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Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people. The Three-City cohort

Isabelle Carrière^{1,2}, Amandine Farré^{1,2}, Joanna Norton^{1,2}, Marilyn Wyart³, Christophe Tzourio^{4,5}, Pernelle Noize^{4,6}, Karine Pérès^{4,5}, Annie Fourrier-Réglat^{4,6,7}, Marie Laure Ancelin^{1,2}

¹ Inserm, U1061, Montpellier, France.

² Univ. Montpellier, U1061, Montpellier, France.

³ Department of Psychiatry, CHU Caremeau, Nîmes, France.

⁴ Inserm, ISPED, Centre U1219 - Bordeaux Population Health Research Center, Bordeaux, France.

⁵ Univ. Bordeaux, ISPED, Centre Inserm U1219 - Bordeaux Population Health Research Center, Bordeaux, France.

⁶ Department of Clinical Pharmacology, CHU Bordeaux, Bordeaux, France.

⁷ Univ. Bordeaux, U1219, Bordeaux, France

Address for correspondence:

Dr Isabelle Carrière

Inserm U1061, Neuropsychiatry: epidemiological and clinical research.

39 avenue Charles Flahault, BP 34493,

34093 Montpellier cedex 05, France

Email: isabelle.carriere@inserm.fr

Tel: +33 499 614 691, Fax: +33 499 614 579

Abbreviated title: SSRIs and risk of falls and fractures

Abstract

Purpose: Increased risk of falls and fractures has been reported in elderly users of selective serotonin reuptake inhibitors (SSRIs). However, biases were insufficiently addressed notably temporality between exposure and outcome and confounding by residual depression. Our objective was to examine the associations between SSRIs and fall or fracture incidence focusing on their chronic use and different types of SSRIs.

Methods: The population-based cohort included participants aged 65 years and above, who had not fallen before inclusion (n=6,599) or free of recent fracture (n=6823) and followed-up twice over 4 years. New fall and fracture events were self-reported and defined as at least two falls and one fracture, respectively, during the previous 2 years. SSRI users were compared with those taking no antidepressants. Hazard ratios (HR) were estimated using Cox models with delayed entry and adjusted for many confounders including residual depressive symptoms.

Results: Incidence of falls was 19.3% over 4 years and that of fractures 9.5%. After multi-adjustment, SSRI intake was significantly associated with a higher risk of falls (HR, 95% CI = 1.58, 1.23-2.03) and fractures (HR, 95% CI = 1.61, 1.16-2.24). The risk was significantly increased by 80% in those continuing the treatment over 4 years. Citalopram intake only was a significant risk for falls and fluoxetine for fractures.

Conclusions: In this large community-dwelling elderly sample, SSRI users were at higher risk of falls and fractures. This association was not due to reverse causality or residual depressive symptoms. Different SSRI drugs may have specific adverse effects on falls and fractures.

Summary:

In this population-based elderly cohort, participants using selective serotonin reuptake inhibitor (SSRI) antidepressants have an increased risk of falls and fractures notably when the treatment was continued over 4 years. Among the various SSRI types citalopram only was at significant risk for falls and fluoxetine for fractures.

Key words: elderly, antidepressants, falls, fractures

Introduction

Antidepressants are among the most commonly prescribed drugs in the Western world, with an annual rate of treatment of 10.1 per 100 persons in the US general population and 13.7 in the elderly[1]. While there are arguments supporting antidepressant effectiveness and favorable benefit-risk ratio for major depression[2], a much lower efficacy has been found for moderate depression[3]. Data on depression in elderly people are scarce despite specific characteristics including the chronicity of symptoms[4], frequent comorbidities and the high prevalence of subsyndromal depression[5] which may be inadequately treated. Over-treatment of subsyndromal depression may increase risk of drug interactions and adverse reactions as aging is also associated with pharmacodynamic alterations (decreased renal clearance, altered hepatic metabolism and increased elimination half-lives).

