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Bone health in Parkinson's disease: a systematic review and meta-analysis

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ABSTRACT

Objective Parkinson's disease (PD) and osteoporosis are chronic diseases associated with increasing age. Single studies have reported associations between them and the major consequence, namely, increased risk of fractures. The aim of this systematic review and meta-analysis was to evaluate the relationship of PD with osteoporosis, bone mineral density (BMD) and fracture risk.

Methods A literature search was undertaken on 4 September 2012 using multiple indexing databases and relevant search terms. Articles were screened for suitability and data extracted where studies met inclusion criteria and were of sufficient quality. Data were combined using standard meta-analysis methods.

Results 23 studies were used in the final analysis. PD patients were at higher risk of osteoporosis (OR 2.61; 95% CI 1.69 to 4.03) compared with healthy controls. Male patients had a lower risk for osteoporosis and osteopenia than female patients (OR 0.45; 95% CI 0.29 to 0.68). PD patients had lower hip, lumbar spine and femoral neck BMD levels compared with healthy controls; mean difference, -0.08 , 95% CI -0.13 to -0.02 for femoral neck; -0.09 , 95% CI -0.15 to -0.03 for lumbar spine; and -0.05 , 95% CI -0.07 to -0.03 for total hip. PD patients were also at increased risk of fractures (OR 2.28; 95% CI 1.83 to 2.83).

Conclusions This systematic review and meta-analysis demonstrate that PD patients are at higher risk for both osteoporosis and osteopenia compared with healthy controls, and that female patients are at greater risk than male patients. Patients with PD also have lower BMD and are at increased risk of fractures.

The Global Longitudinal Study of Osteoporosis in Women (GLOW) study found PD to be the strongest single contributor to fracture risk compared with other studied factors.⁴ Gait impairment, postural instability and falls, polypharmacy and reduced BMD all contribute to fracture risk in PD.⁶ Vitamin D deficiency with secondary hyperparathyroidism may contribute to low BMD but disease duration and severity, age and low body mass index are also implicated.⁷

BMD is traditionally measured using dual x-ray absorptiometry (DEXA), which measures bone density per unit area. The results are normalised to age- and gender-matched members of the general population, generating a Z-score. Normalisation against a population of young healthy adults gives a T-score. Osteoporosis is defined as a T-score <-2.5 SDs from the norm and osteopenia as a T-score between -1 and -2.5 SDs.²

The aim of this systematic review and meta-analysis was to summarise and combine the published data on the association of PD with fracture risk and BMD.

METHODS

Search strategy

The PRISMA 2009 guidelines for systematic review and meta-analysis were followed throughout the study.⁸ A strategy was developed to search PubMed, SciVerse Scopus and Google Scholar with the following terms: 'Osteoporosis and PD', 'Osteopenia and PD', 'Fracture and PD' and 'Bone health and PD'. The search was carried out on 4 September 2012.

The search was restricted to English articles. Article titles and abstracts were reviewed for relevance pertaining to the following three items of interest: (1) risk of osteoporosis/osteopenia in PD; (2) BMD in PD; and (3) fracture risk in PD. Articles were excluded on the basis of title or abstract if they were not relevant to either bone health or fracture risk in PD. The full articles of relevant studies were obtained and reviewed. Reference lists of relevant articles were hand searched for any additional references not picked up by the electronic database searches, as were the reference lists of existing meta-analyses and any review articles identified through the original database search. Three reviewers (KMT, AJN and KMD) reviewed and filtered the articles at each stage and differences in opinion were resolved through discussion.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder which affects 1%–2% of the UK population over 65 years.¹ Osteoporosis describes a reduction of bone mineral density (BMD) which places those affected at increased risk of fragility fractures particularly those involving the hip, wrist and spine.² Multiple factors contribute to the development of osteoporosis including age, gender, height, weight, family history, smoking status and vitamin D levels.³ Poor bone health results in significant morbidity and mortality, as well as being detrimental to quality of life.² There is increasing evidence to suggest neurological conditions including epilepsy, multiple sclerosis, dementia and PD are associated with an excess rate of osteoporosis and fracture risk.^{4–5}



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Inclusion criteria

Published studies were included if the following criteria were fulfilled: (1) observational studies with either a cohort or case-control design; (2) cases were patients with PD according to standard clinical criteria, for example, Queen Square Brain Bank Criteria;⁹ (3) controls were healthy or had no history of neurological disease; (4) original data were reported; (5) BMD was measured using DEXA scans.

Exclusion criteria

Abstracts and published conference proceedings, editorials, commentaries, review articles, case reports, meta-analyses and letters that did not report new data were all excluded. We also excluded studies that: (1) reported on the management of fractures; (2) reported fractures prior to the onset of PD; (3) did not provide adequate details of the control group; (4) reported data for cases not fulfilling clinical criteria for PD; (5) reported data for factors other than BMD or fracture, for example, falls, body mass index, dietary intake or sunlight exposure; (6) were randomised controlled trials; (7) reported risk estimates other than relative risks (RR)/odds ratios (ORs)/hazard ratios (HRs), such as mortality rate and standardised hospitalisation ratios.

Data handling

Three authors (KMT, AJN and KMD) independently collected and tabulated the data into an electronic spread sheet, under the following headings: PubMed ID, author, year of publication, year of study, population studied, study design, number of males, number of females, mean ages and the results for the specific factor of interest (eg, number with fractures, number with osteoporosis, average BMD).

If case-control studies reported data for more than one control group, we used the control group most representative of the general population. In studies that had no calculated risk estimate (RR/OR/HR), we reviewed the crude data and calculated an OR where possible. In studies that reported both crude and adjusted OR, the adjusted figure was used. Where two studies with the same population and overlapping follow-up periods were found, the study with greatest number of subjects was used. If population sizes were equal, the most recent study was used. Where data were not clearly reported, the corresponding author of the article was contacted and data were made available. After application of the above methods, the quality of the remaining articles was assessed using the Newcastle Ottawa Scale (NOS).¹⁰ We set a predetermined threshold of study quality as a score of 7 out of 9 and excluded any studies that scored below this threshold.

Statistical analysis

Where a factor of interest was reported by two or more studies in a consistent manner, these were combined using standard meta-analysis methods to generate a pooled OR and 95% confidence intervals (CIs) for each factor. The OR was used as an estimate of HR or RR in relevant studies. Heterogeneity between studies was assessed using the I^2 statistic and, where statistically significant heterogeneity was found ($p < 0.05$), the random effects model was used to combine results.^{11 12} Publication bias was assessed using the Egger test, and where statistically significant bias was found, the trim and fill method was used to adjust for it.^{13 14} All analyses were performed using Stata V.10 (StataCorp, College Station, Texas, USA).

RESULTS

Search results

The literature search yielded 2243 non-duplicated articles, of which 2063 were excluded on the basis of their title or abstract. Reviewing the full manuscript of the remaining 180 articles led to further exclusions according to the criteria detailed above (see figure 1 for flowchart). After hand searches and subsequent application of NOS quality criteria (see online supplementary tables S1–S3), the final number of articles included in the analysis was 23.

Osteoporosis and osteopenia in PD

Two studies were included in the analysis that reported the diagnosis of osteoporosis in patients with PD versus healthy controls (see figure 2). The combined OR for osteoporosis in PD patients was 2.61; 95% CI 1.69 to 4.03 (see online supplementary table S4A).

A further four studies reported gender comparisons of osteoporosis/osteopenia in patients with PD. The combined OR for osteoporosis in male PD patients compared with female patients was 0.32; 95% CI 0.18 to 0.58 and for osteopenia was 0.64; 95% CI 0.35 to 1.16 (see figure 2). When data for osteoporosis and osteopenia were combined, the OR for male PD patients versus female PD patients was 0.45; 95% CI 0.29 to 0.68 (see online supplementary table S4B,C).

