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## **High risk of osteoporotic fracture in Parkinson's disease: meta-analysis, pathophysiology and management**

Louvois<sup>1</sup> M., Ferrero S<sup>1</sup>., Barnetche T.<sup>2</sup>, Roux CH<sup>1</sup>, Breuil V.<sup>1,3</sup>

1. Université Côte d'Azur (UCA), Service de Rhumatologie, CHU DE NICE - HÔPITAL PASTEUR 2 - 30 Voie Romaine - CS 51069 - 06001 Nice Cedex 1 – France
2. Department of Rheumatology - FHU ACRONIM - CHU Pellegrin, Bordeaux, France
3. UMR E-4320 MATOs CEA/iBEB/SBTN, Université Nice Sophia Antipolis - Faculté de Médecine, 28 avenue de Valombrose, 06 107 Nice Cedex 2 – France

### **Corresponding author:** Véronique Breuil

Université Côte d'Azur (UCA), Service de Rhumatologie, CHU DE NICE - HÔPITAL PASTEUR 2 - 30 Voie Romaine - CS 51069 - 06001 Nice Cedex 1 – France

Téléphone : 04 92 03 55 12

Fax : 04 92 03 90 18

E-mail : [breuil.v@chu-nice.fr](mailto:breuil.v@chu-nice.fr)

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## **INTRODUCTION**

Parkinson's disease (PD) and osteoporosis (OP) are both age-related diseases recognized as a major public health issue with a high prevalence and an increased risk of loss of autonomy, long-term disability and increased mortality [1,2].

OP is the most common metabolic skeletal disorder, characterized by a decrease in bone mass and alterations of the microarchitecture, leading to skeletal fragility and an increased risk of fractures [2]. OP is a multifactorial disease including aging, gonadal insufficiency and vitamin D deficiency [2,3]. In Western populations, the risk of OP fracture occurring in the remaining lifetime from 50 -years -old individuals is 50% for women and 20% for men [4]. The incidence of OP fractures increases with age and so-called "severe" fractures (spine, hip, humerus and pelvis) are associated with increased morbidity and mortality [5]. The diagnosis of OP is based on the combination of low bone mineral density (BMD) measured by Dual energy X-ray absorptiometry and several factors including age, sex, low body mass index and previous fragility fracture [4,6,7]. OP can be revealed by its complication, fragility fractures, but could be diagnosed earlier based on BMD results [2,6,7]. Although OP fractures can occur spontaneously, particularly vertebral fractures, falls from standing height are the leading causes of fragility fractures. Among these falls, 5% are responsible for fractures at any site [8].

PD is the commonest neurodegenerative disorder after Alzheimer's disease, characterized by rigidity, tremor while rest, bradykinesia, postural instability and others non motors symptoms [1]. PD is recognized as a major public health problem because of its high prevalence and the disabilities and deaths related to this condition [1,9]. Indeed, in France in 2010, the prevalence in the population was 308 to 410 per 100 000 persons (depending on the definition used) and it dramatically increases with age [10]. Beside this high risk of falls, PD is associated with low BMD related to multiple risk factors in relation to the specific pathophysiology of PD, that increase the risk of low-trauma fractures

[11,12].

Based on these findings, the increased risk of OP fractures in PD patients has been explored in many studies. The most recent meta-analysis of global fracture risk in PD was published in 2014, reporting an increase of this risk [13]. Since then, new data on fracture risk in PD patients have become available and two meta-analyses have just been published but are restricted to peripheral fractures and one extended to parkinsonism [14,15]. Thus, we performed a meta-analysis of cohort studies to actualize the association between PD and OP fracture risk at all sites, including vertebral fractures.

## **MATERIALS AND METHODS**

### ***Search strategy***

We performed a systematic search on PubMed and Embase up to February the 2th 2019 for prospective and retrospective cohort studies that reported the association between PD and fractures. The search terms were ((((((((((osteopor\*) OR bone fragility) OR BMD) OR "Fractures, Bone"[Mesh]) OR fracture) OR "Bone Density"[Mesh]) OR "Osteoporosis"[Mesh])) OR bone density)) AND (("Parkinson Disease"[Mesh]) OR parkinson). We also performed a review of the reference list of all the articles of interest in order to find any additional literature. The language restriction was French and English.

### ***Study selection criteria***

We included the studies that met the following criteria: studies that had a prospective or retrospective cohort design controlled or not, whose main outcome was the relationship between PD and at least one anatomic site of fracture, whose study population was exclusively primitive PD patients, studies that reported the RR or the HR with their IC 95% and the analyzed fractures having occurred after the diagnosis of PD. Studies that included secondary Parkinsonism or did not report risk estimated or were conference

abstracts were excluded.

