Journal Pre-proof

Vitamin D in Parkinson's disease: A systematic review of randomized controlled trials.

Paraskevi Detopoulou, Gavriela Voulgaridou, Alexandra Saridaki, Ioanna Pylarinou, Elissaios- Minos Argyris, Vasilios Dedes, Constantinos Giaginis, Georgios I. Panoutsopoulos, Sousana K. Papadopoulou

PII: S2667-2685(23)00049-9

DOI: https://doi.org/10.1016/j.nutos.2023.09.005

Reference: NUTOS 320

To appear in: *Clinical Nutrition Open Science*

Received Date: 31 July 2023

Revised Date: 22 September 2023

Accepted Date: 23 September 2023

Please cite this article as: Detopoulou P, Voulgaridou G, Saridaki A, Pylarinou I, Argyris E-M, Dedes V, Giaginis C, Panoutsopoulos GI, Papadopoulou SK, Vitamin D in Parkinson's disease: A systematic review of randomized controlled trials., *Clinical Nutrition Open Science*, https://doi.org/10.1016/j.nutos.2023.09.005.

Vitamin D in Parkinson's disease: A systematic review of randomized controlled trials.

Paraskevi Detopoulou[1,3], Gavriela Voulgaridou[2], Alexandra Saridaki[1,3], Ioanna Pylarinou[3], Elissaios-Minos Argyris[1], Vasilios Dedes[3], Constantinos Giaginis[4], Georgios I Panoutsopoulos[3*], Sousana K. Papadopoulou[2]

[1]Department of Clinical Nutrition, General Hospital Korgialenio Benakio, Athanassaki 2, 11526, Athens, Greece

[2]Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece

[3]Department of Nutritional Science and Dietetics, Faculty of Health Sciences, University of Peloponnese, New Building, Antikalamos, 24100 Kalamata, Greece

[4]Department of Food Science and Nutrition, School of Environment, University of Aegean, Myrina, Lemnos, Greece

*Corresponding author: George I Panoutsopoulos, gpanouts@uop.gr

Abstract:

In recent years, neurodegenerative diseases are a leading cause of morbidity and disability worldwide, with Parkinson's disease (PD) being the most prevalent. Although diet and vitamin status play a crucial role in PD, the results of vitamin D supplementation are scarce and contradictory. Therefore, the present systematic work reviewed the available randomized controlled trials (RCTs) regarding the role of vitamin D supplementation in patients with PD in the Pubmed, Scopus and Cochrane databases and in grey literature. Four RCTs including 321 patients with PD were identified. Various doses of vitamin D were administered (1,000- 10,000 IU/d) and different exposure outcomes were assessed. One study reported beneficial effects of vitamin D on the Hoehn and Yahr scale (HY) and two studies reported null effects on the Unified Parkinson's Disease Rating Scale (UPDRS). Regarding functional tests, heterogeneous results in the timed-up and go (TUG) test were observed in two studies. One study conducted minute walking tests at 6 and 10 minutes and found an improvement only in the 6MWT. In conclusion, a very small number of RCTs have assessed the effects of vitamin D supplementation on PD. Some isolated beneficial effects of vitamin D were

reported on functional scales and tests but more studies are needed to draw safe conclusions regarding its supplementation in PD.

Keywords: vitamin D; Parkinson Disease; randomized clinical trials

Introduction

In recent years, neurodegenerative diseases are a leading cause of morbidity and disability worldwide, with Parkinson's disease (PD) being the most prevalent [1] and having a higher incidence in adults above 60 years (1%) [2]. In Europe, the prevalence of PD is estimated at approximately 183/100.000 per year [3]. PD is characterized by the loss of dopamine-producing cells in the brain, causing problems with movement and emotions [4]. The main symptoms of this disease are slowness of movement and speed (bradykinesia), muscle rigidity, loss of automatic movements, and tremors, in one of the upper limbs [5]. Additional symptoms of PD may include verbal and written disabilities, communication and concentration difficulties, dysphagia, sarcopenia, depression, and short-term memory loss [4,5]. The exact etiology of this disease is not yet fully understood but is believed that it is a complex result of genetic and environmental factors [6].

Of the environmental factors, diet appears to play a crucial role in both reducing the risk of developing PD and alleviating symptoms of established disease [7]. In particular, studies have shown that flavonoids, carotenoids [5], coffee [8], as well as vegetables, fruits, fish, seeds, and nuts may reduce the risk of developing PD [9–12]. On the contrary, frequent intake of dairy products is associated with a greater risk of developing PD [13,14]. Moreover, vitamins may help prevent the onset of PD. Specifically, vitamins B6, B9, and B12, through their participation in homocysteine metabolism, prevent toxic effects on neurons [15]. In addition, vitamin C, found in abundance in the brain, seems to enhance nerve integrity [16]. Especially, supplementing with vitamin B6 [17] and vitamin D [18,19] could improve patient mobility.

Vitamin D belongs to fat-soluble vitamins and is often referred to as a hormone [20]. It can be ingested through foods, such as egg yolks and fatty fish [21], or it can be synthesized in the skin upon sun exposure [22]. Vitamin D is important for maintaining and promoting bone health [23], muscle health, and strength, while it may reduce the risk of falls and fractures in elderly people [23,24]. In addition, Vitamin D helps sharpen memory [25,26], improves mood [27,28], and

promotes the normal functioning of both the nervous [29,30] and immune [31,32] systems.