BMD in PD

Fourteen included studies reported on BMD in PD patients (total number of patients $n=938$) and controls ($n=15\,050$) (see figure 3 and online supplementary table S5). PD patients had significantly lower BMD than controls; overall combined mean difference, -0.06 ; 95% CI -0.08 to -0.03 . The overall figure comprised significant differences in the BMD of patients and controls at the femoral neck, lumbar spine, total hip and total body, as well as non-significant differences at the trochanter and Ward's triangle. The combined mean difference was -0.08 , 95% CI -0.13 to -0.02 for the femoral neck; -0.09 , 95% CI -0.15 to -0.03 for the lumbar spine; and -0.05 , 95% CI -0.07 to -0.03 for total hip. Subgroup gender analysis showed female PD patients had

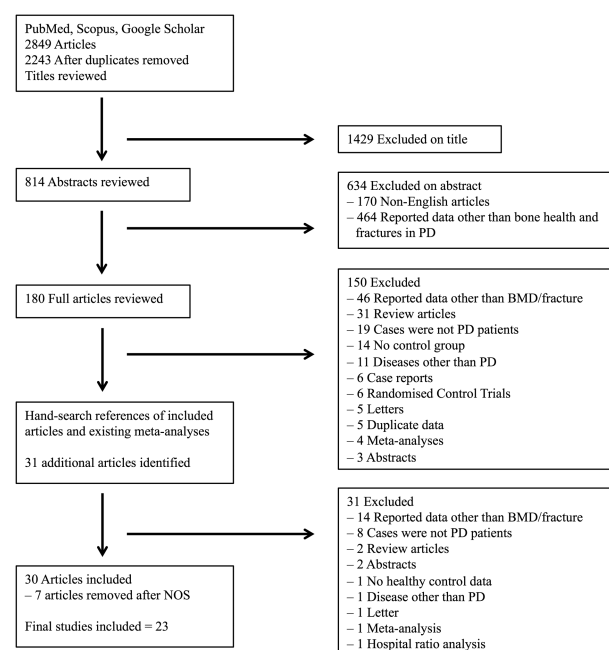


Figure 1 Flowchart of studies included and excluded. PD, Parkinson's disease; BMD, bone mineral density.

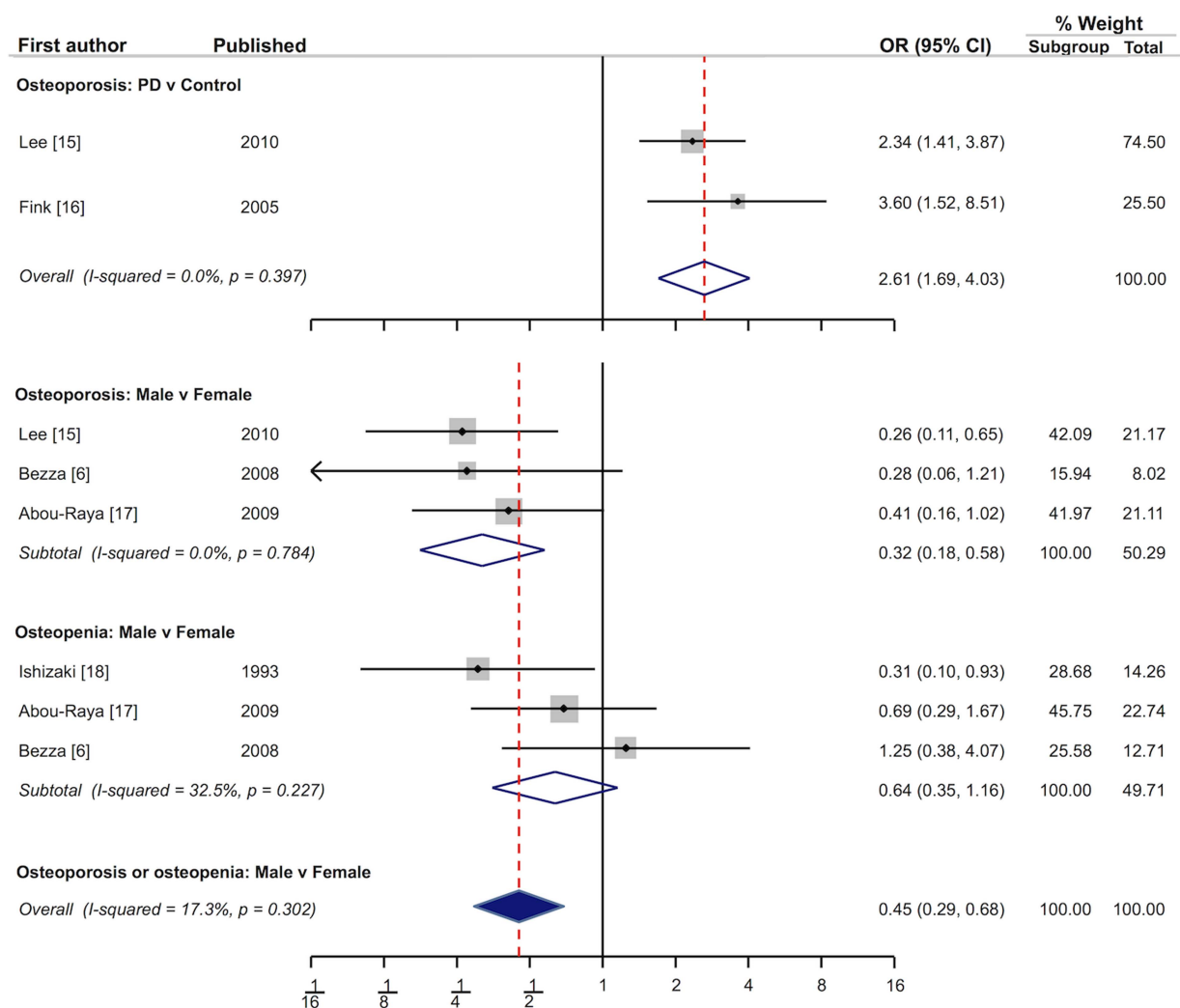


Figure 2 Pooled estimate of OR and 95% CI of Parkinson's disease (PD) and osteoporosis and osteopenia in male versus female patients.

lower BMD at all body sites compared with male PD patients (data not shown).

Five of these 14 studies and one additional study reported Z-scores (see figure 4 and online supplementary table S6). Patients had significantly lower Z-scores than controls; overall combined mean difference, -0.75 ; 95% CI -1.00 to -0.51 . This comprised mean difference of -1.03 ; 95% CI -1.31 to -0.74 for femoral neck; -0.57 , 95% CI -0.67 to -0.48 for lumbar spine; and -0.59 ; 95% CI -0.82 to -0.35 for total body.

Three of the 14 studies reported T-scores (see figure 5 and online supplementary table S7). PD patients had significantly lower T-scores than controls; overall combined mean difference, -1.05 ; 95% CI -1.26 to -0.84 . Separately, the T-scores for lumbar spine, femoral neck and total hip were all significantly lower in PD patients than controls.

Fracture risk in PD

Nine of the included studies reported data pertaining to fracture risk in PD (see figure 6 and online supplementary table S8). The combined effect size was 2.28; 95% CI 1.83 to 2.83. Of these, three studies had a combined HR of 2.10, 95% CI 1.55 to 2.86; four studies had a combined OR of 4.01, 95% CI 1.77 to 9.04; and two studies had a combined RR of 2.13, 95% CI 1.68 to 2.69. Significant publication bias was noted in studies

reporting fracture risk ($p=0.042$). The trim and fill method was used to correct for this yielding a new OR of 1.93; 95% CI% 1.56 to 2.40.

DISCUSSION

The best-established and generalisable risk factors for osteoporosis include age, gender, steroid therapy, low BMI, sedentary lifestyle and smoking.² More recently, neurological diseases have emerged as important causes of secondary osteoporosis. The GLOW found PD to have the strongest association with fractures above all other studied characteristics.⁴

The purpose of this systematic review and meta-analysis was to fully explore the published literature on the risk of osteoporosis, reduction in BMD and fracture risk in patients with PD. The results show that PD patients have significantly increased risk of osteoporosis and osteopenia, and that female patients are more severely affected than male patients. This gender difference in osteoporosis is consistent with that observed in the wider non-PD population. Certain female factors may increase risk of osteoporosis with endocrine and nutritional factors playing an important role.

