MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 666-674
DOI: 10.12659/MSM.912840

Received: 2018.08.21
Accepted: 2018.10.05
Published: 2019.01.23

The Association Between Vitamin D Status, Vitamin D Supplementation, Sunlight Exposure, and Parkinson's Disease: A Systematic Review and Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCE 1 Zonglei Zhou
BDE 2 Ruzhen Zhou
BDF 3 Zengqiao Zhang
ACG 4 Kunpeng Li

1 Department of Epidemiology and Biostatistics, Sichuan University West China School of Public Health, Chengdu, Sichuan, P.R. China
1 Department of Anorectal Surgery, Changhai Hospital of Shanghai, Shanghai, P.R. China
3 School of Rehabilitation Science, Shanghai University of Traditional Chinese Medicine, Shanghai, P.R. China
4 Department of Neurorehabilitation, Shanghai Second Rehabilitation Hospital, Shanghai, P.R. China

Corresponding Author: Kunpeng Li, e-mail: three_stones_SCU@163.com
Source of support: This work was supported by the Shanghai Municipal Commission of Health and Family Planning (Grant number 201540279, 201740184)

Background: This literature review and meta-analysis aimed to determine the association between deficiency of vitamin D, or 25-hydroxyvitamin D, and Parkinson's disease, and whether vitamin D from supplements and sunlight improves the symptoms of Parkinson's disease.

Material/Methods: A literature review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Systematic literature review was performed using databases that included the Web of Science, PubMed, the Cochrane Library, and Embase. The Jadad scale (the Oxford quality scoring system) and the Newcastle-Ottawa scale (NOS) were used to evaluate the quality of the studies.

Results: Eight studies were included in the meta-analysis. Both 25-hydroxyvitamin D insufficiency (<30 ng/mL) (OR, 1.77; 95% CI, 1.29–2.43; P<0.001) and deficiency (<20 ng/mL) (OR, 2.55; 95% CI, 1.98–3.27; P<0.001) were significantly associated with an increased risk of Parkinson's disease when compared with normal controls Sunlight exposure (≥15 min/week) was significantly associated with a reduced risk of Parkinson's disease (OR, 0.02; 95% CI, 0.00–0.10; P<0.001). The use of vitamin D supplements was effective in increasing 25-hydroxyvitamin D levels (SMD, 1.79; 95% CI, 1.40–2.18; P<0.001), but had no significant effect on motor function (MD, –1.82; 95% CI, –5.10–1.45; P=0.275) in patients with Parkinson's disease.

Conclusions: Insufficiency and deficiency of 25-hydroxyvitamin D and reduced exposure to sunlight were significantly associated with an increased risk of Parkinson's disease. However, vitamin D supplements resulted in no significant benefits in improving motor function for patients with Parkinson's disease.

MeSH Keywords: Calcitriol • Meta-Analysis • Parkinson Disease • Sunlight

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912840

3377 3 5 53

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Parkinson's disease is a complex neurodegenerative disease that involves the loss of dopaminergic neurons in the substantia nigra [1]. Parkinson's disease is characterized clinically by motor dysfunction, including a resting tremor, bradykinesia and rigidity, and by non-motor symptoms, including sleep disturbance, cognitive impairment, olfactory disorders, and fatigue [1]. Elderly individuals who are more than 60 years of age are most likely to develop Parkinson's disease [2]. For people who are more than 40 years of age, the incidence of Parkinson's disease is 37.55 and 61.21 per 100,000 person-years, for women and the men, respectively [2]. Worldwide, due to the increase in life expectancy, it has been predicted that the number of patients with Parkinson's disease who are more than 50 years of age will double by 2030 [3]. Both genetic and environmental factors have been reported to contribute to the development of Parkinson's disease, including specific genetic mutations [4], gender [5], exposure to pesticides [6], and the use of calcium channel blockers [7].

Vitamin D, or 25-hydroxyvitamin D, is derived naturally from two main sources, the diet and from the effects of ultraviolet B (UVB) (wavelength, 290–315 nm) from sunlight, on the conversion from the steroid precursor, 7-dehydrocholesterol, in the skin. Therefore, lack of exposure to sunlight can result in low levels of vitamin D [8]. Currently, vitamin D has become regarded not as a vitamin, but as a hormone [9]. Apart from being involved in the metabolism of calcium and phosphorus, vitamin D also has a role in the inflammatory response [10], glucose and lipid metabolism [11,12], and in cardiac and vascular regulation [13]. Vitamin D performs its biological functions by binding to vitamin D receptors (VDRs) [14], which are members of the steroid hormone receptor superfamily. VDRs are widely expressed in many tissues [9], including the kidney, bone, the intestine, muscle, the pancreas, and the central nervous system.

Vitamin D deficiency is associated with a variety of pathological changes in many organ systems [15], and has been shown to be associated with an increased for several chronic diseases, including multiple sclerosis [16–19], cardiovascular disease [20], cancer [21], type 2 diabetes [22], Alzheimer's disease [23] and Parkinson's disease [24]. Vitamin D deficiency has been proposed to act as a suppressor of gene expression [25], one of the key genes that is suppressed in vitamin D deficiency is the tyrosine hydroxylase (TH) gene, which plays an essential role in regulation of dopamine biosynthesis [26] and the expression of neurotrophic factors [9].