Based on case-control studies, patients with established PD typically have lower serum vitamin D concentrations than controls [33]. In addition, vitamin D deficiency (vitamin D levels <50 nmol/L) has been shown to contribute to slowed cognitive function [34] and faster brain aging [35,36]. Vitamin D contributes to the prevention of PD by regulating calcium ions within the dopaminergic nerves [37]. Moreover, vitamin D deficiency increases the risk of developing PD, due to the uncontrolled oxidant [38,39] and neurotoxic reactions in the body [40], as well as the reduced production of the nerve growth factor (NGF) and the brain-derived neurotrophic factor (BDNF) [41,42]. In parallel, lower vitamin D levels are related to increased circulating inflammatory molecules, such as C-reactive protein, which may increase the risk of PD [43].

Several earlier systematic reviews have been conducted investigating the relationship between PD and vitamin D, with the majority of them focusing on the relationship between circulating vitamin D and the risk of PD [18,44–46]. However, the results of vitamin D supplementation are scarce and contradictory [47]. Therefore, the present systematic review includes recent studies [48] and summarizes the results of randomized controlled trials (RCTs), aiming to clarify the role of vitamin D supplementation in protecting PD and managing its symptoms.

Methods

The systematic review was performed in accordance to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Search Strategy

We search randomized clinical trials related to vitamin D and PD published up to June 2023 in research databases Pubmed, Cochrane and Scopus as well as in grey literature (International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov). The search strategy were applied by used the terms: “vitamin D” and “Parkinson Disease”. These terms combined with the Boolean Operator AND,

while for the synonymous words Boolean Operator OR was used. The search strategy was applied to Pubmed presented in more detailed in Table 1. The research question was formed as described in Table 2.

Inclusion and Exclusion Criteria

Studies were are eligible if they 1) were randomized controlled trials, 2) participants have diagnosed PD, 3) compared vitamin D supplementation administered *per os* with placebo. The exclusion criteria is as follows: 1) non-experimental studies, 2) reviews, 3) case reports, 4) case-series, 5) observational studies, 6) there is no control group, 7) intervention with combined or other nutrient supplementation. No language restriction criteria were applied.

Study and Data Collection Process

Risk of Bias and Quality Assessment

Two researchers (P.D. and G.V.) independently assessed the quality of the included RCTs by using the Cochrane Risk of Bias (RoB 2.0) [49] and a senior researcher (S.K.P.) intervened when there was a disagreement.

Data Extraction

In a predefined excel form two researchers extract details from each included article. In more details, the following data were extracted: first authors' name, study duration, journal, registry number, origin where the study took place, ethical permission, the design of RCTs, the method of masking and randomization, mean age, diagnostic criteria for PD, details about the intervention (number of participants, duration, type of supplement, dosage), details about control group (number, sex distribution), inclusion and exclusion criteria, and the outcomes.

Data Synthesis

A narrative synthesis was performed, as it is not possible to conduct a meta-analysis due to the variety of outcomes studied, as well as the variability of the tools used to assess functional capacity.

Results

Out of 1,447 search results, 4 studied met the inclusion criteria and were included in the systematic review. Figure 1 presents the flowchart describing the selection of studies according to PRISMA guidelines.

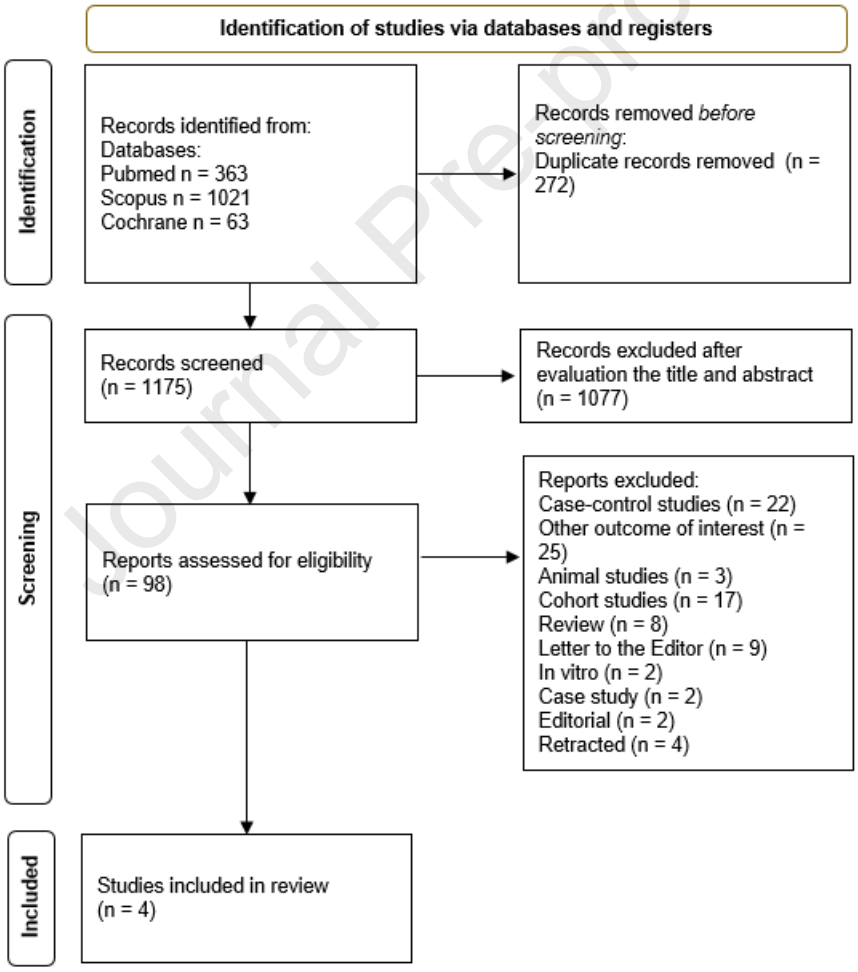

Figure 1. PRISMA flowchart [50] of the selection process of the retrieved studies.