### ***Data extraction and quality assessment***

Two investigators (ML and SF) collected the data using a predetermined form. For each study, we extracted the following data with open office binder : year of publication, type of study, country, age, gender ratio, average follow-up, total cases and total controls, outcomes, outcome assessment (site of fracture), adjustment for confounders, falls, osteoporosis or BMD, and the risk of fracture for each anatomic site, or estimated based on sample size and number of patients with fractures (Hazard ratios (HRs) and Relative risk (RR) for total fractures, hip fractures and vertebral fractures, with their 95% confidence intervals.

### ***Data analysis***

Single RRs were pooled to estimate a RR of fracture within a meta-analysis procedure using the inverse variance approach. Heterogeneity analysis was also performed with Cochran's Q-test and  $I^2$  value. RevMan software was used and p-value less than 5% was defined as significant. The heterogeneity was considered as low if  $I^2 < 25\%$ , moderate if  $I^2$  was between 25 and 50%, and high if  $I^2 > 50\%$ . The risk of bias was calculated by using the Newcastle-Ottawa scale [16].

## **Results**

### ***Literature Search***

The flow for the selection is shown in figure 1. The systematic review of studies database searches identified 1314 records. After removing 490 duplicates, 751 articles were excluded based on their title. From the remaining 73 records, 58 were excluded after reading the abstract :19 were not clearly relevant or had unsuitable data for analysis, 27

were not cohort studies, 6 included secondary Parkinsonism, Alzheimer disease or strokes, 4 were not in English or in French and 2 were retracted. Out of the remaining 15 articles, 3 were excluded after reading the full text as the results were not expressed in HR or had no control group, one that included secondary Parkinsonism and one based on an estimated number of people with PD using a crude prevalence from 2 previous studies [17–21]. We included 2 studies from the manual search and finally a total of 12 cohort studies were included for the meta-analysis [22–33].

### ***Study characteristics***

Table 1 summarizes the main characteristics of the 12 cohort studies included in the analysis: 6 studies were prospective and 6 retrospective. The study population ranged from 52 to 860 388 participants, with a total of 1,246,431 participants (60,226 PD and 1,186,205 controls). Three studies included only women [22,25,28] and 1 only men [24]. For the others, there was a slight male dominance near to one, except for two studies with a majority of women [29,33]. Out of the 12 studies, 6 were conducted in the US, 1 in Germany, 1 in UK, 1 in Australia, 1 in Korea and 2 in Taiwan. Nine studies calculated the RR for hip fractures [22,23,25–27,29–32], 4 the RR for vertebral fractures [23,27,31,33] and 8 included other sites [23–25,27,28,30–32]. Five studies were based on national insurance records [26,29–31,33], 5 on inpatients' records [23–25,27,32] and 2 on self-reported data [22,28]. The follow-up ranged from 1 to 13 years.

### ***Main analysis***

Figure 2 shows a forest plot presenting the individual and overall RR of fractures all sites combined. The meta-analysis of all included studies suggests a significant increase of global fracture risk in PD patient compared to those without PD (overall RR 2.17, 95% CI 1.81-2.59). However, there is substantial heterogeneity between the studies ( $I^2= 94\%$ ). If

we take into account only the 6 studies that specifically report a global risk of fracture, the result of the meta-analysis remains similar (RR 2.06, 95% CI 1.64-2.58;  $I^2$  95%) [23,27,28,30–32].

### ***Subgroup and sensitivity analysis***

#### ***Vertebral fractures***

The individual and overall RR of vertebral fractures is presented in figure 3. The meta-analysis of the 4 included studies suggests an increased risk of vertebral fracture in PD patients compared to controls (RR 1.84, 95% CI (1.46-2.59]). However, the heterogeneity of the studies is high ( $I^2= 53\%$ ).

#### ***Hip fractures***

The individual and overall RR of hip fractures is presented in figure 4, showing a significant increase of hip fractures in PD patients (overall RR 2.55, 95% CI (2.20-2.97)). The heterogeneity is high across the studies ( $I^2=68\%$ ). As one study enrolled exclusively fallers, we carried out a sensitivity analysis of hip fractures excluding this study (figure 5) [32]. It confirms a very significant increase of hip fracture in PD patients (overall RR 2.69, 95% CI 2.45-2.97) with no heterogeneity between the studies ( $I^2 = 0\%$ ).

#### ***Publication Bias***

Table 2 assesses the quality of the studies included in the meta-analysis, using the Newcastle Ottawa Scale (NOS) for cohort studies [16]. Studies included in this meta-analysis were of moderate or high quality, all scoring higher or equal to 4 out of 9 stars. Most studies scored poorly for the item “adequacy of follow-up”, due to a lack of information given in the study report. Five studies scored poorly for the item “representativeness of the exposed cohort”, because four of them [22,24,25,28] did not

include both genders and one included only patients having falls [32]. Due to the use of self-reported assessment, four studies scored poorly for the item “ascertainment of exposure” [22,24,25,28] and one for the item “outcome assessment” [28]. One-year follow-up was not long enough for outcomes to occur [31]. One study did not use a control group and was scored poorly for the item “comparability” [28]. Finally, two studies scored poorly for the item “outcomes of interest not present at the start of study” due to no demonstration of it in the study report [27,32].