Invernizzi *et al*³² reported that osteoporosis and osteopenia affect 91% of female and 61% of male patients. Additionally, Schneider *et al*²³ showed female PD patients to have a 7.3%

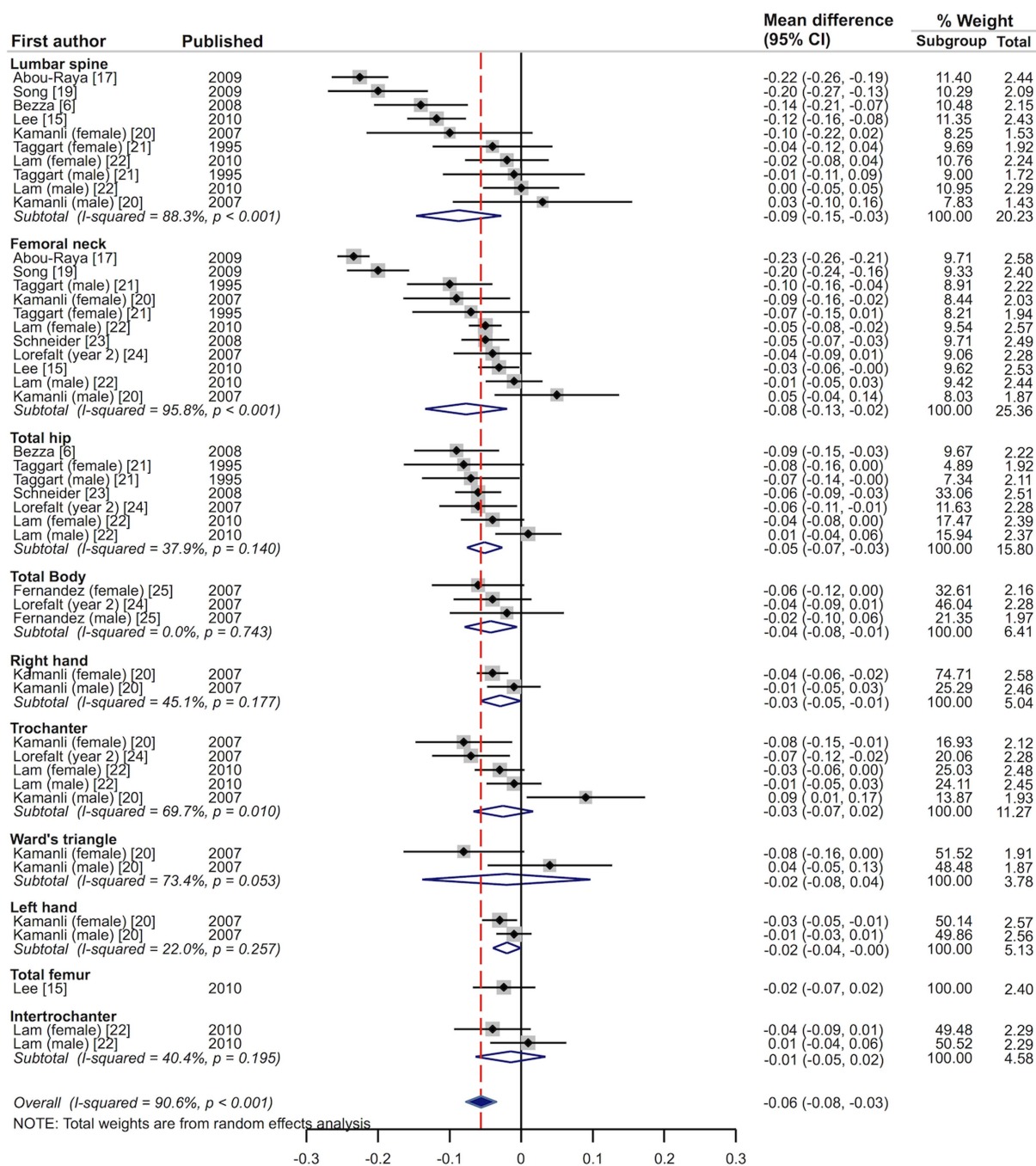


Figure 3 Mean difference and 95% CI of Parkinson's disease and bone mineral density.

lower BMD and an increased risk of fractures (HR 2.6) compared with age-matched controls. Of interest is a recent meta-analysis that found the opposite result.³³ Here the authors found PD male patients to be at a higher risk for osteoporosis than female patients; summary OR 1.16; 95% CI 1.07 to 1.26 for female patients versus OR 2.44; 95% CI 1.37 to 4.34 for male patients. They attributed this difference to higher vitamin D and oestrogen levels in women.^{34 35} However, the authors used different selection criteria for studies including use of abstracts, non-English language articles and an article in which osteoporosis preceded the diagnosis of PD. These differences might account for their findings, which seem counter-intuitive given the well-established gender differences in those without PD.

Through combining data from studies using objective measurements of BMD using DEXA imaging only, PD patients were found to have reduced BMD across a wide range of body regions when compared with healthy controls. In addition, combining data from studies that reported T-scores and Z-scores specifically gave a similar conclusion that BMD was reduced in PD patients compared with controls. Again, gender differences in the PD patient population were apparent. The reduction in BMD in PD patients has been previously reported as being more apparent at the lumbar spine and femoral neck and greatest in older women with advanced disease.⁷ Our findings were in agreement with this observation, with PD patients having most marked changes in BMD levels in the lumbar spine and femoral neck regions.

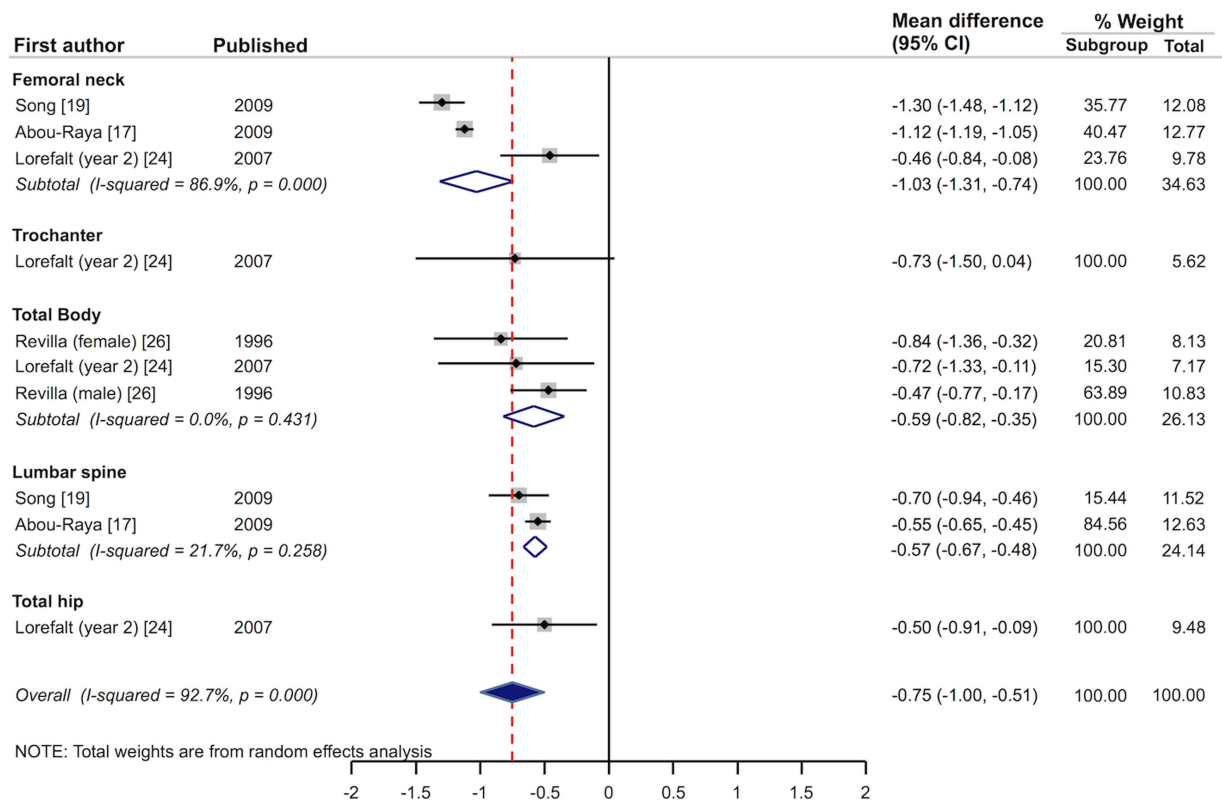


Figure 4 Mean difference and 95% CI of Parkinson's disease and bone mineral density Z-score.