Four double-blind randomized controlled trials including 321 patients with PD were identified [39,48,51,52]. The studies were conducted in Japan [39], Taiwan [51], Poland [48], and Iran [52]

(**Table 3**). The mean age of the patients ranged from 44 to 72 [39] (**Table 4**). Different doses of vitamin D were administered ranging from 1000-1200 IU/d or higher (4000IU/d) to 10,000IU/d, and one of them customized the dosage to the participants' BMI [39,48,51,52] (**Table 5**). Most of the studies (three out of four) had a duration of about 3-4 months [48,51,52] and one of them lasted one year [39]. The studies focused on different outcomes, mainly on the progression of the disease, balance, strength, and the duration of dyskinesia [39,48,51,52]. A more detailed presentation of reported outcomes follows.

Vitamin D levels

Supplementation with vitamin D increased 25(OH)D [39,48,51] and 1,25(OH)D [39,48] in all studies that measured vitamin D status. Regarding other vitamin D metabolites also found increases in 24,25(OH)2D3 and epi-25(OH)D3 [48].

Cognitive impairment

Only one study assessed the effects of vitamin D on cognitive impairment with the use of a Mini-Mental State Examination (MMSE) [39]. No difference in the MMSE was documented [39].

Questionnaires on functional capacity

Two studies reported outcomes regarding several scales of PD [39,52]. One study found that vitamin D prevented the deterioration of the patients using the Hoehn and Yahr scale (HY) [39]. No changes were reported regarding the Unified PD rating scale (UPDRS) [39,52]. However, Suzuki et al. detected a gene interaction between (vitamin D receptor) VDR FokI genotypes and vitamin D effects on HY, UPDRS, and UPDRS part II scales [39]. Moreover, differences in The Parkinson's Disease

Questionnaire (PDQ39) activities of daily living and emotional well-being were documented in one study [39].

Functional tests

The timed up-and-go (TUG) test was improved after vitamin D supplementation in one study [48], while in another one no significant change was observed [51]. Moreover, in one study, vitamin D supplementation improved the 6-minute walking test (6MWT) score, but not the 10-minute walking test (10MWT) [48].

Balance and falls

Only one study reported results on balance and falls and found no significant differences (with an improvement in balance in intermediate measurements) [51].

Risk of bias of the included RCTs

Table 6 summarized the risk of bias of the included studies. Only one study had no concerns about the overall risk of bias. All studies are deemed with low risk of bias regarding the random sequence generation, allocation concealment, blinding of outcomes interest, and selective reporting. Three studies raised concerns about the blinding of participants and personnel.

Discussion

In the present work RCTs on vitamin D supplementation and Parkinson's disease were systematically reviewed. A relatively small number of RCTs (n=4) have been conducted in this field,

with heterogeneous study design and outcome variables [39,48,51,52]. The supplementation with vitamin D led to increases in its serum levels [39,48,51]. Regarding questionnaires on functional capacity only one study reported beneficial effects of vitamin D on the HY scale [39], while no changes were documented in the UPDRS disease scale [39,52]. Regarding functional tests, heterogeneous results in the TUG were observed [48,51], and improvements were detected in the 6-minute walking test (6MWT), but not the 10-minute walking test (10MWT) [50].

Although several doses of vitamin D were tested (from 1000 IU to 10,000 IU), circulating vitamin D increased in three studies [39,48,51], while in one study vitamin D status was not assessed after intervention [52]. Such an effect is expected since supplementary doses of vitamin D are administered. Indeed, as previously reported by our group, the supplementation of vitamin D even in lower doses (200- 300 IU) leads to increases in serum vitamin D levels in a different pathological context [53].

Along with the interpretation of the obtained results several issues should be considered, such as the dosing of vitamin D, participant's age, and country of origin. It is noted that by-design studies running functional tests [48,51] used higher doses of vitamin D (4,000- 10,000 IU/d) than studies assessing functional status with the use of questionnaires (1,000- 1,200 IU) [48,51]. The highest dose of vitamin D was not accompanied by better results. On the contrary, in the study of Hiller et al, which used 10,000 IU/d, the TUG test remained unchanged [51], while in the study of Bytowska using lower levels according to BMI (and up to 6,000 IU/d) favorable effects on the TUG test and 6MWT were reported [48]. It is however obvious that further studies are needed to draw safer conclusions regarding the dosing of vitamin D and its effects on PD.

The age of subjects may play a role in the outcomes achieved. In one study balance measures were improved in younger patients (52–66 y), while in the total sample, no significant differences were documented [51]. However, the effects of vitamin D supplementation on UPDRS were non-

significant both in the study by Suzuki et al. and that of Habibi et al., despite the differences in age and baseline UPDRS (mean age 72, baseline UPDRS 34 vs mean age 44 y, baseline UPDRS 20.52) [39,52]. In parallel, age may be also related to the stage of PD, which may be an additional confounding factor. For example, in the study of Suzuki et al., some patients were in the advanced stage and others in an earlier stage of PD, which may render the identification of potential changes difficult [39]. Older subjects have usually higher rates of vitamin D deficiency due to lower exposure to sunlight and lower capacity of vitamin D hydroxylation [54]. However, others have shown that elevated vitamin D levels are associated with lower severity of PD, but not with disease duration or age [18].

The country of origin of participants should also be considered. The studies were mostly conducted in Asia (Japan [39], Taiwan [51], and Iran [52]) and one study in Europe (Poland [48]). This means that the results may not be generalized to the US or other European populations. In fact, several gene interactions with vitamin D and health outcomes have been reported in the studies assessed [39], which may be population-relevant.

