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REVIEW

Parkinson's disease and risk of hip fracture: systematic review and meta-analysis

Ali Hosseinzadeh[1] · Malahat Khalili[1] · Behnaz Sedighi[2] · Sohrab Iranpour[3] · Ali Akbar Haghdoost[1]

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Abstract

The relationship between Parkinson's disease (PD) and risk of hip fracture yielded inconsistent results. Therefore, we conducted the present systematic review and meta-analysis of published observational studies to assess the association between PD and risk of hip fracture. PubMed, ISI, EMBASE, and Cochrane databases were searched systematically to identify studies assessing the relationship between PD and the risk of hip fracture up to July 01, 2017. In addition, to find related articles, the reference section of retrieved articles was checked. Random-effects model was used for calculation of pooled hazard ratio (HR) and 95% confidence intervals (CI). Thirteen independent studies containing 564,947 participants were included in the meta-analysis. The overall results of included studies showed PD to be associated with the risk of hip fracture ($HR_{overall} = 3.13$, 95% CI 2.53–3.87) in women 3.11 (2.51–3.86) and men 2.60 (2.19–3.09). Our meta-analysis showed the direct association between PD and the risk of hip fracture in both men and women. However, due to the limitations of this study, further well-designed studies are required to confirm our findings.

Keywords Parkinson's disease · Hip fracture · Meta-analysis · Risk factor

Introduction

Parkinson's disease (PD) is a chronic neurological disease that mostly affects the age group of > 50 years of age, and is not prevalent in the age group of < 40. This disease is one of the most prevalent neurodegenerative diseases that its worldwide prevalence increases with age, from 0.6% in ages of 56–69 years to 3% in elderlies of above 80 [1, 2]. In this condition, the loss of dopaminergic neurons, leading to symptoms such as tremor, muscle rigidity, and situational imbalance, increases the risk of falling in patients [3]. Several studies have shown that PD increased the risk of fractures [4–6]. A part of the association between PD and fractures can be related to the increased risk of falling in patients suffering from this disease [7]. On the other hand, PD is associated with other factors that indirectly have an adverse effect on bones [8, 9]; in a way that decrease in the level of 25-hydroxy vitamin D and compensation for high levels of thyroid hormone have been observed in PD patients, and it is possible for these factors to decrease bone density [8]. Both of these factors (falling and decrease in bone density) increase the risk of bone fracture. Besides these factors, due to the side-effects of usual medicines (such as levodopa and dopamine agonist) used for the treatment of PD, including situational blood pressure and reduction of attention or confusion, as well, patient do not have proper protective responses in falling, and thus, the risk of bone fracture increases [10, 11]. A study showed that about 50% of bone fractures happened in PD patients were hip fractures [12].

In addition, studies that have shown the direct association between PD and risk of hip fracture have had a great growth in recent years [6, 13, 14]. Despite this epidemiological evidence, the relationship between PD and the risk of hip fracture has not been systematically assessed; therefore, this relationship has been studied in the present systematic review and meta-analysis.

✉ Ali Akbar Haghdoost
ahaghdoost@gmail.com

[1] Research Center for Modeling in Health, Institute for Future Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

[2] Department of Neurology, Shafa Hospital, Kerman University of Medical Science, Kerman, Iran

[3] Department of Epidemiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Methods

To conduct the current meta-analysis, MOOSE guideline (guideline for meta-analysis of observational studies) was used [15]. PubMed, ISI, EMBASE, and Cochrane databases were searched systematically to identify studies assessing the relationship between PD and risk of hip fracture up to July 01, 2017. In addition, the reference section of retrieved articles was checked to find related articles. The search was performed using medical subheadings such as Parkinson disease or PD, and hip fracture or fracture, in a systematic manner. This search was limited to the studies performed on humans and there were no lingual restrictions.

Inclusion and exclusion criteria of studies

Studies that possessed the following criteria were entered into the meta-analysis: (1) original article; (2) clinical trial, cohort, case–control, and cross-sectional studies; (3) adult human population; (4) relationship index: odds ratio (OR), hazard ratio (HR), or relative risk (RR), reported together with confidence interval (CI) of 95%. Out of 20 epidemiological studies [6, 13, 14, 16–33] that had the inclusion criteria, 18 were cohort studies, 2 were case–control studies, and one was researching news. Studies that had not reported necessary information for calculation of standard error were excluded from the meta-analysis. In addition, in the event that several studies were reported from one population or cohort, only data from the latest study were entered. Two studies were excluded, because they had only reported the point estimate (without CI and standard error) [28, 31], as well as two other studies due to reporting the results of one cohort [13, 14], one study because of ambiguity in reporting the extent of relationship [6], and finally, two studies were excluded from the meta-analysis because of inexplicitness of their report on the extent of relationship [30, 33].