## **Discussion**

On the whole, our study confirms that PD patients are exposed to a significant increased risk of any type of fracture, whether vertebral fractures or hip fractures. These results are consistent with previous systematic reviews and meta-analyses, although some differences in methodology and scope of the previous meta-analysis may account for some slight variations in the magnitude of the increase in fracture risk [13–15]. Indeed, in our meta-analysis, the global risk of fracture appears to be twice as high in PD subjects (RR 2.17), slightly lower than in the previously meta-analysis of Tan et al. (RR=2.66) who selected exclusively prospective cohort studies (Figure 2) [13]. These findings deserve attention as the main risk factor of sustaining a fracture is a previous one, but also because the role of “imminent” fracture appears to be crucial with a dramatic short-term increased risk within the 2 years following vertebral or non-vertebral fracture [34]. This “imminent risk” has been shown in frail osteoporotic subjects with central nervous system diseases or drugs targeting central nervous system [34]. So, PD patients with a recent OP fracture have an imminent risk of new fractures and should be identified in priority in order to receive an immediate treatment [34]. Prompt management is important since, in addition to the increased mortality associated with severe fractures, the costs of care in patients with PD and fall-related fractures are high and affect health economics [35].



Among fractures in PD patients, the increased risk of hip fracture is the highest and the most significant one. We found a RR of hip fracture of 2.69 in PD patients, without any heterogeneity after excluding one study which included exclusively fallers, in agreement with previous studies that report a RR ranging from 2.40 to 3.14 (Figure 4) [14,15,32]. This finding is important as hip fractures are characterized by their severity related to loss of autonomy, increased mortality, predictive of new OP fractures and high direct and indirect costs, as underlined in the report of the International Osteoporosis Foundation [36]. Moreover, it has been shown that a hip fracture in PD patients is associated with a six times higher mortality-rate, longer hospital stays, worse mobility and increased institutionalization [37,38].

Previous meta-analysis had not addressed the risk of vertebral fracture as vertebral fractures are poorly recorded and their identification requires radiographs [14]. Indeed, vertebral fractures can occur spontaneously without fall, induce no or non-specific clinical symptoms and approximately two-thirds of vertebral fractures do not raise clinical attention [39]. However, vertebral fractures are the most common type of OP fracture [39]. They could be suspected on simple strategies, such as monitoring a patient's height loss : height loss  $\geq 4$  cm compared to historical height (at 20 years of age) or loss of height  $\geq 2$  cm as established prospectively during follow-up when followed over 1-3 years is highly predictive of an underlying vertebral fracture [40]. The identification of vertebral fractures is important because they are robust predictors of future fractures, even in the absence of symptoms [41]. Thus, while aware of these limitations and a probable underestimation of vertebral fractures risk, we thought it worth analyzing the risk of vertebral fractures in PD. In the 4 studies selected for meta-analysis, the RR of vertebral fractures ranged from 1.5 to 3.17 depending on the method used to identify these fractures [23,27,31,33]. Our results suggest that PD patients are nearly twice as likely to experience a vertebral fracture (RR=1.84) as controls (Figure 3). One should be aware of the fact that PD patients have an

increased risk of vertebral fractures as these fractures can lead to chronic back pain, increased fear of falling and are associated with substantial morbidity and decreased survival and are predictive of new OP fractures as well [39,40].

In the general population, women are at greater risk of OP than men [4]. Regarding PD, a non-spine, non-hip fracture affected 22% of PD women in the female cohort of Schneider et al. during an average follow-up of 9 years, and 15.2% of PD men in the male cohort of Fink et al. during an average follow-up of 5.1 years [24,25]. The over-risk of fracture due to PD does not appear to be clearly predominant in one sex, as previous meta-analyses report either the same fracture risk for both sexes, a higher risk for women or a higher risk for men, interpreted for the latest as being due in part to a lower fracture rate and a lower relative risk denominator for men without PD than for women [13–15]. These conflicting results may reflect the heterogeneity of the populations observed. Anyway, the key point is that PD is associated with an increased risk of fracture in both men and women compare to subjects without PD [13–15]. In the two studies that included exclusively women and the only study that included exclusively men, the increased risk of hip fracture appears to be comparable in both sexes (respectively HR 2.52, 2.6 ad 2.4) and in the study that only enrolled fallers, males accounted for the greatest proportion of PD-related fall admission but the RR of all fractures and hip fracture remains nearly unchanged after the age and sex-adjusted rate ratio [22,24,25,32].