Despite the low number of RCTs identified, some studies showed a beneficial effect of vitamin D supplementation on some functional tests in PD, confirming the emerging hypothesis of vitamin D implication in the nervous system. Indeed, vitamin D crosses the blood–brain barrier and can directly affect the brain [55]. In parallel, vitamin D has systematic [40] and in-situ anti-inflammatory effects [56,57], which may explain its potential preventive action in brain aging. Moreover, it increases neurotrophin [58], NGF, and BDNF [41,42]. In animal studies vitamin D administration protected against 6-hydroxydopamine-induced neurotoxicity damage [72] and increased glutathione levels in the central nervous system [59].

Last but not least, several limitations should be considered in the studies included. Dosing of vitamin D may be suboptimal in some cases and compliance problems may be present [39]. Moreover, the statistical power of some studies was low [51]. The levels of other vitamins and

background nutritional habits were not assessed. For example, it is known that especially B vitamins may affect PD [15], while dietary patterns may have beneficial effects through the modification of oxidative stress and inflammatory milieu [60].

Regarding gene-phenotype interactions, several polymorphisms affect circulating vitamin D [82]. Indeed, polymorphisms regarding cholesterol synthesis, hydroxylation, vitamin D receptor, and vitamin D transport can have such an effect [19]. However, only one study assessed the potential interaction of genetic makeup with PD related scales, introducing a field that needs more attention [39].

In conclusion, a very small number of RCTs with a relative short supplementation period, have assessed the effects of vitamin D supplementation on PD, and different exposure outcomes were assessed, which renders comparisons between studies even more difficult. Although circulating vitamin D generally increased, some isolated beneficial effects of vitamin D were reported on functional scales (HY but not UPDRS) and in some (TUG, 6MWT) but not all functional tests (10MWT). Further studies are needed to solve the puzzle of vitamin D supplementation in patients with PD.

Abbreviations: ABC: Activities-specific Balance Confidence; EQ-5D: EuroQol 5 Dimension; hs-CRP: high-sensitivity C-reactive protein; HY stage: Hoehn and Yahr scale; MMSE: Mini-Mental State Examination; MWT: min walk test; NHP: Nottingham health profile; PD: Parkinson disease; PDQ39: The Parkinson's Disease Questionnaire; PL: placebo; POMS: Profile of Mood States; SOT: Sensory Organization Test; TUG test: timed up and go test; UPDRS IV sub score: UPDRS: Unified Parkinson's disease rating scale

Funding source: There was no funding source for this study.

References

[1] Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol 2020;27:27–42. https://doi.org/10.1111/ene.14108.

[2] Mischley LK. Nutrition and Nonmotor Symptoms of Parkinson's Disease. International Review of Neurobiology, vol. 134, Elsevier; 2017, p. 1143–61. https://doi.org/10.1016/bs.irn.2017.04.013.

[3] Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm 2017;124:901–5. https://doi.org/10.1007/s00702-017-1686-y.

[4] Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology 2021;20:385–97. https://doi.org/10.1016/S1474-4422(21)00030-2.

[5] Kalia LV, Lang AE. Parkinson's disease. The Lancet 2015;386:896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.

[6] Marras C, Lang A. Parkinson's disease subtypes: lost in translation? Journal of Neurology, Neurosurgery & Psychiatry 2013;84:409–15. https://doi.org/10.1136/jnnp-2012-303455.

[7] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers 2017;3:17013. https://doi.org/10.1038/nrdp.2017.13.

[8] Yadav S, Gupta SP, Srivastava G, Srivastava PK, Singh MP. Role of Secondary Mediators in Caffeine-Mediated Neuroprotection in Maneb- and Paraquat-Induced Parkinson's Disease Phenotype in the Mouse. Neurochem Res 2012;37:875–84. https://doi.org/10.1007/s11064-011-0682-0.

[9] Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology 2012;78:1138–45. https://doi.org/10.1212/WNL.0b013e31824f7fc4.

[10] Gao X, Chen H, Fung TT, Logroscino G, Schwarzschild MA, Hu FB, et al. Prospective study of dietary pattern and risk of Parkinson disease. The American Journal of Clinical Nutrition 2007;86:1486–94. https://doi.org/10.1093/ajcn/86.5.1486.

[11] Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose–response meta-analysis of prospective cohort studies. Eur J Epidemiol 2014;29:613–9. https://doi.org/10.1007/s10654-014-9921-4.

[12] Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease: Coffee, tea and caffeine and PD risk. Geriatrics & Gerontology International 2014;14:430–9. https://doi.org/10.1111/ggi.12123.

[13] Alcalay RN, Gu Y, Mejia-Santana H, Cote L, Marder KS, Scarmeas N. The association between Mediterranean diet adherence and Parkinson's disease: Association of MeDi Adherence and PD. Mov Disord 2012;27:771–4. https://doi.org/10.1002/mds.24918.

[14] Nielsen SS, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. Nicotine from edible *Solanaceae* and risk of Parkinson disease: PD and Edible *Solanaceae*. Ann Neurol 2013;74:472–7. https://doi.org/10.1002/ana.23884.

[15] Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. The Lancet Neurology 2005;4:362–5. https://doi.org/10.1016/S1474-4422(05)70097-1.

[16] Fullard ME, Duda JE. A Review of the Relationship Between Vitamin D and Parkinson Disease Symptoms. Front Neurol 2020;11:454. https://doi.org/10.3389/fneur.2020.00454.

[17] Shen L. Associations between B Vitamins and Parkinson's Disease. Nutrients 2015;7:7197–208. https://doi.org/10.3390/nu7095333.