Quality assessment of studies and data extraction

The following details were extracted and recorded for each of the included studies using a pre-designed data extraction form: publication source (surname of the first author, year of publication of the article, and country of the studied population), name of the study, study design, sample size, follow-up period for cohort studies, age, sex, point estimate together with CI, and variables controlled for in the multivariate model. For each study, we extracted the risk estimations that reflected the greatest degree of control for potential confounders. Study design, participants characteristics, adjustment for potential confounders, and estimates of associations were independently extracted by two reviewers (AH and MKH); disagreements between reviewers were resolved by referring to a third author (AAH).

Eight studies [17–19, 24, 26, 29, 32, 34] had not performed their analyses for men and women separately. However, since estimates were made in presence of adjustment for age and sex, as well as HR and 95% CI, these studies were used in the meta-analysis for men and women. Two studies [23, 24] had reported RR instead of HR, and thus, RR was used in place of HR.

To review the quality of the included studies, 9-Star Newcastle Ottawa Scale (NOS) was used [35]. In a way that 9 points were given to a study with the highest methodological quality, points 4, 2, and 3 were allocated to "choosing study groups", "comparability of study groups", and "outcome assessment and adequacy follow-ups" respectively. Studies with a total score of 0–3, 4–6, and 7–9 were recognized as studies with poor, moderate, and high qualities, respectively.

Statistical analysis

HR was used as the common relationship index for all studies. To assess multivariate-adjusted HRs and its 95% CIs, a forest plot was drawn. In the present meta-analysis, HR logarithm with its standard error was utilized. Summary of HR estimates and its corresponding 95% CIs were calculated using the method of DerSimonian and Laird [36] as well as fixed-effects model and random-effects model. The summary HR estimates from random-effects model were used to investigate the variability between the studies. Statistical heterogeneity of HR between the studies was investigated using Cochran's Q test and I^2 statistic [37]. In case $I^2 \geq 50\%$ and $P \leq 0.05$, heterogeneity was considered statistically significant [38]. The random-effects model was used for pooling the results of the study [36], since this model takes into account study's sample size and between studies variation [39].

Meta-regression and subgroup analysis were done for detection of heterogeneity source. Subgroup analysis was done based on sex, study location, number of participants in a study, age, and quality of the study. In addition, to investigate the potential influence of each of the studies on the overall results, sensitivity analysis was performed.

Publication bias was assessed by the funnel plot [40]. In the funnel plot, HRs were plotted against the inverse of the square of the standard error (a measure of precision). In addition, Begg's test [41] and Egger's test [42] were used to investigate publication bias. All analyses were done using STATA 12.0 software (StataCorp, College Station, TX,

USA) [14]. All *P* values were two sided with a significant level of less than 0.05.

Results

Study characteristics

Based on pre-defined criteria, out of 13 independent studies containing 564,947 participants, a range of 364–498,849 participants was qualified to be included in the meta-analysis. Table 1 shows the characteristics of the included studies in summary [17–27, 29, 32]. Out of the above- mentioned 13 studies, four studies were conducted in the USA [20, 21, 25, 27], five in Europe [17, 18, 23, 26, 29], three in Asia [19, 22, 24], and one in Australia [32]. Two studies [25, 27] were only performed on women and one study [21] only on men, and ten studies [17–20, 22–24, 26, 29, 32] were performed on both men and women. From all the studies, 12 [17–19, 21–27, 29–32] had used HR or RR adjusted for potentially confounding variables as the measure of association, and only in one study [20], adjusted variables were not reported for calculated HR. Table 2 illustrates the results of the quality assessment of studies based on NOS. Ten studies had high quality and three had moderate quality.