Falls play a major role in the occurrence of OP fractures, as they trigger most of them. In PD falls are the first cause of emergency hospitalization and 60% of people with PD fall each year [1,42]. Beside falls, PD is associated with low BMD, accelerated bone loss and BMD is negatively correlated to the severity of PD [24,25,33,43–46]. The pathophysiology of OP in PD involved many factors but is yet partly misunderstood as reported in two reviews [11,12]. Among them, weight and body mass indexes strongly correlate with BMD and PD patients often experience weight loss, with a relationship

between nutritional status and motor and non-motor functions, disease duration and severity of the disease [11,47,48]. In the study of Schneider JL et al., body weight accounted for 72% of the decrease of BMD in PD subjects compared to controls [25]. Sarcopenia, frequently observed in PD, may also contribute to bone loss, by increasing risk of falls and sclerostin levels, a potent inhibitor of bone formation whose secretion is inhibited by loading exercises [12]. Vitamin D deficiency is a risk factor common to OP and PD. Vitamin D is known for its role in regulating calcium homeostasis and metabolism and a high prevalence of vitamin D deficiency is associated with OP in PD in cross sectional studies, consequence of limited UV light exposure and malnutrition [12,49,50]. Vitamin D Receptor (VDR) and 1 $\alpha$ -hydroxylase, the enzyme that converts vitamin D to its active form, are highly expressed in the substantia nigra, leading to the hypothesis that inadequate levels of circulating vitamin D may lead to dysfunction or cell death within the substantia nigra [51]. Based on these findings, many studies have been performed on the association between vitamin D levels and PD: two meta-analysis, including mainly case-control studies, suggest that vitamin D insufficiency or deficiency induces a 1.5 to 2.5-fold increased risk of PD, but two prospective studies on the association between mid-life vitamin D levels and risk of PD and produced conflicting results [51–53]. However, the inverse association between serum vitamin D level and motor symptom severity in cross-sectional studies is consistent and fall risk has been associated with vitamin D in PD [51].

Based on these data, an evaluation of bone status in PD subjects should be proposed including, BMD assessment, search of previous fragility fractures, evaluation of calcium intake and blood test dosing vitamin D levels [2]. If necessary, deficiencies should be corrected by ensuring a total daily intake of calcium of 800–1200 mg and a serum 25-hydroxyvitamin D of at least 50 nmol/L [2,54]. The prevention of falls is crucial, including optimization of PD treatment, environmental management, footwear, and rehabilitation [2,55]. The indication for a specific treatment of OP is based on the presence and type of

previous fragility fracture (severe OP fracture) and, in the absence of fracture, on BMD and other risk factors used for FRAX tool, an algorithm that calculates a person's probability of sustaining hip fracture and major OP fracture over the next 10 years [56]. Recently, Henderson EJ et al. has proposed an algorithm, BONE-PARK, for fracture risk assessment and bone health management in outpatients with PD, that include PD in the secondary OP in the calculation of FRAX [54]. Specific therapies for OP decrease the risk of vertebral and non-vertebral fracture [2]. Among them, zoledronic acid, the most potent bisphosphonate, displays several advantages: it reduces vertebral fractures by 70% and hip fractures by 40%, significantly decreases mortality after hip fracture and is intravenously administered once a year at home in 15 minutes, an advantage for elderly patients with polypharmacy and gastrointestinal dysfunction [2,56,57]. PD patients with severe OP fracture should receive specific treatment against OP, as soon as possible to prevent imminent fracture risk [2,34]. There is no specific study addressing the efficacy of OP therapy in PD patients. However, there is a new trial, TOPAZ (NCT034) ongoing, testing the efficacy of zoledronic acid administered at home once a year for two years in PD patients without any extra-medical visit or BMD testing to prevent OP fractures [12].

There are several limitations in our study. We restricted our search to English and French and thus did not consider studies in other languages, but we would not have been able to accurately assess full text in another language. We included only primary PD to ensure the homogeneity of the results while the very recent meta-analysis of Schini M. et al. included secondary PD [14]. Indeed, parkinsonism corresponds to a wide range of etiologies, with variable response to dopaminergic treatments and the inclusion criteria depended on the studies [58]. However, our results are consistent with Schini's results [14]. We choose to include vertebral fractures although diagnosis is underestimated and the criteria to diagnose vertebral fracture in the included studies could be challenged.

Indeed, in the analysis of vertebral fractures, the heterogeneity was moderate ( $I^2 = 53\%$ )

as vertebral fracture identification criteria were highly variable from one study to another and one study included only compressive fractures [33]. However, despite these limitations and a probable underestimation, vertebral fractures appear more frequent in PD.