[18] Luo X, Ou R, Dutta R, Tian Y, Xiong H, Shang H. Association Between Serum Vitamin D Levels and Parkinson's Disease: A Systematic Review and Meta-Analysis. Front Neurol 2018;9:909. https://doi.org/10.3389/fneur.2018.00909.

[19] Holick M. McCollum Award Lecture, 1994: Vitamin D—new horizons for the 21st century. The American Journal of Clinical Nutrition 1994;60:619–30. https://doi.org/10.1093/ajcn/60.4.619.

[20] Schmid A, Walther B. Natural Vitamin D Content in Animal Products. Advances in Nutrition 2013;4:453–62. https://doi.org/10.3945/an.113.003780.

[21] Lu Z, Chen TC, Zhang A, Persons KS, Kohn N, Berkowitz R, et al. An evaluation of the vitamin D3 content in fish: Is the vitamin D content adequate to satisfy the dietary requirement for vitamin D?

The Journal of Steroid Biochemistry and Molecular Biology 2007;103:642–4. https://doi.org/10.1016/j.jsbmb.2006.12.010.

[22] Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between Vitamin D, Parathyroid Hormone, and Bone Health. The Journal of Clinical Endocrinology & Metabolism 2011;96:E436–46. https://doi.org/10.1210/jc.2010-1886.

[23] Voulgaridou G, Papadopoulou SK, Detopoulou P, Tsoumana D, Giaginis C, Kondyli FS, et al. Vitamin D and Calcium in Osteoporosis, and the Role of Bone Turnover Markers: A Narrative Review of Recent Data from RCTs. Diseases 2023;11:29. https://doi.org/10.3390/diseases11010029.

[24] Maddock J, Zhou A, Cavadino A, Kuźma E, Bao Y, Smart MC, et al. Vitamin D and cognitive function: A Mendelian randomisation study. Sci Rep 2017;7:13230. https://doi.org/10.1038/s41598-017-13189-3.

[25] Shah SA, Yoon GH, Chung SS, Abid MN, Kim TH, Lee HY, et al. Novel osmotin inhibits SREBP2 via the AdipoR1/AMPK/SIRT1 pathway to improve Alzheimer's disease neuropathological deficits. Mol Psychiatry 2017;22:407–16. https://doi.org/10.1038/mp.2016.23.

[26] De Koning EJ, Van Schoor NM, Penninx BWJH, Elders PJM, Heijboer AC, Smit JanH, et al. Vitamin D supplementation to prevent depression and poor physical function in older adults: Study protocol of the D-Vitaal study, a randomized placebo-controlled clinical trial. BMC Geriatr 2015;15:151. https://doi.org/10.1186/s12877-015-0148-3.

[27] Gowda U, Mutowo MP, Smith BJ, Wluka AE, Renzaho AMN. Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. Nutrition 2015;31:421–9. https://doi.org/10.1016/j.nut.2014.06.017.

[28] Bivona G, Gambino CM, Iacolino G, Ciaccio M. Vitamin D and the nervous system. Neurological Research 2019;41:827–35. https://doi.org/10.1080/01616412.2019.1622872.

[29] Häusler D, Weber MS. Vitamin D Supplementation in Central Nervous System Demyelinating Disease—Enough Is Enough. IJMS 2019;20:218. https://doi.org/10.3390/ijms20010218.

[30] Ao T, Kikuta J, Ishii M. The Effects of Vitamin D on Immune System and Inflammatory Diseases. Biomolecules 2021;11:1624. https://doi.org/10.3390/biom11111624.

[31] Yang C-Y, Leung PSC, Adamopoulos IE, Gershwin ME. The Implication of Vitamin D and Autoimmunity: a Comprehensive Review. Clinic Rev Allerg Immunol 2013;45:217–26. https://doi.org/10.1007/s12016-013-8361-3.

[32] Buleu FN, Luca CT, Tudor A, Badalica-Petrescu M, Caraba A, Pah A, et al. Correlations between Vascular Stiffness Indicators, OPG, and 25-OH Vitamin D3 Status in Heart Failure Patients. Medicina 2019;55:309. https://doi.org/10.3390/medicina55060309.

[33] Sleeman I, Aspray T, Lawson R, Coleman S, Duncan G, Khoo TK, et al. The Role of Vitamin D in Disease Progression in Early Parkinson's Disease. JPD 2017;7:669–75. https://doi.org/10.3233/JPD-171122.

[34] Neveu I, Naveilhan P, Baudet C, Brachet P, Metsis M. 1,25-Dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes: NeuroReport 1994;6:124–6. https://doi.org/10.1097/00001756-199412300-00032.

[35] Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Sääksjärvi K, Heliövaara M. Serum Vitamin D and the Risk of Parkinson Disease. Arch Neurol 2010;67. https://doi.org/10.1001/archneurol.2010.120.

[36] Musiol IM, Feldman D. 1,25-Dihydroxyvitamin D_3 Induction of Nerve Growth Factor in L929 Mouse Fibroblasts: Effect of Vitamin D Receptor Regulation and Potency of Vitamin D_3 Analogs [1]. Endocrinology 1997;138:12–8. https://doi.org/10.1210/endo.138.1.4858.

[37] Xie Y, Feng H, Peng S, Xiao J, Zhang J. Association of plasma homocysteine, vitamin B12 and folate levels with cognitive function in Parkinson's disease: A meta-analysis. Neuroscience Letters 2017;636:190–5. https://doi.org/10.1016/j.neulet.2016.11.007.

[38] Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry 2020;91:795–808. https://doi.org/10.1136/jnnp-2019-322338.

[39] Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Noya M, Takahashi D, et al. Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. The American Journal of Clinical Nutrition 2013;97:1004–13. https://doi.org/10.3945/ajcn.112.051664.

