

## Selective serotonin reuptake inhibitors and selective serotonin and norepinephrine reuptake inhibitors use and risk of fractures in adults: a systematic review and meta-analysis

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**Selective Serotonin Reuptake Inhibitors and Selective Serotonin and Norepinephrine  
Reuptake Inhibitors Use and Risk of Fractures in Adults:  
A Systematic review and Meta-Analysis**

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**Running head:** SSRIs and Risk of Fractures

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**Objective:** to evaluate the association between SSRI and SNRI use and risk of fractures in older adults.

**Methods:** We systematically identified and analyzed observational studies comparing SSRI/SNRI use for depression with non-SSRI/SNRI use with a primary outcome of risk of fractures in older adults. We searched for studies in MEDLINE, PsycINFO, EMBASE, DARE, the Cochrane Library, Web of Science clinical trials research registers from 2011 for SSRIs and 1990 for SNRIs to November 29, 2016.

**Results:** Thirty-three studies met our inclusion criteria, 23 studies were included in meta-analysis: 9 case-control studies and 14 cohort studies. A 1.67-fold increase in the risk of fracture for SSRI users compared to non-users was observed (Relative Risk 1.67, 95% CI 1.56-1.79,  $p=0.000$ ). The risk of fracture increases with their long-term use: within 1 year the risk is 2.9% or one additional fracture in every 85 users; within 5 years the risk is 13.4% or one additional fracture in every 19 users. In meta-regression we found that the increase in risk did not differ across age groups (OR=1.006;  $p=0.173$ ). A limited number of studies on SNRIs use and the risk of fractures prevented us from conducting a meta-analysis.

**Conclusions:** Our systematic review showed an association between risk of fracture and the use of SSRIs, especially with increasing use. Age does not increase this risk. No such conclusions can be drawn about the effect of SNRIs on the risk of fracture due to a lack of studies.

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**INTRODUCTION**

The treatment most commonly prescribed for depression in older people is an antidepressant.<sup>1</sup> Due to the recurrent nature of depression, this often leads to a long-term prescription. Although psychological interventions (e.g., psychotherapy) seem to be more effective than antidepressants,<sup>2</sup> they are infrequently used in older age groups, for a variety of reasons (e.g., convenience, availability, eligibility criteria).<sup>2</sup>

According to the National Institute for Health and Clinical Excellence, the first choice of antidepressant is a Selective Serotonin Reuptake Inhibitor (SSRI), prescriptions of which have shown a 47% increase in recent years, irrespective of age.<sup>3</sup> The preference for SSRIs over other antidepressants (e.g., tricyclics) is due to their broad indications, safer side effect profile and efficacy.<sup>4</sup>

However, the use of SSRIs may be associated with a higher risk for all types of fractures compared to no SSRI use, which may be a particular concern in older patients.<sup>5-8</sup> Several guidelines mention the risk of fractures for SSRI use in the elderly: UK guidance on the use and safety of SSRIs indicates a small increased risk of fractures;<sup>9</sup> and the 2015 update of the Beers criteria also lists SSRIs as inappropriate medications in older adults, based on falls risk.<sup>10</sup> Although studies such as the population-based Canadian Multicenter Osteoporosis study showed an increased risk which led to a recommendation that bone health be assessed in patients treated with SSRIs,<sup>11</sup> a recent systematic review of Gebara *et al.* on the risk of falls could not show

causality between SSRI use and the former, stating that there is a lack of evidence to support changes in the current treatment guidelines on the use of SSRIs in older adults.<sup>12</sup>

Another group of antidepressants that is growing in popularity is Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs); however, little is known about their associated risk of fractures. This group of medications is increasingly prescribed in the elderly population for the treatment of a range of conditions such as depression, anxiety, diabetic neuropathic pain, fibromyalgia, and chronic musculoskeletal pain.<sup>13</sup> Venlafaxine and Duloxetine are two SNRIs that are commonly prescribed. Venlafaxine is now reported to be the sixth most frequently prescribed medication for the treatment of depression in older people.<sup>14</sup>

Several systematic reviews on the association of SSRI use and risk of fractures have been published previously, with the most recent being by Rabenda *et al.* in 2013.<sup>8</sup> We conducted an initial scoping review, which found that a considerable number of new, large and higher quality studies had been published since, indicating that an updated review would be appropriate.

Thus, considering an increasing rate of SSRIs and SNRIs prescription, a lack of studies on their comparative safety profile in older adults and a considerable number of new published studies since the last systematic review, we conducted a systematic review and meta-analysis with meta-regression. The specific research questions we sought to address were: (1) what is the association between SSRI and SNRI use versus non-use, on the risk of fracture in older adults? And (2) what is the effect of age on this association?

