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The Risk of Hip and Non-Vertebral Fractures in Patients with Parkinson's Disease and Parkinsonism: A Systematic Review and Meta-Analysis

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that is common in older individuals. PD patients have an increased risk of fractures compared to the general population, perhaps due to multiple falls. However, the fracture risk has not been fully assessed. To assess the impact of PD on the risk of hip and non-vertebral fractures, we conducted a systematic review and meta-analysis.

Comprehensive searches of three key bibliographic databases were conducted to identify reviews and primary studies relating to the risk of fractures in patients with PD. Search terms included all relevant terms for Parkinson's disease and for fractures. We selected observational studies with data on the risk of fractures in adults with PD compared to controls without the diagnosis. Study quality was assessed using the Newcastle Ottawa Scale. The random-effects model was used to pool the results.

Eighteen studies were included in the review. Seventeen independent studies (14 cohort and 3 case-control studies) were included in the hip fracture analysis. Nine studies (all cohorts, no case-control studies) were included in the non-vertebral fracture analysis. Study quality was judged to be moderate to good. Overall, PD patients had an increased risk for both hip fractures (2.40, 95% CI 2.04 to 2.82) and non-vertebral fractures (1.80, 95% CI 1.60 to 2.01) compared to controls. The relative risk for hip fractures was higher in men (2.93, 95% CI 2.05 to 4.18) than in women (1.81, 95% CI 1.61 to 2.04). There were no effects of the study design, geographical region, or criteria for diagnosing Parkinson's disease on these estimates of fracture risk.

There is an increase in the risk of hip and non-vertebral fractures in patients with Parkinson's disease and we recommend a re-evaluation of the clinical guidelines on bone health in patients with PD to address this.

Keywords: Parkinson; Parkinsonism; Fractures; Meta-analysis; Systematic review

Highlights

- There is a positive association between Parkinson's disease and the risk of hip fractures (2.40, 95% CI 2.04 to 2.82)
- There is a positive association between Parkinson's disease and the risk of non-vertebral fractures (1.80, 95% CI 1.60 to 2.01)
- People with PD have a substantially increased risk of fragility fracture, especially of the hip

Introduction

Parkinson's disease is a common neurodegenerative disease with a lifetime risk of 2% for men and 1.3% for women in the USA, taking into account competing risks of death (1). It mainly affects individuals after the age of 50, and the incidence increases with age. A study of seven European community surveys of independently living and institutionalized elderly subjects 65 years of age or older found an overall prevalence of 0.6% in adults aged 65 to 69 years, increasing to 2.6% for those 85 to 89 years (2). The incidence stabilises after the age of 80, probably because of underdiagnosis (3).

Parkinson's disease patients have more than a threefold increase risk in falls compared to age- and gender-matched controls (4). PD has also been linked to higher risk of osteoporosis and lower bone mineral density (BMD) levels (5). These factors contribute to an increased risk of fractures in patients with PD, which has been observed in several studies, with hip fracture being the most common site (5-7).

Despite the numerous individual studies published on the risk of fractures, the relationship between PD and the risk of hip and non-vertebral fractures has not been systematically assessed. Previous meta-analyses have focused on the general risk of fractures (5, 6). A recently published systematic review on the risk of hip fractures excluded studies that only reported event rates without a summary statistic and it excluded studies that included patients with parkinsonism, which may have affected the pooled risk estimate reported (8). Parkinsonism is an atypical form of Parkinson's disease that makes up about 10% of cases and may progress more rapidly than Parkinson's disease and is less responsive to the usual treatment, levodopa.

This review aims to address the question "what is the risk of hip and non-vertebral fractures in adult patients with Parkinson's disease compared to those without Parkinson's disease?" through a systematic review and meta-analysis. It also seeks address the limitations of previous reviews by including a wider pool of studies and to assess whether the risk differs in patients according to age, sex, study quality and presence of dementia. We chose these two classifications of fracture as they are well captured in epidemiological studies, in contrast to vertebral fractures, which require serial radiographs for their accurate identification. It is of particular importance to assess the risk of non-vertebral fractures as this is a major endpoint in clinical trials of fractures.

Materials and methods

Protocol and registration

This systematic review was conducted following key principles outlined in the Cochrane Handbook (9) and in the Centre for Reviews and Dissemination Handbook (10). It has been reported in accordance with the PRISMA statement (11). The protocol for this review was

registered on the PROSPERO database (https://www.crd.york.ac.uk/prospero/), record number CRD42018094911.

Information sources and search strategy

Systematic searches of bibliographic databases were conducted to identify published systematic reviews and update these with more recently published primary studies. An initial full search was conducted in MEDLINE and Embase and updated on 29th March 2019 (MEDLINE only) using free text and thesaurus terms for fractures, Parkinson's disease and study design (Supplemental data 1). The reference lists of key existing reviews (5, 12) were searched and experts in the field consulted for additional primary studies.

Study selection

Retrieved records were uploaded into Endnote and duplicate records were removed. For the study of previous systematic reviews, one reviewer assessed records against the inclusion criteria. A second reviewer independently sifted a 10% sample and the Kappa statistic for agreement was calculated. For the review of primary studies, one reviewer conducted the title and abstract sift, and a second reviewer independently sifted a 10% sample. The Kappa statistic for agreement was calculated. The full text sift was conducted independently by two reviewers and disagreements resolved through discussion, or involvement of a third reviewer.

Systematic reviews and primary studies were eligible for inclusion where they met the following criteria: population included adults aged 18 years and above with a diagnosis of Parkinson's disease (identification of patients through medication records was an acceptable form of diagnosis); included a comparison group of patients without Parkinson's disease; reported outcomes of hip and/or non-vertebral fractures; had an observational design (primary study review) or were a systematic review of studies with an observational design (review of systematic reviews). Studies were excluded if: the Parkinson's disease definition/diagnosis was

unclear; data was not reported separately for Parkinson's disease patients; the diagnosis was made after the fracture event or where the sequence was unclear; the comparator group was not clearly defined; data was only available on vertebral fractures or there was no way to exclude the data from vertebral fractures; fracture risk was based on an algorithm or risk tool; outcome data was unclear, missing or incomplete; the study was not in English; or was a narrative review, letter, editorial, commentary, conference abstract, animal or biological study.

When two or more studies were identified that included or potentially included the same patients (based on recruitment location, database name (where provided) and years of recruitment), and where they reported data relating to the same fracture sites, the study with the largest sample size was used, or which reported protocol-defined subgroup analyses (e.g. by fracture site, age, sex etc). Where both a cohort study or a case-control study were available, the cohort study was selected for inclusion in the review.

