hip fracture was of 1.70 (95 % CI, 1.47–1.98) for antidepressant users, as compared to non-users. Case-control and cohort studies showed similar results: pooled RR, 1.75 (95 % CI, 1.48–2.06) and 1.45 (95 % CI, 1.05–2.02), respectively. The excess risk associated with SSRI use (pooled RR, 1.86; 95 % CI, 1.50–2.31) was numerically but not significantly higher

Table 1 Differences in antidepressant use (in DDDs/1,000 persons/day) in the five large EU countries and the USA calculated by using IMS drug sales data (2009)

Country	Total	SSRIs	TCAs
France	49.94	31.99	3.47
Germany	39.68	18.30	10.20
Italy	38.05	28.71	1.72
Spain	62.48	42.70	2.96
UK	64.95	44.51	9.57
USA	97.50	66.29	5.04

DDDs/1,000/day shown are not corrected for the ratio (mean DDDs/1,000 persons/day)_{online databases}: (DDDs/1,000 persons/day)_{IMS database}

Fig. 2 **a** Forest plot examining the association between antidepressant use and hip fracture risk, RRs/ORs, and their 95 % CIs of individual studies are depicted as extending lines. The size of the *square within the extending lines* is proportional to the weight of the studies, assuming a random effects models. The pooled RR and its 95 % CI are presented as a *diamond*. **b** Forest plot examining the association between SSRI use and hip fracture risk. RRs/ORs and their 95 % CIs of individual studies are depicted as extending lines. The size of the *square within the extending lines* is proportional to the weight of the studies, assuming a random effects models. The pooled RR and its 95 % CI are presented as a *diamond*. **c** Forest plot examining the association between TCA use and hip fracture risk. RRs/ORs and their 95 % CIs of individual studies are depicted as extending lines. The size of the *square within the extending lines* is proportional to the weight of the studies, assuming a random effects models. The pooled RR and its 95 % CI are presented as a *diamond*



than that for TCA use (pooled RR, 1.59; 95 % CI, 1.32–1.93). A test for heterogeneity of effects between studies was highly significant ($p < 0.001$) (Fig. 2).

Estimated prevalence rates of antidepressant use

Country-specific estimates of antidepressant use in the year 2009 are shown in Table 1. The average antidepressant daily consumption (in DDDs) was highest in the USA (97.50 DDDs/1,000 persons/day), followed by the UK (64.95 DDDs/1,000 persons/day), Spain (62.46 DDDs/1,000 persons/day), Germany (39.68 DDDs/1,000 persons/day), and Italy (38.05 DDDs/1,000 persons/day).

Furthermore, Table 1 shows that in all countries except Germany, the consumption of SSRIs was more than double compared to the use of TCAs. Notably, the DDDs/1,000 persons/day for SSRIs was more than ten times higher than that for TCAs (66.29 and 5.04 DDDs/1,000 persons/day, respectively) in the USA, Italy, Spain, and the UK. Furthermore, the consumption of TCAs in Germany, and to a lesser extent in the UK, was high when compared to the other four countries.

Estimated prevalence rates of anytime P_e in the study period (year 2009), and in the countries of interest, ranged from 4.4 % in Italy to 11.2 % in the USA. Similarly, P_e estimates lied between 2.0 % (Germany) and 7.1 % (USA)

Table 2 Estimated prevalence rates (Pe) of antidepressant use in the year 2009 for the studied countries

Category	Country	Estimated Pe (%)
Overall (all anti-depressants)	France	5.71
	Germany	4.54
	Italy	4.35
	Spain	7.14
	UK	7.43
	USA	11.15
SSRIs	France	3.44
	Germany	1.97
	Italy	3.09
	Spain	4.59
	UK	4.79
	USA	7.13
TCAs	France	0.96
	Germany	2.81
	Italy	0.47
	Spain	0.81
	UK	2.63
	USA	1.39

for SSRIs and between 0.5 % (Italy) and 2.8 % (Germany) for TCAs. Table 2 shows country-specific Pe estimates for overall antidepressants, SSRIs, and TCAs; all these Pe rates were corrected using a correction factor as described in Formula 2.