## **METHODS**

We conducted a systematic review and meta-analysis according to the Cochrane recommendations.<sup>15</sup> The review protocol was registered with the international register of systematic review protocols on PROSPERO (CRD42016052926). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework for reporting

the results.<sup>16</sup>

### **Eligibility criteria**

To be included in our review, studies had to meet the following criteria:

- Population: adults on an SSRI or SNRI, with or without a formal diagnosis of depression.
- Exposure: SSRI or SNRI use - Fluoxetine, Citalopram, Escitalopram, Paroxetine, Sertraline, Fluvoxamine, Venlafaxine, Duloxetine (a full list is provided in Supplementary material).
- Comparison: none or some other form of anti-depressant treatment.
- Primary outcome: fracture (any type of fracture at any anatomical sites either self-reported or identified in the hospital records).
- Study design: randomized-controlled trials, case-control (e.g., patients with a fracture compared to patients without a fracture), cohort studies (e.g., SSRI users compared to non SSRI users).

We included studies using any dose or duration of use of SSRI or SNRI, and recorded these factors as potential modifiers of treatment effect. For completeness when searching for studies, we also included those comparing SSRIs to SNRIs, different types of SSRIs/SNRIs, and different doses of SSRI/SNRI. These studies are described in the text, but have been excluded from any pooled statistical analysis (see below).

### **Search strategy and data sources**

A specialist librarian in systematic reviews assisted with the literature search. We performed a systematic search for articles without language restrictions in the following electronic bibliographic databases: MEDLINE, PsycINFO, EMBASE, DARE - Database of Abstracts or Reviews of Effects, the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane

Central Register of Controlled Trials (CENTRAL), Web of Science (science and social science citation index), clinical trials research registers (ClinicalTrials.gov and the WHO's International Clinical Trials Registry Platform). We searched for studies on SSRIs published from April 2011 (the most recent systematic review on the relationship between SSRIs and fractures included studies published up to this date)<sup>8</sup> to November 29, 2016. The search for studies on SNRIs ranged from 1990 to November 29, 2016. The first SNRI - Venlafaxine was marketed in 1994,<sup>17</sup> therefore we searched from 4 years prior to the marketing date to ensure that all pre-marketing trials were captured. We searched for the studies published in English, French, Dutch or Russian. The key words were “selective serotonin reuptake inhibitor”, “serotonin norepinephrine reuptake inhibitor”, “fracture”, “osteoporosis”, “osteopenia”, and “bone mineral density”. (See Supplementary material for an example, of the complete MEDLINE search terms). Additionally, reference lists from identified papers and reviews were checked for additional relevant studies. All companion articles of the included studies were also examined. If more than one publication described the same study, it was treated as one study. The full articles relating to any identified conference abstracts were obtained whenever possible. Literature search results were uploaded to the Endnote X7 reference management software package.

### **Study Selection**

We used a 2-step approach to study selection. First, 2 reviewers (VK, JH) independently examined the references (titles and abstracts) based on the eligibility criteria. Second, full texts of the selected references were retrieved and read. At each step, differences in coding were resolved by consensus. We included conference abstracts if they provided sufficient data.

### **Data Collection Process and Items**

One of the reviewers (VK) independently performed data extraction from each study using a standardized data collection form that included author, publication date, country, study design,

setting, medication type (SSRI, SNRI or both) or specific medication (e.g., Venlafaxine), duration of use (current, past), dose (e.g., defined daily dose – DDD), sample size, participant characteristics (mean age, male sex, variables controlled in analysis - age, sex, depression, BMD, body mass index - BMI, previous fracture, smoking, alcohol, glucocorticoids, number of comorbidities, Charlson comorbidity index and others), duration of the study and outcomes such as incidence of a new fracture (hip, spine, non-vertebral fractures) and other (e.g., BMD change, risk of fracture depending on 5-HTT affinity). Treatment effect estimates for each reported outcome were extracted including relative risk (RR) estimates (odds ratio - OR; hazard ratio - HR), associated 95% confidence intervals (95% CI), and/or *p* values. Where more than one effect estimate was reported for any outcome, the most stringently adjusted estimate was selected. Estimates of fracture risk for current and past SSRI and/or SNRI use were extracted separately, and an estimate of current use was used in a meta-analysis to derive an overall estimate across studies.<sup>11, 18-20</sup> For studies where multiple levels of DDD were investigated, results for the level closest to one DDD were selected.<sup>19, 21</sup> The primary outcome was fracture at any of the anatomical sites assessed in a study, which in most cases included multiple sites (e.g. hip, wrist or spine).<sup>22-25</sup> Where results were reported for both osteoporotic and non-osteoporotic fractures, results for the former were used.<sup>26</sup>

One of the authors (DR) checked the form and performed a quality control check by randomly selecting 60% of studies and conducting 100% verification of the data collected from these for meta-analysis.