Studies included in the selected systematic review (6) were further assessed based on the current inclusion and exclusion criteria and the data from the selected studies was fully extracted as described below.

Data extraction

A standardized data extraction form was developed and agreed with the clinical team. Data from all the studies selected, were extracted by one reviewer and checked by another. Disagreements were resolved through discussion. A blank sample of the data extraction form is provided in Supplemental material 2.

Quality assessment

The quality of the existing systematic review was assessed using AMSTAR (13) by one reviewer and checked by a second. The quality of primary studies was assessed using the Newcastle Ottawa Scale (NOS) (14) for cohort and case-control studies by one reviewer and

checked by a second; disagreements were resolved through discussion. A maximum score of 9 stars could be assigned to a study. The scoring guidelines are provided in Supplemental material 3.

Narrative synthesis

A narrative synthesis was conducted, including tabulation of study characteristics, and a description of the available data. Subgroups were defined a-priori and included gender, study location (continent), type of effect size reported (relative risk, hazard ratio, odds ratio, or incidence risk ratio), type of study design (cohort or case-control). Parkinson's disease is a disorder that requires clinical diagnosis and there is no available imaging or laboratory method to confirm the diagnosis; previous meta-analyses excluded studies with Parkinsonism. For these reasons, it was decided to subgroup the studies further in three different ways wherever possible: clear definition of clinical criteria used for the diagnosis of PD, diagnosis used in the study (Parkinson's disease or Parkinsonism), method of PD diagnosis (self-report only or other).

Data analysis

Hip, vertebral and non-vertebral fractures are the groupings usually used in clinical trials of drugs to prevent fractures. However, the group of vertebral fractures is captured poorly in observational studies, as it requires regular spinal radiographs to identify morphometric fractures. Therefore, this analysis included only hip and non-vertebral fractures. The available measures of effect size (ES) and their 95% confidence intervals (CI) were extracted from the studies. These included relative risk (RR), hazard ratio (HR), odds ratio (OR) and incidence risk ratio (IRR). If multiple effect sizes were reported from one study because of different adjustments, the one with the fewer adjustments was used for the meta-analysis, as many adjustments would increase the heterogeneity between studies. For studies that did not report an effect size, this was calculated using the raw data for fractures reported in the study (15, 16).

In these cases, the relative risk, its standard error and 95% confidence interval were calculated (17). In the case of studies that reported zero fractures in one subgroup, this number was substituted with 0.5 to allow further calculations (18, 19).

For studies that reported separate risks for hip and femur fracture, a pooled effect size was used in the main analysis (20). For the non-vertebral fracture analysis, one effect size per study was used. Therefore, if a study reported several effect sizes according to different fracture sites, then these effect sizes were pooled to get an overall estimate (15, 16, 20-25). Effect sizes on skull fractures were excluded. The non-vertebral fracture analysis only included studies that reported the risk of more than one non-vertebral site or reported the overall risk of "non-spine" fractures. Studies where the only outcome was hip fracture were not included in the non-vertebral analysis.

A meta-analysis of the natural logarithms of the effect sizes and their confidence intervals was performed and presented using forest plots. The random-effects model was used to pool the results (26). If a study only reported separate estimates by gender, and an overall estimate was not given, then the separate estimates where used for the meta-analysis (27, 28).

Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic (29). Since the chi-squared test has low power, the p value of 0.10, was used to determine statistical significance. Where the pooled effect had considerable heterogeneity, further analyses were conducted to identify possible reasons for the observed heterogeneity. A leave-one-out sensitivity analysis, was used to check how each individual study affected the overall estimate and a meta-regression analysis was performed to investigate the extent to which heterogeneity could be related to one or more characteristics of the studies.

Subgroup analyses were carried out according to predefined groups. If there was no overlap of the confidence intervals, then we concluded that there was statistical significance between the

subgroups (9, 30). A sensitivity analysis was performed limiting the pooled studies to those having a high-quality assessment score according to the Newcastle Ottawa scale (≥7).

Publication bias was assessed through visual inspection of a funnel plot (31). A formal statistical assessment, was performed using Egger's test (32). When statistically significant bias was identified, the trim-and-fill method was used to adjust for that (33, 34). Testing for publication bias was only performed when there were more than 10 studies in the analysis (32).

All statistical analyses were done using the Stata/IC 15.1 software (StataCorp LLC).

Results

Study selection

The review of systematic reviews database searches identified 452 unique records. Based on the title or the abstract, 388 records were excluded. From the remaining 64 records, one systematic review met the inclusion criteria for the review (6). The kappa statistic for agreement between reviewers was 1.00 (95% CI 1.00, 1.00) indicating very good agreement.

The systematic review of primary studies database searches identified 355 records (four from the update search in March 2019), of which 233 were unique. Hand searching of existing reviews and contact with experts in the field retrieved a further 28 records. In total, 261 unique records were considered for inclusion in the review. Of these, 180 were excluded based on the title or abstract, and the full text of 81 records was retrieved for assessment against the inclusion criteria. A further 63 were excluded after consulting the full text (full list with reasons provided in Supplemental material 4), leaving a total of 18 (15, 16, 20-25, 27, 28, 35-42) primary studies that met the inclusion criteria and were included in the review. Of these, 17 were included in the meta-analysis for hip fracture (15, 16, 20-25, 27, 28, 35-38, 40-42) and 9 were included in

the meta-analysis for non-vertebral fractures (15, 16, 20-25, 39). The study statistic for agreement between reviewers was 0.697 (95% CI 0.297, 1.000) , indicating good agreement. The flow chart for the selection is shown in Figure 1.