Studies on the association between vitamin D deficiency and Parkinson's disease have shown conflicting findings. One cohort study [27] reported that there was insufficient evidence to support the hypothesis that vitamin D deficiency had a role in the pathogenesis of Parkinson's disease, or on the integrity of the dopaminergic system. However, other studies [9,28] have reported a high prevalence of vitamin D deficiency in patients with Parkinson's disease, with an inverse relationship between serum levels of 25-hydroxyvitamin D and the severity of Parkinson's disease [29–31]. Vitamin D supplements have been shown to reduce the rate of deterioration of motor function, as determined by both the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS) [32]. Preclinical animal experiments have also shown that vitamin D treatment was beneficial in reducing neuroinflammation and dopaminergic neurodegeneration [33]. However, controversy remains regarding the relationship between vitamin D status and the risk of Parkinson's disease. One study in Finland showed that increased vitamin D levels could reduce the risk of developing Parkinson's disease [24]. A further prospective cohort study that included a 17-year follow-up period showed that there was no association between vitamin D levels and the risk of developing Parkinson's disease [34].

Most previously published studies have focused on the prevalence of vitamin D deficiency or insufficiency in patients with Parkinson's disease, but published cohort studies, case-controlled studies, or randomized controlled trials (RCT) are scarce. Findings on the association between vitamin D status and the risk of Parkinson's disease are inconsistent, and it is unclear whether the degree of vitamin D deficiency affects the risk of Parkinson's disease. Also, although vitamin D deficiency is more common in patients with Parkinson's disease, it is unknown whether vitamin D supplements and exposure to sunlight can be regarded as an effective therapy to reduce the symptoms of Parkinson's disease.

Therefore, this literature review and meta-analysis aimed to determine the association between deficiency of vitamin D, or 25-hydroxyvitamin D, and Parkinson's disease, and whether vitamin D from supplements and sunlight improves the symptoms of Parkinson's disease. The normal serum reference range for total 25-hydroxyvitamin D is 20–100 ng/mL, and in this study, vitamin D insufficiency was defined as a serum level <30 ng/mL, and vitamin D deficiency was defined as a serum level <20 ng/mL.

Material and Methods

Literature search

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*http://www.prisma-statement.org*).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. The search strategy for PubMed.

Search	Query
#1	Idiopathic Parkinson disease [Title/Abstract] OR Parkinsonism [Title/Abstract] OR primary Parkinsonism [Title/Abstract] OR Parkinsonian disorder [Title/Abstract] OR Parkinsonian syndrome [Title/Abstract] OR Parkinson [Title/Abstract] OR PD [Title/Abstract] OR paralysis agitans [Title/Abstract] OR lewy body [Title/Abstract]
#2	Parkinson disease [Mesh]
#3	#1 OR #2
#4	Cholecalciferol [Title/Abstract] OR ergocalciferol [Title/Abstract] OR 25-Hydroxyvitamin D [Title/Abstract] OR 25(OH)D [Title/Abstract] OR vitamin D analog [Title/Abstract]
#5	Vitamin D [Mesh]
#6	#4 OR #5
#7	#3 AND #6

A systematic literature search was performed using four electronic databases from their inceptions to May 2018m with publications in the English language, The databases included PubMed, Embase, the Cochrane Library, and the Web of Science. The keywords used in the searches included: 'vitamin D,' 'cholecalciferol,' 'ergocalciferol,' '25-hydroxyvitamin D,' '25(OH)D,' 'vitamin D analog,' and 'Parkinson's disease,' 'Parkinsonism,' 'Parkinsonian disorder,' 'PD,' 'paralysis agitans,' 'Lewy body.' Variations or synonyms of keywords were also used to ensure that a comprehensive search was undertaken. Reference lists from review articles were also viewed to ensure that no potentially eligible studies were omitted. The detailed search strategy for the PubMed database is presented in Table 1.

Publication selection

Two reviewers independently reviewed the titles and abstracts of the retrieved publications. The full text of the publications was reviewed for studies where the inclusion eligibility could not be determined from the titles and abstracts alone. Inclusion criteria were case-controlled studies, cohort studies, or randomized clinical trials (RCTs) that included patients with a diagnosis of Parkinson's disease and serum vitamin D (25-hydroxyvitamin D) measurement to determine whether there was insufficiency or deficiency. Inclusion criteria also required details of the use of vitamin D supplements and sunlight exposure, the relative risk (RR) or odds ratio (OR), and changes in serum vitamin D levels. The use of the Unified Parkinson's Disease Rating Scale (UPDRS) (Part III) over time was an inclusion criteria or could be calculated from reported data.

Published studies were excluded if they were cross-sectional studies, case reports, review articles, animal studies, editorials, or letters, or if they had incomplete data. In the latter case, there were attempts to contact the authors to supply missing data. Only studies selected by both reviewers were included in the meta-analysis. Any disputes regarding publication inclusion criteria were resolved by discussion or referral to a third reviewer.

Data extraction and quality assessment of the study methods using the Jadad scale (the Oxford quality scoring system) and the Newcastle-Ottawa scale (NOS)

Data from the included studies were independently extracted by two reviewers, with the use of a data extraction checklist. Confirmation of data extraction was performed and any inconsistent data were verified by a third reviewer. Extracted publication data included the first author, the year of publication, the region, the study type, the characteristics of the study participants, including age, gender, body mass index (BMI), Hoehn and Yahr stage, and baseline levels of 25-hydroxyvitamin D. Exposure measurement, effect size, adjusted factors for cohort or case-controlled studies, and treatment methods, time of follow-up for RCTs were also recorded. Any disagreements were resolved by discussion until a consensus was reached.