## **Conclusion**

Our study confirms that PD patients have a greater risk of OP fractures, especially hip fracture recognized as a severe fracture associated with increased morbidity and mortality that require specific treatment. Numerous factors contribute to this increased risk in PD, although the pathophysiology is still not fully understood. The assessment of fracture risk remains a challenge in PD, as there are multiple motor and non-motor symptoms competing for attention in these frail patients. We suggest that assessment of fracture risk should be included in guidelines for PD patients care.

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## Figures legend

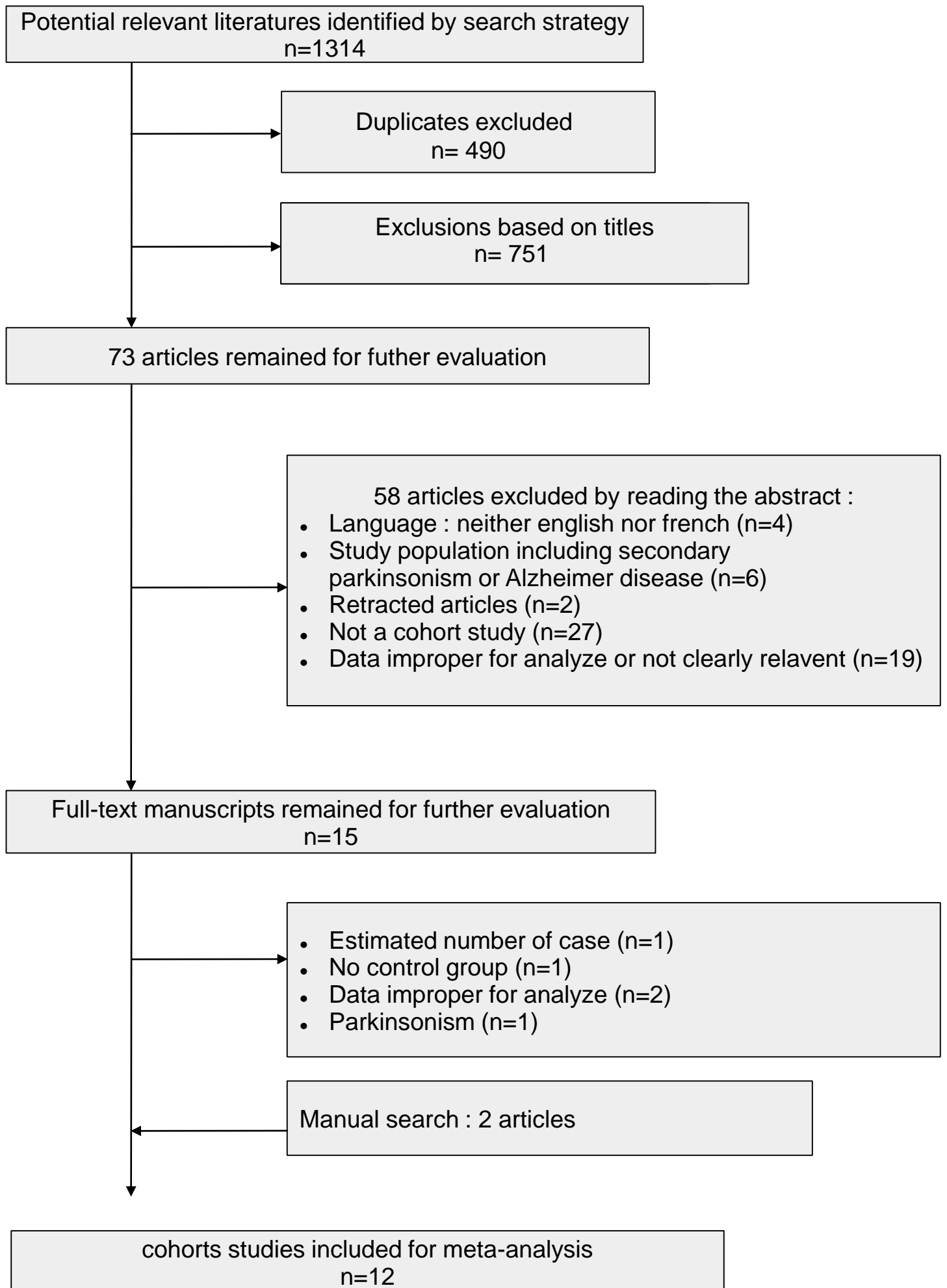
**Figure 1:** Flowchart for the study selection process