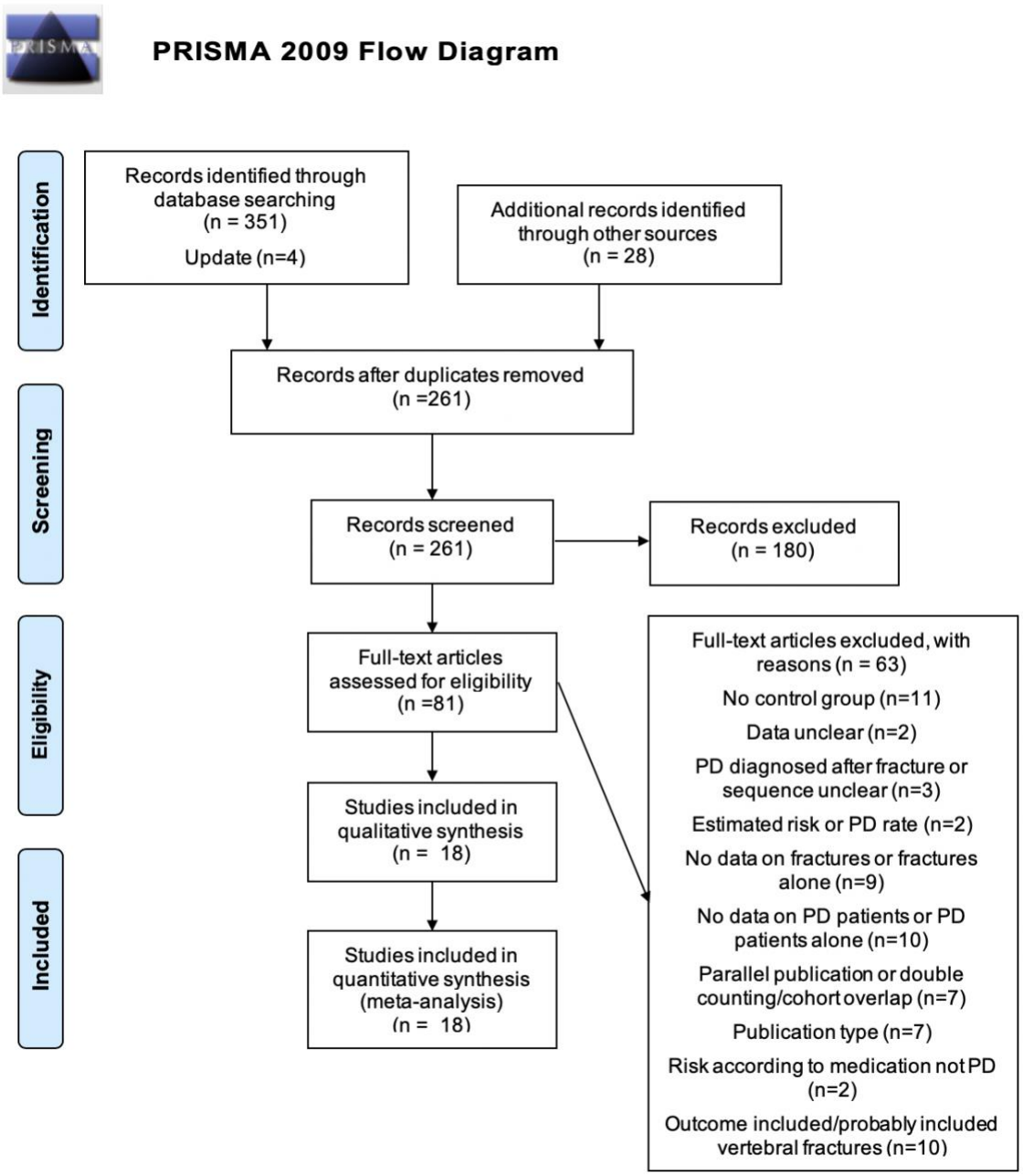

Figure 1: PRISMA flow chart for the study selection process

Study characteristics

Table 1 summarises the main characteristics of the 18 studies included in the analyses. In total, three studies had a case-control design (28, 37, 40) and the rest were cohort studies. The study population ranged from 52 to 1,276,891 participants, with a total of 2,335,361. Average follow-up varied between 1 and 14 years. All the studies started patient recruitment after 1975.

Three studies included males only (38-40), one study consisted of females only (25). Only four studies reported ethnicity, with the majority of the participants being Caucasian. Only a few studies reported the prevalence of dementia, but none reported the risk of fractures according to dementia status, which was one of the planned subgroup analyses.

Three studies reported data on bone mineral density (BMD) measurements according to PD status, with two of them showing significantly lower BMD results in PD patients compared to controls [0.876 g/cm2 vs 0.958 g/cm2 respectively, $p<0.001$ and 0.68± 0.14 vs 0.74 ±0.13 g/cm2 respectively, p 0.005 (25, 39)]. One cohort showed no statistical difference in BMD (16). There was one cohort study that reported BMD measurements according to hip fracture status [femoral neck BMD (g/cm2): no hip fracture 0.79 ± 0.13 g/cm2, hip fracture 0.67 ± 0.11 g/cm2 ($p<0.001$)] (38).

In terms of diagnosis, three studies evaluated people with parkinsonism (23, 28, 36), while the others evaluated people with Parkinson's disease (15, 16, 20-22, 24, 25, 27, 35, 37-42). Three studies gave the criteria used for the diagnosis of PD. Only two studies used self-report alone as a method of diagnosis (28, 40). One study identified patients with idiopathic PD using dispensed medication and reported two models; model I ('possible' idiopathic PD patients) and model II ('probable' idiopathic PD patients) (27). We used the results from model II for the analysis.

Study (year)	Study design	Country	Study population	Diagnosis for PD/ Parkinsonism	Study size, Number of PD patients, Number of incident fractures	Age	Female (%)	Average follow-up
Abey-Nesbit (2019) **(35)**	Cohort	New Zealand	InterRAI-HC geriatric assessment record	PD; Assessment, including observations, interviews with the individual and their family members, and medical records	45044 1781 3010	≥65	61.5	Median 13.9 m
An (2017) **(36)**	Cohort	South Korea	National Health Insurance Service (NHIS) National Sample Cohort (NSC)	Parkinsonism; Insurance registry	15498 2583 325	>40	59.7	NR, maximum 11 y
Arbouw (2011) **(37)**	Case-control	Netherlands	Dutch PHARMO Record Linkage System (RLS) Institute for Drug Outcome Research	PD; Medical records (history of hospitalisation)	33104 64 6763	≥18	73	Cases: 5.8 y Controls: 5.7 y
Benzinger (2014) **(27)**	Cohort	Germany	Allgemeine Ortskrankenkasse Bayern (AOK Bavaria)	PD; Registry of discharges and medication	872779 12391 34147	≥65	62.7 cases 63.3 controls	Cases: 4.50y (2.47 to 4.50) Controls: 4.50y (4.50 to 4.50)
Cauley (2016) **(38)**	Cohort	USA	The Osteoporotic Fractures in Men (MrOS) Study	PD; Self-report, interview or examination	5876 48 178	≥65	0	8.6 y
Fink (2008) **(39)**	Cohort	USA	The Osteoporotic Fractures in Men (MrOS) Study	PD; Self-report, interview or examination	5937 46 NR	≥65	0	Cases: 4.1y (0-6 to 6), Controls: 5.1y (0 to 6.8)
Genever (2005) **(15)**	Cohort	United Kingdom	PD register of the Movement Disorder Clinic at Chesterfield and North Derbyshire Royal Hospital	PD; Outpatient department registry, diagnosed by a consultant Care of the Elderly physician, specialised in movement disorders, using the United Kingdom Parkinson's Disease Society Brain Bank criteria	400 200 NR	>40	52	5.94 y
Grisso (1997) **(40)**	Case-control	USA	34 Hospitals in Philadelphia (Pennsylvania) and Kaiser Permanente Medical Care Programme in Northern California	PD; Self-report	758 25 356	≥45	0	NR
Huang (2015) **(21)**	Cohort	Taiwan	Taiwan National Health Insurance Research Database	PD; Insurance registry: At least 3 outpatient visits or inpatient medical services with principal diagnosis of PD required	7115 1423 1142	≥40	44.6	NR
Jørgensen (2014) **(22)**	Cohort	Denmark	Danish Civil registration System, Danish National Patient registry, Danish National Prescription registry, Income Statistics registry	PD; Registries of admissions and prescriptions	1276891 NR NR	≥65	58.5	NR
Kalilani (2016) **(20)**	Cohort	USA	Truven Health MarketScan1 Commercial Claims (CCMC) and the Truven Health MarketScan Medicare Supplemental and Coordination of Benefits (Medicare Supplemental; MDCR) insurance databases	PD; Insurance registry, claims plus prescriptions	56550 28275 881	>40	46.7	57,922 person-years