Main analysis

The results of each study together with their overall results were presented in the forest plot (Fig. 1). Out of 13 studies, 12 studies [17, 18, 20–24, 26, 27, 29, 32] had reported a positive significant relationship between PD and the risk of hip fracture, and one study [25] had reported a positive but not significant relationship between PD and the risk of hip fractures (Table 1). The overall results of included studies showed that based on the random-effect model; PD has a direct association with the risk of hip fracture ($HR_{overall} = 3.13$, 95% CI 2.53–3.87). However, heterogeneity was statistically significant ($P_{hetrogenisity} = 0.00$ $I^2 = 93.4\%$). Based on meta-regression results, the sample size was the most important factor in creating heterogeneity. With regard to the results of subgroup analysis, studies conducted by Walker et al. [23] and Jorgensen et al. [29] had the most part in creating heterogeneity due to having large sample sizes. In addition, the study of Paul et al. [32], which was done in Australia, also caused heterogeneity. In the analysis conducted after excluding the above-mentioned studies, there was no major change in the relationship between PD and hip fracture ($HR_{overall} = 2.87$, 95% CI 2.43–3.38); and the heterogeneity test was not statistically significant ($I^2 = 5.2\%$; $P_{heterogeneity} = 0.39$) (Fig. 2).

Sensitivity and subgroup analyses

Subgroup analysis was performed based on sex, study location, number of participants in the study, age, follow-up period, and quality of performed studies (Table 3). Based on the obtained results, it can be observed that the effect of PD on hip fracture in women 3.11 (2.51–3.86), is slightly higher than that of men 2.60 (2.19–3.09). However, regarding study location, the effect of PD on hip fracture is considerably higher in the studies performed in Europe 4.85 (1.79–13.17) than those performed in the USA 2.96 (1.79–4.89), as well as in Asia 2.63 (2.17–3.19), and in Australia 2.06 (1.95–2.17). In addition, the effect of PD on hip fracture in the group of above 60 years of age old 4.16 (1.81–9.57) was considerably higher than the group of below 60 years old 2.68 (1.96–3.68). The analysis that was performed based on the duration of the follow-up period showed that the highest value of HR was in the study group that had the follow-up period of fewer than 5 years 5.48 (1.78–16.88); and in the studies with follow-up periods of between 5–10 years and above 10 years, HR were, respectively, 2.44 (1.98–2.99) and 2.79 (1.66–4.69). Likewise, the effect of PD on hip fracture in the high-quality study group was 4.03 (2.52–6.43), which is almost twice the amount of the low-quality study group 1.92(1.63–2.26).

In the sensitivity analysis, that in it, one study was omitted each time, and overall results were then calculated, there were no significant changes in the overall results of HR. The scope of results in the sensitivity analyses was between HR = 2.41 (95%, CI 2.06–2.80) and HR = 3.65 (95%, CI 2.50–5.33).

Publication bias

Begg's test and Egger's test showed some evidence for the existence of publication bias in the studies on PD and hip fracture ($P \leq 0.05$). Therefore, to evaluate and also adjust the effect of publication bias on the results of the meta-analysis, the method of Trim and Fill was used. The overall results obtained by this method HR = 3.32 (2.23–2.7) were slightly different from the overall results obtained from the meta-analysis HR = 2.87 (2.42–3.38).

Discussion

The findings from this meta-analysis indicate that PD almost tripled the risk of hip fracture. Subgroup and sensitivity analyses showed that the overall results of this analysis had enough stability.

To explain the relationship between PD and hip fracture, numerous factors have been pointed out in different texts. One of the factors that increases the risk of hip fracture is

Table 1 Characteristics of epidemiological studies of Parkinson's disease and risk of fracture included in the meta-analysis