Several meta-analyses and reviews have reported an increased risk of falls in the elderly[6-9] as well as fractures[10, 11], although not consistently. However, biases are insufficiently addressed notably due to a lack or limited consideration of (i) criteria of temporality between exposure and outcome, (ii) pattern of use and treatment chronicity and (iii) potential confounders and channeling bias (related to underlying burden of physical and mental illness). Separating the effect of depression from the effect of treatment is notably a critical point [11]. While most of the earlier studies found the class of tricyclic antidepressants (TCAs) to be a risk factor for falls and fractures[8, 12], more recent studies focused on selective serotonin reuptake inhibitors (SSRIs)[13, 14] which are now first-line therapy among older patients. Although being considered safer than TCAs, SSRIs have been found to be associated with an increased risk of bone mineral density loss and fracture[10, 15-17]. This led to consider SSRIs as potentially inappropriate in older adults with a history of falls or fractures[18]. However, two recent systematic reviews concluded that evidence of causation was lacking due to the absence of a demonstrated mediating pathway between SSRIs and falls[19] or osteoporosis[20]. As the effects of antidepressants on falls and fractures in elderly people have never been evaluated in randomized clinical trials, only well-designed analyses of large population-based cohorts can help address these relationships, evaluating long-term effects and taking into account the temporality between exposure and outcome and the main confounders.

The purpose of this study was to examine the longitudinal associations between antidepressant use and (i) falls and (ii) fractures, in a large elderly community-dwelling cohort, for which information on a wide range of potential confounding factors including residual depressive symptoms was available. The analyses focused on SSRIs, their chronic use and different types of SSRIs.

Method

Study sample

Subjects were recruited as part of a multi-site cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of three French cities (Bordeaux, Dijon, and Montpellier) between 1999 and 2001[21]. The study protocol was approved by the Ethical Committee of the Bicêtre University-Hospital (France) and written informed consent was obtained from each participant. A standardized evaluation with a face-to-face interview and a clinical examination was undertaken at baseline and after 2 and 4 years. The follow-up was then extended but data on falls were not collected after 4 years. Of the 9,294 participants included in the cohort, 503 were excluded because of a diagnosis of prevalent or incident dementia. The incidence study on falls was carried out on 6,599 participants, after further excluding 600 who declared at least 2 falls before inclusion, 908 with no follow-up assessments, 214 treated with other antidepressants(only SSRI antidepressants were considered in the present study) and 470 with missing data for at least one of the 16adjusting covariates. The incidence study on fractures was performed on 6,823 participants, after further excluding 613 who declared a fracture before inclusion, 1,087 with no follow-up assessments, 216 treated with other antidepressants and 52 with missing data for at least one of the 9adjusting covariates.

Compared with the analyzed sample for fall incidence, those excluded were older ($p<.001$), more frequently women ($p=0.002$), non-smokers ($p<.001$) and taking other medications ($p<.001$). They had more often cognitive, visual and hearing impairment, physical and activity limitations, fear of falling, daytime sleepiness, depressive symptoms, cardiovascular diseases, osteo-articular pains and orthostatic hypotension ($p<.001$ for all comparisons).

Outcomes

At baseline, participants were asked about the occurrence of falls during the preceding months and at follow-up examinations about the occurrence of falls since the preceding examination. Participants who reported having fallen were asked about the number of falls. At each follow-up visit those who reported at least 2 falls in the last 2 years were classified as fallers.

For fractures, participants were asked identically at baseline and at each follow-up examination about the occurrence of fractures with and without hospitalization, during the 2 preceding years. All body sites were considered: hip, wrist, spine (including compression), upper limb (arm, shoulder and collarbone), lower limb and any other site. The outcome was defined as reporting at least one fracture in the last 2 years.