The Jadad scale (the Oxford quality scoring system) [35] was used to evaluate the quality of the study methods used for RCTs, and the Newcastle-Ottawa scale (NOS) [36] was used to evaluate the study quality for cohort or case-controlled studies. The requirements of the Jadad scoring system included the generation of a random sequence, allocation concealment, participants, investigators and assessors who were blinded to the study, the integrity of data, selective reporting, and evaluation of sources of bias. The maximum score using the Jadad scale was 7 points, and studies with a Jadad score of >4 points were considered to be of high quality. The NOS was mainly used to assess the methodological quality of non-RCTs, including cohort and case-controlled studies. The maximum score using the NOS was 9 points, and studies with a NOS score of >6 points were considered to be of high quality.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

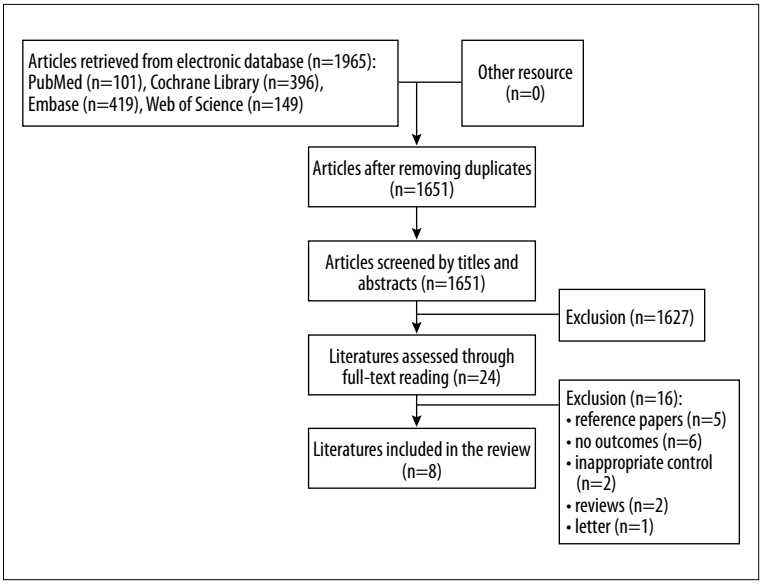

Figure 1. Flow diagram of the study design and screening of the published literature.

Data synthesis and statistical analysis

The primary outcomes evaluated in this review and meta-analysis included the association between vitamin D status and the risk of Parkinson's disease and the effects of vitamin D supplements on serum levels of vitamin D (25-hydroxyvitamin D) and motor function for individuals with Parkinson's disease. The secondary outcome was the relationship between sunlight exposure and the risk of Parkinson's disease. The normal serum reference range for total 25-hydroxyvitamin D is 20–100 ng/mL. In this study, vitamin D insufficiency was defined as a serum level <30 ng/mL (<75 nmol/L), and vitamin D deficiency was defined as a serum level <20 ng/mL (<50 nmol/L) [37]. A cutoff value of 15 min/week was used to evaluate the effects of sunlight exposure on the prevention of Parkinson's disease, as previously reported [38].

The RR or OR with a 95% confidence interval (CI) were pooled for dichotomous outcomes. Continuous outcomes measured using the same method were summarized as the weighted mean difference (MD) with 95% CI. The pooled standardized mean difference (SMD) and 95% CI were calculated for outcomes with different measures. The I^2 statistic was used to determine heterogeneity across studies. A fixed-effects pooled analysis method was used to combine the results if no or low heterogeneity existed (I^2<50%), or a random-effects meta-analysis was performed. Visual interpretation of funnel plots and Egger's test [39] were used to determine publication bias, where appropriate. Sensitivity analysis, based on the quality of the study methods, was performed to test the stability of the studies, where required. Stata version 12.0 statistical software was used to perform the meta-analysis and to create forest plots.

Results

Publication search results

A flow diagram of the study publication screening method is shown in Figure 1. A total of 1,965 publications were initially identified according to the search criteria. Then, the titles and abstracts of 1,651 publications were reviewed after removing duplicate studies, and 1,627 non-relevant publications were removed. For the remaining 24 publications, the full texts were retrieved for further assessment, and 16 publications were excluded. Finally, eight studies [28,31,32,40–44] were included in the meta-analysis (Figure 1).

Characteristics and quality of the methods used in the included studies

Of eight studies, three studies [28,40,44] originated from the United States, three [31,32,43] studies were from Japan, one study was from Canada [41], and one study was from Egypt [42]. Of the eight studies, there were five case-controlled studies [31,40–43], one cohort study [28] and two randomized clinical studies (RCTs) [32,44]. The characteristics of cohort study, case-controlled studies, and RCTs are presented in Tables 2 and 3. All studies were considered to be of high-quality, except for one study [43]. The details of the Newcastle-Ottawa scale (NOS) or the Jadad scale (the Oxford quality scoring system) for each study are shown in Tables 2 and 3.

Synthesis of meta-analysis: Vitamin D status and the risk of Parkinson's disease

Three studies that included 966 patients with Parkinson's disease and 813 controls investigated the influence of low vitamin

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Characteristics and methodological quality of studies for analysis of 25(OH)D level, sunlight exposure and risk of PD.