[40] Alfieri DF, Lehmann MF, Oliveira SR, Flauzino T, Delongui F, De Araújo MCM, et al. Vitamin D deficiency is associated with acute ischemic stroke, C-reactive protein, and short-term outcome. Metab Brain Dis 2017;32:493–502. https://doi.org/10.1007/s11011-016-9939-2.
[41] Shirazi HA, Rasouli J, Ciric B, Rostami A, Zhang G-X. 1,25-Dihydroxyvitamin D3 enhances neural stem cell proliferation and oligodendrocyte differentiation. Experimental and Molecular Pathology 2015;98:240–5. https://doi.org/10.1016/j.yexmp.2015.02.004.
[42] Fahmy EM, Elawady ME, Sharaf S, Heneidy S, Ismail RS. Vitamin D status in idiopathic Parkinson's disease: an Egyptian study. Egypt J Neurol Psychiatry Neurosurg 2020;56:45. https://doi.org/10.1186/s41983-020-00175-2.
[43] Naveilhan P, Neveu I, Wion D, Brachet P. 1,25-Dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor: NeuroReport 1996;7:2171–5. https://doi.org/10.1097/00001756-199609020-00023.
[44] Lv Z, Qi H, Wang L, Fan X, Han F, Wang H, et al. Vitamin D status and Parkinson's disease: a systematic review and meta-analysis. Neurol Sci 2014;35:1723–30. https://doi.org/10.1007/s10072-014-1821-6.
[45] Rimmelzwaan LM, Van Schoor NM, Lips P, Berendse HW, Eekhoff EMW. Systematic Review of the Relationship between Vitamin D and Parkinson's Disease. JPD 2016;6:29–37. https://doi.org/10.3233/JPD-150615.
[46] Zhou Z, Zhou R, Zhang Z, Li K. The Association Between Vitamin D Status, Vitamin D Supplementation, Sunlight Exposure, and Parkinson's Disease: A Systematic Review and Meta-Analysis. Med Sci Monit 2019;25:666–74. https://doi.org/10.12659/MSM.912840.
[47] Pignolo A, Mastrilli S, Davì C, Arnao V, Aridon P, dos Santos Mendes FA, et al. Vitamin D and Parkinson's Disease. Nutrients 2022;14:1220. https://doi.org/10.3390/nu14061220.
[48] Bytowska ZK, Korewo-Labelle D, Berezka P, Kowalski K, Przewłócka K, Libionka W, et al. Effect of 12-Week BMI-Based Vitamin D3 Supplementation in Parkinson's Disease with Deep Brain Stimulation on Physical Performance, Inflammation, and Vitamin D Metabolites. IJMS 2023;24:10200. https://doi.org/10.3390/ijms241210200.
[49] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
[50] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.
[51] Hiller AL, Murchison CF, Lobb BM, O'Connor S, O'Connor M, Quinn JF. A randomized, controlled pilot study of the effects of vitamin D supplementation on balance in Parkinson's disease: Does age matter? PLoS ONE 2018;13:e0203637. https://doi.org/10.1371/journal.pone.0203637.
[52] Habibi AH, Anamoradi A, Shahidi GA, Razmeh S, Alizadeh E, Moradian Kokhedan K. Treatment of Levodopa-induced dyskinesia with Vitamin D: A Randomized, double-blind, placebo-controlled trial. Neurol Int 2018;10. https://doi.org/10.4081/ni.2018.7737.
[53] Detopoulou P, Papadopoulou SK, Voulgaridou G, Dedes V, Tsoumana D, Gioxari A, et al. Ketogenic Diet and Vitamin D Metabolism: A Review of Evidence. Metabolites 2022;12:1288. https://doi.org/10.3390/metabo12121288.
[54] Ding H, Dhima K, Lockhart KC, Locascio JJ, Hoesing AN, Duong K, et al. Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. Neurology 2013;81:1531–7. https://doi.org/10.1212/WNL.0b013e3182a95818.
[55] Won S, Sayeed I, Peterson BL, Wali B, Kahn JS, Stein DG. Vitamin D Prevents Hypoxia/Reoxygenation-Induced Blood-Brain Barrier Disruption via Vitamin D Receptor-Mediated NF-kB Signaling Pathways. PLoS ONE 2015;10:e0122821. https://doi.org/10.1371/journal.pone.0122821.
[56] Furman I, Baudet C, Brachet P. Differential expression of M-CSF, LIF, and TNF-? genes in normal and malignant rat glial cells: Regulation by lipopolysaccharide and vitamin D. J Neurosci Res 1996;46:360–6. https://doi.org/10.1002/(SICI)1097-4547(19961101)46:3<360::AID-JNR9>3.0.CO;2-I.
[57] Garcion E, Nataf S, Berod A, Darcy F, Brachet P. 1,25-Dihydroxyvitamin D3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic

encephalomyelitis. Molecular Brain Research 1997;45:255–67. https://doi.org/10.1016/S0169-328X(96)00260-4.

[58] Riaz S, Malcangio M, Miller M, Tomlinson DR. A vitamin D 3 derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats. Diabetologia 1999;42:1308–13. https://doi.org/10.1007/s001250051443.

[59] Cass WA, Peters LE, Fletcher AM, Yurek DM. Evoked dopamine overflow is augmented in the striatum of calcitriol treated rats. Neurochemistry International 2012;60:186–91. https://doi.org/10.1016/j.neuint.2011.11.010.

[60] Bisaglia M. Mediterranean Diet and Parkinson's Disease. IJMS 2022;24:42. https://doi.org/10.3390/ijms24010042.