Population attributable risks

Table 3 shows that the attributable excess risk of hip fractures associated with antidepressant use (PARs) varied significantly between countries, with the lowest PAR being found in Italy (2.95 %; 95 % CI, 2.00–4.09), and the highest in the USA

(7.24 %; 95 % CI, 4.98–9.85). Furthermore, a significantly higher PAR was observed for SSRI users compared to TCA users in all countries. Only Germany and the UK showed nonsignificant numerical differences in PARs for hip fracture risk related to SSRI vs. TCA use.

Our sensitivity analysis showed that PARs in a population of women aged 65 years or older, was relatively higher than the estimates for the whole population in the five EU countries and the USA (ranges, 11–13 and 3–7 %, respectively; Table 4). There were statistically significant differences in PARs between genders in the elderly (65 years or older) populations from Denmark and Norway: PAR_{Denmark} (12.78 % (95 % CI, 8.96–17.02) for women and 6.47 % (95 % CI, 4.44–8.83) for men) and PAR_{Norway} (10.92 % (95 % CI, 7.61–14.65) for women and 4.90 % (95 % CI, 3.35–6.73) for men.

Discussion

We have shown a wide heterogeneity in the quantitative consumption of antidepressant drugs (overall and class specific) within the EU and compared to the USA. In all countries, SSRIs were the most consumed class of antidepressants.

Our literature review reveals that there is considerable data pointing towards an increased hip fracture risk among antidepressant users: overall, users of antidepressants appear at a 70 % higher risk, with SSRI users at almost 90 % increased risk and TCA users at about 60 % excess risk.

Following this, our data shows that the potential contribution of antidepressant use to the population rate of hip fractures (PAR) in five large EU countries, and the USA varies from just below 3 % for Italy to more than double (7.2 %) in the USA. When different classes of antidepressants are compared, SSRI use appears associated with a significantly higher attributable risk than TCA use in most countries.

Our estimations of the PAR were comparable to those reported by authors from Denmark and the Netherlands

Table 3 Estimation of the association between use of antidepressants and risk of hip fracture in the five large EU countries and the USA, expressed as population attributable risks (PAR) with 95 % confidence intervals

Country	% population ≥65 years ^a (%)	% women amongst those aged ≥65 years (%)	PAR (All anti-depressants)	PAR (SSRIs)	PAR (TCAs)
France	16.70	58.90	3.84 % [2.61–5.30]	2.87 % [1.69–4.31]	0.56 % [0.30–0.88]
Germany	21.00	57.45	3.08 % [2.09–4.26]	1.66 % [0.97–2.51]	1.63 % [0.89–2.54]
Italy	20.30	57.96	2.95 % [2.00–4.09]	2.59 % [1.52–3.89]	0.28 % [0.15–0.44]
Spain	16.65	57.52	4.76 % [3.25–6.54]	3.80 % [2.25–5.68]	0.48 % [0.26–0.75]
UK	16.48	55.87	4.94 % [3.37–6.78]	3.95 % [2.34–5.90]	1.53 % [0.84–2.39]
USA	13.04	51.11	7.24 % [4.98–9.85]	5.78 % [3.44–8.54]	0.81 % [0.44–1.27]

Different studies used to calculate RR in the three categories. Hence, figures on SSRIs and TCAs cannot be added

^a Institut National de la Statistique et des Etudes Economiques (www.insee.fr), DESTATIS-Statistisches Bundesamt (www.destatis.de), Geo Demo Istat (www.demo.istat.it), Instituto Nacional de Estadística (www.ine.es), Office for National Statistics (www.ons.gov.uk), and United States Census Bureau (www.census.gov)

Table 4 Estimated PAR antidepressants (all) for hip fracture by country, gender and age, using distribution data from Denmark

	Males				Females			
	Age ≥65 years		Age <65 years		Age ≥65 years		Age <65 years	
	Pe (%)	PAR (%)	Pe (%)	PAR (%)	Pe (%)	PAR (%)	Pe (%)	PAR (%)
Denmark (reference)	11.4	7.39	4.2	2.86	18.9	11.68	7.6	5.05
France	8.8	5.80	3.2	2.19	14.5	9.21	5.9	3.97
Germany	7.0	4.67	2.6	1.79	11.6	7.51	4.7	3.19
Italy	6.6	4.42	2.5	1.72	11.1	7.21	4.5	3.05
Spain	11.0	7.15	4.1	2.79	18.2	11.30	7.3	4.86
UK	11.4	7.39	4.2	2.86	19.0	11.74	7.6	5.05
USA	17.2	10.75	6.3	4.22	28.4	16.58	11.4	7.40

Pe was estimated by country/age/sex according to the following: value in cell Denmark × national overall Pe (Table 2)/Denmark overall Pe (Table 2)
Population Attributable Risks % (PAR) were calculated using a RR 1.70 and the estimated Pe values

(Abrahamsen et al. [33] and Van den Brand et al. [28]). However, we found no other study that investigated the PAR of antidepressant use and hip fractures in other countries.