Kauppi (2014) **(41)**	Cohort	Finland	Health 2000 Survey	PD; Questions and diagnostic assessments, clinical examination	2300 10 96	≥55	57.9	Mean 9.8 y
Lau (2001) **(28)**	Case-control	Singapore, Malaysia Thailand, Philippines	Asian Osteoporosis Study (AOS)	Parkinsonism; Self-reported questionnaire	2338 NR 1176	≥50	61.2	NR
Lorefält (2007) **(16)**	Cohort	Sweden	Linkçping cohort	PD; Outpatient departments, using UK Parkinson's Disease Society Brain Bank criteria	52 26 7	≥60	65.4	1 y
Melton (2006) **(23)**	Cohort	USA	Rochester Epidemiology Project	Parkinsonism; Medical record, according to following criteria: at least two of four cardinal signs (resting tremor, bradykinesia, rigidity, or impaired postural reflexes) with all three of the following: (1) no secondary cause; (2) no documentation of unresponsive- ness to levodopa treatment (applicable only to treated patients); and (3) no prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia or dysautonomia) not otherwise explained	392 196 211	>40	39	Median 13 y (0.4 to 27)
Pouwels (2013) **(24)**	Cohort	United Kingdom	UK General Practice Research Database (GPRD)	PD; Diagnosis in medical records plus two prescriptions for PD medication	9374 4687 NR	≥40	42	4 y
Schneider (2008) **(25)**	Cohort	USA	Study of osteoporotic fractures (SOF)	PD; Questionnaire, physical examination, medication for verification	8105 73 NR	≥65	100	8 y non-spine, non-hip 9 y hip cohort
Wiklund (2016) **(42)**	Cohort	Sweden	Umeå 85+/ Gerontological Regional Database (GERDA)	PD; Interviews, review of medical records to confirm diagnoses	953 15 96	≥85	65.8	Mean 2.7 y (1–1827 days)

Table 1: Summary of included studies examining the association between Parkinson's disease and the risk of hip and non-vertebral fractures

Y: years; m: months; NR: not reported

Quality assessment

The selected systematic review by Tan et al (6) was found to be of good quality, scoring well on eight out of eleven items on the AMSTAR checklist. The scores are provided in Supplemental material 5. The review scored poorly for not reporting a priori design, excluding conference abstracts, and not providing a full list of excluded studies. However, the review also addressed the question of risk of fractures in patients with PD, and was conducted to a high standard with duplicate study selection, comprehensive literature searches, quality assessment and appropriate methods of analysis with no conflicts of interest.

A summary of the judgement of the quality of the included primary studies is provided in Table 2 (cohort studies) and Table 3 (case-control studies). Justifications for the scores given are provided in Supplementary data 5. Overall, cohort studies were of good quality, with all scoring more than or equal to 7 out of 9 stars. Most studies scored poorly for the item "adequacy of follow-up"; this was largely due to no information being given in the study report.

Case-control studies (n=3) generally scored less well than cohort studies, with no study scoring 7 or more out of 9 possible stars. All studies failed to report whether cases were consecutive and failed to present data that would allow a judgement to be made about the representativeness of the recruited population. All studies scored poorly for their definition of controls, because cases were defined as first instance of hip fracture (i.e. patients with previous hip fracture were excluded), but patients with previous hip fracture were not excluded from the control group, or this was unclear.

Author, year	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start	Comparability of groups	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total stars awarded
Abey- Nesbit, 2019 **(35)**	*	*	*	*	**	*	*	*	9
An, 2017 **(36)**	-	*	*	*	**	*	-	*	7
Benzinger, 2014 **(27)**	*	*	*	*	**	*	*	-	8
Cauley 2016**(38)**	-	*	*	*	**	*	*	*	8
Fink, 2007 **(39)**	-	*	*	*	**	*	*	*	8
Genever, 2005 **(15)**	*	-	*	*	**	*	*	-	7
Huang, 2015 **(21)**	-	*	*	*	**	*	*	*	8
Jørgensen, 2014 **(22)**	*	*	*	*	**	*	-	*	8
Kalilani 2016 **(20)**	*	*	*	*	**	*	*	-	8
Kauppi, 2014 **(41)**	-	*	*	*	**	*	*	-	7
Lorefält, 2007 **(16)**	*	*	*	*	**	*	*	-	8
Melton, 2006**(23)**	*	*	*	*	**	*	*	-	8
Pouwels 2013 **(24)**	*	*	*	*	**	*	*	-	8
Schneider, 2008 **(25)**	_	*	*	*	**	*	*	-	7
Wiklund, 2016 **(42)**	-	*	*	*	**	*	*	-	7

Table 2: Authors' judgement for the quality of included studies, scored using the Newcastle Ottawa Scale (14) for cohort studies

First author, year	Is case definition adequate?	Representativeness of cases	Selection of controls	Definition of controls	Comparability of groups	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total stars rated
Arbouw 2011 **(37)**	*	-	*	-	**	*	*	-	6
Grisso 1997 **(40)**	*	-	*	-	**	-	*	-	5
Lau, 2001 **(28)**	*	-	*	-	**	-	*	*	6

Table 3: Authors' judgement for the quality of included studies, scored using the Newcastle Ottawa Scale (14) for case-control studies

Main analysis

Hip fractures

Seventeen studies (14 cohort and 3 case-control), with a total of 2,329,424 participants, were included in the meta-analysis for hip fractures (Supplementary data 6). Overall, the meta-analysis of the included studies based on the random effects model, showed that PD patients have an increased risk for hip fractures compared to controls (2.40, 95% CI 2.04 to 2.82; Figure 2A). However, there was substantial heterogeneity between results of the studies (I^2=87.4%, p value <0.001).