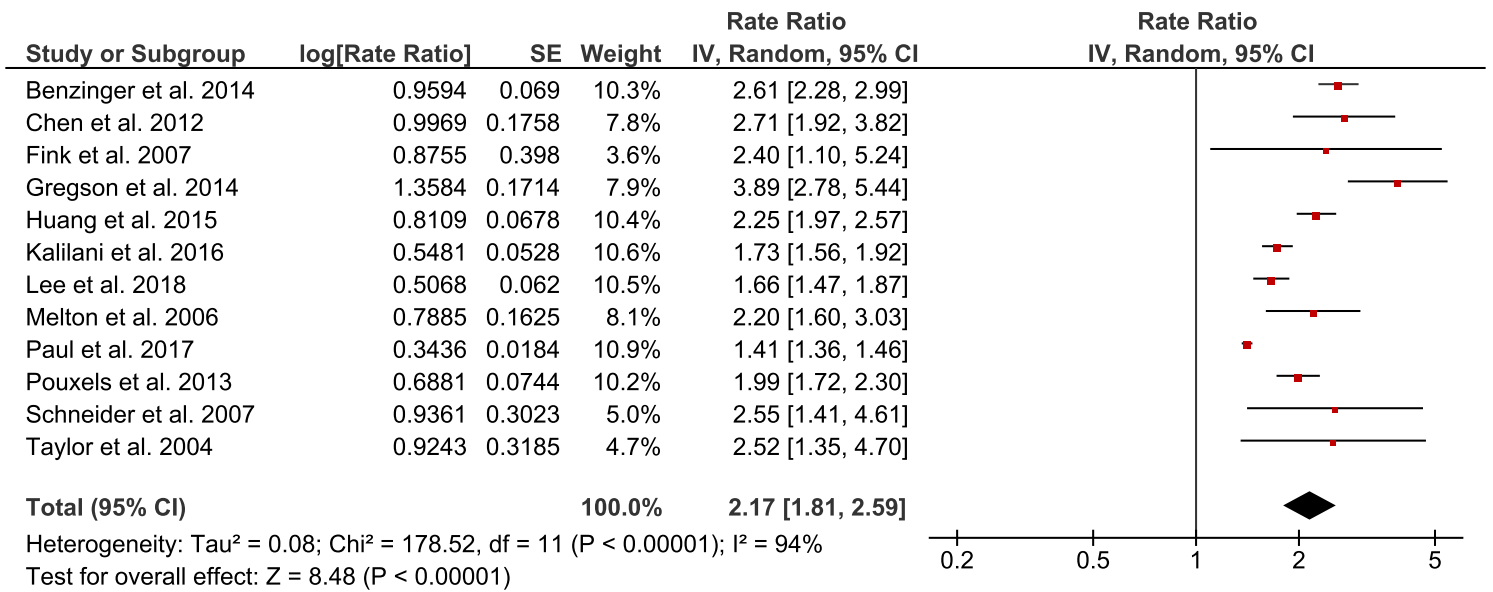
**Figure 2:** Forest plot of the association between Parkinson's disease and the risk of fracture all sites combined. Single Rate Ratios (RR) were pooled to estimate an overall RR of fracture, using the inverse variance approach. The squares and the horizontal lines respectively represent the RR and 95% Confidence Intervals (CI) of each individual study. The black diamond represents the pooled RR.

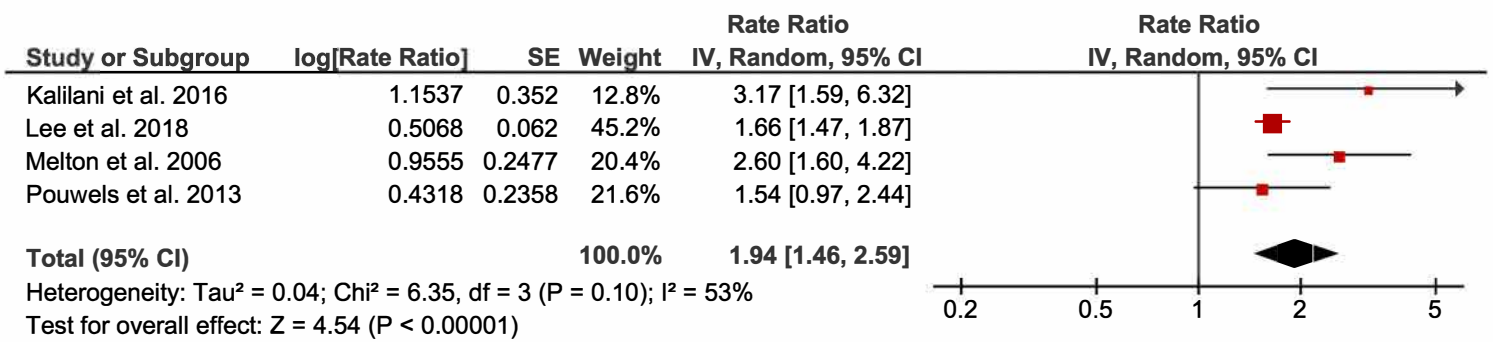
**Figure 3:** Forest plot of the association between Parkinson's disease and the risk of vertebral fracture. Single Rate Ratios (RR) were pooled to estimate an overall RR of fracture, using the inverse variance approach. The squares and the horizontal lines respectively represent the RR and 95% Confidence Intervals (CI) of each individual study. The black diamond represents the pooled RR.