Studies; years of publication; region	Types of studies	Number; age (years); Male %; BMI		Disease duration (years); Hoehn and Yahr stage	Exposure measures	OR (95% CI)	Adjustment	NOS score
		PD	Control					
Wang et al. [40]; 2014; USA	Case-control	478; 64±12; 63%; NA	431; 70±8; 35%; NA	7.6±6.24; NA	Exposure: E_a, insufficiency, 25(OH)D <30 ng/mL; E_b, deficiency, 25(OH)D <20 ng/mL. Non-exposure: normal status, 25(OH)D ≥30 ng/mL	E_a: 2.64 (1.88, 3.71)* E_b: 2.13 (1.58, 2.89)*	Age, sex, and season	9
Ding et al. [41]; 2013; Canada	Case-control	388; 65.7±9.6; 64.4%; 26.5±4.9	283; 68.0±10.4; 37.5%; 26.5±4.9	4.5±4.8; 2.1±0.6		E_a: 1.35 (0.99, 1.84)** E_b: 1.80 (1.06, 3.10)*	Age, sex, race, and vitamin D supplementation	6
Evatt et al. [28]; 2008; USA	Cohort	100; 65.4; 57%; NA	99; 65.7; 57%; NA	7.6±5.4; NA		E_a: 2.14 (1.21, 3.78)** E_b: 2.66 (1.19, 5.93) **	Race, APOE genotype, sex, and residence	7
Abou-Raya et al. [42]; 2009; Egypt	Case-control	82; 67.5±7.5; 52.4%; 23.9±5.7	68; 67.0±6.9; 52.9%; 23.5±3.8	6.5±3.5; 3.0±0.5	Exposure: sunlight exposure <15 min/w; Non-exposure: sunlight exposure ≥15 min/w	0.08 (0.04, 0.18)**	Age, sex, BMI	7
Sato et al. [31]; 2005; Japan	Case-control	142; 69.9±7.7; 45.1%; 21.4±3.5	99; 68.8±3.4; 42.4%; 22.2±2.0	6.2±3.7; 3.3±1.1		0.01 (0.00, 0.02)**	Age	7
Sato et al. [43]; 1997; Japan	Case-control	71; 69.93; 45.1%; 21.35	33; 68.8±3.5; 51.5%; 22.3±2.0	PD_a: 4.1±2.3; 1.86±0.48 PD_b: 7.1±3.8; 3.84±0.77		0.05 (0.01, 0.46)** 0.01 (0.00, 0.05)**	Age	5

25(OH)D – 25-hydroxyvitamin D; PD – Parkinson's disease; BMI – body mass index; NOS – Newcastle-Ottawa quality assessment scale; NA – not available. * Adjusted value from original articles; ** value calculated according to counts of events and total number of two groups in each study. Data were presented as mean ± standard deviation.

Table 3. Characteristics and methodological quality of studies for analysis of effects of vitamin D supplement on patients with PD.

Studies; years of publication; region	Type of studies	Number; age (years); Male %; BMI		Disease duration (years); Hoehn and Yahr stage		Baseline 25(OH)D (ng/ml)		Intervention		Follow-up	JADAD score
		T	C	T	C	T	C	T	C		
Suzuki et al. [32]; 2013; Japan	RCT	56; 72.5±6.6; 52%; 22.7±2.8	58; 71.2±6.9; 53%; 22.8±3.7	2; 2.27	1.08; 2.16	22.5±9.7	21.1±8.8	Vit. D_3 1200 IU/d	Placebo	12 m	6
Dubose et al. [44]; 2011; USA	RCT	16; 64±7.9; 63.3%; 29.3±3.3	14; 65±7.3; 68.8%; 28.2±5.6	2.19; NA	2.21; NA	20.2±8.6	24.9±8.6	Vit. D_3 50000 IU/w plus vit. D 600 IU/d	Placebo plus vit. D 600 IU/d	6 m	6

T – treatment group; C – control group; 25(OH)D – 25-hydroxyvitamin D; PD – Parkinson's disease; BMI – body mass index; NA – not available; vit. D – vitamin D. Data were presented as mean ± standard deviation.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

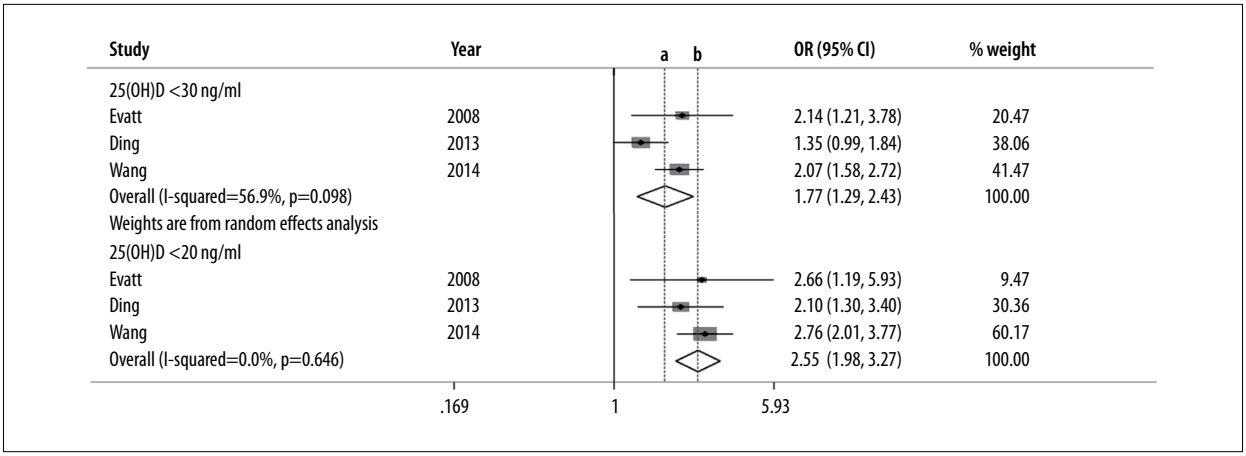

Figure 2. Forest plots of the association between vitamin D insufficiency and deficiency and the risk of Parkinson's disease. a) Forest plots of the association between vitamin D insufficiency and the risk of Parkinson's disease. b) Forest plots of the association between vitamin D deficiency and the risk of Parkinson's disease.