Study	Country of study	Study population	Length of follow-up (year)	Gender	Study size	Age	Adjusted HR (95% CI)	Adjustment for covariates
Kauppi	Finland	This prospective study is based on the health survey, a comprehensive health examination survey which was conducted in Finland in 2000–2001	10 (2013)	F/M	2300	≥ 55	7.08 (2.19–22.93)	Gender, age, height, waist circumference, QUI, handgrip strength, walking speed, number of prescribed CNS active medication
Pouwel	UK	General practice Research Database (GPRD)	4 (2012)	F/M	9374	≥ 40	3.24 (2.15–4.9)	Age, sex, medication
Huang	Taiwan	Taiwan's National Health Insurance Program	8 (2014)	F/M	7115	≥ 40	2.56 (2.02–3.26)	Age, sex, urbanization, low income, stay in teaching hospital, coexisting medical conditions, and medication use. Additionally adjusted for fracture-repair surgery in the model of post-fracture mortality
Melton	USA	Rochester Epidemiology Project	13 (2005)	F/M	364	≥ 40	3.2 (1.9–5.5)	Age
Cauley	USA	Osteoporotic fractures in Men Study (MrOS)	8.6 (2015)	M	5994	≥ 65	3.32 (1.21–9.07)	Age, race, clinic
Yen-Yu Chen	Taiwan	An 8-year follow-up study in Taiwan	8 (2011)	F/M	4334	≥ 50	2.71 (1.92–3.83)	Age, gender, state of co-morbid hypertension, diabetes, diabetic neuropathy, osteoporosis, hyperlipidemia
Yamanashi	Japan	A total of 714 patients prospectively followed in Japan	3 (2004)	F/M	714	≥ 65	3.27 (1.28–8.35)	Age and sex
Schousboe	USA	The Study of Osteoporotic Fractures and Medicare claims data	20 (2012)	F	5008	≥ 65	1.77 (0.91–3.24)	Age, femoral neck BMD, clinic site
Wiklund	Sweden	Umeå 85+/Gerontological Regional Database (GERDA) study	5 (2015)	F/M	953	≥ 85	5.12 (1.82–14.44)	Currently smoking,underweight, age, sex, delirium
Cauley	USA	Study subjects were participants in the ongoing SOF cohort	10.5 (2008)	F	8945	≥ 65	9.09 (2.09–39.5)	Age, fracture history, maternal history of hip fracture, contrast sensitivity, weight, alcohol consumption
Paul	Australia	Residents of New South Wales (NSW), Australia	8.5	F/M	5045	≥ 65	2.06 (1.95–2.17)	Age, sex
Jørgensen	Denmark	Danish National Patient Registry and the National Population Registry	13	F/M	15,952	≥ 52	1.74 (1.67–1.8)	Age, gender, household size, calendar year, and comorbidity
Walker	England	Northumbria Healthcare NHS Foundation Trust England	2	F/M	498,849	≥ 60	14.1 (9.8–20.3)	Age

QUI quantitative ultrasound index, *CNS* central nervous system, *HR* hazard ratio

Table 2 Methodological quality of studies included in the meta-analysis

Studies	Selection				Comparability	Outcome			Score
	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcome to occur	Adequacy of follow-up of cohorts	
Kauppi	*	*	**	*	*	*	*	*	9
Pouwel	*	*	*	*	*	*	*	–	7
Huang	*	*	*	*	*	*	*	–	7
Melton	*	*	*	*	–	*	*	*	7
Cauley	*	*	–	*	*	*	*	**	8
Yen-Yu Chen	*	*	*	*	**	*	*	*	9
Walker	*	*	*	*	*	*	–	*	7
Yamanashi	*	*	*	*	*	–	*	–	6
Schousboe	*	*	*	*	**	*	*	*	9
Wiklund	*	*	*	*	**	–	*	*	8
Cauley	*	*	*	*	*	–	*	*	7
Paul	*	*	*	–	*	*	*	–	6
Jørgensen	*	*	–	–	*	*	*	–	4