395

396 **Table 1.** Search strategy in Pubmed.

#1 "Parkinson Disease"[Mesh] OR "Parkinson Disease"[tiab] OR "Parkinson's Disease"[tiab] OR Parkinson*[tiab] OR Parkinsonism[tiab]
#2 "vitamin D" [Mesh] OR "vitamin D"[tiab] OR "vitamin D2"[tiab] OR "vitamin D3"[tiab] OR "1,25 dihydroxycholecalciferol"[tiab] OR ergocalciferol*[Mesh] OR ergocalciferol*[tiab] OR calcitriol[tiab] OR "25-Hydroxyvitamin D"[tiab] OR "1-alpha hydroxyvitamin D3"[tiab] OR cholecalciferol[Mesh] OR cholecalciferol[tiab] OR alfacalcidol[tiab] OR doxercalciferol[tiab] OR "1,25-dihydroxyvitamin D3"[tiab] OR "25 hydroxycholecalciferol"[tiab] OR calcifediol[tiab]
#1 AND #2

397

398

399 **Table 2.** Research question formulated as PICO.

P (Population) Patients with diagnosed PD
I (Intervention) Vitamin D *per os* administration as supplement
C (Comparator) Placebo
O (Outcome) - Increase vitamin D serum levels - Improve physical function

400

401 **Table 3:** Characteristics of the included studies.

Study name	Study duration	Publication year	Journal	Origin	Registry	Ethical permission	RCT design	Randomization	Masking
Suzuki et al [39]	12 months	2013	Am J Clin Nutr	Tokyo, Japan	UMIN Clinical Trials Registry (UMIN000001841)	Ethics committee of Jikei University School of Medicine and the clinical study committee of the Katsushika Medical Center	parallel	yes	double-blind
Hiller et al [51]	16 weeks	2018	PLoS ONE	Taiwan	ClinicalTrials.gov: NCT01119131	Portland VA Medical Center (IRB #2393), OHSU institutional review board (IRB#6482)	parallel	yes (Those with < 20 ng/ml baseline vitamin D (25-OH) levels were enrolled into the vitamin D supplementation arm)	double-blind
Bytowska et al [48]	12 weeks	2023	IJMS	Poland	Clinical Trials.gov (NCT04768023)	Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/522-648/2019)	parallel	yes	double-blind
Habibi et al [52]	3 months	2018	Neurol Int.	Iran	-	Ethical Committee of the Iran University of	parallel	yes	double-blind

						Medical Sciences			

402

403

404 **Table 4.** General characteristics of participants and inclusion/exclusion criteria of patients in the randomized controlled trials.

Study name	Patients (n)	Men (n)	Age mean ±SD (y)	Parkinson Criteria	Intervention (n)	Control (n)	Inclusion/Exclusion Criteria
Suzuki et al [39]	114	60	72.5± 6.6	criteria of the UK Parkinson's Disease Society Brain Bank	55	57	Inclusion: 1) PD diagnosis by >2 neurologists 2) age 45–85 y, and 3) not having first- or second-degree relatives with PD. Exclusion: 1) history of stones in the urinary tract 2) vitamin D supplements 3) Osteoporosis or bone fractures 4) severe dementia or depression 5) severe psychosis and hallucinations, or 6) being capable for participation in the study by the neurologists
Hiller et al [51]	58	68	66.57± 8.07	National Institute of Neurological Disorders and Stroke (NINDS) criteria	28	30	Inclusion: 1) diagnosis of PD (NINDS criteria) 2) Ability to ambulate 50 feet without the assistance of another person. 3) Ability to cooperate with balance testing. 4) 50 + years of age. 5) Serum Vitamin D (25-OH): 21- 39 ng/ml. 6) Balance dysfunction indicated by: a score of ≥1 on the pull test or 1 fall in last month or 2 near falls in the last month. Exclusion: 1) Significant cognitive deficits as defined by a Mini Mental Status Exam (MMSE) of <25. 2) Other neurological or orthopedic deficit that impairs gait or cognition (e.g. stroke, fracture). 3) History of renal stones or renal disease (history of renal transplant, currently on dialysis, or a creatinine > 1.5 at baseline testing)

							4) Vitamin D supplementation of > 600 IU a day 5) Hypercalcemia (based on ionized calcium level). 6) Known untreated tuberculosis infection. 7) Pregnancy 8) Soy Allergy
Bytowska et al [48]	29	19	vitD group 63 ± 9 PL Group 66 ± 6		13	16	Inclusion: 1)Willingness to participate 2) subthalamic nucleus deep brain stimulation treatment 3) no previous supplementation of vitamin D3 4) no serious comorbidity (tumor, cerebrovascular disease 5) cardiorespiratory compromise, forced dementia, etc.) Exclusion: not meeting the inclusion criteria
Habibi et al [52]	120	NR	VitD group 44.02±13.2 PL group 49.9±11.4		60	60	Inclusion: 1) patients with Parkinson disease that have levodopa induced dyskinesia 2) written informed consent Exclusion: NOT meeting the inclusion criteria

405 NR: Not reported; PL: Placebo; SD: Standard deviation

406

407

408

409

410

411 **Table 5.** Intervention details and outcomes of the included studies.