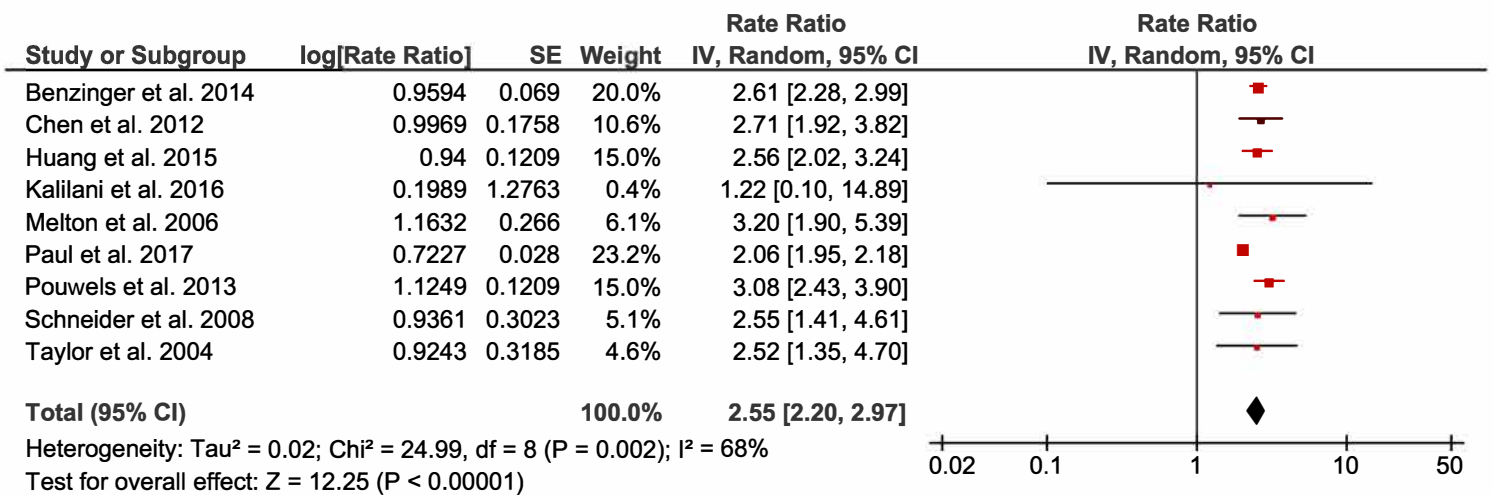
**Figure 4:** Forest plot of the association between Parkinson's disease and the risk of hip fracture. Single Rate Ratios (RR) were pooled to estimate an overall RR of fracture, using the inverse variance approach. The squares and the horizontal lines respectively represent the RR and 95% Confidence Intervals (CI) of each individual study. The black diamond represents the pooled RR.

**Figure 5:** Forest plot of the sensitivity analysis of the association between Parkinson's disease and the risk of hip fracture. Single Rate Ratios (RR) were pooled to estimate an overall RR of fracture, using the inverse variance approach. The squares and the horizontal lines respectively represent the RR and 95% Confidence Intervals (CI) of each individual study. The black diamond represents the pooled RR.