### **Risk of Bias in Individual Studies**

The quality of each included study was assessed independently by 2 reviewers (VK, JH) using the Newcastle-Ottawa scale, designed for case-control and cohort studies.<sup>27</sup> Low quality was defined as a Newcastle-Ottawa score <7 and high quality as a score  $\geq 7$  (maximum score 9).<sup>5</sup>



## **Synthesis of Results**

We summarized the data in tables such as characteristics of included studies for case-control and cohort studies. When applying meta-analysis, we made an a priori assumption that studies were heterogeneous and adopted the DerSimonian-Laird random-effects model.<sup>28</sup> Depending on their design, studies reported effect sizes as odds-ratios, hazard ratios, relative risks or standardized incidence ratios, but for analysis purposes we treated all forms of effect as approximating an RR and amenable to pooling since the baseline incidence rate of fractures was typically low. We combined effect estimates across case-control and cohort studies but also included a comparison between these designs. The  $I^2$  statistic was used to measure heterogeneity. Analysis was conducted using the Stata v14 Metan and Metareg commands using an alpha value for statistical significance of 5%.<sup>29</sup>

### **Meta-analyses**

For our primary meta-analysis, we pooled studies regardless of the type(s) of SSRIs used or the site(s) of fracture studied, but restricted the comparison to non- or past-users of SSRIs (e.g., we excluded studies directly comparing different anti-depressants). We also conducted a sensitivity analysis using only the studies rated as high quality (NOS score  $\geq 7$ ) and subgroup meta-analyses (See Table S4).

### **Meta-regression**

There was wide variation between studies in participant age profiles, ranging in means from 43 years to 78 years. Therefore to investigate the relationship between age and risk of fracture when using SSRIs, we conducted meta-regression analyses of (log) effect sizes on the average age (usually mean age but for one study the median<sup>30</sup>) of the participants in each study. We then repeated this analyses including study design (cohort or case-control) and percentage male participants as covariates. Due to the limited number of studies for meta-regression, we did not

include any further study-level covariates.

### **Number needed to harm**

To estimate the number of additional users of SSRIs associated with one additional case of fracture (number needed to harm, or NNH) we used as a baseline the absolute rates of people 65 years and over not on anti-depressants experiencing a fracture, of 1.76% over 1 year, 3.26% over two years and 8.06% over 5 years, reported by Coupland *et al.*<sup>31</sup> These rates are based on analysis of patient records for 570 general practitioners practices from the QResearch primary care database. QResearch is reported to be reasonably representative of the UK primary care population.<sup>14</sup>

### **Risk of Bias Across Studies**

To examine the potential for publication bias amongst the final set of included studies, we produced a funnel plot, plotting the study standard errors against the logarithm of the risk ratios, as per the Cochrane recommendations.

## **RESULTS**

We identified 2,122 articles in the initial search, of which we reviewed 141 full articles (Figure 1). Our final sample consists of thirty-three studies: 11 case-control studies and 22 cohort studies. No relevant randomized controlled studies were found. Sixteen studies were included from the previous systematic review<sup>20-26, 30, 32-39</sup> and 17 studies were identified as new in the databases (Figure 1).<sup>11, 18, 19, 31, 40-52</sup>

The studies we found were published between 1998<sup>37</sup> and 2016,<sup>19, 42-44, 49</sup> with eleven studies since 2013.<sup>11, 19, 40, 41, 43-46, 48, 49, 52</sup> Two studies were reported across multiple articles and each was treated as a single distinct study: Vestergaard *et al.*<sup>21, 53, 54</sup> and Souverein *et al.*<sup>49, 55, 56</sup> One study reported results from both a cohort<sup>49, 55</sup> and a nested case-control analysis.<sup>49, 56</sup> Estimates of effect

size were very similar, but for meta-analyses where both sets of results were available we kept those from the cohort analysis, as precision was higher, and dropped the case-control results. Four conference abstracts were identified.<sup>40, 42, 47, 48</sup> All studies were published in English. The characteristics of the included studies are presented in Table 1 and 2.

### **Study characteristics**

*Participants:* In the 11 case-control studies, the numbers of case and control subjects ranged from 34<sup>49</sup> to 14,958<sup>53</sup> and from 412<sup>34</sup> to 373,962<sup>21</sup> respectively. In the 22 cohort studies, the numbers of participants ranged from 18<sup>20</sup> to 906,422<sup>41</sup> and the mean follow-up period from 6 months<sup>47</sup> to 10 years.<sup>11</sup> Five studies concerned patients with depression only and one, people with Parkinson's disease. Eight studies reported depression status based on a validated depression assessment tool (e.g., the geriatric depression scale). Nine and three studies respectively concerned only women or only men. Three studies examined the incidence of fractures for different age groups of participants.

*SSRI and SNRI:* 29 studies evaluated the effect of SSRIs, seven looked at SNRIs,<sup>14, 19, 21, 31, 44, 45, 47, 48, 53, 54</sup> and two studies grouped these drug classes together.<sup>11, 24</sup> Seven studies provided results for specific SSRI or SNRI medications;<sup>14, 19, 31, 35, 42-44, 54</sup> the remainder pooled across different medications. Data on SSRI and SNRI use were retrieved either from the national prescription database or self-reported and verified from drug containers. Thirteen studies categorized participants into current, recent or past users.<sup>11, 18-20, 24, 26, 35, 37-39, 41, 43, 52</sup>

*Comparisons:* Most studies (n=22) used non-users of SSRIs as the comparison group, though provided little detail on what other treatments individuals in the comparison group might be using. A few studies (n=9) compared SSRIs or SNRIs with other antidepressants (e.g., tricyclics),<sup>24, 32, 47</sup> SNRIs with SSRIs,<sup>45, 48</sup> current with past users,<sup>49</sup> individual SSRI medication

(Paroxetine) with other SSRIs,<sup>42</sup> with SSRIs of different adherence to the treatment<sup>50</sup> and no comparator description.<sup>36</sup>

*Outcome:* From 33 studies reporting fractures as an outcome, 3 studies reported separately on fractures and falls,<sup>31, 38, 43</sup> and 2 studies fractures and change in BMD.<sup>23, 38</sup> Occurrence of fractures was based on hospital records or national health databases, general practice databases, self-reporting adjudicated by medical records, and self-reporting. Hip was the most frequently reported anatomical site of a fracture followed by non-vertebral fractures and spine.

Six studies examined fracture incidence relative to SSRI daily dose (DDD)<sup>19-21, 31, 39, 46</sup> and 3 studies relative to affinity for 5-HTT.<sup>24, 26, 39</sup> Two studies reported the outcome for different follow-up periods.<sup>45, 52</sup>

*Study location:* Twelve studies were conducted in Europe (excluding the UK), 11 in the USA, 4 in the UK, 4 in Canada, 2 in Asia, and one in Israel. Four studies enrolled patients from multiple countries. One study included three different cohorts of patients; from the UK, Denmark and Spain.<sup>49, 55, 56</sup> The results of these cohorts were used independently in our meta-analyses.

*Quality of the studies:* Of the 29 studies (conference abstracts were not included in the quality assessment), 26 were high quality ( $\geq 7$ ) and 3 low quality (score  $< 7$ ) (Table S2 and Table S3).

### **Main meta-analytic results**

Of the 33 studies included in this systematic review, 23 studies were included in the primary meta-analysis: 9 case-control studies and 14 cohort studies. Ten studies were dropped from meta-analysis for reasons of lack of data (one conference abstract), qualitatively different population (Parkinson's disease), poorly matched or non-relevant comparison group (8 studies): see Table S1 for the specific reasons for exclusion from the meta-analysis. SSRI use and risk of fracture were significantly associated: RR 1.67, 95% CI 1.56-1.79,  $p=0.001$ ,  $I^2=88.4\%$  (Figure 2).

Sensitivity analysis based on only those studies rated as being high quality (n=18) found a very similar result: RR 1.68, 95% CI 1.54-1.84, p=0.001, I<sup>2</sup>=88.4% (Table S4).

Six studies examined the association between SNRI use and risk of fracture: 2 case-control and 4 cohort studies (Table S5). Effect of SNRI use was compared to non-use, SSRI use and tricyclics use. Two studies evaluated the effect of an individual SNRI (Venlafaxine). We did not conduct a meta-analysis on SNRIs due to their excessive heterogeneity and the limited number of studies. However, two studies reported a significantly increased risk associated with SNRI use (Table 3).

### **Meta-regression**

The meta-regression found no significant relationship between study effect size and average participant age, either without (OR=1.006; p=0.173) or with control for design type and gender balance (OR=1.006; p=0.175) (Figure 3). Design and gender were themselves not significant moderators of effect size (p=0.602 and p=0.640 respectively).

### **Subgroup meta-analyses**

Subgroup meta-analyses are presented in Table S4. In most subgroup analyses the number of studies was small (<5) and heterogeneity was high. In line with the finding of the meta-regression, the association between SSRI use and the risk of fracture was similar in both case-control and cohort studies: RR 1.74, 95% CI 1.50-2.02, p=0.001, I<sup>2</sup>=92.8% and RR 1.63, 95% CI 1.49-1.79, p=0.001, I<sup>2</sup>=84.8% respectively. RRs also varied by only a small degree between different anatomical sites of fracture.

Results for individual SSRI medications were available from only four studies, and subgroup analysis showed only small differences in relative risks with widely overlapping confidence intervals. However, the effect sizes were all well below the overall RR of 1.67 across all included studies, suggesting that this is an unrepresentative subset.

For the remaining subgroup analyses, the sub-category level effects likewise had highly overlapping confidence intervals in almost all cases, indicating either only small differences or that study numbers were too small to detect differences.

### **Number needed to harm**

On the basis of the overall pooled relative risk of 1.67 from our meta-analysis and baseline absolute fracture rates of 1.76% over 1 year, 3.26% over two years and 8.06% over 5 years,<sup>31</sup> the estimated fracture rate over one year's exposure to SSRIs is 2.9% with an NNH of 85; over two years 5.4% with NNH=46; and over 5 years 13.4% with NNH=19.

### **Publication bias**

The funnel plot was asymmetrical; showing a shortage of smaller studies with lower, possibly non-significant, effect sizes. This could indicate a publication bias against such studies (Figure 4).

## **DISCUSSION**

Our meta-analysis showed a pooled 1.67-fold increase in the risk of fracture for older SSRI users in comparison to non-users. This level of increased risk is in line with the findings of previous systematic reviews,<sup>5, 6, 8, 57, 58</sup> but is based on a much larger and higher-quality evidence base. SSRIs are typically taken over a long period and the associated risk of fracture within 5 years use was 13.4% or one additional fracture in every 19 users. At least part of any increased risk of fracture could be related to possible side effects of SSRIs that may be more prominent at their initiation: orthostatic hypotension, dizziness, falling, and tachyphylaxis.<sup>59-61</sup> However, we found that the risk was still significantly elevated over 5 years of use in contrast to the findings of Eom *et al.* who showed a higher risk of fractures with a shorter duration of SSRIs.<sup>5</sup>

Despite age having a well-known association with fracture risk,<sup>62</sup> in meta-regression we found the increase in risk from SSRI use to be much the same in all the studied age groups, from 40

years up to 80 years, and the same for males and females. Our meta-analysis thus indicated that SSRIs play an independent role from age and gender in increased risk of fracture.<sup>6</sup>

### **Strengths and limitations**

Our systematic review is the most comprehensive review to date on the use of SSRIs (and SNRIs) and the risk of fracture. The last meta-analysis on SSRIs was published in 2013 and included 16 studies published up to April 2011.<sup>8</sup> The great majority of the studies we included were individually statistically significant, but nonetheless, there was high heterogeneity in effect size and some evidence of possible publication bias against smaller, non-significant studies.

Although the large majority of studies were rated high quality, the cohort studies generally fell down on giving details of exposure, and the case-control studies on details of exposure and non-response rate. The control condition was frequently poorly described and differed across studies, but in most cases combined non-users of anti-depressants with users of other types of anti-depressants. This may have led to some degree of underestimation of the fracture risk for SSRIs compared to an entirely anti-depressant free population. We did not have individual patient data for meta-regression, so were limited to using study mean ages and gender balance, which will have limited our power to detect an association with risk. The limited number of the studies on SNRIs use and a risk of fracture did not allow us to conduct a meta-analysis and to provide their safety profile.

We found no relevant randomized controlled trials; hence our review is based entirely on observational studies that have the potential for bias. We extracted the data adjusted for confounders such as osteoporotic risk factors (e.g., BMI, previous fracture), study design, methodological quality, age, type of fracture, and duration of the treatment. However, there is still a risk of unobserved bias. For example, as Gebara *et al.* indicate, a study design based on an administrative database<sup>11, 45</sup> will not adequately capture the diagnosis of depression.<sup>12</sup> An absence

of randomization in observational studies also introduces the risk of allocation bias. In this context, older patients with higher risk of falls tend to have SSRIs or SNRIs prescribed, instead of other antidepressants (e.g., tricyclic antidepressants). We found indications of publication bias against smaller non-significant studies, but this is unlikely to fully account for our overall result, derived mostly from a substantial number of very large observational investigations.

There were considerable differences in design between studies, including variations in study design, populations, comparison groups, SSRI medications, doses and duration, and non-adjustment (or non-reporting) of important variables. However, we excluded 10 studies from meta-analysis that were markedly different in quality of reporting, population, or selection of comparison group (e.g., tricyclics). We were limited in our ability to investigate the effects of this heterogeneity on study results, due to the number of studies and the available information on each. Most of the sub-group analyses were based on very small numbers of studies (2, 3 or 4) and results for these should be treated with considerable caution, as the addition of just one extra study – particularly given the high heterogeneity - could cause a substantial change in the effect estimate or confidence interval.<sup>63</sup>

## **Conclusion**

There is sufficient albeit non-randomized evidence that use of SSRIs substantially increases fracture risk in adults, from at least age 40 years and above, particularly when used over long periods; but counter to expectations, the degree of increased risk is largely independent of age.



## **Key points**

- ✓ SSRIs are the first choice of antidepressants in elderly patients with depression. They are associated with higher risk of fractures. Depression plays an independent role in increased risk of fractures.
- ✓ Our study found that age does not increase the risk of fractures associated with SSRIs use. Long-term use of SSRIs leads to higher risk of fractures.
- ✓ A number of methodological limitations of the published trials suggest the actual risk may be higher than our estimate.

The authors have no conflicts to declare.

Contributors: VK, DR, HvM – were involved in the conception and design of the review. VK and JH – performed study selection and quality assessment. VK and DR – extracted data from included studies. VK and DR – were involved in the data analysis. VK, JH, DR, HvM – were involved in the interpretation and discussion of results. VK, JH, DR, HvM – drafted the manuscript. All authors approved the final version of the article. VK – is the guarantor.

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## REFERENCES

1. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848-56.
2. Collins N, Corna L. General practitioner referral of older patients to Improving Access to Psychological Therapies (IAPT): an exploratory qualitative study. *BJPsych bulletin* 2018;42(3):115-18.
3. *Prescription cost analysis: England 2009*. The Health and Social Care Information Centre, 2010.
4. Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. *Prim Care Companion J Clin Psychiatry*. 2001;3(1):22-7.
5. Eom CS, Lee HK, Ye S, Park SM, Cho KH. Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. *J Bone Miner Res*. 2012;27(5):1186-95.
6. Wu Q, Bencaz AF, Hentz JG, Crowell MD. Selective serotonin reuptake inhibitor treatment and risk of fractures: a meta-analysis of cohort and case-control studies. *Osteoporos Int*. 2012;23(1):365-75.
7. Rizzoli R, Cooper C, Reginster JY, Abrahamsen B, Adachi JD, Brandi ML, et al. Antidepressant medications and osteoporosis. *Bone*. 2012;51(3):606-13.
8. Rabenda V, Nicolet D, Beaudart C, Bruyere O, Reginster JY. Relationship between use of antidepressants and risk of fractures: a meta-analysis. *Osteoporos Int*. 2013;24(1):121-37.
9. *Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs): use and safety*. Medicines and Healthcare products regulatory agency, 2014.
10. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63(11):2227-46.

11. Moura C, Bernatsky S, Rahme E, Beauchamp ME, Bessette L, Adachi J, et al. Psychotropic medication use and 10-year incident fracture risk in men and women ages 50 and older in the population-based Canadian Multicentre Osteoporosis Study (CaMoS). *J Popul Ther Clin Pharmacol*. 2014;21 (1):e116.
12. Gebara MA, Lipsey KL, Karp JF, Nash MC, Iaboni A, Lenze EJ. Cause or Effect? Selective Serotonin Reuptake Inhibitors and Falls in Older Adults: A Systematic Review. *Am J Geriatr Psychiatry*. 2015;23(10):1016-28.
13. Nelson JC, Oakes TM, Liu P, Ahl J, Bangs ME, Raskin J, et al. Assessment of falls in older patients treated with duloxetine: a secondary analysis of a 24-week randomized, placebo-controlled trial. *Prim Care Companion CNS Disord*. 2013;15(1).
14. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ*. 2011;343:d4551.
15. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Baltimor, MD: 2011.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-41.
17. Redrobe JP, Bourin M, Colombel MC, Baker GB. Dose-dependent noradrenergic and serotonergic properties of venlafaxine in animal models indicative of antidepressant activity. *Psychopharmacology*. 1998;138(1):1-8.
18. Rabenda V, Bruyere O, Reginster JY. Risk of nonvertebral fractures among elderly postmenopausal women using antidepressants. *Bone*. 2012;51(4):674-9.

19. Wang CY, Fu SH, Wang CL, Chen PJ, Wu FL, Hsiao FY. Serotonergic antidepressant use and the risk of fracture: a population-based nested case-control study. *Osteoporos Int*. 2016;27(1):57-63.
20. Ziere G, Dieleman JP, van der Cammen TJ, Hofman A, Pols HA, Stricker BH. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of nonvertebral fractures. *J Clin Psychopharmacol*. 2008;28(4):411-7.
21. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. *Osteoporos Int*. 2006;17(6):807-16.
22. Abrahamsen B, Brixen K. Mapping the prescription to fractures in men--a national analysis of prescription history and fracture risk. *Osteoporos Int*. 2009;20(4):585-97.
23. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, et al. Depressive symptoms, bone loss, and fractures in postmenopausal women. *J Gen Intern Med*. 2008;23(5):567-74.
24. Gagne JJ, Patrick AR, Mogun H, Solomon DH. Antidepressants and fracture risk in older adults: a comparative safety analysis. *Clin Pharmacol Ther*. 2011;89(6):880-7.
25. Diem SJ, Blackwell TL, Stone KL, Cauley JA, Hillier TA, Haney EM, et al. Use of antidepressant medications and risk of fracture in older women. *Calcif Tissue Int*. 2011;88(6):476-84.
26. Verdel BM, Souverein PC, Egberts TC, van Staa TP, Leufkens HG, de Vries F. Use of antidepressant drugs and risk of osteoporotic and non-osteoporotic fractures. *Bone*. 2010;47(3):604-9.
27. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa, ON: Ottawa Hospital Research Institute.

28. Kontopantelis E, Springate DA, Reeves D. A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. *PloS one*. 2013;8(7):e69930.
29. Stata Statistical Software. 2015 [cited April 20, 2017]; Available from.
30. Schneeweiss S, Wang PS. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. *J Clin Psychopharmacol*. 2004;24(6):632-8.
31. Coupland CA, Dhiman P, Barton G, Morriss R, Arthur A, Sach T, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. *Health Technol Assess*. 2011;15(28):1-202, iii-iv.
32. Bolton JM, Metge C, Lix L, Prior H, Sareen J, Leslie WD. Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol*. 2008;28(4):384-91.
33. Ensrud KE, Blackwell T, Mangione CM, Bowman PJ, Bauer DC, Schwartz A, et al. Central nervous system active medications and risk for fractures in older women. *Arch Intern Med*. 2003;163(8):949-57.
34. French DD, Campbell R, Spehar A, Cunningham F, Foulis P. Outpatient medications and hip fractures in the US: a national veterans study. *Drugs Aging*. 2005;22(10):877-85.
35. Hubbard R, Farrington P, Smith C, Smeeth L, Tattersfield A. Exposure to tricyclic and selective serotonin reuptake inhibitor antidepressants and the risk of hip fracture. *Am J Epidemiol*. 2003;158(1):77-84.
36. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, et al. Predictors of non-spine fracture in elderly men: the MrOS study. *J Bone Miner Res*. 2007;22(2):211-9.
37. Liu B, Anderson G, Mittmann N, To T, Axcell T, Shear N. Use of selective serotonin-reuptake inhibitors or tricyclic antidepressants and risk of hip fractures in elderly people. *Lancet*. 1998;351(9112):1303-7.

38. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, Prior JC, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med.* 2007;167(2):188-94.
39. van den Brand MW, Pouwels S, Samson MM, van Staa TP, Thio B, Cooper C, et al. Use of anti-depressants and the risk of fracture of the hip or femur.[Erratum appears in *Osteoporos Int.* 2009 Oct;20(10):1715]. *Osteoporos Int.* 2009;20(10):1705-13.
40. Adachi J, Lacroix AZ, Lindsay R, March L. Fracture patterns with selective serotonin receptor inhibitor, proton pump inhibitor and glucocorticoids use in GLOW. *Conference abstract: Osteoporos Int.* 2014;25((Suppl 2)):119.
41. Bakken MS, Engeland A, Engesaeter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age Ageing.* 2013;42(4):514-20.
42. Bali V, Aparasu R, Johnson ML, Chen H, Carnahan R. Comparative safety of paroxetine and other SSRIs for the risk of hip fracture in elderly nursing home residents with depression. *Conference Abstract: Value in Health.* 2016;19 (3):A183-A4.
43. Carriere I, Farre A, Norton J, Wyart M, Tzourio C, Noize P, et al. Patterns of selective serotonin reuptake inhibitor use and risk of falls and fractures in community-dwelling elderly people: the Three-City cohort. *Osteoporos Int.* 2016;27(11):3187-95.
44. Cheng BH, Chen PC, Yang YH, Lee CP, Huang KE, Chen VC. Effects of depression and antidepressant medications on hip fracture A population-based cohort study in Taiwan. *Medicine.* 2016;95 (36) (no pagination)(e4655).
45. Lantaigne A, Sheu YH, Sturmer T, Pate V, Azrael D, Swanson SA, et al. Serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor use and risk of

fractures: a new-user cohort study among US adults aged 50 years and older. *CNS Drugs*. 2015;29(3):245-52.

46. Pouwels S, Bazelier MT, de Boer A, Weber WE, Neef C, Cooper C, et al. Risk of fracture in patients with Parkinson's disease. *Osteoporos Int*. 2013;24(8):2283-90.

47. Schink T, Jobski K, Schmedt N, Kollhorst B, Garbe E. Antidepressants and the Risk of Hip Fractures. *Conference Abstract: Pharmacoepidemiol Drug Saf*. 2015;24:554.

48. Sheu YH, Lantaigne A, Sturmer T, Pate V, Azrael D, Miller M. Fracture Risk among Depressed Patients Initiating SNRIs vs SSRIs Antidepressants. *Conference Abstract: Pharmacoepidemiol Drug Saf*. 2014;23:273.

49. Souverein PC, Abbing-Karahagopian V, Martin E, Huerta C, de Abajo F, Leufkens HGM, et al. Understanding inconsistency in the results from observational pharmacoepidemiological studies: The case of antidepressant use and risk of hip/femur fractures. *Pharmacoepidemiol Drug Saf*. 2016;25:88-102.

50. Zucker I, Chodick G, Grunhaus L, Raz R, Shalev V. Adherence to treatment with selective serotonin reuptake inhibitors and the risk for fractures and bone loss: a population-based cohort study. *CNS Drugs*. 2012;26(6):537-47.

51. Hanyu R, Wehbi VL, Hayata T, Moriya S, Feinstein TN, Ezura Y, et al. Anabolic action of parathyroid hormone regulated by the beta2-adrenergic receptor. *Proc Natl Acad Sci U S A*. 2012;109(19):7433-8.

52. Sheu YH, Lantaigne A, Sturmer T, Pate V, Azrael D, Miller M. SSRI use and risk of fractures among perimenopausal women without mental disorders. *Inj Prev*. 2015;21(6):397-403.

53. Vestergaard P, Prieto-Alhambra D, Javaid MK, Cooper C. Fractures in users of antidepressants and anxiolytics and sedatives effects of age and dose. *Osteoporos Int*. 2012;23:S70.

54. Vestergaard P, Rejnmark L, Mosekilde L. Selective serotonin reuptake inhibitors and other antidepressants and risk of fracture. *Calcif Tissue Int.* 2008;82(2):92-101.
55. Ali MS, Groenwold RH, Belitser SV, Souverein PC, Martin E, Gatto NM, et al. Methodological comparison of marginal structural model, time-varying Cox regression, and propensity score methods: the example of antidepressant use and the risk of hip fracture. *Pharmacoepidemiol Drug Saf.* 2016;25 Suppl 1:114-21.
56. De Groot MCH, Candore G, Uddin MJ, Souverein PC, Ali MS, Belitser SV, et al. Case-only designs for studying the association of antidepressants and hip or femur fracture. *Pharmacoepidemiol Drug Saf.* 2016;25:103-13.
57. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf.* 2007;30(2):171-84.
58. Oderda LH, Young JR, Asche CV, Pepper GA. Psychotropic-related hip fractures: meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. *Ann Pharmacother.* 2012;46(7-8):917-28.
59. Pacher P, Ungvari Z. Selective serotonin-reuptake inhibitor antidepressants increase the risk of falls and hip fractures in elderly people by inhibiting cardiovascular ion channels. *Med Hypotheses.* 2001;57(4):469-71.
60. Donaldson LJ, Reckless IP, Scholes S, Mindell JS, Shelton NJ. The epidemiology of fractures in England. *J Epidemiol Community Health.* 2008;62(2):174-80.
61. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med.* 1998;339(13):875-82.
62. Ensrud KE. Epidemiology of fracture risk with advancing age. *J Gerontol A Biol Sci Med Sci.* 2013;68(10):1236-42.



63. Friede T, Rover C, Wandel S, Neuenschwander B. Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. *Biom J.* 2017;59(4):658-71.

Figures legends:

**Figure 1.** Flow Chart

**Figure 2.** SSRI use and risk of fracture

**Figure 3.** Meta-regression of log effect size on average age of study participants.

**Figure 4.** Funnel plot of RR vs standard error of the log