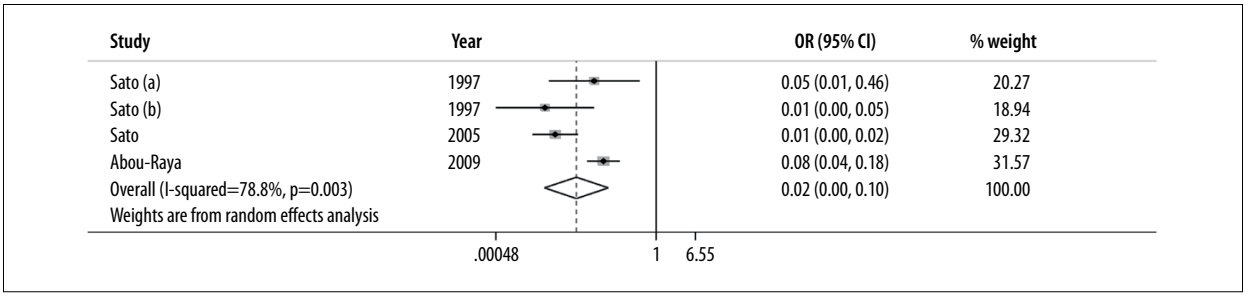

Figure 3. Forest plots of the association between sunlight exposure and the risk of Parkinson's disease.

D level on the risk of Parkinson's disease (Figure 2) [28,40,41]. The results of pooled random-effects analysis showed that vitamin D insufficiency (serum level <30 ng/mL or <75 nmol/L) measured as serum 25-hydroxyvitamin D, significantly increased the risk of Parkinson's disease by >1.5-fold (OR, 1.77; 95% CI, 1.29–2.43; P<0.001) with low heterogeneity across studies (I^2=56.9%; P=0.098). Vitamin D deficiency (serum level <20 ng/mL or <50 nmol/L) measured as serum 25-hydroxyvitamin D, significantly increased the risk of Parkinson's disease by almost 2.5-fold (OR, 2.55; 95% CI, 1.98–3.27; P<0.001), and there was no study heterogeneity (I^2=0.0%; P=0.646). Compared with vitamin D insufficiency, vitamin D resulted in a significant increase in the risk of Parkinson's disease (Figure 2).

Synthesis of meta-analysis: Sunlight exposure and the risk of Parkinson's disease

Three case-controlled studies involving 295 patients with Parkinson's disease and 200 controls evaluated the association between exposure to sunlight and the risk of Parkinson's disease (Figure 3) [31,42,43]. There was high heterogeneity across studies (I^2=78.8%; P=0.003), and a random-effects meta-analysis was performed to combine data. Exposure to sunlight (≥15 min/week) was associated with a significantly reduced risk of Parkinson's disease (OR, 0.02; 95% CI, 0.00–0.10; P<0.001). Similar results were obtained for the sensitivity analysis (OR, 0.03; 95% CI, 0.00–0.26; P<0.001) (Figure 3).

Synthesis of meta-analysis: Vitamin D supplements and vitamin D levels in patients with Parkinson's disease

Two RCTs involving 144 patients reported the effects of vitamin D supplement on vitamin D level for individuals with Parkinson's disease [32,44]. There was no heterogeneity between published trials (I^2=0.0%; P=0.783). In the fixed-model analysis of pooled data, the standardized mean difference (SMD) was 1.79 (95% CI, 1.40–2.18; P<0.001) indicating that vitamin D supplements increased serum levels of vitamin D (Figure 4).

Synthesis of meta-analysis: Vitamin D supplements and motor function in patients with Parkinson's disease

Motor function in patients with Parkinson's disease evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) (Part III) was reported in two RCTs (three intervention groups) [32,44]. Vitamin D supplementation had no significant effect on motor function in patients with Parkinson's disease (MD,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

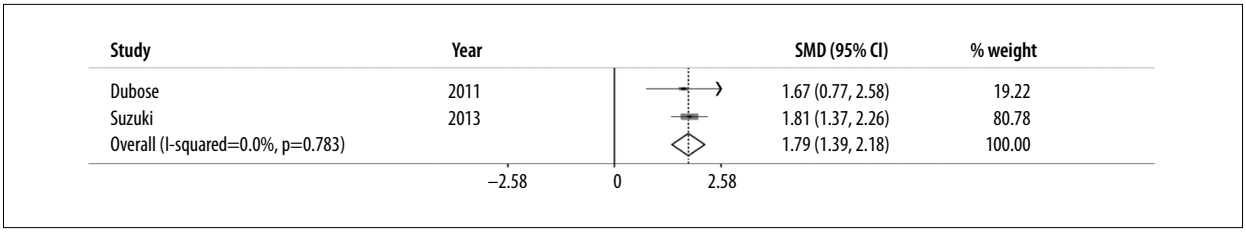

Figure 4. Forest plots of the effects of vitamin D supplementation on vitamin D levels in patients with Parkinson's disease.