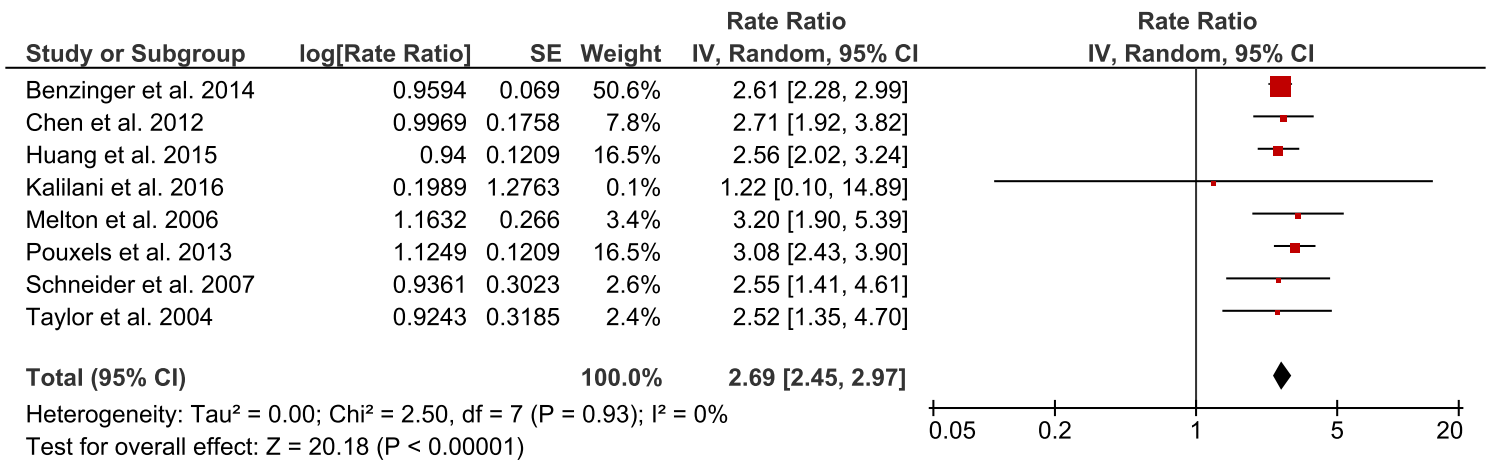












**Table 1 – Summary of included studies examining the association between Parkinson’s disease and the risk of fractures.**

<b>Study</b>	<b>Study design</b>	<b>Study location</b>	<b>Ratio of males (%)</b>	<b>Age (Y)</b>	<b>Total cases / total controls</b>	<b>Follow up (Y)</b>	<b>Outcomes assessment</b>	<b>Site of fractures</b>	<b>Adjustment for confounders</b>
<b>Lee (2018) [33]</b>	Retrospective cohort	Korea	40.8	> 60	3,370 / 16,850	9	National records	vertebral	Age, gender
<b>Paul (2017) [32]</b>	Retrospective cohort	Australia	PD: 51% Controls: 33.3%	> 65	5,045 / 201,562	8.5	Inpatient records	Hip, any site	Age, gender
<b>Kalilani, (2016) [31]</b>	Retrospective cohort	US	53.3	> 40	28,275 / 28,275	1	National insurance records	Hip, vertebral, any site	age, gender, region of residence, and duration of enrollment.
<b>Huang (2015) [30]</b>	Retrospective cohort	Taiwan	55.4	> 40	1,423 / 5,692	8	National insurance records	Hip, any site	gender,, urbanization, low income, coexisting medical conditions, and medication use
<b>Benzinger (2014) [29]</b>	Retrospective cohort	Germany	PD: 37.3% Controls: 36.7%	>65	12,391 / 860,388	4.5	National insurance records	Hip	functional impairment and gender
<b>Gregson (2014) [28]</b>	Prospective cohort	US, Europe, Canada	0	> 55	2,945 / 43,832	3	Self-reported	Any site	Non available
<b>Pouwels (2013) [27]</b>	Retrospective cohort	UK	57.7	> 40	4,687 / 4,687	4	Inpatient records	Hip, vertebral, any site	Age, gender
<b>Chen (2012) [26]</b>	Prospective cohort	Taiwan	49	68.6 (mean)	394 / 3,940	8	National insurance records	Hip	Age, gender, state of comorbidities
<b>Schneider, (2008) [25]</b>	Prospective cohort	US	0	> 65	850 / 8,105	Non-hip, non-spine fractures: 8 Hip fractures: 9	Inpatient records	Hip, non-hip non vertebral	Age
<b>Fink (2008) [24]</b>	Prospective cohort	US	100	>65	46 / 5,891	PD: 4.1 Controls: 5.1	Inpatient records	Non vertebral	Age
<b>Melton (2006) [23]</b>	Prospective cohort	US	61	71 (median)	196 / 196	13	Inpatient and outpatient records	Hip, vertebral, any site	Non available
<b>Taylor (2004) [22]</b>	Prospective cohort	US	0	73.3 (mean)	604 / 6,787	8.9	self-reported and radiological review	Hip	Age

**Table 2 - Quality of cohorts included in the meta-analysis : The Newcastle Ottawa Scale [16]**

Study	Selection				Comparability	Outcomes			Total scores
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcomes of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough	Adequacy of follow up of cohorts	
Lee (2018) [33]	*	*	*	*	**	*	*	-	8
Paul (2017) [32]	-	*	*	-	**	*	*	-	6
Kalilani (2016) [31]	*	*	*	*	**	*	-	*	8
Huang (2015) [30]	*	*	*	*	**	*	*	*	9
Benzinger (2014) [29]	*	*	*	*	**	*	*	-	8
Gregson (2014) [28]	-	*	-	*	-	-	*	*	4
Pouwels (2013) [27]	*	*	*	-	**	*	*	-	7
Chen (2012) [26]	*	*	*	*	**	*	*	-	8
Schneider (2008) [25]	-	*	-	*	**	*	*	-	6
Fink (2008) [24]	-	*	-	*	**	*	*	*	7
Melton (2006) [23]	*	*	*	*	**	*	*	-	8
Taylor (2004) [22]	-	*	-	*	**	*	*	-	6