Deterioration in bone health in patients with PD can have grave consequences and a significant increase in fracture risk in this patient group compared with healthy controls was observed. Factors that contribute to loss of BMD in PD include vitamin D deficiency with secondary hyperparathyroidism, reduced sunlight exposure, disease duration and severity, age

and low body mass index. Factors that increase risk of fractures from falls in the context of reduced BMD include postural instability, orthostatic hypotension, motor fluctuations, cognitive impairment and physical deconditioning. In all, 50% of PD patients report falling more than once during a 3-month period and 13% report falling more than once a week.^{36 37}

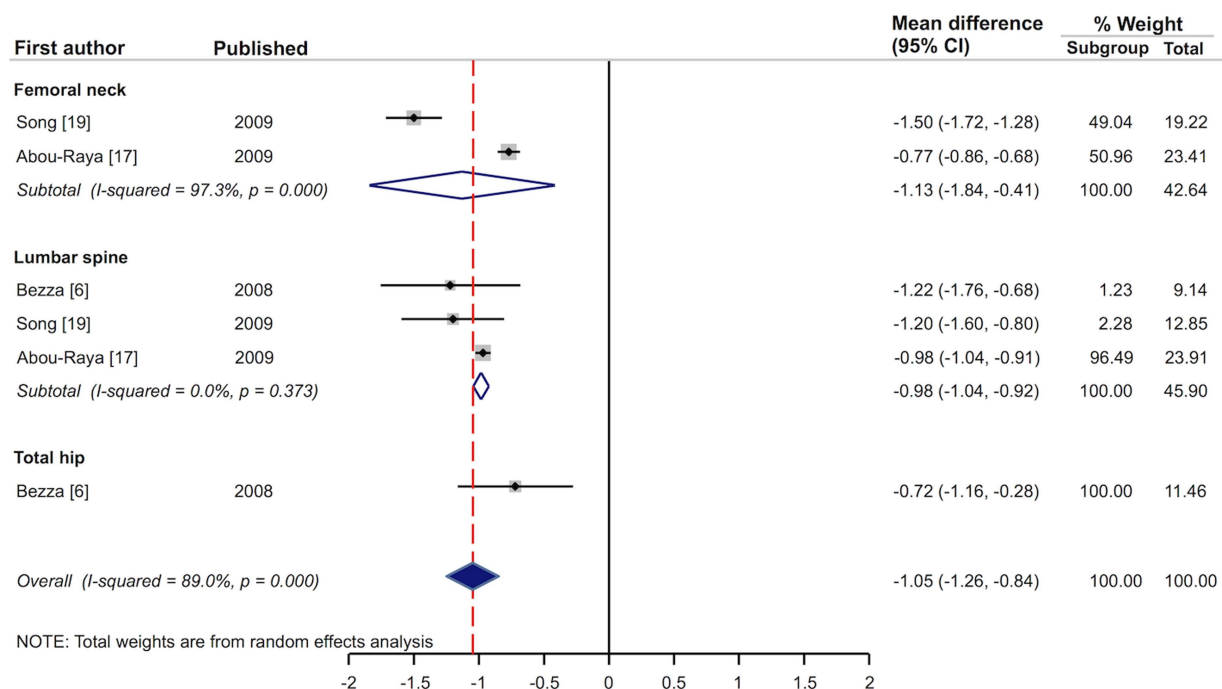


Figure 5 Mean difference and 95% CI of Parkinson's disease and bone mineral density T-score.

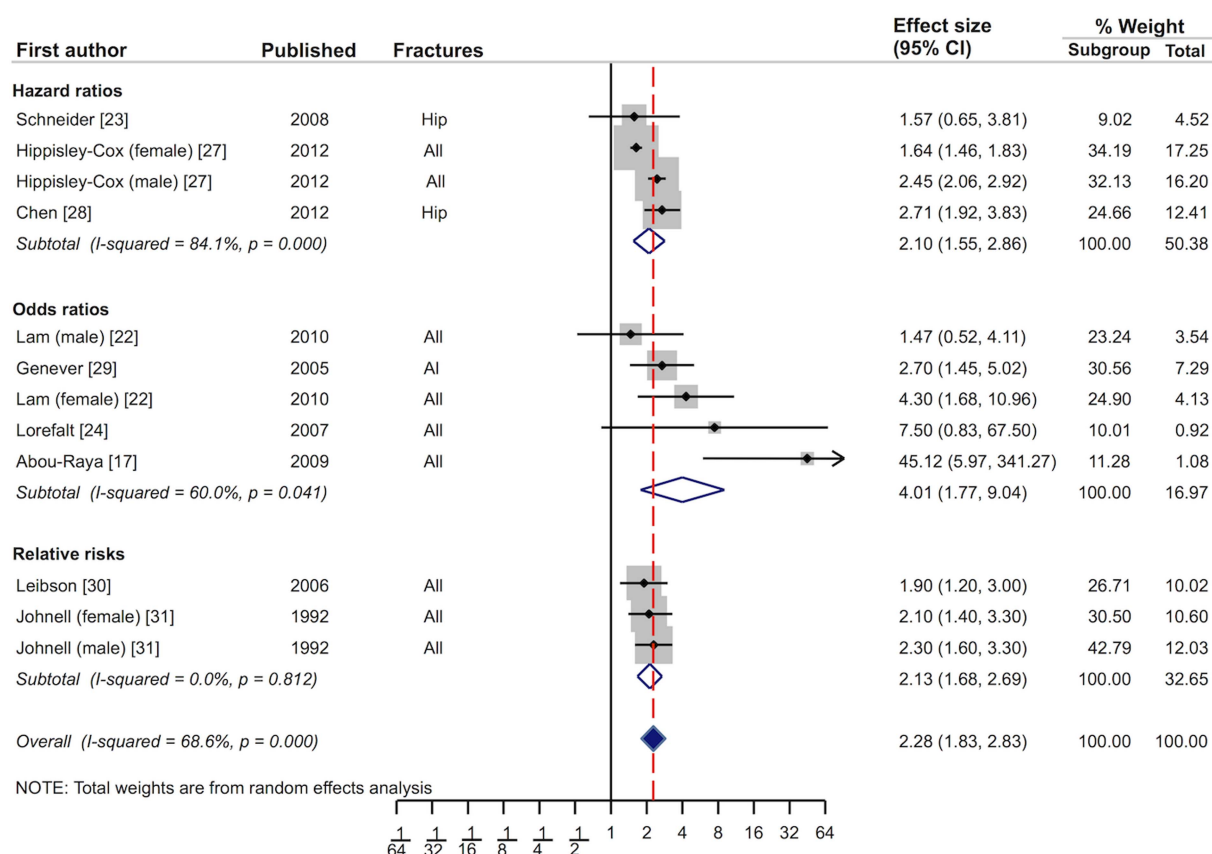


Figure 6 Pooled estimate of effect size (ES) and 95% CI of Parkinson's disease and fracture risk.

The most common fracture is that of the hip, which accounts for 50% of all fractures in PD patients.³⁸ In non-PD subjects, the most common fragility fractures are vertebral.² The prevalence of vertebral fractures may be underestimated in PD as the typical or expected stooped posture may not solicit investigation for osteoporosis (figure 7). Hip fractures are associated with higher medical costs and greater morbidity than all other osteoporotic fractures.³⁹ They also carry a 1-year mortality rate of 30%.⁴⁰ The predisposition for hip fractures in PD may reflect the nature of the falls themselves in that they are often in a sideways or backward direction.^{29–31} Elderly subjects with a rapid gait are more likely to fall forward while those with a shuffling gait tend to fall backward or to the side and suffer a hip fracture.^{41–42} Lower BMD levels at the hip may also contribute to the excess rate of hip fractures in PD patients. Of interest is a previous community-based study of PD patients showing that falls risk was significantly greater in patients with dyskinesia and tended to be greater in those with motor fluctuations.⁴³ The nine studies that were included in the fracture meta-analysis were reviewed further to see whether an explanation for the difference in fracture site could be determined. None of the studies provided information on motor fluctuations, two provided information on falls and one provided information on walking speed showing that patients were slower than controls and more likely to fall. The reason for the excess risk of hip fracture in PD is an important matter for further study.

Levodopa is central to the drug treatment of PD, but has been implicated as an independent risk factor for fracture and reduced BMD in some studies and the risk may be dose-dependent.^{41–44} Alongside a possible deleterious effect on

BMD, levodopa improves some motor deficits in PD but tends not to improve postural stability, meaning that patients are potentially more mobile but are perhaps at an increased risk of falls. Side effects of levodopa such as orthostatic hypotension, visual hallucinations and excessive daytime somnolence can further increase risk of falls.⁴¹ Levodopa can also induce hyperhomocysteinemia which has been reported as a potential risk factor for fractures.⁴⁵ Furthermore, a significant proportion of patients with PD suffer from depression and it is noteworthy that the concomitant use of antidepressants with levodopa has been associated with a threefold to fivefold increase in the risk of hip/femur fractures.^{41–46} Antidepressants inhibit serotonin transport systems and have a detrimental effect on the microarchitecture of the bone and thus reduce BMD.⁴⁷

The management of fracture risk is an important aspect of the holistic care of patients with PD. The National Institute of Health and Care Excellence recommends that assessment with either FRAX⁴⁸ or Qfracture²⁷ risk calculators should be 'considered' in all patients with possible secondary osteoporosis and should be used to determine those who should undergo formal BMD measurement using dual-energy X-ray absorptiometry (DEXA) imaging.³ The treatment of osteoporosis should follow local guidelines and should be considered on an individual basis. Bisphosphonates are important in the treatment of osteoporosis but side effects such as nausea are relatively common. Correcting vitamin D and calcium levels using supplementation should also be routine in these patients.

Non-pharmacological measures such as exercise programmes, dietary advice, smoking cessation, regular medication review, occupational therapy and physiotherapy assessment, visual



Figure 7 Osteoporotic collapse in a Parkinson's disease patient with camptocormia. This patient has a completely collapsed posture on standing (A and B—standing lateral radiograph). When supine, there is normal sagittal alignment of the spine and no flexed joint contractures (C). Supine CT imaging through the midline demonstrates several osteoporotic vertebral fractures. There is complete wedging of T11 (red arrow) and partial collapse of lumbar vertebrae 1–3 (D).

assessment, and falls education and risk management can contribute to reducing falls risk. Specific exercise programmes focusing on strength, balance and flexibility reduce falls rate and risk in community dwelling elderly people.⁴⁹ Ultimately, an integrated approach including falls risk assessment, fracture risk assessment and investigations into secondary causes of osteoporosis in PD patients is needed to prevent falls and fractures in these patients.

There were a number of identifiable limitations when undertaking this review. We restricted our search to articles written in English and therefore reports written in other languages were not included in the analysis. However, this was an important decision since the quality of the studies included was a key consideration and could not be assessed adequately if the authors reviewed non-English articles and their abstracts. Even carefully planned search strategies can miss articles of interest and underestimate the available published literature. To overcome this, we used overlapping search terms, three indexing databases and hand searched the reference list of suitable articles. Reassuringly, the hand search yielded no additional suitable articles that could be included in the final analysis, suggesting that our electronic search strategy was adequate. By following this sequence, we have taken numerous steps to ensure that missing information was kept to a minimum. Low quality studies may distort the overall findings of meta-analysis. We therefore devised and

followed stringent inclusion and exclusion criteria, followed by the additional step of employing a recognised quality scoring system for the remaining articles, the NOS scale. ORs, HRs and RRs were considered to be equivalent for the purposes of combining and analysing data. They are not equivalent, however, and in addition some articles did not report an OR and simply gave the raw data. In this situation, two authors independently calculated the OR from the raw data and then cross-referenced their answers. Significant heterogeneity was observed in most of the analyses. This is expected because of differences between individual studies in, for example, study population characteristics and whether crude or adjusted risk estimates were reported.

In conclusion, we have used a comprehensive systematic review and meta-analysis to demonstrate a significant positive association in risk of osteoporosis, reduction in BMD and risk of fractures in patients with PD. Further research is required to look at the basic mechanisms that underpin these observations, as well as more detailed study of the epidemiology, leading onto strategies for pharmacological and non-pharmacological primary and secondary prevention.

Contributors KMT, AJN and KMD: design and conceptualisation of the study, acquisition of data, analysis of the data, interpretation of the data, drafting the manuscript, approval of final version. JB: analysis of the data, interpretation of the data, drafting the manuscript, approval of final version. RD: design and conceptualisation of the study, approval of final version. AJL: design and conceptualisation of the study, interpretation of the data, revision of the manuscript for intellectual content, approval of final version.

Competing interests KMT reports no disclosures. AJN: Travel support from the National Institute of Health Research for presentations at MDS Congresses and Association of British Neurologists Meetings; grants from Parkinson's UK Innovation Grant (K-1006), Parkinson's UK Career Development Award (F-1201), National Institute of Health Research Academic Clinical Fellowship, Élan/Prothena Pharmaceuticals and GE Healthcare. KMD: beneficiary of a Reta Lila Weston Scholarship and received a Parkinson's UK Innovation Grant (K-1010). JPB reports no disclosures. RD reports no disclosures. AJL: Board membership for Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion, BIAL, Noscira, Roche; consultancy for Genus; grants from PSP Association, Weston Trust—Reta Lila Howard Foundation; speaking fees from Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion, BIAL, Noscira and Roche.

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Supplementary Table 1 - Details of Studies included in the meta-analysis

Author	Year	Sample year(s)	Study Design	Country	Population	Cohort size	PD Cases (no.)	Females	Males	Mean age	Controls	Females	Males	Mean Age
Abou-Raya	2009	NK	Case-Control	Egypt	Department of Internal Medicine, University of Alexandria	-	82	39	43	67.5	68	32	36	67.0
Bezza	2008	NK	Case-Control	Morocco	Neurology department, Military Hospital Mohammed V	-	52	16	36	60.0	52	16	36	59.6
Chen	2012	1999-2000	Case-Control	Taiwan	National Health Insurance Research Database	-	394	201	193	68.6	3940	2010	1930	68.6
Fink	2005	2000-2002	Cohort	US	Six USA clinical sites	5995	52	0	52	75.1	5943	0	5943	73.6
Genever	2005	NK	Nested case-control	UK		-	200	104	96	75.6	200	104	96	74.36
Hippisley-Cox	2012	1993-2011	Cohort Study	UK	Primary care popluation	3142673	7809							
Ishizaki	1993	NK	Case-control	Japan		-	64	41	23	66.9	42	23	19	62.9
Ishizaki	1993	NK	Case-control	Japan		-	64	41	23	66.9	42	23	19	62.9
Johnell	1992	1967-1979	Population based Case-Control	Minnesota	Olmsted County	-	138			72.3	138			72.4
Kamanli	2007	NK	Case-Control	Turkey		-	12	12	-	67.2	18	18	-	62.1
Melton	2006	1976-1995	Cohort	Minnesota	Olmsted County	-	196	76	120		196	76	120	

Melton	2006	1976-1995	Cohort	Minnesota	Olmsted County	-	120		120		120		120	
Melton	2006	1976-1995	Cohort	Minnesota	Olmsted County	-	76	76			76	76		
Pang	2009	NK	Cross sectional	China	Parkinson's disease Association	-	34	34	0	64.2	30	30	0	65.5
Pang	2009	NK	Case-Control	China	Parkinson's disease Association	-	43	21	22	63.9	29	13	16	61.3
Sato	1997	1996	Case-Control	Japan	Futase Social Insurance Hospital-group 1	-	20	11	9	69	33	16	17	69.8
Sato	1997	1996	Case-Control	Japan	Futase Social Insurance Hospital-group 2	-	51	28	23	70.3	33	16	17	69.8
Sato	2005	2000-2003	Case-Control	Japan	Department of geriatric neurology, Mitate Hospital	-	142	78	64	69.9	99	57	42	68.8
Schneider	2008	1986-1988	SOF Cohort	US	4 Clinical centres-Baltimore, Minneapolis, Portland, Pittsburgh	8105	73	73	0	78.3	8032	8032	0	77
Song	2009	2006-2007	Case-Control	Korea	Catholic medical centre, Korea, Soonchunhyang University hospital	-	107	61	46	67.9	100	49	51	65.3
Lee	2010	2006-2007	Case-Control	Korea	Asan Medical Centre, Seoul, Korea	-	95	53	42	67.6	285	159	126	67.6
Lorefalt	2007	NK	Case-Control	Sweden		-	26	17	9	74	26	17	9	74
Fernandez	2007	NK	Case-Control	Argentina		-	22	12	10	67	104	44	44	67
Fernandez	2007	NK	Case-Control	Argentina		-	12	12	-	67.3	44	44	-	66.4
Fernandez	2007	NK	Case-Control	Argentina		-	10	-	10	67.4	44	-	44	67.1