Non-vertebral fractures

Nine cohort studies, with a total of 1,356,711 participants, were included in the meta-analysis for non-vertebral fractures (Supplementary data 6). Overall, the meta-analysis of the included studies based on the random effects model showed that PD patients have an increased risk for non-vertebral fractures compared to controls (1.80, 95% CI: 1.60 to 2.01; Figure 2B). The heterogeneity observed between the studies was not statistically significant (I^2=30.1%, p value= 0.18).

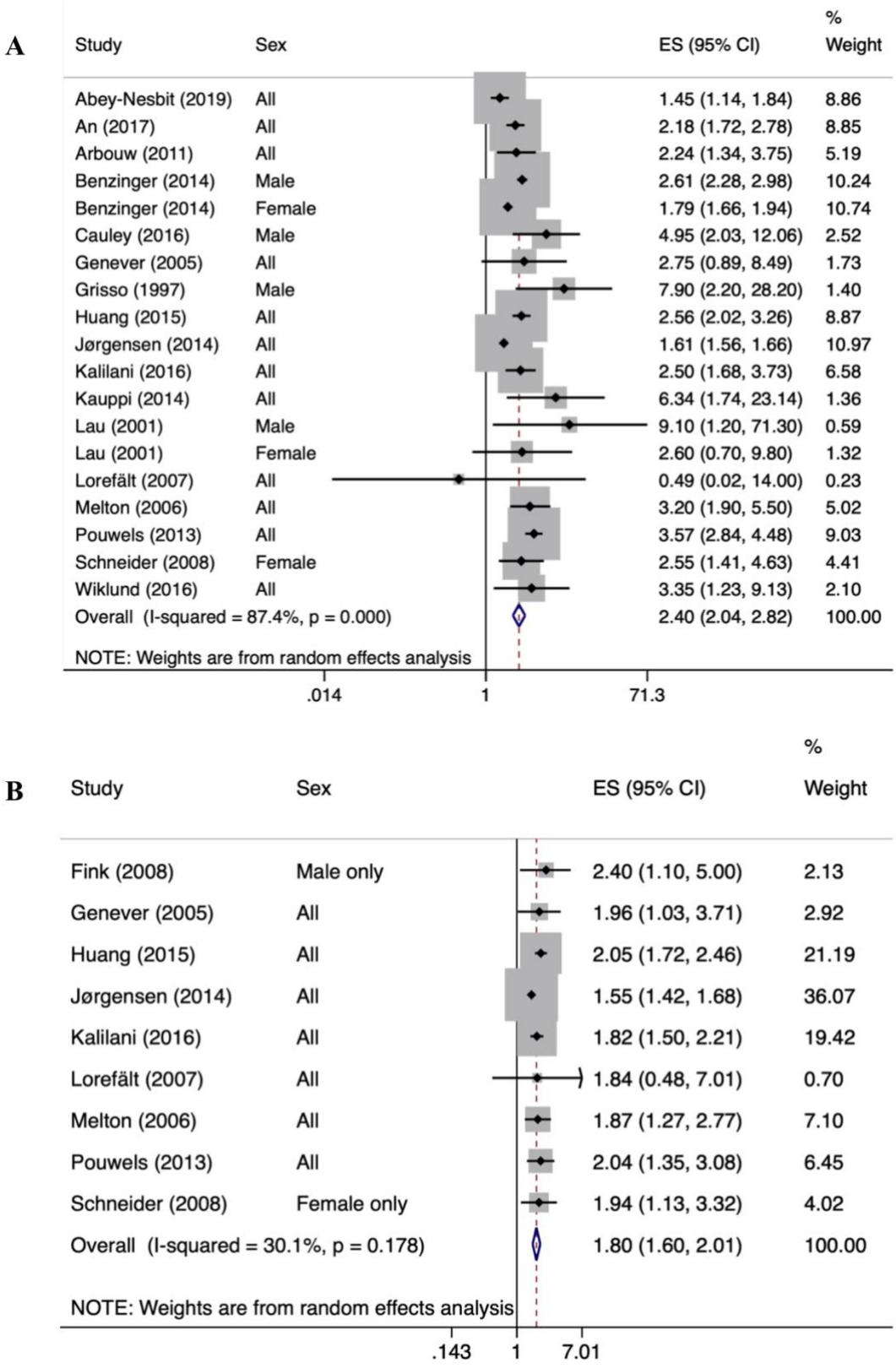

Figure 2: Forest plots of the association between Parkinson's disease (PD) and the risk of hip (A) and non-vertebral (B) fractures. Random effects model was used to pool the overall effect size (ES) and 95% confidence intervals (CIs). The diamond represents the pooled ES and the squares and horizontal lines represent the ES and 95% CI respectively for each individual study

Subgroup and sensitivity analyses

Hip fractures

Table 4 shows the effects of PD on hip fracture risk from the different subgroup analyses performed. Only the gender subgroup analysis suggested a significant difference between groups, as the confidence intervals did not overlap (Figure 3). The relative risk for hip fractures was higher in men (2.93, 95% CI 2.05 to 4.18) than in women (1.81, 95% CI 1.61 to 2.04). The difference here may be due in large part to the lower rate of fractures, and a smaller denominator, in men. There were no significant effects of the geographical location, use of specific clinical criteria for diagnosing Parkinson's disease, study design, type of effect size reported (e.g. HR, RR), whether the diagnosis of Parkinson's disease or Parkinsonism was used or whether self-report was the only method of identifying patients with PD.

A sensitivity analysis was performed using the studies that scored ≥7 out of 9 stars in the Newcastle Ottawa Scale. Three case-control studies were removed from the analysis (28, 36, 37, 40). The overall effect size was found to be 2.34, 95% CI: 1.98, 2.27, which was similar to the one calculated for all the studies (2.40, 95% CI 2.04 to 2.82).

In order to identify possible reasons for the increased heterogeneity observed, a leave-one-out sensitivity analysis was performed. No single study affected the overall heterogeneity, with all the leave-one-out analyses having I_2 values greater than 80% (data not shown). Meta-regression analysis suggested that gender and location, accounted for 74.1% of the variance between studies.

Factors	Number of studies	Effect size (95% CI)	Heterogeneity I_2 (%) between studies	p value for heterogeneity
Gender				
Male	7 (23, 27, 28, 35, 36, 38, 40)	**2.93 (2.05, 4.18)**	68.0	0.005
Female	6 (23, 25, 27, 28, 35, 36)	**1.81 (1.61, 2.04)**	11.1	0.345

Effect size				
HR	10 (21, 23-25, 27, 35, 36, 38, 41, 42)	2.50 (2.03, 3.08)	85.5	<0.001
RR	3 (15, 16, 28)	2.92 (1.35, 6.30)	0	0.509
OR	2 (37, 40)	3.65 (1.10, 12.18)	69.0	0.072
IRR	2 (20, 22)	1.91 (1.26, 2.92)	78.5	0.031
Study design				
Cohort	14 (15, 16, 20-25, 27, 35, 36, 38, 41, 42)	2.34 (1.98, 2.77)	89.5	<0.001
Case-control	3 (28, 37, 40)	3.42 (1.72, 6.79)	34.1	0.208
Clinical criteria reported for diagnosis of PD				
Yes [a]	3 (15, 16, 23)	3.00 (1.86, 4.83)	0	0.549
No	14 (20-22, 24, 25, 27, 28, 35-38, 40-42)	2.37 (2.00, 2.79)	89.0	<0.001
Diagnosis				
Parkinson's	14 (15, 16, 20-22, 24, 25, 27, 35, 37, 38, 40-42)	2.36 (1.98, 2.81)	89.3	<0.001
Parkinsonism	3 (23, 28, 36)	2.46 (1.87, 3.26)	11.2	0.337
Only self-report used for the definition of PD				
Yes	2 (28, 40)	2.33 (1.99, 2.74)	88.0	<0.001
No	15 (15, 16, 20-25, 27, 35-38, 41, 42)	5.18 (2.24, 11.95)	0	0.415
Study location				
Asia	3 (21, 28, 36)	2.39 (2.02, 2.82)	0	0.468
Europe	8 (15, 16, 22, 24, 27, 37, 41, 42)	2.32 (1.87, 2.89)	92.1	<0.001
Oceania	1 (35)	1.45 (1.14, 1.84)	NA	NA
USA	5 (20, 23, 25, 38, 40)	3.03 (2.26, 4.05)	12.4	0.335

Table 4: Summary effect sizes from the different subgroup analyses performed for the association between Parkinson's disease (PD) and the risk of hip fracture. Only the effect sizes for gender did not have overlapping confidence intervals (shown in bold)

[a] Genever et al (15): diagnosed by a consultant Care of the Elderly physician, specialised in movement disorders, using the United Kingdom Parkinson's Disease Society Brain Bank criteria; Lorefält et al (16):diagnosis in geriatric and neurological departments, UK Parkinson's Disease Society Brain Bank criteria; Melton et al (23): at least two of four cardinal signs: resting tremor, bradykinesia, rigidity, or impaired postural reflexes with all three of the following: (1) no secondary cause; (2) no documentation of unresponsiveness to levodopa treatment (applicable only to treated patients); and (3) no prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia or dysautonomia) not otherwise explained

CI: Confidence interval; HR: Hazard ratio; RR: Relative risk; OR: Odds ratio; IRR: Incidence risk ratio; NA: Not available

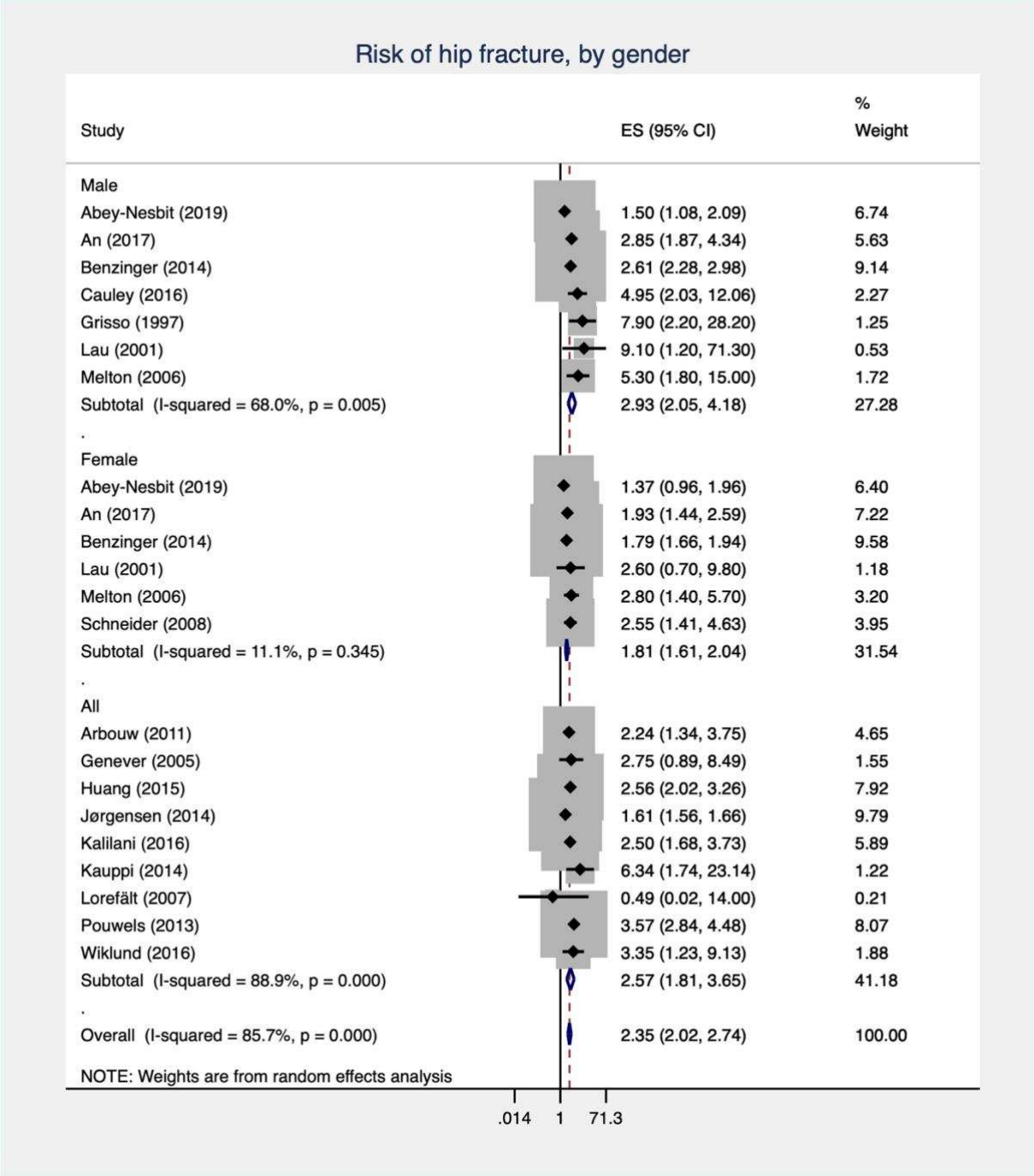

Figure 3: Forest plots of the subgroup analysis based on gender of the association between Parkinson's disease (PD) and the risk of hip fractures. Random effects model was used to pool the overall effect size (ES) and 95% confidence intervals (CIs). The diamond represents the pooled ES and the squares and horizontal lines represent the ES and 95% CI respectively for each individual study

Non-vertebral fractures

In order to perform the gender subgroup analysis, individual effect sizes from one study had to be calculated for the male group, as described in the methods (23). The individual effect sizes

for fracture sites were then pooled using random effects model to calculate the overall effect size by gender (Supplementary material 6). The forest plot of the gender subgroup analysis is shown in Figure 4. Overall, the effect size for non-vertebral fractures in male patients with PD (2.26, 95% CI: 1.37 to 3.73), was higher than the one in women (1.82, 95% CI: 1.33 to 2.48), but the confidence intervals overlapped.

Table 5 shows the effects of PD on non-vertebral fracture risk from the different subgroup analyses performed. There were no significant effects of the geographical location, use of specific clinical criteria for diagnosing Parkinson's disease, effect size reported by the study, or whether the diagnosis of Parkinson's disease or Parkinsonism was used. No sensitivity analysis was performed for study quality, as all the studies included scored ≥7 out of 9 stars.

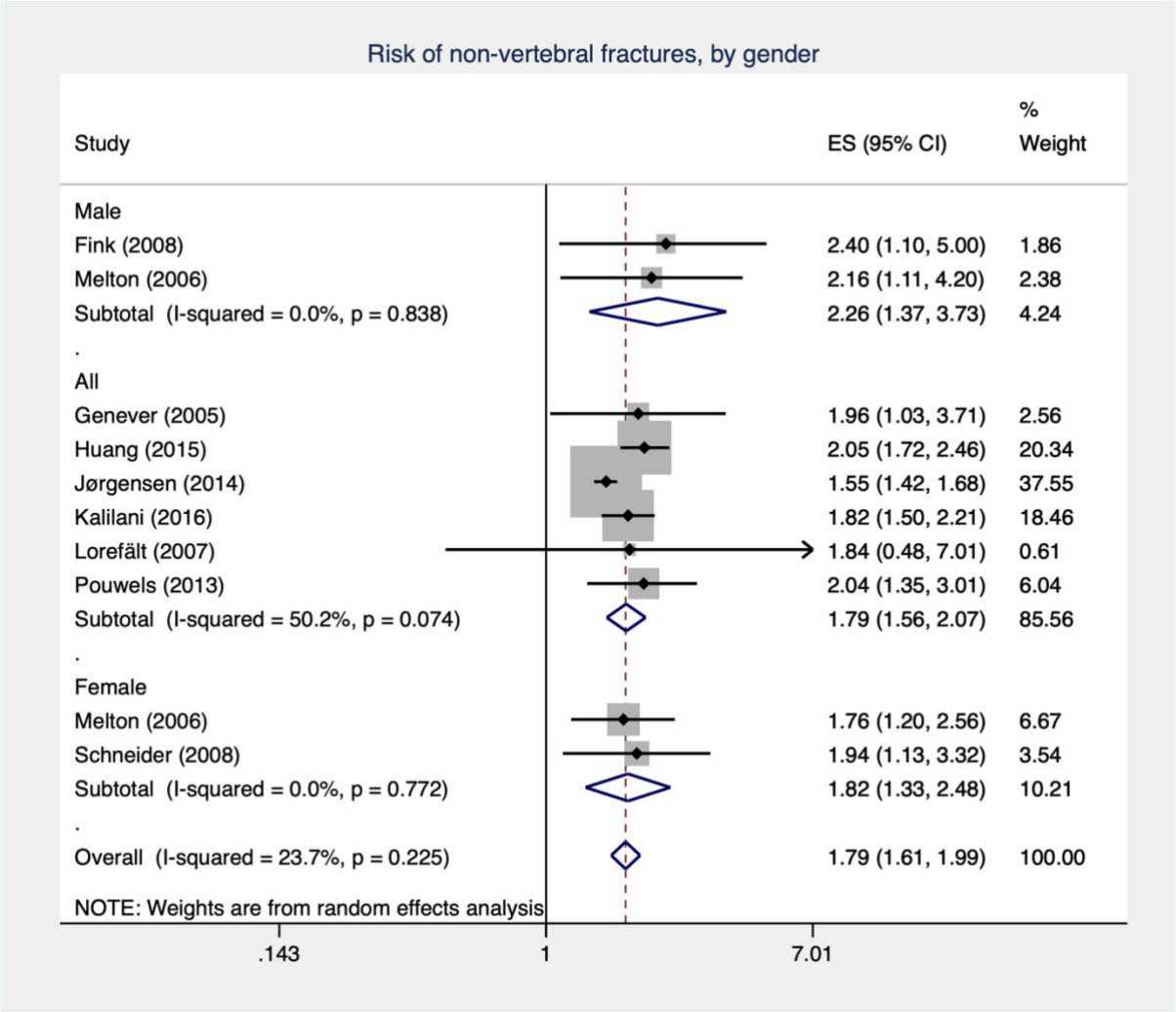

Figure 4: Forest plots of the subgroup analysis based on gender of the association between Parkinson's disease (PD) and the risk non-vertebral fractures. Random effects model was used to pool the overall effect size (ES) and 95% confidence intervals (CIs). The diamond represents the pooled ES and the squares and horizontal lines represent the ES and 95% CI respectively for each individual study

Factors	Number of studies	Effect size (95% CI)	Heterogeneity I_2 between studies (%)	p value for heterogeneity
Gender				
Male	2 (23, 39)	2.26 (1.37, 3.73)	0	0.838
Female	2 (23, 25)	1.82 (1.33, 2.48)	0	0.772
Effect size				
HR	5 (21, 23-25, 39)	2.03 (1.76, 2.34)	0	0.983
RR	2 (15, 16)	1.94 (1.09, 3.45)	0	0.934
IRR	2 (20, 22)	1.64 (1.41, 1.90)	55.0	0.136
Clinical criteria reported for diagnosis of PD				
Yes [a]	3 (15, 16, 23)	1.89 (1.37, 2.61)	0	0.992
No	6 (20-22, 24, 25, 39)	1.82 (1.57, 2.10)	54.1	0.053
Diagnosis				
Parkinson's	8 (15, 16, 20-22, 24, 25, 39)	1.80 (1.59, 2.05)	37.2	0.132
Parkinsonism	1 (23)	1.87 (1.27, 2.76)	NA	NA
Study location				
Asia	1 (21)	2.05 (1.71, 2.45)	NA	NA
Europe	4 (15, 16, 22, 24)	1.57 (1.45, 1.71)	0	0.542
USA	4 (20, 23, 25, 39)	1.86 (1.58, 2.19)	0	0.917

Table 5: Summary effect sizes from the different subgroup analyses performed for the association between Parkinson's disease (PD) and the risk of non-vertebral fractures

[a] *Genever et al (15): diagnosed by a consultant Care of the Elderly physician, specialised in movement disorders, using the United Kingdom Parkinson's Disease Society Brain Bank criteria; Lorefält et al (16):diagnosis in geriatric and neurological departments, UK Parkinson's Disease Society Brain Bank criteria; Melton et al (23): at least two of four cardinal signs: resting tremor, bradykinesia, rigidity, or impaired postural reflexes with all three of the following: (1) no secondary cause; (2) no documentation of unresponsiveness to levodopa treatment (applicable only to treated patients); and (3) no prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia or dysautonomia) not otherwise explained. HR: Hazard ratio; RR: Relative risk; IRR: Incidence risk ratio; NA: Not available*

Publication bias

The funnel plot of the meta-analysis data on hip fractures was not in perfect symmetric distribution (Supplemental material 6). The Egger's test suggested evidence of significant bias ($p = 0.001$). This finding should be treated cautiously, as it can probably be explained by the high heterogeneity observed between studies. The adjusted estimate using the trim and fill method was 2.26, 95% CI: 1.93 to 2.65. The non-vertebral fracture analysis had fewer than 10 studies so a test for publication bias was not performed.

Discussion

Overall, this study showed that there is an increase in the risk of hip and non-vertebral fractures in patients with Parkinson's disease. This is a clinically important increased risk of hip fracture; for example, the risk is similar to the increased risk of hip fracture in analyses of patients who ever used corticosteroids (2.07 in female and 2.62 in male) (43). This study also showed a higher relative risk of hip fractures in male than in female patients; in the general population, hip fractures are more common in female (44). The higher relative risk in men may be due in part to a lower rate of fractures and a smaller denominator for relative risk in men without Parkinson's than women.

The increase in the risk of fractures in patients with PD has been reported in systematic reviews and meta-analyses previously (5, 6, 8). Despite the differences in methodologies and scope, our review found similar increases in risks. Tan et al conducted a meta-analysis on the risk of fractures. Overall, that study showed that PD patients had an increased risk of fractures compared to controls (pooled HR= 2.66, 95% CI= 2.10 to 3.36), with male patients with PD having similar risks to female PD patients. The hip fracture subgroup analysis included four studies and reported an HR of 2.66 (2.07, 3.42), which was similar to our findings. The non-

vertebral fracture subgroup analysis only included two studies, but showed, similarly to our report, an increased risk in PD patients, with a pooled HR= 1.61 (0.70, 3.73). (6). The Torsney et al review, published around the same period as the Tan et al review, also reported the risk of fractures in general, and did not use a site-specific approach. Their overall effect size was 2.28 (95% CI 1.83 to 2.83) (5). The most recently published related meta-analysis focused on evaluating the risk for hip fractures and found an overall HR of 3.13 with 95% CI= 2.53 to 3.87 (8). Our study selection included nine more studies (15, 16, 20, 25, 28, 35-37, 40).

A major cause of fractures in patients with Parkinson's disease may be their increased risk of multiple falls (4). There may also be a contribution from low BMD. In a cross-sectional study, BMD was found to be 7% lower than in controls (25). It has been shown in men that the rate of bone loss is three times the expected level (39). The reduction in BMD might relate to lower body weight; women with PD weigh on average 6 kg less than controls (25).

Hip fractures are particularly important in patients with PD. The mortality rate of patients with this disorder has been reported to be doubled after a hip fracture compared with those without the disease (45). They also have a greater impact on the health care system, with more complications and longer hospital admissions (46).

The high risk of fractures in patients with Parkinson's disease is recognised in fracture scores like QFracture (47), but not in others like FRAX. The fracture risk would be better estimated by FRAX once it includes falls in the assessment of risk as they are an independent risk factor for fracture (48). The problem arises from the fact that some recommendations for the treatment of osteoporosis use score outcomes to assess the initiation of treatment to reduce fractures (49). This results in a small percentage of patients with PD receiving treatments for osteoporosis. A recent study showed that only 40% of the PD patients diagnosed with fragility fractures were receiving evidence-based treatment for osteoporosis and not all of them were assessed by

physiotherapists (50). PD available guidelines do not address the issue of bone health in detail (51-53). PD-specific algorithms for the assessment and management of bone health have been suggested in some studies, but national and international guidelines also have to be revised. Fracture risk assessment and evidence based treatment for osteoporosis should be part of the care in patients with PD (54). Clinical trial evidence is also needed to check whether anti-osteoporotic treatment given on top of falls prevention strategies would further reduce the risk of fractures in this group of patients. One trial to address this issue is underway (ClinicalTrials.gov Identifier: NCT03924414).

There were several limitations in our study. First, we only included studies published in English language, thus data from specific geographic areas might have been missed. The majority of the published studies have data from white/Caucasian population and were mainly oriented in Europe and the USA; therefore, this might have affected the results. The diagnosis of Parkinson's disease was not necessarily performed by a neurologist. This might have resulted in misclassification of the diagnosis in some patients. If patients diagnosed with PD did not actually have the disorder, then the analysis would only lead to an underestimation of the risk of fractures. Our study also assumed that the risk of fractures in patients with Parkinsonism and Parkinson's disease was similar and included all the studies in the overall analysis. The subgroup analysis supported our assumption, as there was no difference in the risks between the two groups. Significant heterogeneity was also an issue in this study. The random effects model allows for heterogeneity, so using this model gives a quantified result. Moreover, different sensitivity analyses were performed to identify possible reasons for this heterogeneity. The meta-regression analysis suggested that gender and location, accounted for 74.1% of the variance between studies. The heterogeneity was also probably the cause for the funnel plot asymmetry observed, as the number of studies was not substantially more than 10 (32). Although it would be interesting to check the effect on BMD and falls on the effect size, not

many studies included BMD and falls data. The effect of PD medication would also be an interesting subgroup analysis, but it was not included in our priori analyses, so the data were not extracted.

This comprehensive systematic review and meta-analysis demonstrates a strong association between Parkinson's disease and risk of hip and non-vertebral fractures. Patients with PD should have fracture risk assessment in their standard care.

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