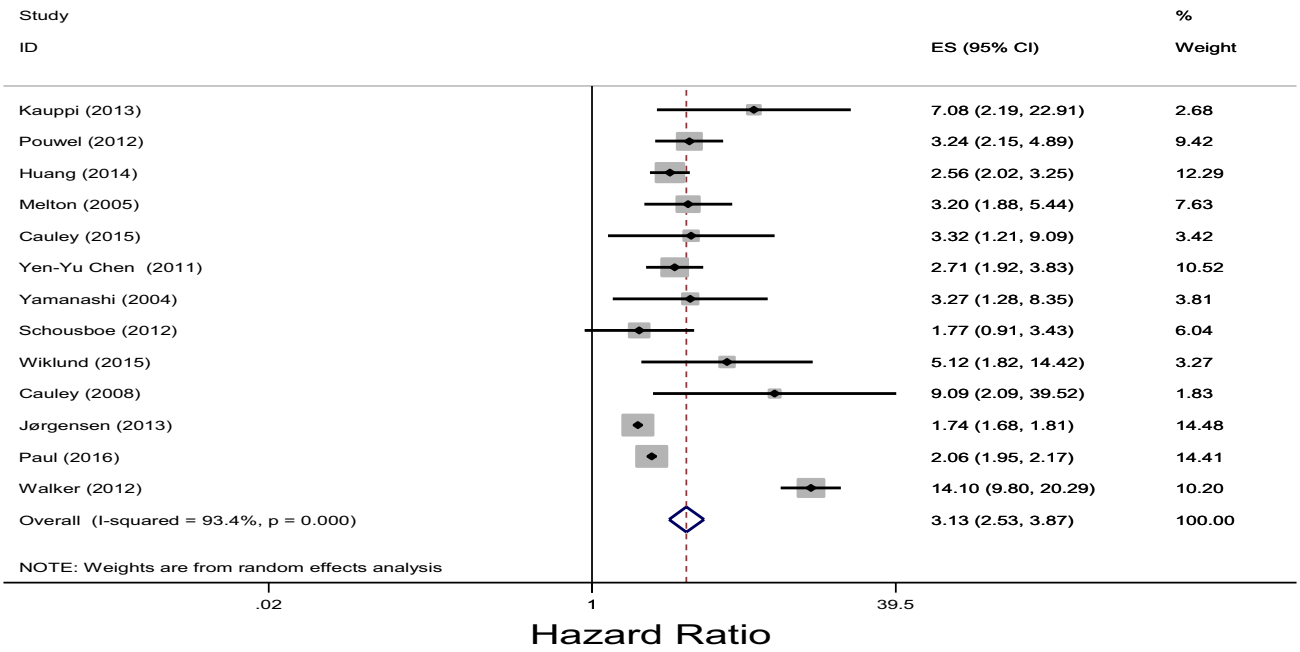

Fig. 1 Forest plot of the association between Parkinson's disease and risk of hip fracture. Random-effects model was used to pool the overall hazard ratios (HRs) and 95% confidence intervals (CIs). The diamond represents the pooled HR, and the squares and the horizontal lines, respectively, represent the HR and 95% CI of each individual study

vitamin D deficiency. In a study conducted by Dhanwal et al., it was demonstrated that about 75% of those who suffer from hip fracture had vitamin D deficiency [43]. In addition, several other studies have pointed out the relationship between vitamin D deficiency and hip fracture [43–47]. Vitamin D deficiency is caused by hypocalcemia and compensatory hyperparathyroidism; and if the parathyroid hormone is more than the required amount, it can cause bone loss by stimulating the activity of osteoclasts [48].

Therefore, due to the fact that vitamin D has a vital role in bone metabolism, it is clear that its deficiency increases the risk of falling and hip fracture [49]; while it has been