Revilla	1996	NK	Case-Control	Spain		-	52	24	28	63.1	80	40	40	64
Taggart	1995	2 years	Case-Control	UK		-	55	29	26	75	55	29	26	75
Taggart	1995	2 years	Case-Control	UK		-	29	29	-	76.8	29	29	-	76.7
Taggart	1995	2 years	Case-Control	UK		-	26	-	26	74.3	26	-	26	74.7
Leibson	2006	1976-1995	Case-Control	USA	Olmsted County	-	197	77	120	70	197			
Lam	2010	2004-2005	Case-Control	Hong Kong		-	50	-	50	66.8	100	-	100	66.9
Lam	2010	2004-2005	Case-Control	Hong Kong		-	58	58	-	68.8	116	116	-	69

Supplementary Table 2 – BMD, Z-score , T-score values and fracture rates of studies included in the meta-analysis

Author	Year	Factor of interest	BMD PD	SD	BMD control	SD	Z-score PD	SD	Z-score control	SD	T-score PD	SD	T-score control	SD	PD	Controls	p-value	OR	HR	RR	CI (Lower)	CI (Upper)
Abou-Raya	2009	Femoral neck	0.723	0.09	0.957	0.05											0.005					
Abou-Raya	2009	Femoral neck					-0.99	0.26	0.125	0.17							0.001					
Abou-Raya	2009	Femoral neck									-2.04	0.29	-1.27	0.25			0.001					
Abou-Raya	2009	Lumbar spine	0.889	0.17	1.114	0.06											0.001					
Abou-Raya	2009	Lumbar spine					-0.73	0.35	-0.183	0.28							0.005					
Abou-Raya	2009	Lumbar spine									-1.75	0.16	-0.78	0.21			0.001					
Abou-Raya	2009	Previous Fall Osteoporosis													38	2	0.005					
Abou-Raya	2009	(female)													19	0		0.408			0.163	1.018
Abou-Raya	2009	Osteoporosis (male)													12	0						
Abou-Raya	2009	Osteopenia (female)													18	0		0.6914			0.2861	1.671
Abou-Raya	2009	Osteopenia (male)													16	0						
Abou-Raya	2009	All Fractures													33	1	0.001					
Bezza	2008	Lumbar spine	1.03	0.17	1.17	0.17											<0.001					
Bezza	2008	Lumbar spine									-1.3	1.4	-0.08	1.4			<0.001					
Bezza	2008	Total Hip	0.96	0.15	1.05	0.16											0.03					
Bezza	2008	Total Hip Osteoporosis									-0.6	1.1	0.12	1.2			0.02					
Bezza	2008	(both)													9	0						
Bezza	2008	Osteopenia (both)													28	0						
Bezza	2008	Osteoporosis (female)													5	0		0.275			0.062	1.211
Bezza	2008	Osteoporosis (male)													4	0						

Bezza	2008	Osteopenia (female)						8	0		1.25	0.384	4.068
Bezza	2008	Osteopenia (male)						20	0				
Chen	2012	Hip fracture						41	160	<0.001	2.71	1.92	3.83
Fink	2005	>2 falls						28.60%	11.70%	<0.001	2.9	1.55	5.46
Fink	2005	Osteoporosis (male)						6	208	0.002	3.596	1.52	8.515
Fink	2005	Lumbar spine	1.022	No SD	1.073	No SD				0.04			
Fink	2005	Total hip	0.908	No SD	0.958	No SD				0.007			
Fink	2005	Femoral neck	0.75	No SD	0.785	No SD				0.45			
Fink	2005	Trochanter	0.729	No SD	0.766	No SD				0.03			
Genever	2005	All fractures						38	16	0.007			
Genever	2005	Limb						27	13	0.038			
Genever	2005	Femoral						11	4	0.07			
Genever	2005	Forearm						8	5				
Genever	2005	Vertebra						8	3				
Genever	2005	Ankle						3	3				
Genever	2005	Humerus						3	0				
Genever	2005	Rib						3	0				
Genever	2005	Pelvis						1	1				
Genever	2005	Tibia						1	0				
Hippisley-Cox	2012	Fracture (female)									1.64	1.46	1.83
Hippisley-Cox	2012	Hip fracture (female)									2.03	1.75	2.35

Hippisley-Cox	2012	Fracture (male)									2.45	2.06	2.92	
Hippisley-Cox	2012	Hip fracture (male)									3	2.37	3.79	
Ishizaki	1993	Osteopenia (female)						22	6	0.305		0.1	0.929	
Ishizaki	1993	Osteopenia (male)						6	2					
Ishizaki	1993	Asymmetrical osteopenia and PD symptoms						95%						
Johnell	1992	All Fracture						88	39	0.002		2.3	1.6	3.3
Johnell	1992	Male fractures						25	9			2.8	1.3	6.2
Johnell	1992	Female fractures						63	30			2.1	1.4	3.3
Johnell	1992	Vertebra						20	18			1.1	0.6	2.1
Johnell	1992	Ribs						27	8			3.4	1.6	7.7
Johnell	1992	Distal forearm						8	4			2	0.6	7
Johnell	1992	Proximal humerus						6	3			2	0.5	8.6
Johnell	1992	Pelvis						6	0			-	2	>100
Johnell	1992	Proximal femur						20	1			20	4	>100
Johnell	1992	Ankle						1	5			0.2	0.02	1.3
Johnell	1992	Proximal Tibia						0	0			-	0	>100
Kamanli	2007	Right hand	0.34	0.03	0.38	0.03				<0.05				
Kamanli	2007	Left hand	0.33	0.04	0.36	0.02				<0.05				
Kamanli	2007	Lumbar spine	0.84	0.18	0.94	0.12								
Kamanli	2007	Femoral neck	0.66	0.11	0.75	0.09				<0.05				
Kamanli	2007	Ward's triangle	0.49	0.13	0.57	0.09								
Kamanli	2007	Trochanter	0.57	0.1	0.65	0.08								

Kamanli	2007	Right hand	0.45	0.06	0.46	0.03
Kamanli	2007	Left hand	0.44	0.02	0.45	0.04
Kamanli	2007	Lumbar spine	1.09	0.15	1.06	0.17
Kamanli	2007	Femoral neck	0.89	0.09	0.84	0.13
Kamanli	2007	Ward's triangle	0.72	0.09	0.68	0.13
Kamanli	2007	Trochanter	0.86	0.09	0.77	0.12

Melton	2006	Skull					7	1		7.6	0.9	64
Melton	2006	Distal forearm					13	8		1.7	0.7	4.6
Melton	2006	Clavicle/scapula/sternum					6	3		2.6	0.7	9.9
Melton	2006	Ribs					20	14		1.8	0.9	3.6
Melton	2006	Vertebrae					74	33		2.6	1.6	4.1
Melton	2006	Pelvis					9	3		4	1.2	14
Melton	2006	Proximal femur					42	16		3.2	1.9	5.5
Melton	2006	After ten years follow up, fracture number					46%	29%				
Melton	2006	Skull					4	1		4.3	0.5	39
Melton	2006	Distal forearm					5	0		-	-	-
Melton	2006	Clavicle/scapula/sternum					3	1		2.9	0.5	17
Melton	2006	Ribs					14	6		2.5	0.9	7.1
Melton	2006	Vertebrae					34	11		3.2	1.5	6.7
Melton	2006	Pelvis					3	0		-	-	-
Melton	2006	Proximal femur					19	4		5.3	1.8	15
Melton	2006	Skull					3	0		-	-	-
Melton	2006	Distal forearm					8	8		1	0.4	2.9
Melton	2006	Clavicle/scapula/sternum					3	2		1.7	0.3	9.2
Melton	2006	Ribs					6	8		1.4	0.5	4.1

Melton	2006	Vertebrae									40	22		2.4	1.3	4.4
Melton	2006	Pelvis									6	3		2.8	0.8	9.1
Melton	2006	Proximal femur									23	12		2.8	1.4	5.7
Pang	2009	Had a fall in the last year									15	3	0.006			
Pang	2009	Total hip Osteopenia (female)	0.779	0.113			0.2	1.0		-1.0	1.1					
Pang	2009	Osteoporosis (female)										12	0			
Pang	2009											3	0			
Pang	2009	Lumbar spine Falls in the past year	0.848	0.165						-1.4	1.5					
Pang	2009											15	4	0.046		
Sato	1997	BMD right second metacarpal (CXD used)	2.346	0.38	2.553	0.366						2.346	2.553	0.0002		
Sato	1997	Z-score BMD right second metacarpal					0.648	1.197	0.227	1.138		-0.648	0.227	<0.05		
Sato	1997		2.139	0.486	2.553	0.366								0.0002		
Sato	1997	Z-score					-1.61	1.624	0.227	1.138				<0.0001		
Sato	2005	BMD	2.2	0.46	2.55	0.36								<0.0001		
Sato	2005	T-score								-2.29	1.59	0.39	1.2	<0.0001		
Schneider	2008	Hip	0.68	0.14	0.74	0.13								0.005		
Schneider	2008	Femoral neck	0.58	0.1	0.63	0.12								0.005		
Schneider	2008	Hip Fracture												1.57	0.65	3.81

Schneider	2008	Non-spine, non-hip fracture																1.02	0.42	2.46	
Song	2009	Lumbar spine	0.7	0.2	0.9	0.3														<0.001	
Song	2009	Femoral neck	0.4	0.1	0.6	0.2														<0.001	
Song	2009	Lumbar spine					-1.7	0.1	-1	1.2										<0.001	
Song	2009	Lumbar spine									-3.4	1.5	-2.2	1.4						<0.001	
Song	2009	Femoral neck					-1.9	0.1	-0.6	0.9										<0.001	
Song	2009	Femoral neck									-3.9	0.1	-2.4	1.1						<0.001	
Lee	2010	Osteoporosis (both)													36	59	0.001	2.337		1.412	3.869
Lee	2010	Osteoporosis present (female)													27	48	0.008	0.263		0.105	0.654
Lee	2010	Osteoporosis present (male)													9	11	0.05				
Lee	2010	Lumbar spine	0.837	0.184	0.955	0.151														<0.001	
Lee	2010	Femoral neck	0.702	0.127	0.733	0.118														0.056	
Lee	2010	Total femur	0.819	0.195	0.843	0.168														0.288	
Lorefalt	2007	Fracture													6	1		NS			
Lorefalt	2007	Total Body Year 1	0.98	0.1	1.01	0.2														NS	
Lorefalt	2007	Total Body Year 1					-0.15	0.8	0.36	1.3										NS	
Lorefalt	2007	Total Hip Year 1	0.77	0.1	0.81	0.1														NS	
Lorefalt	2007	Total Hip Year 1					-0.25	0.7	0.12	0.6										<0.05	
Lorefalt	2007	Femoral neck Year 1	0.65	0.1	0.69	0.1														<0.05	
Lorefalt	2007	Femoral neck Year 1					-0.22	0.9	0.16	0.6										<0.05	
Lorefalt	2007	Trochanter	0.58	0.1	0.63	0.1														<0.05	

[illegible]

Taggart	1995	Lumbar spine	0.92	0.21	0.93	0.15				NS	-0.11	0.09	
Taggart	1995	Total hip	0.81	0.14	0.88	0.11				NS	-0.15	-0.01	
Taggart	1995	Neck of femur	0.65	0.11	0.75	0.11				<0.002	-0.17	-0.04	
Leibson	2006	Fracture						73	46	<0.01	1.9	1.2	3
Leibson	2006	Hip Fracture						25	5	<0.01	5.6	2.1	15
Lam	2010	Lumbar Spine	0.9	0.16	0.9	0.15				0.95			
Lam	2010	Femoral neck	0.68	0.12	0.69	0.11				0.48			
Lam	2010	Trochanter	0.61	0.12	0.62	0.1				0.72			
Lam	2010	Intertrochanter	0.97	0.16	0.96	0.15				0.81			
Lam	2010	Total Hip	0.82	0.14	0.81	0.13				0.49			
Lam	2010	Fracture Male						7	10	0.522			
Lam	2010	Lumbar Spine	0.73	0.2	0.75	0.15				0.39			
Lam	2010	Femoral neck	0.53	0.11	0.58	0.1				0.005			
Lam	2010	Trochanter	0.46	0.12	0.49	0.09				0.04			
Lam	2010	Intertrochanter	0.76	0.18	0.8	0.15				0.14			
Lam	2010	Total Hip	0.63	0.15	0.67	0.12				0.09			
Lam	2010	Fracture Female						14	8	0.012			

Supplementary Table 3 – NOS scoring of studies included in the meta-analysis

Author	Year	NOS
Abou-Raya	2009	8
Bezza	2008	7
Chen	2012	7
Fink	2005	8
Genever	2005	8
Hippisley-Cox	2012	9
Ishizaki	1993	7
Johnell	1992	8
Kamanli	2007	9
Melton	2006	9
Pang	2009	8
Pang	2009	8
Sato	1997	7
Sato	2005	9
Schneider	2008	8
Song	2009	8
Lee	2010	8
Lorefalt	2007	9
Fernandez	2007	8
Revilla	1996	8
Taggart	1995	7
Leibson	2006	9
Lam	2010	8
Abrahamsen	2009	5
Arbouw	2011	5
Dennison	2012	4
Di Monaco	2006	6
Sato	2001	6
Pressley	2012	5
Rico	1987	5

Author, year	PD Cases	Controls	Osteoporosis in PD	Osteoporosis in Controls	p-value	OR	95% CI
Fink et al, 2005	52	5943	6	208	0.002	3.596	[1.52, 8.52]
Lee et al, 2010	95	285	36	59	0.001	2.337	[1.41, 3.87]

Supplementary table 4a. Summary of the studies included in the analysis of risk of osteoporosis in PD.

Author,(year	PD(Cases	Females	Males	Osteoporosis(Osteoporosis(OR	95%(CI
				in(female(PD(in(male(PD(
Lee#et#l,#2010	95	53	42	patients	patients	0.263	[0.12,#0.65]
Bezza#et#l,#2008	52	16	36	5	4	0.275	[0.06,#.21]
Abou;Raya#et#l,#2009	82	39	43	19	12	0.408	[0.16,#.02]

Supplementary table 4b. Summary of the studies included in the analysis of risk of osteoporosis in female and male PD patients.

Author,(year	PD(Cases	Females	Males	Osteopenia(Osteopenia(OR	95%(CI
				in(female(PD(in(male(PD(
Bezza#et#l,#2008	52	16	36	patients	patients	1.25	[0.38,#.07]
Abou;Raya#et#l,#2009	82	39	43	18	16	0.69	[0.29,#.67]
Ishizaki#et#l,#1993	64	41	23	22	6	0.31	[0.1,#0.93]

Supplementary table 4c. Summary of the studies included in the analysis of risk of osteopenia in female and male PD patients.