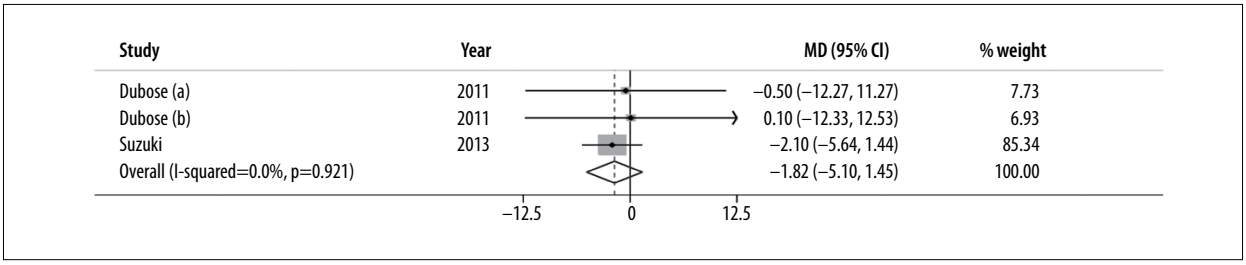

Figure 5. Forest plots of the effects of vitamin D supplementation on motor function in patients with Parkinson's disease.

−1.82; 95% CI, −5.10–1.45; P=0.275) (Figure 5). There was no heterogeneity between studies (I^2=0.0%, P=0.921) (Figure 5).

Discussion

A systematic literature review identified eight studies that included five case-controlled studies, one cohort study, and two randomized clinical trials (RCTs). Meta-analysis was performed to investigate the associations between vitamin D status, as determined by the serum levels of 25-hydroxyvitamin D, sunlight exposure, and the risk of Parkinson's disease. The therapeutic effects of vitamin D supplements on serum levels of vitamin D and on motor function for patients with Parkinson's disease were also investigated in the meta-analysis. To our knowledge, this was the first systematic review and meta-analysis to investigate the relationship between vitamin D supplements and sunlight exposure and the risk of Parkinson's disease. This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [45]. Keywords and their variations or synonyms were used to search electronic publication databases, and reference lists of eligible studies were also reviewed. Of the eight identified studies that underwent quantitative data synthesis, the Jadad scale (the Oxford quality scoring system) and the Newcastle-Ottawa scale (NOS) were used to evaluate the quality of the methods used in the studies.

Pooled meta-data analysis showed that individuals with vitamin D insufficiency (serum 25-hydroxyvitamin D <30 ng/mL) were significantly more likely to develop Parkinson's disease (OR, 1.77; 95% CI, 1.29–2.43; P<0.001), and individuals with vitamin D deficiency (serum 25-hydroxyvitamin D <20 ng/mL) had a 2.5-fold increased risk of developing Parkinson's disease, when compared with control groups (OR, 2.55; 95% CI, 1.98–3.27; P<0.001).

Previously published studies have reported that patients with Parkinson's disease had reduced serum levels of vitamin D when compared with normal individuals [46,47]. A prospective cohort study that included 3,173 participants with a 29-year follow-up, showed that vitamin D could protect individuals from Parkinson's disease [24]. Also, increased vitamin D receptors (VDRs) and enzymes involved in the formation of active vitamin D have been reported in the substantia nigra, an area associated with the development of Parkinson's disease [48]. The neuroprotective function of vitamin D may occur due to the regulation of neurotrophic factors, antioxidative mechanisms, immunoregulation, regulation of calcium-binding protein, and modulation of neuronal excitation [24,48,49]. Together, the results of the present meta-analysis and the findings from previous studies provide evidence that supports the beneficial effects of vitamin D in reducing the risk of Parkinson's disease.

However, this meta-analysis showed that the use of vitamin D supplements increased the serum levels of vitamin D (25-hydroxyvitamin D) in patients with Parkinson's disease (SMD, 1.79; 95% CI, 1.40–2.18; P<0.001), but there were no significant effects from the use of vitamin D supplements on motor function (MD, −1.82; 95% CI, −5.10–1.45; P=0.275). In support of these findings, a previously published cross-sectional study from Iran showed that vitamin D status was not associated with Hoehn and Yahr stage and the Unified Parkinson's Disease Rating Scale (UPDRS) score in subjects with Parkinson's disease [50].

The findings of this present study also showed that exposure to sunlight (≥15 min/week) had a significant role in preventing

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Parkinson's disease (OR, 0.02; 95% CI, 0.00–0.10; P<0.001). Sensitivity analysis was also performed to determine the quality of the methods used in the published studies, which showed similar results (OR, 0.03; 95% CI, 0.00–0.26; P<0.001). One study [51] also reported that exposure to UVB was associated with a reduced risk of developing Parkinson's disease. UVB is a component of sunlight, and cutaneous synthesis of vitamin D requires UVB radiation [52], and this process has an important role in controlling serum vitamin D levels [53]. Sunlight exposure reduces the risk of Parkinson's disease by increasing serum levels of vitamin D.

Because there is evidence to support that vitamin D has a potential role in the prevention of Parkinson's disease, for individuals with vitamin D insufficiency, especially those who are at high risk of developing Parkinson's disease, it might be important to take vitamin D supplements or to include foods in the diet that are rich in vitamin D, including fish, liver, and nuts, to maintain D levels within the normal range. Spending more time outdoors to increase the duration of sunlight exposure, might be a better option. However, in patients with established Parkinson's disease, currently, there is no evidence that vitamin D should be recommended for symptom control. Therefore, with regard to the effects of vitamin D on Parkinson's disease, currently, vitamin D appears to have a more important role in the prevention rather the treatment of Parkinson's disease

This study had several limitations. Only eight studies were identified, which included a small number of study participants and short-term follow-up. In the study design, although comprehensive keywords and search strategies were used to identify relevant published studies, there was still a possibility that some studies were missed, particularly studies with negative results, which are more likely not to be published. There was also the possibility of study bias, as publications were limited to those in the English language, and the possibility of publication bias was not explored due to the limited number of published studies. This analysis only investigated the influence of vitamin D supplements on serum concentrations of vitamin D and on motor function for patients with Parkinson's disease, an overall evaluation on effects of vitamin D supplement was not made due to limited or unavailable data. Only two RCTs [32,44] reported the effects of vitamin D supplements, and this and other limitations may result in non-representative results. Future large-scale, multi-center, controlled, randomized clinical studies are required to provide evidence on the association between vitamin D and Parkinson's disease, which include long-term follow-up, particularly for the effects of vitamin D on motor function and other rehabilitation outcomes.

Conclusions

Vitamin D levels below the normal range are associated with an increased risk of Parkinson's disease, which increases with decreasing levels of vitamin D. Also, sunlight exposure (≥15 min/week) is beneficial in reducing the risk of developing Parkinson's disease. Vitamin D supplementation is beneficial for increasing vitamin D levels in patients with Parkinson's disease but has no effects on motor function. Therefore, maintenance of normal vitamin D levels from a combination of diet, sunlight, and supplements are low-cost approaches to prevent Parkinson's disease, but vitamin D supplementation might not be a suitable addition to the treatment regime and patient rehabilitation in patients with established Parkinson's disease. Due to the few included studies in this meta-analysis, high-quality multicenter studies are still needed to confirm the conclusions and to explore the effectiveness of vitamin D supplements on non-motor symptoms and quality of life for patients with Parkinson's disease.

Acknowledgments

We are grateful to the authors of the primary studies included in this meta-analysis and acknowledge the statistical assistance provided by Maowen Li.

Conflict of interest

None.

References:

1. Poewe W, Seppi K, Tanner CM et al: Parkinson disease. Nat Rev Dis Primers, 2017; 3: 17013
2. Hirsch L, Jette N, Frolkis A et al: The incidence of Parkinson's disease: A systematic review and meta-analysis. Neuroepidemiology, 2016; 46: 292–300
3. Dorsey E, Constantinescu R, Thompson J et al: Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology, 2007; 68: 384–86
4. Corti O, Lesage S, Brice A: What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev, 2011; 91: 1161–218
5. de Lau LM, Breteler MM: Epidemiology of Parkinson's disease. Lancet Neurol, 2006; 5: 525–35
6. Allen MT, Levy LS: Parkinson's disease and pesticide exposure – a new assessment. Crit Rev Toxicol, 2013; 43: 515–34
7. Lang Y, Gong D, Fan Y: Calcium channel blocker use and risk of Parkinson's disease: A meta-analysis. Pharmacoepidemiol Drug Saf, 2015; 24: 559–66
8. Sato Y, Iwamoto J, Honda Y: Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in Parkinson's disease. Parkinsonism Relat Disord, 2011; 17: 22–26
9. Evatt ML, DeLong MR, Kumari M et al: High prevalence of hypovitaminosis D status in patients with early Parkinson disease. Arch Neurol, 2011; 68: 314–19
10. Kempker JA, Tangpricha V, Ziegler TR, Martin GS: Vitamin D in sepsis: From basic science to clinical impact. Crit Care, 2012; 16: 316
11. Lee S, Clark SA, Gill RK, Christakos S: 1,25-dihydroxy vitamin D3 and pancreatic beta-cell function: Vitamin D receptors, gene expression, and insulin secretion. Endocrinology, 1994; 134: 1602–10

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

12. Salamon H, Bruiners N, Lakehal K et al: Vitamin D regulates lipid metabolism in Mycobacterium tuberculosis infection. J Immunol, 2014; 193: 30–34
13. Carthy EP, Yamashita W, Hsu A, Ooi BS: 1,25-Dihydroxyvitamin D3 and rat vascular smooth muscle cell growth. Hypertension, 1989; 13 (6 Pt 2): 954–59
14. Wang Y, Zhu J, DeLuca HF: Where is the vitamin D receptor? Arch Biochem Biophys, 2012; 523: 123–33
15. Wrzosek M, Lukaszkiewicz J, Wrzosek M et al: Vitamin D and the central nervous system. Pharmacol Rep, 2013; 65: 271–78
16. Rotstein DL, Healy BC, Malik MT et al: Effect of vitamin D on MS activity by disease-modifying therapy class. Neurol Neuroimmunol Neuroinflamm, 2015; 2: e167
17. Koduah P, Paul F, Dörr JM: Vitamin D in the prevention, prediction and treatment of neurodegenerative and neuroinflammatory diseases. EPMA J, 2017; 8: 313–25
18. Behrens JR, Rasche L, Gieß RM et al: Low 25-hydroxyvitamin D, but not the bioavailable fraction of 25-hydroxyvitamin D, is a risk factor for multiple sclerosis. Eur J Neurol, 2016; 23: 62–67
19. Pierrot-Deseilligny C, Souberbielle JC: Vitamin D and multiple sclerosis: An update. Mult Scler Relat Disord, 2017; 14: 35–45
20. Giovannucci E, Liu Y, Hollis BW, Rimm EB: 25-Hydroxyvitamin D and Risk of Myocardial Infarction in Men: A Prospective Study. Arch Intern Med, 2008; 168: 1174–80
21. Kilkkinen A, Knekt P, Heliövaara M et al: Vitamin D status and the risk of lung cancer: A cohort study in Finland. Cancer Epidemiol Biomarkers Prev, 2008; 17: 3274–78
22. Knekt P, Laaksonen M, Mattila C et al: Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology, 2008; 19: 666–71
23. Littlejohns TJ, Henley WE, Lang IA et al: Vitamin D and the risk of dementia and Alzheimer disease. Neurology, 2014; 83: 920–28
24. Knekt P, Kilkkinen A, Rissanen H et al: Serum vitamin D and the risk of Parkinson disease. Arch Neurol, 2010; 67: 808–11
25. Wang TT, Tavera-Mendoza LE, Laperriere D et al: Large-scale in silico and microarray-based identification of direct 1,25-dihydroxy vitamin D3 target genes. Mol Endocrinol, 2005; 19: 2685–95
26. Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK: Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Brain Res Mol Brain Res, 1996; 36: 193–96
27. Fullard ME, Xie SX, Marek K et al: Vitamin D in the parkinson associated risk syndrome (PARS) study. Mov Disord, 2017; 32: 1636–40
28. Evatt ML, Delong MR, Khazai N et al: Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol, 2008; 65: 1348–52
29. Peterson AL, Murchison C, Zabetian C et al: Memory, mood, and vitamin D in persons with Parkinson's disease. J Parkinsons Dis, 2013; 3: 547–55
30. Meamar R, Shaabani P, Tabibian SR et al: The effects of uric acid, serum vitamin D3, and their interaction on Parkinson's disease severity. Parkinsons Dis, 2015; 2015: 463–83
31. Sato Y, Honda Y, Iwamoto J et al: Abnormal bone and calcium metabolism in immobilized Parkinson's disease patients. Mov Disord, 2005; 20: 1598–603
32. Suzuki M, Yoshioka M, Hashimoto M et al: Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. Am J Clin Nutr, 2013; 97: 1004–13
33. Calvello R, Cianciulli A, Nicolardi G et al: Vitamin D treatment attenuates neuroinflammation and dopaminergic neurodegeneration in an animal model of Parkinson's disease, shifting M1 to M2 microglia responses. J Neuroimmune Pharmacol, 2017; 12: 327–39
34. Shrestha S, Lutsey PL, Alonso A et al: Serum 25-hydroxyvitamin D concentrations in mid-adulthood and Parkinson's disease risk. Mov Disord, 2016; 31: 972–78
35. Higgins JP, Green S: Cochrane handbook for systematic reviews of interventions version 5.1.0. Naunyn Schmiedebergs Arch Pharmakol, 2011; 5: S38
36. Wells GA, Shea BJ, O'Connell D et al: The Newcastle-Ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Appl Eng Agric, 2014; 18: 727–34
37. Rosen CJ: Clinical practice. Vitamin D insufficiency. N Engl J Med, 2011; 364: 248–54
38. Komar L, Nieves J, Cosman F et al: Calcium homeostasis of an elderly population upon admission to a nursing home. J Am Geriatr Soc, 1993; 41: 1057–64
39. Egger M, Davey SG, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997; 315: 629–34
40. Wang L, Evatt ML, Maldonado LG et al: Vitamin D from different sources is inversely associated with Parkinson disease. Mov Disord, 2015; 30: 560–66
41. Ding H, Dhima K, Lockhart KC et al: Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. Neurology, 2013; 81: 1531–37
42. Abou-Raya S, Helmii M, Abou-Raya A: Bone and mineral metabolism in older adults with Parkinson's disease. Age Ageing, 2009; 38: 675–80
43. Sato Y, Kikuyama M, Oizumi K: High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. Neurology, 1997; 49: 1273–78
44. Dubose S: Effects of vitamin D supplementation on motor symptoms of patients with Parkinson's disease. Masters Thesis. Emory University 2011. Available at [URL]: *https://vmch-etd.library.emory.edu/view/record/pid/emory: 944r1*
45. Moher D, Liberati A, Tetzlaff J, Altman D: [Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement.] Revista Española De Nutrición Humana Y Dietética 2009; 18: e123 [in Spanish]
46. Nguyen TH, Minh TL. Vitamin D status in patients with Parkinson's disease. Mov Disord 2014; 29: S80.
47. Moghaddasi M, Mamarabadi M, Aghaii M: Serum 25-hydroxyvitamin D3 concentration in Iranian patients with Parkinson's disease. Iran J Neurol, 2013; 12: 56–59
48. Eyles D, Smith S, Kinobe R et al: Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat, 2005; 29: 21–30
49. Buell JS, Dawsonhughes B: Vitamin D and neurocognitive dysfunction: Preventing "D"ecline? Mol Aspects Med, 2008; 29: 415–22
50. Chitsaz A, Maracy M, Basiri K et al: 25-hydroxyvitamin d and severity of Parkinson's disease. Int J Endocrinol, 2013; 2013: 689149
51. Kravietz A, Kab S, Wald L et al: Association of UV radiation with Parkinson disease incidence: A nationwide French ecologic study. Environ Res, 2017; 154: 50–56
52. Holick MF, MacLaughlin JA, Clark MB et al: Photosynthesis of previtamin D3 in human skin and the physiologic consequences. Science, 1980; 210: 203–5
53. Holick MF: Vitamin D deficiency. N Engl J Med, 2007; 357(3): 266–81

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]