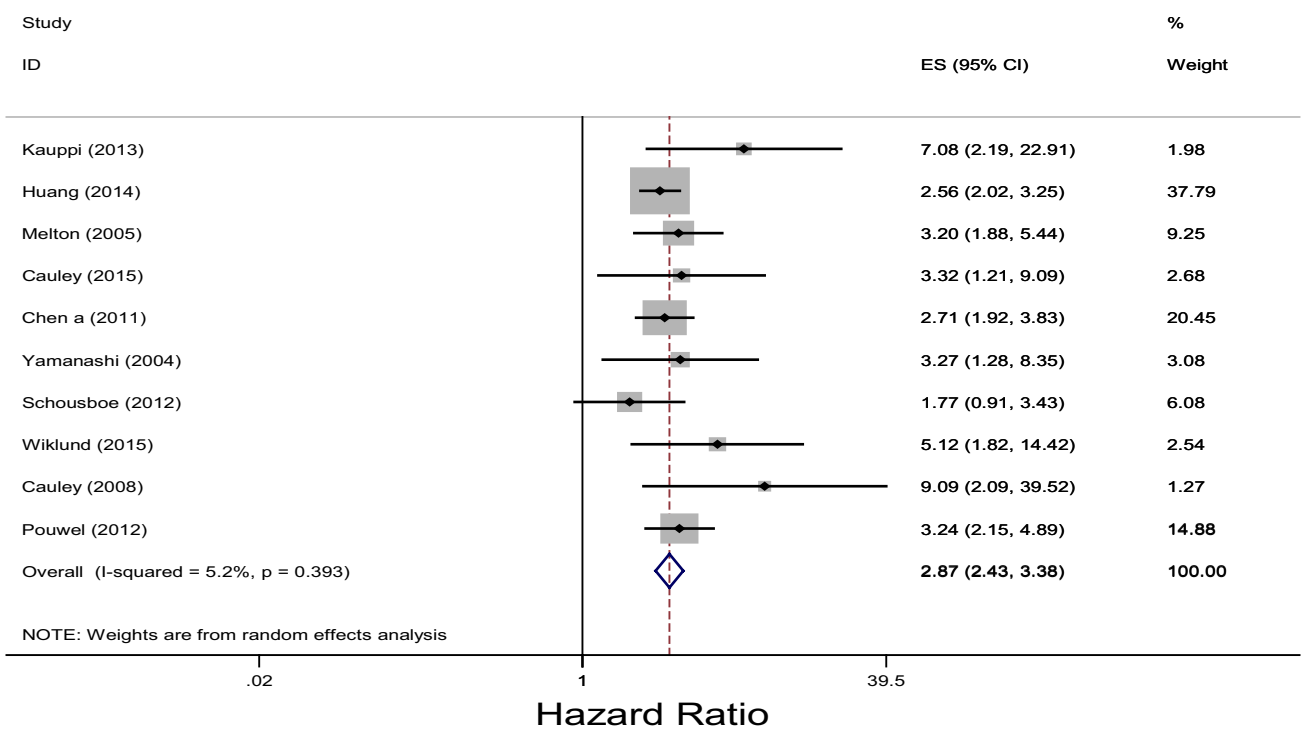

Fig. 2 Forest plot of the association between Parkinson's disease and risk of hip fracture. Random-effects model was used to pool the overall hazard ratios (HRs) and 95% confidence intervals (CIs). The diamond represents the pooled HR, and the squares and the horizontal lines, respectively, represent the HR and 95% CI of each individual study

Table 3 Risk estimates of the association between Parkinson's disease and risk of hip fracture

Factors	No. of studies	Summary adjusted HR (95%)	Heterogeneity I^2 (%)	Publication bias (*P*)
Gender				
Male	11	2.60 (2.19–3.09)	87.1	< 0.05
Female	12	3.11 (2.51–3.86)	93.2	< 0.05
Study location				
USA	4	2.96 (1.79–4.89)	35.5	≥ 0.05
Europe	5	4.85 (1.79–13.17)	96.8	≥ 0.05
Asia	3	2.63 (2.17–3.19)	0	≥ 0.05
Australia	1	2.06 (1.95–2.17)	NA	NA
Study size				
< 5000	5	3.12 (2.41–4.05)	0	< 0.05
5000–9000	5	2.31 (1.84–2.89)	49.6	≥ 0.05
> 9000	3	4.34 (1.21–15.57)	93.3	≥ 0.05
Age				
< 60	6	2.68 (1.96–3.68)	85.3	< 0.05
> 60	7	4.16 (1.81–9.57)	94.7	≥ 0.05
Follow-up				
< 5	3	5.48 (1.78–16.88)	93.4	≥ 0.05
5–10	5	2.44 (1.98–2.99)	54.9	≥ 0.05
> 10	5	2.79 (1.66–4.69)	73.9	≥ 0.05
Quality score				
≥ 7	10	4.03 (2.52–6.43)	87.6	≥ 0.05
< 7	3	1.92 (1.63–2.26)	92.6	≥ 0.05

NA not available, *HR* hazard ratio

demonstrated that prevalence of vitamin D deficiency in PD patients was significantly higher compared to healthy individuals or the Alzheimer's disease patients. This matter shows a special relationship between vitamin D deficiency and PD [8, 50, 51]. Vitamin D deficiency decreases muscle strength [48]. Muscle strength has an indirect correlation with bone density, and it affects bone formation and reconstruction through mechanical signals which it creates [52–54].

In a way that isokinetic muscle strength of PD patients is decreased compared to healthy individuals, even at the beginning stages of the disease, and it is reduced even more by disease's progression; although the reason behind this is unknown [55]. The next factor that explains the relationship between PD and hip fracture is the lack of movement or low physical activity in PD patients. Lack of movement or low physical activity causes bone loss and increases the risk of hip fracture [48, 56, 57]. Because of the low activity of PD patients [58], bone density in these patients is lower than healthy individuals [13, 20, 59].

One of the reasons which immobility causes a decrease in bone density is that the bone tissue is sensitive to its mechanical environment, and is constantly stimulated by muscle contractions and the movements that cause weight bearing. When bones are under pressure, a fluid flow is created that osteocytes are able to recognize through their dendritic connections. In response to these tensions, osteocytes create warning molecules that stimulate bone reconstruction via osteoclasts and osteoblasts [60, 61]. Therefore, unusual mechanical pressure as a result of immobility or low physical activity leads to bone loss and decrease in bone density [62]; and this matter increases the risk of hip fracture.

Another factor that has a negative effect on bone density and increases the risk of hip fracture is malnutrition [57]. The PD patients are exposed to malnutrition for several reasons including impaired hand–mouth coordination, dysphagia, decreased bowel movement, depression, cognitive impairment, and side-effects of drugs. At the same time, considering the muscle strength and involuntary movements in these patients, energy requirement tends to increase. Furthermore, malnutrition can lead to decreased levels of vitamin D, folic acid, and vitamin B12, which have negative effects on bone formation and strength [63, 64].

In addition, using different drugs for treating PD patients might be related to the risk of fracture. In a study performed by Vastergaard, it was shown that Levodopa was generally related to increased risk of fracture and in higher doses, increased the risk of hip fracture [65]. This matter could be due to the fact that Levodopa can create hyperhomocysteinemia as a result of its metabolism [66].

The risk of hip fracture in women was slightly higher than men in the subgroup analysis. This result is compatible with the results of the study of Joseph Melton III that had shown that the risk of hip fracture during lifetime was 17.5% for women and 6% for men. The bigger percentage of hip fracture in women is related to osteoporosis [67]. Osteoporosis can happen due to low bone mass or because of bone loss. Bone loss in women is increased after the menopause period due to decreased estrogen levels, and thus, the possibility of osteoporosis and hip fracture is increased [68]. Considering the fact that, in the present review study, most studies were done in ages of post menopause, therefore, it is possible that this is the reason for the observed difference between the two sexes.

In addition, based on the subgroup analysis, the greatest risk of hip fracture was in the continent of Europe, while the lowest risk was in Australia. These results are compatible with the study conducted by Dhanwal et al.; based on their results, same as the results obtained in this study, the highest rate of hip fractures had happened in European countries and the rate of such fractures in Asian countries was moderate [69]. Furthermore, a North-to-South geographical pattern has been seen, especially in Europe and USA, in a way that the most amount of hip fractures had happened in Northern regions [70]. Observed geographical differences can be related to demographical factors, race, latitude, physical activity, and vitamin D deficiency in Northern regions due to less sunlight [69]. Regarding the placement of Australia in a low latitude, the existence of the North-to-South pattern might explain the low amount of fracture risk in Australia. Although considering the fact that there was only one study from there, the results are not entirely reliable.

In addition, based on the obtained results from subgroup analysis, the risk of hip fracture in individuals of above 60 years of age was considerably higher than those of below 60 years. This finding is compatible with the findings of the previous studies [17, 19, 22, 23]. According to the World Health Organization's declaration in 2015, one of the possible reasons for increased risk of hip fracture in individuals of above 60 years of age is osteoporosis that its prevalence is increased with aging; in a way that about 15% of Caucasians suffer from osteoporosis at the age of 50 and about 70% at the age of 80; and this matter is more prevalent in women [68, 70]. In the present study, the effect of PD on hip fracture was higher in studies with less follow-up period, and the more the duration of the follow-up period, the less the risk of fracture. We do not have an explanation for this matter, but it may be due to that the risk of PD on hip fracture is high at the beginning, but with increased follow-up period, that risk is reduced; and this reduction is not because of decreased risk of PD, but because of the increased risk in the control group.

Restrictions

There were several limitations in this study. First, there was a significant heterogeneity in the overall analysis ($I^2 = 93.4\%$); and as it was demonstrated in the subgroup analysis, sex, study location, and sample size probably had a role in the observed heterogeneity. Second, there might be uncontrolled confounders. These residual confounders such as the history of hip fracture, taking corticosteroids or other medicines used in the treatment of PD, and serum status of vitamin D may confound the obtained results. Third, participants in the studies were mainly from Europe and America, and therefore, findings of this study may not be applicable for other populations. Another limitation of this study was publication bias; although, using the Trim and Fill method showed that the obtained results from this method were not majorly different from the meta-analysis results. Although, the possibility of the existence of publication bias is omnipresent in all meta-analyses.

Conclusion

The result from this meta-analysis showed a direct association between PD and the risk of hip fracture in both men and women. Despite the observational studies which we analyzed, it does not seem that the observed relationship was due to confounder factors alone. However, due to the limitations of this study, further well-designed studies are required to confirm our findings.

Compliance with ethical standards

Conflict of interest Ali Hosseinzadeh, Malahat Khalili, Behnaz Sedighi, Sohrab Iranpour, and Ali Akbar Haghdoost declare that they have no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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