Author, year	PD patients	Controls	Site for BMD	BMD (PD Patients)	BMD (Controls)	P-value	Mean Difference	95% CI
Abou-Raya et al, 2009	82	68	Femoral neck	0.723	0.957	0.005	-0.23	[-0.26, -0.21]
Abou-Raya et al, 2010	82	68	Lumbar spine	0.889	1.114	0.001	-0.22	[-0.26, -0.19]
Bezza et al, 2008	52	52	Lumbar spine	1.03	1.17	<0.001	-0.14	[-0.21, -0.07]
Bezza et al, 2009	52	52	Total Hip	0.96	1.05	0.03	-0.09	[-0.15, -0.03]
Kamanli et al, 2007	12	18	Right hand (female)	0.34	0.38	<0.05	-0.04	[-0.06, -0.02]
Kamanli et al, 2008	12	18	Left hand (female)	0.33	0.36	<0.05	-0.03	[-0.05, -0.01]
Kamanli et al, 2009	12	18	Lumbar spine (female)	0.84	0.94		-0.10	[-0.22, 0.02]
Kamanli et al, 2010	12	18	Femoral neck (female)	0.66	0.75	<0.05	-0.09	[-0.16, -0.02]
Kamanli et al, 2011	12	18	Ward's triangle (female)	0.49	0.57		-0.08	[-0.16, 0.00]
Kamanli et al, 2012	12	18	Trochanter (female)	0.57	0.65		-0.08	[-0.15, -0.01]
Kamanli et al, 2013	12	13	Right hand (male)	0.45	0.46		-0.01	[-0.05, 0.03]
Kamanli et al, 2014	12	13	Left hand (male)	0.44	0.45		-0.01	[-0.03, 0.01]
Kamanli et al, 2015	12	13	Lumbar spine (male)	1.09	1.06		0.03	[-0.10, 0.16]
Kamanli et al, 2016	12	13	Femoral neck (male)	0.89	0.84		0.05	[-0.04, 0.14]
Kamanli et al, 2017	12	13	Ward's triangle (male)	0.72	0.68		0.04	[-0.05, 0.13]
Kamanli et al, 2018	12	13	Trochanter (male)	0.86	0.77		0.09	[0.01, 0.17]
Schneider et al, 2008	73	8032	Hip	0.68	0.74	0.005	-0.06	[-0.09, -0.03]
Schneider et al, 2009	73	8032	Femoral neck	0.58	0.63	0.005	-0.05	[-0.07, -0.03]
Song et al, 2009	107	100	Lumbar spine	0.7	0.9	<0.001	-0.20	[-0.27, -0.13]
Song et al, 2010	107	100	Femoral neck	0.4	0.6	<0.001	-0.20	[-0.24, -0.16]
Lee et al, 2010	95	285	Lumbar spine	0.837	0.955	<0.001	-0.12	[-0.16, -0.08]
Lee et al, 2011	95	285	Femoral neck	0.702	0.733	0.056	-0.03	[-0.06, -0.00]
Lee et al, 2012	95	285	Total femur	0.819	0.843	0.288	-0.02	[-0.07, 0.02]
Lorefalt et al, 2007	26	26	Total Body Year 2	0.97	1.01	NS	-0.04	[-0.09, 0.01]
Lorefalt et al, 2008	26	26	Total Hip Year 2	0.74	0.8	<0.05	-0.06	[-0.11, -0.01]
Lorefalt et al, 2009	26	26	Femoral neck Year 2	0.63	0.67	<0.01	-0.04	[-0.09, 0.01]
Lorefalt et al, 2010	26	26	Trochanter Year 2	0.56	0.63	<0.05	-0.07	[-0.12, -0.02]
Fernandez et al, 2007	12	44	BMD (female)	0.958	1.018	<0.05	-0.06	[-0.12, 0.00]
Fernandez et al, 2008	10	44	BMD (male)	1.176	1.196	NS	-0.02	[-0.10, 0.06]
Taggart et al, 1995	29	29	Lumbar spine (female)	0.76	0.8	NS	-0.04	[-0.12, 0.04]
Taggart et al, 1996	29	29	Total hip (female)	0.64	0.72	NS	-0.08	[-0.16, 0.00]
Taggart et al, 1997	29	29	Neck of femur (female)	0.55	0.62	NS	-0.07	[-0.15, 0.01]
Taggart et al, 1998	26	26	Lumbar spine (male)	0.92	0.93	NS	-0.01	[-0.11, 0.09]
Taggart et al, 1999	26	26	Total hip (male)	0.81	0.88	NS	-0.07	[-0.14, -0.00]
Taggart et al, 2000	26	26	Neck of femur (male)	0.65	0.75	<0.002	-0.10	[-0.16, -0.04]
Lam et al, 2010	50	100	Lumbar Spine (male)	0.9	0.9	0.95	0.00	[-0.05, 0.05]
Lam et al, 2011	50	100	Femoral neck (male)	0.68	0.69	0.48	-0.01	[-0.05, 0.03]
Lam et al, 2012	50	100	Trochanter (male)	0.61	0.62	0.72	-0.01	[-0.05, 0.03]
Lam et al, 2013	50	100	Intertrochanter (male)	0.97	0.96	0.81	0.01	[-0.04, 0.06]
Lam et al, 2014	50	100	Total Hip (male)	0.82	0.81	0.49	0.01	[-0.04, 0.06]
Lam et al, 2015	58	116	Lumbar Spine (female)	0.73	0.75	0.39	-0.02	[-0.08, 0.04]
Lam et al, 2016	58	116	Femoral neck (female)	0.53	0.58	0.005	-0.05	[-0.08, -0.02]
Lam et al, 2017	58	116	Trochanter (female)	0.46	0.49	0.04	-0.03	[-0.06, 0.00]
Lam et al, 2018	58	116	Intertrochanter (female)	0.76	0.8	0.14	-0.04	[-0.09, 0.01]
Lam et al, 2019	58	116	Total Hip (female)	0.63	0.67	0.09	-0.04	[-0.08, 0.00]

Supplementary table 5. Summary of the studies included in the analysis of BMD levels in PD patients and controls.

Author, year	PD patients	Controls	Area studied	Z-score (PD)	Z-score (control)	P-value	Mean Difference	95% CI
Abou-Raya et al, 2009	82	68	Femoral neck	-0.996	0.125	0.001	-1.12	[-1.19, -1.05]
	82	68	Lumbar spine	-0.735	-0.183	0.005	-0.55	[-0.65, -0.45]
Lorefalt et al, 2007	26	26	Total Body Year 2	-0.31	0.41	<0.01	-0.72	[-1.33, -0.11]
	26	26	Total Hip Year 2	-0.32	0.18	<0.05	-0.50	[-0.91, -0.09]
	26	26	Femoral neck Year 2	-0.3	0.16	<0.01	-1.03	[-1.31, -0.74]
	26	26	Trochanter Year 2	-0.41	0.32	<0.01	-0.73	[-1.50, 0.04]
Song et al, 2009	107	100	Lumbar spine	-1.7	-1	<0.001	-0.70	[-0.94, -0.46]
	107	100	Femoral neck	-1.9	-0.6	<0.001	-1.30	[-1.48, -1.12]
Revilla et al, 1996	52	80	Total body (male)	-0.47	0		-0.47	[-0.77, -0.17]
	52	80	Total body (female)	-0.84	0		-0.84	[-1.36, -0.32]

Supplementary table 6. Summary of the studies included in the analysis of Z-scores in PD patients and controls.

Author, year	PD patients	Controls	Area studied	T-score (PD)	T-score (control)	P-value	Mean Difference	95% CI
Abou-Raya et al, 2009	82	68	Femoral neck	-2.037	-1.266	0.001	-0.77	[-0.86, -0.68]
			Lumbar spine	-1.753	-0.778	0.001	-0.98	[-1.04, -0.91]
Bezza et al, 2008	52	52	Lumbar spine	-1.3	-0.08	<0.001	-1.22	[-1.76, -0.68]
			Total Hip	-0.6	0.12	0.02	-0.72	[-1.16, -0.18]
Song et al, 2009	107	100	Lumbar spine	-3.4	-2.2	<0.001	-1.20	[-1.60, -0.80]
			Femoral neck	-3.9	-2.4	<0.001	-1.50	[-1.72, -1.28]

Supplementary table 7. Summary of the studies included in the analysis of T-scores in PD patients and controls.

Author, year	PD patients	Control	Fracture site	PD patients with fracture	Control with fracture	P-value	HR	95% CI
Schneider et al, 2008	73	8032	Hip Fracture				1.57	[0.65, 3.81]
Hippisley-Cox et al, 2012	7809		Fracture (female)				1.64	[1.46, 1.83]
Hippisley-Cox et al, 2012	7809		Fracture (male)				2.45	[2.06, 2.92]
Chen et al, 2012	394	3940	Hip fracture	41	160	<0.001	2.71	[1.92, 3.83]

Author, year	PD patients	Control	Fracture site	PD patients with fracture	Control with fracture	P-value	OR	95% CI
Lam et al, 2010	50	100	Fracture Male	7	10	0.522	1.47	[0.52, 4.11]
Lam et al, 2010	58	116	Fracture Female	14	8	0.012	4.30	[1.68, 10.98]
Genever et al, 2005	200	200	All fractures	38	16	0.007	2.70	[1.45, 5.02]
Abou-Raya et al, 2009	82	68	All Fractures	33	1	0.001	45.12	[5.97, 341.27]
Lorefalt et al, 2007	26	26	Fracture	6	1	NS	7.50	[0.83, 67.50]

Author, year	PD patients	Control	Fracture site	PD patients with fracture	Control with fracture	P-value	RR	95% CI
Johnell et al, 1992	138	138	Male fractures	25	9		2.80	[1.3, 6.2]
Johnell	138	138	Female fractures	63	30		2.10	[1.4, 3.3]
Leibson et al 2006	197	197	Fracture	73	46	<0.01	1.90	[1.2, 3]

Supplementary table 8. Summary of the studies included in the analysis of fractures in PD patients and controls.