To our knowledge, this is the first study that compares antidepressant consumption data from IMS Health between various countries. Our findings of a relatively higher consumption of TCAs in Germany (when compared to other European countries and the USA), and of a predominant use of SSRIs above other antidepressants, were also seen by Bauer et al. [34]

Our pooled RRs are in line with a previous meta-analysis [35]. In addition to our study, various reports [27, 28, 31] have observed higher hip fracture risks in first time users of antidepressants, as compared to patients with prolonged use. However, the underlying mechanism for an increased fracture risk associated with antidepressant use is still unclear.

Bone physiology and risk of falling, both associated with fracture risk, may be affected by antidepressant use [9, 36]. SSRIs, but also other antidepressants with properties of serotonin transporter inhibition, could reduce bone mineral density [8, 10, 28, 36]. This is supported by both in vitro and animal studies [8, 37]. However, studies in humans have demonstrated controversial results [25, 38–40]. Furthermore, anticholinergic and cardiovascular adverse effects of TCAs may cause an increased tendency to fall, leading to an increased fall-associated fracture risk [10, 28]. Compared to TCAs, SSRIs have a favorable safety profile. According to some authors, the increased fracture risk with SSRI use reported in different studies can be the consequence of a selection bias: in patients with a higher fall risk (i.e., elderly), a SSRI prescribing preference may exist [24, 31, 36]. In addition, depression is also a potential risk factor for both falls and fractures and thus confounding by indication may also lead to an overestimated excess risk [32, 36].

One of the strengths of our study is that we used a common source of data for drug consumption estimates (IMS).

Limitations in the use of PAR have been described elsewhere [21]. However, we believe that PARs in this study are a useful tool to express the attributable impact of antidepressant use on the rate of hip fractures at a population level and to enable comparisons between countries. Another limitation of this study is the extrapolation of antidepressant use in Northern European countries to the consumption of antidepressants in other European nations and the USA. Under this assumption, we made it possible to estimate Pes and thus PARs for these countries. Antidepressant use is higher among elderly women [41, 42], a high-risk population for hip fractures. This may lead to an underestimation of PARs as it was assumed in the current study that antidepressant use is equally distributed over the whole population. Our sensitivity analysis, which showed that the PAR is indeed higher for the elderly and especially for older women, confirms this. The limited breadth of data available made it impossible for us to account for differences in age and gender distribution between the studied countries and this is a limitation of our study. Similarly, the lack of information on the doses of drugs used did not allow us to explore further dose or drug-related effect sizes.

The findings of our pooled RR analyses are limited by the high degree of heterogeneity between studies. This may be the result of bias introduced by the use of only observational studies, mostly based on healthcare utilization data. Furthermore, adjusting for unmeasured, potential confounders is limited in population-based studies [36]. However, Schneeweiss and Wang [43] demonstrated a persisting, significant association between SSRI use and hip fractures after correcting for bias by potential confounders not measured in Medicare utilization data. Nonetheless, the uncertainty with regard to the causal relationship between AD use and hip fracture suggests cautious interpretation of the PARs that we presented.

Finally, it must be acknowledged that the observational nature of the data used in this study does not allow us to draw

conclusions on causal associations between use of drugs and the excess risk of hip fractures observed at a population level. In addition, the observed attributable risks might not be fully reversible, as some part of the effects observed might be related to the disease process itself or to unavoidable therapies. However, this information will be useful for a more informed decision based on the potential risks and benefits of these treatments.

In conclusion, our results suggest that the potential contribution of antidepressant use to the population rate of hip fractures in France, Germany, Italy, Spain, the UK, and the USA varies between 3 and 7 %. This is the first study comparing the attributable excess risk related to antidepressant utilization worldwide.

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