Antidepressant exposure

At baseline and follow-up examinations, the questionnaire included an inventory of all drugs regularly used during the preceding month. To reduce underreporting, participants were asked to provide medical prescriptions, drug packages and any other relevant material. Drug exposure has previously been validated in this cohort in comparison with the reimbursement data from the health care insurance system[22, 23].The drugs were systematically coded using the Anatomical Therapeutic Chemical (ATC) classification system.**Participants treated with antidepressants other than SSRIs were excluded from the analyses.** SSRI drugs included: citalopram (N06AB04), fluoxetine (N06AB03),fluvoxamine (N06AB08),paroxetine (N06AB05), andsertraline (N06AB06). We also examined the chronicity of use over the 4 years of follow-up;the analysis compared the group of participants reporting SSRI use at baseline and at both follow-up visits (the group is referred to hereafter as the "continuing group") and the group of those reporting SSRI use only at baseline ("discontinuing group") with the group of those never treated with any antidepressants ("never users").

Socio-demographic and clinical variables

The standardized interview included questions on socio-demographic characteristics, smoking, visual and hearing impairment,difficulties standing up from a chair, problems of balance during walking, fear of falling, excessive daytime sleepiness, and cardiovascular pathologies. Osteo-articular pain included reported pain or treatment with anti-inflammatory or antirheumatic agents.Use of benzodiazepines and other drugsacting on the central nervous system (CNS) as well as the total number of other medications were derived from reported drugs. For the fracture study, use of anti-osteoporosis drugs (calcium, bisphosphonates, vitamin D, calcitonin, raloxifene and teriparatide), hormonal replacement therapy and corticosteroids were also considered. A hierarchical indicator of disability[24]combined three scales: Rosow and Breslau mobility scale[25],Lawton-Brody Instrumental Activity of Daily Living (IADL) scale[26] and Katz's Activity of Daily Living (ADL) scale[27].This indicator defines 4 levels of disability: full independence, mild disability (only mobility restriction), moderate disability (mobility and IADL restriction), and severe disability (mobility, IADL and ADL restriction).Cognitive impairment was defined as a Mini Mental State Examination (MMSE) score<26[28].Severity of depressive symptoms was assessed by the Center for Epidemiologic Studies-Depression scale (CES-D)[29]and history of major depressive episode (MDE) was diagnosed using the Mini International Neuropsychiatric Interview[30].Orthostatic hypotension was defined as a blood pressure reduction of at least 20 mmHg systolic or 10 mmHg diastolic between lying and standing position. Low standing blood

pressure (LSBP) was defined as $\leq 90/60$ mmHg[31] and body mass index (BMI) as weight divided by height squared.

Statistical analyses

Comparison of baseline characteristics between included and excluded participants was performed using Chi-square tests and Wilcoxon rank-sum tests. Two main outcomes were examined in this study, i.e. the occurrences of falls and fractures. To avoid reverse causality and clarify temporality we only considered the subjects who did not report the outcome of interest in the period preceding inclusion. The risk associated with SSRI use was evaluated using Cox models with delayed entry taking age as the basic time scale and birth as the time origin. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). This method enables a better adjustment for age and is preferred, especially for an elderly sample, over the standard model which uses study time as the time scale[32]. The assumptions of proportional hazards over time and the linearity of continuous covariates were verified.

To control for confounding effects, three nested models were constructed. Model 0 was adjusted for gender, centre and age (time scale). Model 1 included additional covariates that were associated with fall or fracture incidence ($p < 0.20$ in Model 0). This model thus included 14 and 7 additional covariates for fall and fracture outcomes, respectively. Model 2 further included potential mediators such as poor balance and daytime sleepiness. These models were performed for participants with no missing data on any of the covariates. All analyses were conducted using the statistical software SAS version 9.4 for Windows.

Results

The median time of follow-up (interquartile range) was 3.6 (3.4-3.8) years. Regarding falls, 19.3% of the 6,599 participants declared having fallen at least twice at the 2-year (10.2%) or 4-year follow-up (9.1%). The differences between fallers and non-fallers adjusted for age, sex, and center are shown in Table 1. Nearly all baseline characteristics were associated with fall incidence, except for visual impairment, orthostatic hypotension, LSBP, and benzodiazepine use. Regarding fractures, 9.5% of the 6,823 participants had at least one fracture over the follow-up: 4.5% at 2 years and 5.0% at 4 years. Table 2 presents the differences between participants who reported a fracture and those who did not. Participants with incident fracture were significantly older, more often women, non-smokers, users of CNS and anti-osteoporosis drugs and had more frequently a history of MDE.

Table 3 gives the risk of falls at follow-up for baseline SSRI intake compared with no antidepressant intake. The same pattern of associations was found in minimally adjusted (Model 0) and multi-adjusted (Model 1) models. SSRI intake was significantly associated with a higher risk of falls (HR, 95% CI = 1.58, 1.23-2.03). Further adjustments for possible mediators (poor balance during walking and daytime sleepiness) did not change the results (HR, 95% CI = 1.62, 1.23-2.12, p<0.001). No interaction was found between SSRI intake and gender (p=0.44). In the analysis by SSRI drugs, citalopram was associated with the highest adjusted hazard ratio for falls (HR, 95% CI = 2.31, 1.35-3.96) although it was not the most commonly prescribed SSRI. We then examined the risk of falls according to the pattern of SSRI use during the 4 years. Compared to the group of "never users" an increased adjusted risk of falls at 4 years was found for the "continuing group" (HR, 95% CI = 1.88, 1.36-2.61); the association was not significant for the "discontinuing group".

Baseline SSRI intake was also associated with an increased 4-year risk of fracture (Table 4) after multiple adjustments (HR, 95% CI = 1.61, 1.16-2.24); further adjusting for poor balance did not modify the result (HR, 95% CI = 1.63, 1.18-2.27). No interaction was found between SSRI use and gender (p=0.60) or anti-osteoporosis drug use (p=0.22). The most prescribed SSRI drugs were paroxetine and fluoxetine, however only fluoxetine was associated with a two-fold increase in the risk of fractures (multi-adjusted HR, 95% CI = 2.07, 1.28-3.32). In the multivariate analysis of the fracture risk according to the pattern of SSRI use during the 4 years, compared to the group of "never users", an increased risk was found for the "continuing group" (HR, 95% CI = 1.78, 1.15-2.78).

Discussion

In this large prospective study, we found a very significant increase of about 60% in the 4-year risk of falls and fractures for participants taking SSRIs at baseline and an even greater increase (around 80%) in chronic users. These associations remained significant after adjustment for a large range of other confounders. Conversely, the risk was not significant after treatment discontinuation. Examining individual SSRI drugs, a more than two-fold increased risk was found for falls in citalopram users only and for fractures in fluoxetine users.

A higher risk of falling has already been reported with SSRIs in distinct settings; a nursing home sample[33], elderly patients from a primary care database[13] and community-dwelling older women[34]. Falls are highly multi-factorial and in contrast with most previous studies, we adjusted for a large range of potential confounders including disability, difficulties standing up from a chair, osteo-articular pain, fear of falling, systolic blood pressure, cardiovascular diseases as well as use of benzodiazepines, other CNS drugs, and polypharmacy. As depression is a well-known risk factor for falls we also adjusted for residual depressive symptoms (including low energy, fatigue, attention difficulties,...) and severity using a validated scale and a diagnostic instrument for lifetime MDE. We actually found that depressive symptomatology was the main confounder together with fear of falling and disability which have rarely been considered before. In our multi-adjusted analysis, the hazard ratio for SSRI users remained high and significant suggesting that the SSRIs themselves rather than the underlying burden of illness are independently associated with the risk of falls.

This effect on falls appeared lower in participants who discontinued treatment in the first two years. Other findings showed that regardless of the antidepressant class, the risk of falls increased shortly after treatment initiation and then decreased, with a peak within 8 months for SSRIs[16]. In this elderly sample, fluoxetine and paroxetine were the most frequently prescribed antidepressants and although fluoxetine has the highest half-life elimination time, we found no significant differences for the risk of falls between these two SSRIs (data not shown). Conversely, despite lower statistical power, the risk of falling with citalopram was highly significant. This has also been reported in elderly patients from a primary care database[13], and further stresses that different SSRI drugs may have distinct effects on the risk of falls.

The temporality and possible reversibility of the risk after treatment discontinuation observed in this longitudinal study, together with the consistency of the associations in different populations and settings and possible dose-effects[35], lend support to a causative link between SSRIs and falls in the elderly. We hypothesized a number of reasons for this effect. Serotonergic adverse effects included digestive symptoms, headache, restlessness, tremors, dizziness, anxiety and weakness[6, 36]. SSRIs also have sedative effects but this is less frequent than in patients

taking TCAs[37].Poor sleep efficiency is common with SSRIs, with long sleep latency and sleep fragmentation, resulting in multiple long wake episodes[38] which could lead to elderly people getting out of bed at night, thus increasing the risk of falls. Visual function is also a key risk factor for falls[39] and SSRIs may be associated with adverse ocular effects[40]. In our large cohort we were able for the first time to examine many of these potential mediating factors, e.g. orthostatic hypotension, LSBP, poor balance and daytime sleepiness, visual impairment as well as headache, anxiety and osteoporosis (data not shown) but they all failed to explain even partially the observed relationships.

Long-term SSRI treatment has been linked to osteoporosis in late-life[41] which together with falls is a common pathway leading to fractures. A higher risk of fractures has previously been reported in SSRI users, with a duration- and dose- dependent effect; the higher the doses, the longer the use, and the higher the risk[10, 11, 14, 42, 43]. However, most studies using administrative data, could not fully control for important confounders such as osteoporosis and related factors, e.g. use of anti-osteoporosis drugs and supplements (e.g., calcium, vitamin D or hormone therapy in women) and smoking. The role of depression has also not been taken into account. However, people with long-term history of depression may have lower physical activity or performances and poorer nutritional status which could be associated with fractures[44]. In our study, we were able to adjust for both history of depression, behavioral characteristics, and use of anti-osteoporosis drugs and supplements, yet SSRI use was still associated with a 60% increased risk of fractures, reaching 80% in long-term users. These results thus provide further support for a causative link between SSRI intake and fractures in community-dwelling elderly people. We also found that fluoxetine increased the risk of fractures but not paroxetine which was just as frequently prescribed. The fact that citalopram was a risk factor for falls and fluoxetine for fractures remains to be elucidated but suggests that fractures are not a simple consequence of falling and could indicate differences in the nature and severity of adverse reactions.

Serotonin is found in blood platelet, gastrointestinal tract and the CNS and has been implicated in various physiological functions. Peripheral serotonin has been implicated in platelet aggregation, vascular tone, hypertension, and intestinal motility. In CNS, serotonin has been associated with mood, temperature regulation, circadian rhythm, vomiting, and energy balance. Regulation of bone metabolism is complex, involving different signaling pathways and opposite functions. Brain-derived serotonin increases osteoblast numbers and decreases bone resorption, therefore increasing bone mass. Conversely, gut-derived serotonin acts to inhibit bone formation and increased circulating serotonin has been associated with lower bone density[45]. Age-related

changes in drug absorption, metabolism, and blood-brain barrier permeability may also influence levels of serotonin. Depending on their pharmacological properties and bioavailability, and degree of serotonin reuptake inhibition, SSRIs may have distinct effects on bone.

Strengths of this study include its multicentric longitudinal design and the size of the sample with more than 6,500 elderly participants from the general population. Antidepressant use was ascertained at baseline and during follow-up by examining the prescriptions and boxes, thus minimizing exposure misclassification. Exposure to both current and chronic antidepressant medication has previously been shown within this cohort to be highly valid in comparison with the reimbursement data from the health care insurance system [22, 23]. Although in observational studies residual confounding may always subsist, our analyses overcame several limitations of previous studies. History of falls or fractures can be both a predictor and a possible risk factor for depression and studies are exposed to reverse causality. In our longitudinal study the temporality of the associations has been addressed by excluding the participants with falls or fractures in the period preceding inclusion and restricting analyses to incident falls or fractures. To our knowledge this is also the first study which adjusted for such a large range of different key factors including blood pressure, physical and activity limitations as well as physical and mental health.

Our study has several limitations. As in most previous observational studies, falls and fractures were self-reported. We however excluded prevalent and incident cases of dementia to avoid unreliable responses and potential overestimation of the association since behavioral disturbances in dementia are a major cause of falls. In addition, incident falls were retrieved from 2 questions and covered a 2-year period which may lead to under-reporting. No data were available on the duration of the treatment before inclusion but we were able to evaluate the effect of long-term treatment during the follow-up. Poor balance and daytime sleepiness were also self-reported. We were not able to consider specific insomnia criteria such as frequent night awakenings and also some aspects of the visual functioning including contrast vision. Another potential limitation is that we did not use propensity score methods in our analyses to account for confounders. However, it should be noted that these methods do not always adequately account for unmeasured confounders. They estimate marginal effects at a population level while multivariate models as used in this study estimate individual conditional effects [46] and are more suitable for explanatory investigations with the additional advantage of allowing the evaluation of the impact of mediating factors.

In conclusion, this study showed that in community-dwelling elderly people, SSRI users are at high risk of falls and fractures. These associations are not due to reverse causality or residual depressive symptoms. The possible pathways explaining these associations remain to be explored. Differences may exist between SSRI drugs regarding the risk of falls and fractures. Precautions taken when prescribing TCAs to elderly patients should be extended to SSRIs along with an objective diagnosis of depression, an adapted treatment and an evaluation of risk factors for falls and fractures.

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Conflicts of interest:

Isabelle Carrière, Amandine Farré, Joanna Norton, Marilyn Wyart, Christophe Tzourio, Pernelle Noize, Karine Péres, Annie Fourrier-Réglat, and Marie Laure Ancelin declare that they have no conflict of interest.

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Table 1. Baseline Characteristics and Risk of Falls over 4 Years, n=6599

	Non fallers		Fallers		HR [95%CI] ^a	P value
	N=5326	N=1273	n	%		
Categorical variables						
Sex (male)	2282	42.85	364	28.59		<0.0001 ^b
Smoking						.
Never	3185	59.80	800	62.84	-	.
Former	1847	34.68	416	32.68	1.27 [1.11;1.45]	0.0007
Current	294	5.52	57	4.48	1.12 [0.85;1.47]	0.41
Body Mass Index (kg/m ²)						.
Normal (<25)	2529	47.48	602	47.29	-	.
Overweight (25-30)	2105	39.52	509	39.98	1.14 [1.01;1.29]	0.03
Obese (≥ 30)	692	12.99	162	12.73	1.12 [0.94;1.33]	0.20
MMSE						.
≥ 26	4666	87.61	1078	84.68	-	.
< 26	660	12.39	195	15.32	1.16 [1.00;1.36]	0.05
Hierarchical disability indicator						.
Fully independent	3196	60.01	593	46.58	-	.
Mild disability	1881	35.32	551	43.28	1.09 [0.96;1.23]	0.19
Moderate to severe disability	249	4.68	129	10.13	1.39 [1.13;1.71]	0.002
Visual impairment ^c (n=6266)	692	13.66	204	16.99	1.02 [0.88;1.19]	0.78
Hearing impairment ^d	325	6.10	116	9.11	1.22 [1.00;1.48]	0.05
Difficulties standing up from a chair	535	10.05	208	16.34	1.34 [1.15;1.55]	0.0002
Poor balance during walking (n=6573)	848	15.96	356	28.23	1.52 [1.34;1.72]	<0.0001
Osteo-articular pain	958	17.99	287	22.55	1.21 [1.06;1.38]	0.006
Orthostatic hypotension (n=5608)	565	12.40	132	12.57	0.96 [0.80;1.16]	0.70
Low standing blood pressure (n=5624)	93	2.03	29	2.75	1.17 [0.81;1.70]	0.40
Fear of falling	860	16.15	353	27.73	1.39 [1.22;1.57]	<0.0001
Daytime sleepiness (n=6162)	813	16.28	252	21.59	1.34 [1.16;1.55]	<0.0001

	Non fallers		Fallers		HR [95%CI] ^a	P value
	N=5326		N=1273			
Categorical variables	n	%	n	%		
Time since first MDE ≥ 2 years	368	6.91	111	8.72	1.22 [0.99;1.50]	0.06
Benzodiazepine use	935	17.56	290	22.78	1.11 [0.97;1.26]	0.14
Other CNS drugs ^e	154	2.89	60	4.71	1.45 [1.12;1.88]	0.005
Number of other medications ≥ 5	1794	33.68	558	43.83	1.24 [1.11;1.39]	0.0002
Continuous variables	Median	IQR	Median	IQR	HR [95%CI]*	P value
Age (years)	73	69-77	75	70-79		<0.0001 ^b
Sitting systolic blood pressure (cm Hg)	14.6	13-16	14.4	13-16	0.96 [0.93;0.99]	0.003
Number of cardiovascular diseases ^f	0	0-1	0	0-1	1.09 [1.02;1.16]	0.007
Depressive symptomatology (CES-D score)	7	3-13	9	5-16	1.01 [1.01;1.02]	<0.0001

^aCox model adjusted for sex, center and age

^bChi square test for sex and Wilcoxon test for age

^cVisual impairment defined as having a corrected near visual acuity (Parinaud scale) of less than 2 or difficulties recognizing a familiar face at 4 meters.

^dHearing impairment defined as deafness or only able to hear a conversation when a single person speaks loudly.

^eAnti-Parkinson, antiepileptic and psycholeptic drugs

^f Cardiovascular diseases include stroke, angina pectoris, myocardial infarction, cardio-vascular surgery, arrhythmia, heart failure, and peripheral artery disease; 73.1% of participants did not declare a cardiovascular disease, 18.0% had only one cardiovascular disease

CES-D: Center for Epidemiologic Studies–Depression scale, CI: confidence interval, CNS: central nervous system, HR: Hazard ratio, IQR: inter quartile range, MDE major depressive episode, MMSE: Mini Mental State Examination

Table 2. Baseline Characteristics and Risk of Fractures over 4 Years, n=6823

	No Fracture		Fracture		HR [95%CI] ^b	P value
	N=6173		N=650			
Categorical variables ^a	n	%	n	%		
Sex (male)	2599	42.10	159	24.5		<0.0001 ^c
Smoking						
Never	3728	60.39	426	65.54	-	.
Former	2109	34.16	193	29.69	1.29 [1.06;1.57]	0.01
Current	336	5.44	31	4.77	1.20 [0.83;1.74]	0.33
Difficulties standing up from a chair	720	11.68	107	16.51	1.17 [0.95;1.45]	0.14
Poor balance during walking (n=6786)	1154	18.79	166	25.78	1.17 [0.98;1.41]	0.08
Osteo-articular pains	1146	18.56	145	22.31	1.17 [0.97;1.41]	0.10
Time since first MDE ≥ 2 years	425	6.88	64	9.85	1.41 [1.07;1.86]	0.01
Benzodiazepine use	1132	18.34	163	25.08	1.20 [1.00;1.43]	0.05
Other CNS drugs ^d	189	3.06	32	4.92	1.52 [1.06;2.16]	0.02
Anti-osteoporosis drugs	614	9.95	110	16.92	1.33 [1.08;1.64]	0.008
Corticosteroid use						
No	5882	95.29	605	93.08		
Oral	88	1.43	17	2.62	1.62 [1.00;2.62]	0.05
Inhaled	203	3.29	28	4.31	1.33 [0.91;1.95]	0.14
Continuous variables	Median	IQR	Median	IQR	HR[95%CI]*	P value
Age (years)	73	69-77	74	71-78		<0.0001 ^c

^aAll other variables in table 1 are non significant (p>0.20) as well as hormonal replacement therapy in women^bCox model adjusted for sex, center and age^cChi square test for sex and Wilcoxon test for age^dAnti-Parkinson, antiepileptic and , psycholeptic drugs

CI: confidence interval, CNS: central nervous system, HR: Hazard ratio, IQR: inter quartile range, MDE major depressive episode

Table 3. Four-year Risk of Falls and SSRI Antidepressant Use at Baseline

	Non fallers	Fallers	Model 0 ^a		Model 1 ^b	
			HR [95%CI]	P value	HR [95%CI]	P value
SSRI use (n=6599)						
No antidepressant	5196	1202				
SSRI	130	71	1.84 [1.45;2.35]	<0.0001	1.58 [1.23;2.03]	0.0003
SSRI drugs (n=6589)^c						
No antidepressant	5196	1202				
Fluoxetine	48	23	1.58 [1.04;2.39]	0.03	1.38 [0.91;2.10]	0.14
Citalopram	15	14	2.92[1.72;4.95]	<0.0001	2.31[1.35;3.96]	0.002
Paroxetine	48	23	1.75 [1.16;2.65]	0.008	1.50 [0.99;2.28]	0.06
Sertaline	12	8	1.84 [0.92;3.70]	0.16	1.65 [0.82;3.33]	0.16
SSRI usage patterns						
(n=6118)						
Never users ^d	4876	1094	-	-	-	-
Continuing ^e	58	40	2.17 [1.58;2.99]	<0.0001	1.88 [1.36;2.61]	0.0001
Discontinuing ^f	35	15	1.51 [0.90;2.52]	0.12	1.27 [0.76;2.13]	0.36

^aModel 0 adjusted for sex, age and center^bModel 1 adjusted for age, center, sex, smoking, BMI, cognitive impairment, disability, benzodiazepines, other CNS drugs, difficulties standing up from a chair, osteo-articular pains, fear of falling, time since first MDE, number of other medications, sitting systolic blood pressure, number of cardiovascular diseases, and CES-D score^c10 participants taking fluvoxamine (3 fallers, 7 non fallers) were excluded due to small numbers.^dNo antidepressant at baseline nor at the 2- and 4- year follow-up^eSSRI used at baseline and at both follow-up visits^fSSRI used at baseline and not at the 2- and 4- year follow-up

Table 4. Four-year Risk of Fracture and SSRI Antidepressant Use at Baseline

	No fracture	Fracture	Model 0 ^a		Model 1 ^b	
			HR [95%CI]	P value	HR [95%CI]	P value
SSRI use (n=6823)						
No antidepressant	5987	609				
SSRI	186	41	1.77 [1.28;2.43]	0.0005	1.61 [1.16;2.24]	0.004
SSRI drugs (n=6811)^c						
No antidepressant	5987	609				
Fluoxetine	60	18	2.31 [1.44;3.69]	0.005	2.07 [1.28;3.32]	0.003
Citalopram	27	5	1.71 [0.71;4.14]	0.23	1.49 [0.61;3.64]	0.38
Paroxetine	71	11	1.34 [0.74;2.44]	0.33	1.25 [0.68;2.28]	0.47
Sertaline	19	4	1.37 [0.51;3.68]	0.53	1.31 [0.49;3.51]	0.60
SSRI usage pattern						
(n=6309)						
Never users ^d	5588	552	-	-	-	-
Continuing ^e	90	22	1.98 [1.29;3.03]	0.002	1.78 [1.15;2.78]	0.01
Discontinuing ^f	47	10	1.69 [0.90;3.17]	0.10	1.59 [0.84;2.99]	0.15

^aModel 0 adjusted for sex, age and center^bModel 1 adjusted for age, center, sex, smoking, benzodiazepines, other CNS drugs, osteo-articular pains, time since first MDE, anti-osteoporosis drugs, and oral corticosteroids^c12 participants taking fluvoxamine (3 fallers, 9 non fallers) were excluded due to small numbers^dNo antidepressant at baseline nor at the 2- and 4- year follow-up^eSSRI used at baseline and at both follow-up visits^fSSRI used at baseline and not at the 2- and 4- year follow-up