Study name	Intervention Details	Comparator Details	Duration	Timepoints of measurements	Primary Outcomes	Secondary Outcomes	Results
Suzuki et al [39]	1200 IU/d vit D3	Placebo (identical tablets without vitD)	12 months	t=0, t=12 months	HY stage, UPDRS, UPDRS part II, MMSE	PDQ39, EQ-5D	Vitamin D3 prevented the deterioration of the HY stage in patients [difference between groups: P = 0.005; mean ± SD change within vitamin D3 group: +0.02 ± 0.62 (P = 0.79); change within placebo group: +0.33 ± 0.70 (P = 0.0006)]. No difference in UPDRS and MMSE. Difference in PDQ39 activities of daily living Difference in PDQ39 emotional well-being Interaction of VDR FokI genotypes with vitD3 on changes in the HY stage (P-interaction = 0.045), UPDRS total (P-interaction = 0.039), and UPDRS part II (P-interaction = 0.021).
Hiller et al [51]	vitamin D (10,000 IU/day), Ca 1000 mg/d	Placebo (identical tablets without vitD+ Ca)	16 weeks	t=0, t=16 weeks	Composite score of static and dynamic balance (Sensory Organization Test using dynamic posturography)	Gait measures (iMOBILITY device, TUG test) Strength measures (leg flexion and extension using a dynamometer) Falls Quality of life (NHP, PDQ-	↑ 25(OH)D (T0:30.2 ng/ml T1: 61.1 ng/ml) no improvement in balance (SOT) improvement in the SOT of 10.6 points in ages 52–66 vs ages 67–86 of the cohort (p = 0.012) no differences in secondary outcomes

						39, ABC, POMS) biochemical measurements 25(OH)D, Ca, P, Creatine	
Bytowska et al [48]	for BMI under 25, 4000 International Units (IU)/day; for BMI between 25 and 30, 5000 IU/day; and for BMI over 30, 6000 IU/day	placebo vegetable oil (identical bottles)	12 weeks	t=0, t= 6weeks, t= 12weeks	Functional Tests (TUG, 6 MWT, 10 MWT) Vitamin D Metabolites 25(OH)D3 25(OH)D2 24,25(OH)2D3 epi-25(OH)D3	C-Reactive Protein	↑ 25(OH)D3 after vitamin D3 supplementation in the VitD group no changes in the serum concertation of 25(OH)D2 in both groups at T0 and T2 ↑24,25(OH)2D3 in the VitD group (T0: 2.09 ± 1.09 ng/mL vs T2: 2.77 ± 1.02 ng/mL) ($p < 0.05$) no change in the PL group (T0: 1.67 ± 1.15 ng/mL vs T2: 1.32 ± 0.81 ng/mL) ↑ epi-25(OH)D3 in the VitD group (T0: 1.03 ± 0.37 vs T2: 1.67 ± 0.70 ng/mL ($p < 0.005$) no change in PL group (T0: 0.83 ± 0.54 ng/mL vs T2 0.79 ± 0.54 ng/mL) positive correlation between 25(OH)D3 and 24,25(OH)2D3 ($p < 0.0001$) positive correlation between 25(OH)D3 concentration and epi-25(OH)D3 ($p < 0.0001$) ↓ TUG in the VitD group after supplementation (T0: 13.69 ± 5.10 sec vs T1:11.96 ± 3.44 sec and T2: 11.46 ± 3.80 sec) ($p < 0.05$) no changes in TUG in the PL group (T0: 10.65 ± 2.44 sec, T1:10.56 ± 2.73 sec, T2: 9.86 ± 1.63 sec).

							↑6 MWT in VitD group (T0 vs T2) (T0: 316.68 ± 93.45 m, T1:339.99 ± 91.43 m, T2: 350.29 ± 96.28 m) ($p < 0.05$) no changes in the PL group (T0:381.23 ± 74.74 m, T1:379.99 ± 56.5 m, T2:377.61 ± 75.6 m) No change in 10 MWT at all three time points in the PL and the VitD group, respectively (T1:9 ± 1.59 sec, 10.39 ± 3.24 sec; T2:8.46 ± 1.00 sec, 9.88 ± 2.38 sec; T3:8.66 ± 1.43 s, 9.31 ± 2.47 sec no changes in hs-CRP in both groups
Habibi et al [52]	vitamin D3 (1000 IU/d)	placebo	3 months	t=0, t=3 months	UPDRS part IV and UPDRS	-	no effects of vitD in improvement of levodopa induced dyskinesia (UPDRS and UPDRS part IV) positive correlation of the duration of dyskinesia (years) with severity in both groups positive correlation of the duration of dyskinesia (years) with dyskinesia duration per day in vitD group. Age, sex, duration of dyskinesia and Parkinson disease (years) had no effect on the treatment outcomes

ABC: Activities-specific Balance Confidence; EQ-5D: EuroQol 5 Dimension; hs-CRP: high-sensitivity C-reactive protein; HY stage: Hoehn and Yahr scale; MMSE: Mini-Mental State Examination; MWT: min walk test; NHP: Nottingham health profile; PD: Parkinson disease; PDQ39: The Parkinson's Disease Questionnaire; PL: placebo; POMS: profile of Mood States; SOT: Sensory Organization Test; TUG test: timed up and go test; UPDRS IV sub score: UPDRS: Unified Parkinson's disease rating scale

Table 6. Risk of bias of the included RCTs

	Suzuki et al., 2013 [39]	Bytowska et al., 2023 [48]	Hiller et al., 2018 [51]	Habibi et al., 2018 [52]
Random sequence generation (Selection bias)	⊕	⊕	⊕	⊕
Allocation concealment (Selection bias)	⊕	⊕	⊕	⊕
Blinding of participants and personnel (Performance bias)	⊕	⊕	⊕	⊕
Blinding of outcomes assessment (Detection bias)	○	⊕	○	○
Incomplete outcome data (Attrition bias)	⊕	⊕	⊕	⊕
Selective reporting (Reporting bias)	⊕	⊕	⊕	⊕
Other bias	⊕	○	⊕	○

⊕ yes, ⊗ no, ○ non-answer

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: