# The Role of Vitamin D in Parkinson's Disease

Fatma Öznur Afacan[1,*] and Didem Önay Derin[2]

[1] *University of Health Sciences, Institute of Hamidiye Health Sciences, Department of Nutrition and Dietetics, 34668, Istanbul, Turkiye*

[2] *Selçuk University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 42250, Konya, Turkiye*

**Abstract**

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by tremor, rigidity, bradykinesia, and postural instability, along with non-motor symptoms that can cause disability. Vitamin D, a fat-soluble secosteroid, influences gene expression by binding to the vitamin D receptor (VDR). It is essential for calcium homeostasis and metabolism and is also linked to various health conditions, including PD. In recent years, a high prevalence of vitamin D deficiency has been observed in PD patients. The enzymes converting vitamin D to its active form, VDR, and 1α-hydroxylase, are highly expressed in the substantia nigra. These findings indicate that low vitamin D levels may cause dysfunction or cell death in this brain region. Vitamin D impacts several biological processes in the central nervous system, including neurotransmission in dopaminergic circuits. Studies show lower vitamin D levels in Parkinson's patients compared to healthy controls. Links have been found between vitamin D levels and non-motor symptoms like mood disorders, orthostatic hypotension, and olfactory dysfunction, as well as motor severity. However, information on vitamin D's effects on non-motor symptoms is limited. This review seeks to critically examine the relationship between vitamin D and PD, focusing on the potential mechanisms through which vitamin D may influence the development, progression, and clinical management of PD. Additionally, it aims to evaluate the role of vitamin D in the prevention of PD and its therapeutic potential as an adjunctive treatment in patients with Parkinson's disease.

***Keywords:*** Vitamin D, Medical nutrition therapy, Parkinson's disease.

**Review Article** / *Received: 27 February 2025, Accepted: 17 April 2025, Published Online: 5 May 2025.*

## 1. Introduction

Vitamin D refers to a group of fat-soluble secosteroids that can be synthesized in the skin through exposure to sunlight or obtained through dietary intake (Fullard & Duda, 2020). The biological effects of vitamin D are primarily mediated by its binding to the vitamin D receptor (VDR), which modulates gene expression both directly and indirectly (Shirvani et al., 2020). Initially recognized for its essential role in regulating calcium homeostasis and bone metabolism, vitamin D was also noted in the 1930s and 1940s for its beneficial effects in treating conditions such as psoriasis, asthma, and rheumatoid arthritis (McCullough et al., 2019). Over time, its association with a broad range of health conditions—including cardiovascular disease, cancer, autoimmune disorders, and neurodegenerative diseases such as Parkinson's disease (PD)—has become increasingly evident (Bouillon, 2018). The potential neuroprotective effects of vitamin D have garnered significant attention, particularly in relation to neurodegenerative diseases. Several mechanisms through which vitamin D may exert neuroprotection have been proposed. One such mechanism involves the influence of vitamin D on neurotrophic factors, which are essential for the survival, development, and function of neurons. By promoting the synthesis of these factors, vitamin D can support neuronal health and protect against degeneration. Additionally, vitamin D has been shown to regulate nerve growth, further contributing to neuronal maintenance and repair processes (Garcion et al., 2002). Furthermore, vitamin D's neuroprotective role is thought to be mediated through its ability to protect neurons from cytotoxicity. Cytotoxicity, which results from the accumulation of toxic substances or oxidative stress, is a critical factor in the pathogenesis of neurodegenerative diseases. Vitamin D's antioxidant properties may help reduce oxidative damage, thereby preserving neuronal function and reducing the progression of neurodegenerative disorders like PD. These mechanisms, including the regulation of neurotrophic factors, nerve growth, and cytotoxicity,

* Corresponding Author: Fatma Öznur Afacan
Email: ftmznr@gmail.com
https://doi.org/10.56479/ijgr-47

 

collectively contribute to the neuroprotective properties of vitamin D, which may play a significant role in the prevention and management of neurodegenerative diseases such as Parkinson's disease. Further research is needed to fully elucidate these mechanisms and their impact on PD pathophysiology (Liewellyn et al., 2010).

PD is the second most common degenerative disease of the central nervous system (CNS) after Alzheimer's disease. PD is a complex and progressive neurodegenerative disorder characterized by motor symptoms such as bradykinesia, resting tremor, rigidity, postural instability, and gait disturbances (Barichella et al., 2022). In addition, PD is characterized by various non-motor symptoms (e.g., hyposmia, constipation, urinary dysfunction, orthostatic hypotension, cognitive impairment, depression, and rapid eye movement sleep behavior disorder), which may lead to disability. These non-motor symptoms can emerge several years, or even decades, before the onset of motor features (Bloem et al., 2021). The pathophysiology of PD is defined by the presence of intraneuronal cytoplasmic inclusions, primarily composed of α-synuclein aggregates known as Lewy bodies, leading to dopaminergic loss in the substantia nigra pars compacta (SNpc) and other nuclei within the CNS (Tolosa et al., 2021). The underlying molecular pathogenesis involves α-synuclein proteostasis, encompassing mitochondrial function, oxidative stress, calcium homeostasis, axonal transport, and neuroinflammation, along with other pathways and mechanisms (Poewe et al., 2017). Although the pathophysiology of PD has been well characterized, its exact etiology remains unclear. Recently, among various etiological factors, low vitamin D status has emerged as a potentially modifiable risk factor for PD (Barichella et al., 2022). This review aims to examine the relationship between vitamin D and Parkinson's disease, as well as the role of vitamin D in the prevention and treatment of the disease.

## 2. Sources and Metabolism of Vitamin D

Vitamin D is primarily synthesized in the skin from 7-dehydrocholesterol under the influence of ultraviolet B radiation. Although it is a fat-soluble hormone, it can also be obtained from dietary sources. Vitamin D3 is biologically inert and requires two hydroxylation steps to become active (Barichella et al., 2022). The first hydroxylation occurs in the liver, where the enzyme vitamin D-25-hydroxylase converts vitamin D into 25-hydroxyvitamin D3 (25-OH-D3) or calcidiol, which is the circulating form. Subsequently, 25-OH-D3 is converted into 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3), also known as calcitriol, by 25-hydroxyvitamin D-1α-hydroxylase or 1α-hydroxylase (Fullard & Duda, 2020). This second step takes place in the kidneys, particularly in the proximal convoluted tubule cells, and is regulated by blood calcium and phosphorus levels (Plum & DeLuca, 2010). After sun exposure, the skin converts 7-dehydrocholesterol into cholecalciferol (Bytowska et al., 2023). Therefore, insufficient exposure to sunlight may result in low vitamin D levels (Zhou et al., 2019).

Vitamin D can also be obtained from certain dietary sources. In nature, dietary vitamin D exists in two forms: vitamin D3 (25-OH-D3) or cholecalciferol, which is found in animal-derived sources such as bluefish, egg yolk, and meat, and vitamin D2 (25-OH-D2) or ergocalciferol, which is primarily present in nuts, almonds, walnuts, mushrooms, beans, and leafy green vegetables (Barichella et al., 2022). Similar to cholecalciferol, ergocalciferol must undergo hydroxylation at the 25 and 1α positions to become active. The total amount of cholecalciferol and ergocalciferol is generally referred to as 25-OH-D (Sosa & Gómez, 2020). Since only a limited number of foods provide a reasonable amount of vitamin D, dietary intake is often insufficient (Barichella et al., 2022).

Currently, vitamin D is considered a hormone rather than a vitamin (Zhou et al., 2019). In addition to its role in calcium and phosphorus metabolism, vitamin D also plays a role in inflammatory response (Kempker et al., 2012), glucose and lipid metabolism (Salamon et al., 2014), and cardiac and vascular regulation (Carthy et al., 1989). The biological functions of vitamin D are mediated through its binding to vitamin D receptors (VDRs), which belong to the steroid hormone receptor superfamily. VDRs are widely expressed in various tissues, including the kidneys, bones, intestines, muscles, pancreas, and central nervous system (Zhou et al., 2019).

## 3. Vitamin D Deficiency: Definition and Prevalence

The clinical practice guidelines on vitamin D issued by the Endocrine Society Task Force have defined a threshold level of 50 nmol/L (or 20 ng/mL) as vitamin D deficiency. A threshold of <30 nmol/L (or 12 ng/mL) has been shown to significantly increase the risk of osteomalacia and nutritional rickets and is, therefore, considered severe vitamin D deficiency. Serum 25-OH-D concentrations between 50 nmol/L and 75 nmol/L (<30 ng/mL) should be classified as vitamin D

insufficiency. In contrast, 25-OH-D concentrations ranging from 75 to 150 nmol/L represent the normal range (Holick et al., 2011). In summary, serum vitamin D levels are generally defined as deficient at <20 ng/mL, insufficient at 20–30 ng/mL, and sufficient at >30 ng/mL. Low vitamin D status, or hypovitaminosis D, encompasses both deficiency and insufficiency and has emerged as a highly prevalent condition worldwide (Barichella et al., 2022).

Low vitamin D levels are more frequently observed in childhood and older age. Severe vitamin D deficiency has been reported with a prevalence ranging from 85% to 99%, particularly in patients affected by liver and/or kidney failure (Amrein et al., 2020). Vitamin D deficiency has been associated with various pathological changes in multiple organ systems and has been linked to an increased incidence of several chronic diseases, including multiple sclerosis (Koduah et al., 2017), cardiovascular disease (Giovannucci et al., 2008), cancer (Kilkkinen et al., 2008), type 2 diabetes (Knekt et al., 2008), Alzheimer's disease (Littlejohns et al., 2014), and Parkinson's disease (Bytowska et al., 2023).

## 4. Parkinson's Disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, characterized by the loss of dopaminergic neurons in the substantia nigra (Zhou et al., 2019). Individuals over the age of 60 are at a higher risk of developing PD (Hirsch et al., 2016). Due to the aging population, the incidence of PD is expected to increase further in the future (Bytowska et al., 2023). The etiology of PD remains unknown and is likely multifactorial. The exact mechanism underlying neurodegeneration in PD has not yet been fully elucidated (Lv et al., 2020). Both genetic and environmental factors, including specific genetic mutations (Corti et al., 2011), sex, pesticide exposure (Allen & Levy, 2013), and the use of calcium channel blockers (Lang et al., 2015), have been reported to contribute to the development of Parkinson's disease. Due to its uncertain etiology, no medication has been proven to cure PD (Lv et al., 2020). Therefore, PD currently remains an incurable disease. The primary goals are to alleviate symptoms, reduce discomfort, and slow disease progression to help patients better manage their daily activities (Bytowska et al., 2023).

Symptoms can be classified as motor and non-motor. The main motor symptoms include bradykinesia, postural instability, and resting tremors. Non-motor symptoms include depression, dementia, sleep disorders, and mild personality changes. In Parkinson's disease, dopamine production is impaired due to the degeneration of the substantia nigra (Jankovic & Tan, 2020). Studies conducted on rodent models of PD have observed that vitamin D treatment exerts a protective effect on dopaminergic neurons in the substantia nigra (Rimmelzwaan et al., 2016).

## 5. The Relationship of Vitamin D to Parkinson's Disease

Vitamin D deficiency in Parkinson's disease (PD) was first identified by Sato et al. in 1997 (Sato et al., 1997). Since then, numerous studies have observed that the prevalence of vitamin D deficiency and insufficiency in PD is higher compared to controls (Ding et al., 2013; Fullard & Duda, 2020). After the discovery that vitamin D receptors (VDR) and 1α-hydroxylase, the enzyme responsible for converting vitamin D into its active form, are highly expressed in the substantia nigra, it has been hypothesized that insufficient circulating vitamin D levels may lead to dysfunction or cell death in the substantia nigra (Eyles et al., 2005). A long-term cohort study found that the incidence of PD was three times higher in individuals with the lowest serum 25(OH)D concentrations compared to those with the highest concentrations (Knekt et al., 2010). In a study conducted on 300 individuals selected from the Clinical Research in Neurology database (100 Parkinson's patients, 100 Alzheimer's patients, and 100 healthy controls), the prevalence of vitamin D deficiency (defined as concentrations below 30 ng/mL) was reported to be significantly higher in Parkinson's patients (55%) compared to both healthy controls (36%) and Alzheimer's patients (41%). Additionally, 47.2% of Parkinson's patients were found to have vitamin D insufficiency (20-30 ng/mL) (Evatt et al., 2008).

In the Mini-Finland Health Survey (Mini-Fin Study), which examined the correlation between vitamin D levels and the incidence of Parkinson's disease (PD), higher vitamin D levels were observed to be associated with a lower risk of developing PD over a 29-year follow-up period (Knekt et al., 2010). It was reported that the risk of PD was 65% lower in individuals with serum vitamin D concentrations above 50 nmol/L compared to those with concentrations below 25 nmol/L (Knekt et al., 2010). In a prospective observational study comparing 145 Parkinson's patients with 94 healthy controls, it was observed that at baseline, Parkinson's patients had significantly lower serum vitamin D concentrations than age-matched controls. Similarly, after an 18-month follow-up, individuals with PD were found to have lower mean

serum 25(OH)D concentrations compared to controls (Sleeman et al., 2017). Since dermal synthesis is the primary source of vitamin D, some studies have focused on the relationship between outdoor work and the risk of Parkinson's disease. One study found that Danish men who worked outdoors had a lower likelihood of developing PD compared to those who worked indoors (Kenborg et al., 2011). A study conducted on 69,010 Parkinson's patients in France reported that the number of prescriptions for Parkinson's medications was lower in geographic regions with higher UV-B radiation. However, the role of diet and dietary vitamin D intake in the risk of PD has not been sufficiently explored in the literature (Kravietz et al., 2017). One study reported an inverse relationship between the risk of Parkinson's disease and serum levels of all forms of vitamin D, including dietary 25-OH D2, which is independent of sun exposure (Wang et al., 2015). These findings suggest the possibility that the risk of Parkinson's disease associated with vitamin D may not be solely due to a lack of sun exposure. Other mechanisms, such as gastrointestinal dysfunction—a common non-motor dysfunction in PD—which may impair vitamin D2 absorption, could also be involved (Lubomski et al., 2020).

In addition to studies demonstrating an association between vitamin D and PD, there are also studies that do not support this relationship. In a prospective study with an average follow-up of 17 years, although an increase in PD risk was reported between vitamin D levels >30 ng/mL and <20 ng/mL, no significant association was found between vitamin D status and the risk of Parkinson's disease (Shrestha et al., 2016). In the Parkinson Associated Risk Syndrome (PARS) study, no significant difference was found in total plasma vitamin D levels among high-risk patients compared to all other groups (Fullard et al., 2017). The inconsistent findings regarding the relationship between vitamin D and Parkinson's disease are thought to be due to differences in the geography, dietary habits, physical activity, and socioeconomic conditions of the studied populations (Barichella et al., 2022).

Due to the limited mobility and gastrointestinal symptoms observed in PD patients, low vitamin D levels may also be a consequence of the disease (Ly et al., 2020). However, several studies have suggested that vitamin D deficiency may be associated with the etiology of Parkinson's disease (Newmark & Newmark, 2007; Evatt et al., 2008; Fullard et al., 2017). A study reported that even in Parkinson's patients with normal ambulation and gastrointestinal function, the prevalence of vitamin D deficiency was still higher (Evatt et al., 2011). Newmark and colleagues concluded that chronic vitamin D deficiency may not simply be a result of the disease but could be linked to the pathogenesis or progression of Parkinson's disease (Newmark & Newmark, 2007; Knekt et al., 2010).

Despite numerous studies reporting a link between low serum vitamin D levels and Parkinson's disease (PD), inconsistencies remain due to variations in vitamin D measurement standards and threshold definitions. These methodological differences hinder cross-study comparisons and affect the interpretation of results. Additionally, geographic factors (e.g., sun exposure), dietary habits, and genetic variations—particularly in vitamin D receptor (VDR) polymorphisms—further contribute to heterogeneity in findings. To address these challenges, future research should adopt standardized measurement protocols, account for environmental and genetic influences, and conduct large-scale randomized controlled trials to clarify the potential causal role and therapeutic efficacy of vitamin D in PD.

## 6. Pathophysiology of Vitamin D and Parkinson's Disease

The pathophysiological cause of Parkinson's disease (PD) is the loss of dopaminergic neurons (DA) in the substantia nigra (SN) of the midbrain, primarily characterized by the formation of Lewy bodies, which consist of α-synuclein protein aggregations (Lv et al., 2020). Vitamin D plays a fundamental role in various diseases, including dermatological conditions, cardiovascular disorders, autoimmune diseases, and neurological disorders such as Parkinson's disease, exerting biological effects on multiple processes (Barichella et al., 2022). Since vitamin D is a fat-soluble hormone capable of crossing the blood-brain barrier, it exerts effects on the CNS. Additionally, the CNS has the ability to synthesize its own vitamin D. Vitamin D has been reported to influence cellular proliferation, differentiation, calcium signaling, neuroprotection, synaptogenesis, amyloid clearance, and the prevention of neuronal death through the CNS (Di Somma et al., 2017). Furthermore, vitamin D has been implicated in dopaminergic neurotransmission as well as in cellular processes such as neurogenesis and neurite outgrowth (DeLuca & Li, 2011). It has been determined that vitamin D increases the expression of tyrosine hydroxylase enzyme in chromaffin cells of the adrenal medulla, which exhibit surface vitamin D receptors (VDRs), enhances catecholamine production, and plays a role in both dopamine synthesis and storage in the CNS (Pertile et al., 2016). In an experimental study,

vitamin D was observed to mitigate neurotoxicity induced by 6-hydroxydopamine (a toxic compound) in rats, providing protection against dopamine depletion in the SNpc (Wang et al., 2001). In vitro studies have demonstrated that vitamin D may upregulate the expression of glial cell line-derived neurotrophic factor (GDNF), particularly in the striatum, suggesting its protective role in PD (Sanchez et al., 2002). Moreover, vitamin D has been reported to counteract oxidative stress in the brain by reducing reactive oxygen species through various mechanisms, including PARP1 inhibition (Barichella et al., 2022). A study indicated that vitamin D may prevent α-synuclein aggregation through the expression of calbindin-D28k, a calcium-binding protein, thereby exhibiting a neuroprotective role (Rcom et al., 2017). These effects, alongside others, suggest that vitamin D may influence the pathophysiology of Parkinson's disease via mechanisms such as neuroinflammation, oxidative stress, and dopamine production, which may contribute to disease progression. In conclusion, inadequate vitamin D status may contribute to the loss of dopaminergic neurons in the brain and thus play a role in the development of PD (Pignolo et al., 2022).

VDR and 1α-hydroxylase, which converts vitamin D into its active form, are expressed in the neurons of the substantia nigra in Parkinson's disease (PD) (Suzuki et al., 2013). The active form of vitamin D, 1,25-$(OH)_2D_3$, binds to the vitamin D receptor (VDR), activating it and regulating gene transcription. Both VDR and the 1α-hydroxylase enzyme are also expressed in other tissues, including neuronal and glial cells (Rimmelzwaan et al., 2016). Therefore, vitamin D has been suggested to play a role in brain development and neurodegenerative diseases such as PD and dementia, exerting neuroprotective effects on brain function (Eyles et al., 2005). In particular, VDR expression in dopaminergic regions of the brain implies a direct regulatory influence of vitamin D on the survival and function of these neurons, further supporting its potential involvement in PD pathophysiology. Moreover, vitamin D is believed to modulate microglial activation and inflammatory cytokine production, which are key contributors to neuroinflammation in PD. This modulation of immune responses may reduce chronic inflammation in the substantia nigra, thereby preventing or delaying dopaminergic neuron degeneration.

Genetic studies have demonstrated an association between VDR gene polymorphisms and the risk of PD (Butler et al., 2011). Muscle and motor impairments have been observed in VDR knockout mice (Burne et al., 2005). The FokI C allele of VDR, which is thought to enhance signal transduction efficiency, has been reported to be associated with milder forms of PD (Suzuki et al., 2012). Among the genes regulated by VDR in the hippocampus, several have been implicated in the pathophysiology of PD, including CCAAT/enhancer-binding protein beta (CEBPB), Peripheral myelin protein 22 (PMP22), Plasma membrane calcium-transporting ATPase 3 (ATP2B3), Glutamate receptor AMPA 3 (GRIA3), Neurotrophic receptor tyrosine kinase 2 (NTRK2), DNA methyltransferase 3 alpha (DNMT3A), Tenascin R (TNR), and Glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A). These findings suggest that vitamin D levels and VDR gene polymorphisms may be associated with the incidence and progression of PD (Lang et al., 2020). These polymorphisms may influence individual responses to vitamin D and contribute to variability in susceptibility and clinical progression of PD. Therefore, the consideration of genetic variability in future clinical trials may enhance understanding of differential therapeutic responses to vitamin D supplementation.

1,25-$(OH)_2D_3$ is synthesized in the human brain and influences the function of various structures, including the substantia nigra. Since 1,25-$(OH)_2D_3$ is a potent regulator of neuronal gene expression, it has been classified as a neurosteroid (Landel et al., 2018). In neurons, vitamin D suppresses oxidative stress, inhibits inflammation, and stimulates neurotrophin production. In addition to preventing vascular damage, vitamin D exerts neuroprotective effects through the upregulation of neurotrophins, improved metabolism, and positive effects on cardiovascular function (AlJohri et al., 2019; Lang & Leibrock, 2019; Lang et al., 2020). Moreover, vitamin D has been shown to stimulate the differentiation of dopaminergic neurons and upregulate dopamine synthesis and metabolism (Pertile et al., 2016; AlJohri et al., 2019). These findings underscore the multi-faceted role of vitamin D in maintaining dopaminergic neuron health and regulating critical processes involved in PD pathogenesis. Nonetheless, despite these promising mechanisms, current evidence remains inconclusive, and conflicting findings persist in the literature regarding the extent of vitamin D's protective effects in PD.

In neuroblastoma cells, vitamin D has been shown to reduce cell proliferation and promote differentiation. Thus, vitamin D supports the growth, survival, proliferation, and differentiation of neurons and neural stem cells (AlJohri et al., 2019). Vitamin D deficiency may compromise neuronal development, dopamine transport, and metabolism. Additionally,

vitamin D is a potent inhibitor of cyclooxygenase (COX), an inflammatory enzyme reported to play a role in the pathophysiology of PD. Consequently, vitamin D is thought to have a beneficial impact on the clinical course of Parkinson's disease (Lang et al., 2020). Given the complexity of PD etiology and the interplay between environmental and genetic factors, future studies should adopt stratified approaches based on vitamin D status, genetic background, and clinical phenotype to more precisely delineate the role of vitamin D in PD. Randomized controlled trials are particularly needed to evaluate vitamin D's efficacy, focusing on parameters such as disease stage, motor and non-motor symptoms, and relevant biomarkers.

## 7. Effects of Vitamin D on PD Symptoms and Prognosis

Vitamin D deficiency may have an impact on the progression of Parkinson's disease (PD) as well as on its clinical motor and non-motor symptoms (Pignolo et al., 2022). Studies conducted in humans have reported that serum 25(OH)D levels are lower in Parkinson's patients compared to controls, and higher 25(OH)D levels have been associated with better motor function (Topal et al., 2010; Evatt et al., 2011). In one study, low 25(OH)D levels were observed to be associated with severe postural instability, freezing of gait, and postural abnormalities (Moghaddasi et al., 2013). Additionally, higher 25(OH)D levels have been linked to neuroprotection in rodent models of PD (Wang et al., 2001; Rimmelzwaan et al., 2016). Other studies have reported an inverse relationship between serum 25-hydroxyvitamin D levels and the severity of Parkinson's disease (Hiller et al., 2018; Bytowska et al., 2023). Vitamin D supplementation has been shown to reduce the rate of motor function deterioration, as determined by both the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale (UPDRS) (Suzuki et al., 2013). In a case-control study, higher serum 25(OH)D$_3$ levels were found to be associated with better automatic postural responses in Parkinson's disease (Peterson et al., 2013), while a clinical study reported that the administration of 1200 IU of vitamin D supplementation prevented the worsening of scores on scales (H&Y and UPDRS) measuring the severity of Parkinson's disease (Suzuki et al., 2013). In addition to its symptomatic effects on motor function, vitamin D may also exert neurotrophic or neuroprotective effects in Parkinson's disease. Higher vitamin D levels have been associated with better balance, and vitamin D supplementation has been reported to have a positive impact on PD motor symptoms (Peterson et al., 2013; Suzuki et al., 2013). Studies have indicated that as 25(OH)D$_3$ concentrations decrease in Parkinson's patients, the severity of motor symptoms increases (Suzuki et al., 2012; Zhou et al., 2019). Prospective observational studies have also found a negative relationship between baseline vitamin D status and the severity of PD motor symptoms during disease progression (Suzuki et al., 2013; Sleeman et al., 2017). Therefore, vitamin D supplementation may delay the worsening of symptoms in Parkinson's patients. A cross-sectional observational study also reported an association between postural balance and serum vitamin D levels (Peterson et al., 2013).

Limited data are available regarding the relationship between vitamin D and non-motor symptoms in PD. In general, individuals with low 25(OH)D$_3$ levels have been reported to experience worsening non-motor symptoms such as excessive daytime sleepiness, olfactory dysfunction, and cognitive decline (Kim et al., 2018; Plantone et al., 2022). A study investigating olfactory dysfunction, a symptom observed in PD, reported that 25(OH)D$_3$ levels correlated with the severity of olfactory impairment in Parkinson's disease (Kim et al., 2018). In addition to its association with dementia and olfactory function in PD patients, serum 25(OH)D$_3$ concentrations may also influence gastric emptying time (Kwon et al., 2016) and orthostatic hypotension (Jang et al., 2015).

It has been suggested that vitamin D is a regulator of the renin-angiotensin system (RAS). RAS plays a role in blood pressure regulation and affects the sympathetic nervous system; therefore, vitamin D-related dysfunction in RAS may lead to sympathetic system impairment (Fullard et al., 2020). Numerous studies involving both PD patients and the general population have associated vitamin D status with orthostatic hypotension (Duval et al., 2015; Ometto et al., 2016). In one study, 55 PD participants were divided into two groups based on the presence or absence of orthostatic hypotension, and it was determined that serum 25-hydroxyvitamin D and calcitriol levels were significantly lower in the group with orthostatic hypotension (Jang et al., 2015).

Olfactory dysfunction is also a common non-motor symptom in Parkinson's disease, with a prevalence of 50–90% (Fullard et al., 2020). It has been reported that vitamin D plays a role in the pathogenesis of olfactory dysfunction in Parkinson's disease through various potential mechanisms involving calcitriol, the active form of vitamin D (Kim et al., 2018). Additionally, alterations in dopamine and

acetylcholine signaling have been shown to contribute to olfactory dysfunction in Parkinson's disease (Bohnen et al., 2011). Calcitriol has been reported to increase the activity of choline acetyltransferase and tyrosine hydroxylase, which are enzymes responsible for the synthesis of acetylcholine and dopamine, thereby exhibiting a neuroprotective effect (Wrzosek et al., 2013). In addition to the regulation of acetylcholine, vitamin D may also play a role in the clearance of amyloid-beta, both of which are involved in the pathogenesis of cognitive impairment in Parkinson's disease (Fullard et al., 2020). Multiple studies have demonstrated that VDR and enzymes involved in D3 metabolism are expressed in the central nervous system, particularly in hippocampal regions (Yilmazer et al., 2013; Fullard et al., 2020). Animal studies have shown that vitamin D deficiency negatively affects hippocampal learning and memory through gene expression and neural development (Liang et al., 2018). These studies propose potential mechanisms for the impact of vitamin D on cognitive decline in Parkinson's disease; however, further research is needed to determine whether vitamin D status influences cognition in PD and whether supplementation may help prevent or improve cognitive decline (Fullard et al., 2020).

## 8. Osteoporosis and Fracture Risk in Parkinson's Disease

An increased prevalence of osteoporosis and osteopenia has been reported in patients with Parkinson's disease (PD), and PD is considered a cause of secondary osteoporosis (Lv et al., 2020). A study conducted in Korea determined that 6542 out of 35,663 patients with Parkinson's disease (18.3%) experienced osteoporosis, with fractures occurring most frequently within the first six months following the onset of Parkinson's disease and decreasing three years after diagnosis (Park et al., 2019). Bone loss and fractures in Parkinson's disease are reported to be multifactorial, with vitamin D deficiency being one of the contributing factors (Sato et al., 1997; Metta et al., 2017). Vitamin D deficiency is a well-known risk factor for osteoporosis and bone fractures (Suzuki et al., 2013). A meta-analysis of randomized controlled trials has reported that vitamin D supplementation reduces the risk of falls in elderly individuals, suggesting that vitamin D deficiency may increase the risk of falls (Bischoff-Ferrari et al., 2009). Patients with Parkinson's disease have lower bone mineral density and a higher risk of falls and hip fractures compared to age-matched controls; however, these risks may also result from factors unrelated to PD, such as advanced age, low body mass index, and limited sun exposure (Suzuki et al., 2013).

A decline in bone mass is a common finding in Parkinson's disease, affecting 91% of women and 61% of men (Barichella et al., 2022). According to the World Health Organization, osteoporosis is defined as bone mineral density that is 2.5 standard deviations below the mean, whereas osteopenia is defined as bone mineral density between 1.0 and 2.5 standard deviations below the mean for age, race, and sex (Reid, 2020). The reduced bone mass observed in Parkinson's disease appears to be primarily due to decreased mobility, similar to other neurological disorders. However, vitamin D deficiency, along with other endocrine, nutritional, and iatrogenic factors, may play a significant role in bone mass depletion (Barichella et al., 2022). In a cross-sectional study involving Parkinson's patients and healthy controls, lower bone mineral density was observed in the PD group, and an inverse relationship was identified between bone mineral density at the hip and disease severity. These findings suggest a link between osteoporosis and the progression of Parkinson's disease (Gao et al., 2015).

## 9. Vitamin D Receptor Polymorphisms and Parkinson's Disease

The biological functions of $1,25(OH)_2D_3$ are mediated by the vitamin D receptor (VDR), a member of the nuclear receptor superfamily of transcription factors. Upon ligand binding, VDR interacts with the retinoid X receptor (RXR) to form a heterodimer, which subsequently binds to vitamin D response elements (VDREs) in target genes. It is estimated that $1,25(OH)_2D_3$ regulates more than 200 genes by influencing various cellular processes (Lv et al., 2020).

VDR serves as the principal mediator of vitamin D functions. A transcriptome-wide screening has revealed increased VDR gene expression in blood cells of patients with early-stage Parkinson's disease (Scherzer et al., 2007). Consequently, it has been suggested that polymorphic variants of VDR may also play a role in the pathogenesis of Parkinson's disease. In recent years, the most frequently studied polymorphisms have been BsmI (rs1544410), FokI (rs10735810), ApaI (rs7975232), and TaqI (rs731236) (Lv et al., 2020). Several studies have investigated the association between VDR polymorphisms and Parkinson's disease; however, conclusive results have not always been obtained. Four classical VDR polymorphisms (TaqI, ApaI, BsmI, and FokI) have been examined for their potential associations with

Parkinson's disease, with the FokI genotype appearing to be the most strongly associated with Parkinson's disease risk (Barichella et al., 2022). A study has reported that Parkinson's patients with higher vitamin D levels exhibit lower motor severity symptoms and that the VDR FokI CC genotype is more prevalent among these individuals. Based on this finding, it has been suggested that the worsening of motor severity in Parkinson's patients carrying the FokI TT or CT genotypes may be prevented through vitamin D supplementation (Suzuki et al., 2012). A meta-analysis evaluating the associations between all VDR polymorphisms and the risk of Parkinson's disease has identified a relationship between FokI and susceptibility to Parkinson's disease in the general population (Gao et al., 2020).

In polymerase chain reaction-based restriction analysis of VDR gene polymorphisms, the BsmI (B/b) polymorphism has been reported to potentially influence the pathogenesis of Parkinson's disease (PD) (Kim et al., 2005). Additionally, studies conducted in Hungarian, Japanese, and Chinese populations have suggested that the FokI (C/T) polymorphism is significantly associated with PD and that the C allele may increase the risk of the disease (Han et al., 2012; Tanaka et al., 2017). The most significant start codon polymorphism of the VDR gene is the FokI polymorphism, which consists of a long version (T allele) and a shorter protein variant shortened by three amino acids (C allele). Compared to T-VDR, C-VDR has been found to have a better capacity for calcium absorption in the intestines. Consequently, the C allele may contribute to higher vitamin D levels and a reduced risk of PD (Lv et al., 2020). However, research findings also suggest that rather than serving as a protective factor, the C allele may act as a risk factor for Parkinson's disease (Han et al., 2012; Tanaka et al., 2017). A stronger association between the FokI CC genotype and milder forms of PD has been identified in one study (Suzuki et al., 2012). Moreover, the Parkinson Environment Gene (PEG) study, a population-based case-control study on PD, has reported a connection between the FokI polymorphism and cognitive decline in PD (Gatto et al., 2016). However, some studies have failed to establish any relationship between VDR genotypes (BsmI, FokI, ApaI, and TaqI loci) and the risk of Parkinson's disease (Kang et al., 2016; Lv et al., 2020). These findings indicate that the impact of VDR gene polymorphisms on PD risk and their association with vitamin D levels may be influenced by factors such as ethnic differences, environmental exposures, gene-gene and gene-environment interactions, or small sample sizes. Therefore, future research should focus on the interactions between vitamin D levels and VDR gene polymorphisms in PD while also considering environmental factors (Lv et al., 2020). Additionally, it has been suggested that vitamin D deficiency may act as a suppressor of gene expression. One of the key genes suppressed under vitamin D deficiency is the tyrosine hydroxylase (TH) gene, which plays a crucial role in the regulation of dopamine biosynthesis and the expression of neurotrophic factors (Zhou et al., 2019). In conclusion, the FokI (C/T) polymorphism has been reported to be significantly associated with PD, and its presence may influence the risk, severity, and cognitive function of Parkinson's patients, as well as the effectiveness of vitamin D3 supplementation in these individuals (Lv et al., 2020).

## 10. Vitamin D Supplementation in Parkinson's Disease

Low vitamin D levels are frequently observed in patients with Parkinson's disease (PD) (Evatt et al., 2008; Evatt et al., 2011; Ding et al., 2013), which has been associated with inadequate intake of vitamin D and various micronutrients (Barichella et al., 2022). Only a limited number of studies have investigated the effects of vitamin D supplementation on PD risk and disease progression. Some studies have demonstrated that vitamin D supplementation and outdoor work significantly reduce the risk of developing Parkinson's disease (Kwon et al., 2013). In a randomized, placebo-controlled study that examined the effects of 1200 IU/day vitamin D supplementation for 12 months in patients with Parkinson's disease, serum vitamin D levels were reported to have doubled in the supplemented group, whereas no increase was observed in the placebo group. Additionally, while no change in motor severity was reported in the supplementation group, deterioration was observed in the control group (Suzuki et al., 2013). In another study that evaluated the effects of 1000 IU/day vitamin D supplementation or placebo in 120 Parkinson's patients, no changes in dyskinesia or motor severity were observed after three months (Habibi et al., 2018). A study aiming to assess the effects of high-dose vitamin D (10,000 IU/day) for 16 weeks on balance in Parkinson's patients using the Sensory Organization Test found no overall improvement in balance; however, it was reported that vitamin D had an effect on balance in the younger subset of the group (mean age: 60 years) (Hiller et al., 2018). Additionally, vitamin D supplementation has been observed to reduce camptocormia in Parkinson's patients (Sato et

al., 2011). In a randomized controlled trial investigating vitamin D supplementation, vitamin D3 was found to temporarily delay PD progression in patients with the FokI CT and TT genotypes (Suzuki et al., 2013). The administration of 1200 IU/day vitamin D supplementation for 12 months (Suzuki et al., 2013) or 10,000 IU/day for 16 weeks (Hiller et al., 2018) did not lead to adverse effects such as hypercalcemia. Thus, vitamin D supplementation appears to be a promising approach in Parkinson's disease; however, the dose of vitamin D that may induce toxicity remains uncertain (Lv et al., 2020).

## 11. Conclusion and Recommendations

Serum vitamin D levels have been consistently reported to be lower in individuals with Parkinson's disease (PD). Higher concentrations of vitamin D have been associated with reduced disease risk and severity, as well as improved cognitive function and psychological well-being. However, upon examination of the current literature, it is evident that findings regarding the preventive or therapeutic efficacy of vitamin D supplementation in PD remain inconsistent. Therefore, insufficient evidence currently exists to support the routine use of vitamin D as a standard adjunctive treatment in clinical practice. These conflicting results are thought to arise from variations in the methods used to measure vitamin D, as well as the application of different threshold values across studies. Additionally, environmental factors such as geographic location, sunlight exposure, dietary habits, physical activity levels, and socioeconomic conditions are considered to significantly influence outcomes and limit the generalizability of findings. Genetic factors are also believed to play a critical role in this association. Specifically, polymorphisms in the vitamin D receptor (VDR) gene may affect both the susceptibility to PD and the individual response to vitamin D supplementation. This suggests that the relationship between vitamin D and PD may be modulated by personalized biological mechanisms, thereby highlighting the importance of incorporating genetic profiling into future investigations. In order to clarify the potential role of vitamin D in the pathophysiology and clinical progression of PD, there is a need for large-scale, multicenter, randomized controlled trials. Such studies should systematically assess a range of parameters, including serum 25(OH)D levels, motor symptom severity, non-motor symptoms (e.g., cognitive impairment, depression, and sleep disturbances), quality of life, disease progression rates, and potential adverse effects. Furthermore, classification of patients according to disease stage and clinical phenotype is essential for obtaining more specific and clinically relevant results. In conclusion, although an increasing body of evidence suggests a potential role for vitamin D in the pathogenesis and symptomatology of Parkinson's disease, the inconsistency of findings precludes definitive recommendations at this time. Further high-quality research is warranted to elucidate underlying mechanisms and to inform evidence-based clinical decision-making regarding the use of vitamin D in PD management.

## Declaration of Competing Interest

The authors declare that they have no financial or non-financial competing interests.

## Financial Disclosure

The authors declare that no financial support was received in the conduct of this research.

## Author's Contributions

F. Ö. Afacan (0000-0002-3138-3257): *Concept/Design, Design, Analysis and Interpretation, Literature Search, Writing, Critical Review*
D. Önay Derin (0000-0003-0624-5714): *Supervision / Advising, Analysis and Interpretation, Critical Review*

## References

Allen, M. T., & Levy, L. S. (2013). Parkinson's disease and pesticide exposure – a new assessment. *Critical Reviews Toxicology, 43,* 515–34. https://doi.org/10.3109/10408444.2013.798719

AlJohri, R., AlOkail, M., Haq,S.H. (2019). Neuroprotective role of vitamin D in primary neuronal cortical culture. *Neurological Science, 14,* 43-48. https://doi.org/10.1016/j.ensci.2018.12.004

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., ... & Malle, O. (2020). Vitamin D deficiency 2.0: An update on the current status worldwide. *European Journal of Clinical Nutrition*, *74*(11), 1498-1513. https://doi.org/10.1038/s41430-020-0558-y

Barichella, M., Garrì, F., Caronni, S., Bolliri, C., Zocchi, L., Macchione, M. C., ... & Pezzoli, G. (2022). Vitamin D status and Parkinson's disease. *Brain Sciences*, *12*(6), 790. https://doi.org/10.3390/brainsci12060790

Bischoff-Ferrari, H. A., Dawson-Hughes, B., Staehelin, H. B., Orav, J. E., Stuck, A. E., Theiler, R., ... & Henschkowski, J. (2009). Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*, *339*. https://doi.org/10.1136/bmj.b3692

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet*, *397*(10291), 2284-2303. https://doi.org/10.1016/S0140-6736(21)00218-X

Bohnen, N. I., & Albin, R. L. (2011). The cholinergic system and Parkinson disease. *Behavioural brain research*, *221*(2), 564-573. https://doi.org/10.1016/j.bbr.2009.12.048

Bouillon, R. (2018). Extra-skeletal effects of vitamin D. *Vitamin D in Clinical Medicine*, *50*, 72-88. https://doi.org/10.1159/000486072

Burne, T. H., McGrath, J. J., Eyles, D. W., & Mackay-Sim, A. (2005). Behavioural characterization of vitamin D receptor knockout mice. *Behavioural Brain Research*, *157*(2), 299-308. https://doi.org/10.1016/j.bbr.2004.07.008

Butler, M. W., Burt, A., Edwards, T. L., Zuchner, S., Scott, W. K., Martin, E. R., ... & Wang, L. (2011). Vitamin D receptor gene as a candidate gene for Parkinson disease. *Annals of Human Genetics*, *75*(2), 201-210. https://doi.org/10.1111/j.1469-1809.2010.00631.x

Bytowska, Z. K., Korewo-Labelle, D., Berezka, P., Kowalski, K., Przewłócka, K., Libionka, W., Kaczor, J. J. (2023). 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. *International Journal of Molecular Sciences*, *24*(12), 10200. https://doi.org/10.3390/ijms241210200

Carthy, E. P., Yamashita, W., Hsu, A., & Ooi, B. S. (1989). 1, 25-Dihydroxyvitamin D3 and rat vascular smooth muscle cell growth. *Hypertension*, *13*(6_pt_2), 954-959. https://doi.org/10.1161/01.HYP.13.6.954

Corti, O., Lesage, S., & Brice, A. (2011). What genetics tells us about the causes and mechanisms of Parkinson's disease. *Physiological reviews*. *91*(4), 1161-1218. https://doi.org/10.1152/physrev.00022.2010

DeLuca, G. C., Li, G., & Ramagopalan, S. (2011). Parkinson disease and vitamin D: an interplay between genes and the environment?. *Archives of neurology*, *68*(12), 1615-1616. https://doi.org/10.1001/archneurol.2011.1078

Ding, H., Dhima, K., Lockhart, K. C., Locascio, J. J., Hoesing, A. N., Duong, K., ... & Scherzer, C. R. (2013). Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study. *Neurology*, *81*(17), 1531-1537. https://doi.org/10.1212/WNL.0b013e3182a95818

Di Somma, C., Scarano, E., Barrea, L., Zhukouskaya, V. V., Savastano, S., Mele, C., ... & Marzullo, P. (2017). Vitamin D and neurological diseases: an endocrine view. *International journal of molecular sciences*, *18*(11), 2482. https://doi.org/10.3390/ijms18112482

Duval, G. T., Brangier, A., Barré, J., Launay, C. P., Beauchet, O., & Annweiler, C. (2015). Vitamin D deficiency and incident onset of orthostatic hypotension in older adults: preliminary results from the'MERE'study. *Journal of the American Geriatrics Society*, *63*(6), 1245-1247.

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & McGrath, J. J. (2005). Distribution of the vitamin D receptor and 1α-hydroxylase in human brain. *Journal of chemical neuroanatomy*, *29*(1), 21-30. https://doi.org/10.1016/j.jchemneu.2004.08.006

Evatt, M. L., DeLong, M. R., Khazai, N., Rosen, A., Triche, S., & Tangpricha, V. (2008). Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Archives of neurology*, *65*(10), 1348-1352. https://doi.org/10.1001/archneur.65.10.1348

Evatt, M. L., DeLong, M. R., Kumari, M., Auinger, P., McDermott, M. P., Tangpricha, V., & Parkinson Study Group DATATOP Investigators. (2011). High prevalence of hypovitaminosis D status in patients with early Parkinson disease. *Archives of neurology*, *68*(3), 314-319. https://doi.org/10.1001/archneurol.2011.30

Fullard, M. E., Xie, S. X., Marek, K., Stern, M., Jennings, D., Siderowf, A., ... & Chen-Plotkin, A. S. (2017). Vitamin D in the Parkinson associated risk syndrome (PARS) study. *Movement Disorders*, *32*(11), 1636-1640. https://doi.org/10.1002/mds.27127

Fullard, M. E., Duda, J. E. (2020). A review of the relationship between vitamin D and Parkinson disease symptoms. *Frontiers in neurology*, *11*, 529840. https://doi.org/10.3389/fneur.2020.00454

Garcion, E., Wion-Barbot, N., Montero-Menei, C. N., Berger, F., & Wion, D. (2002). New clues about vitamin D functions in the nervous system. *Trends in Endocrinology & Metabolism*, *13*(3), 100-105. https://doi.org/10.1016/S1043-2760(01)00547-1

Gao, H., Wei, X., Liao, J., Wang, R., Xu, J., Liu, X., ... & Wang, Q. (2015). Lower bone mineral density in patients with Parkinson's disease: a cross-sectional study from Chinese Mainland. *Frontiers in aging neuroscience*, *7*, 203. https://doi.org/10.3389/fnagi.2015.00203

Gao, J., Teng, J., Liu, Z., Cai, M., & Xie, A. (2020). Association between vitamin D receptor polymorphisms and susceptibility to Parkinson's disease: an updated meta-analysis. *Neuroscience Letters*, *720*, 134778. https://doi.org/10.1016/j.neulet.2020.134778

Gatto, N. M., Paul, K. C., Sinsheimer, J. S., Bronstein, J. M., Bordelon, Y., Rausch, R., & Ritz, B. (2016). Vitamin D receptor gene polymorphisms and cognitive decline in Parkinson's disease. *Journal of the Neurological Sciences*, *370*, 100-106. https://doi.org/10.1016/j.jns.2016.09.013

Giovannucci, E., Liu, Y., Hollis, B. W., & Rimm, E. B. (2008). 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Archives of internal medicine*, *168*(11), 1174-1180. https://doi.org/10.1001/archinte.168.11.1174

Habibi, A. H., Anamoradi, A., Shahidi, G. A., Razmeh, S., Alizadeh, E., & Kokhedan, K. M. (2018). Treatment of Levodopainduced dyskinesia with Vitamin D: A Randomized, double-blind, placebo-controlled trial. *Neurology International*, *10*(3), 7737. https://doi.org/10.4081/ni.2018.7737

Han, X., Xue, L., Li, Y., Chen, B., & Xie, A. (2012). Vitamin D receptor gene polymorphism and its association with Parkinson's disease in Chinese Han population. *Neuroscience Letters*, *525*(1), 29-33. https://doi.org/10.1016/j.neulet.2012.07.033

Hiller, A. L., Murchison, C. F., Lobb, B. M., O'Connor, S., O'Connor, M., & Quinn, J. F. (2018). A randomized, controlled pilot study of the effects of vitamin D supplementation on balance in Parkinson's disease: Does age matter?. *PloS one*, *13*(9), e0203637. https://doi.org/10.1371/journal.pone.0203637

Hirsch, L., Jette, N., Frolkis, A., Steeves, T., & Pringsheim, T. (2016). The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology*, *46*(4), 292-300. https://doi.org/10.1159/000445751

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., ... & Weaver, C. M. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology & metabolism*, *96*(7), 1911-1930. https://doi.org/10.1210/jc.2011-0385

Jang, W., Park, J., Kim, J. S., Youn, J., Oh, E., Kwon, K. Y., ... & Kim, H. T. (2015). Vitamin D deficiency in Parkinson's disease patients with orthostatic hypotension. *Acta*

*Neurologica Scandinavica*, *132*(4), 242-250. https://doi.org/10.1111/ane.12390

Jankovic, J., & Tan, E. K. (2020). Parkinson's disease: etiopathogenesis and treatment. *Journal of Neurology, Neurosurgery & Psychiatry*, *91*(8), 795-808. https://doi.org/10.1136/jnnp-2019-322338

Kang, S. Y., Park, S., Oh, E., Park, J., Youn, J., Kim, J. S., ... & Jang, W. (2016). Vitamin D receptor polymorphisms and Parkinson's disease in a Korean population: revisited. *Neuroscience Letters*, *628*, 230-235. https://doi.org/10.1016/j.neulet.2016.06.041

Kempker, J. A., Tangpricha, V., Ziegler, T. R., & Martin, G. S. (2012). Vitamin D in sepsis: from basic science to clinical impact. *Critical Care*, *16*, 1-6. https://doi.org/10.1186/cc11252

Kenborg, L., Lassen, C. F., Ritz, B., Schernhammer, E. S., Hansen, J., Gatto, N. M., & Olsen, J. H. (2011). Outdoor work and risk for Parkinson's disease: a population-based case–control study. *Occupational and environmental medicine*, *68*(4), 273-278. https://doi.org/10.1136/oem.2010.057448

Kilkkinen, A., Knekt, P., Heliövaara, M., Rissanen, H., Marniemi, J., Hakulinen, T., & Aromaa, A. (2008). Vitamin D status and the risk of lung cancer: a cohort study in Finland. *Cancer Epidemiology Biomarkers & Prevention*, *17*(11), 3274-3278. https://doi.org/10.1158/1055-9965.EPI-08-0199

Kim, J. S., Kim, Y. I., Song, C., Yoon, I., Park, J. W., Choi, Y. B., ... & Lee, K. S. (2005). Association of vitamin D receptor gene polymorphism and Parkinson's disease in Koreans. *Journal of Korean medical science*, *20*(3), 495-498. https://doi.org/10.3346/jkms.2005.20.3.495

Kim, J. E., Oh, E., Park, J., Youn, J., Kim, J. S., & Jang, W. (2018). Serum 25-hydroxyvitamin D3 level may be associated with olfactory dysfunction in de novo Parkinson's disease. *Journal of Clinical Neuroscience*, *57*, 131-135. https://doi.org/10.1016/j.jocn.2018.08.003

Knekt, P., Laaksonen, M., Mattila, C., Härkänen, T., Marniemi, J., Heliövaara, M., ... & Reunanen, A. (2008). Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiology*, *19*(5), 666-671. https://doi.org/10.1097/EDE.0b013e318176b8ad

Knekt, P., Kilkkinen, A., Rissanen, H., Marniemi, J., Sääksjärvi, K., & Heliövaara, M. (2010). Serum vitamin D and the risk of Parkinson disease. *Archives of neurology*, *67*(7), 808-811. https://doi.org/10.1001/archneurol.2010.120

Koduah, P., Paul, F., & Dörr, J. M. (2017). Vitamin D in the prevention, prediction and treatment of neurodegenerative and neuroinflammatory diseases. *Epma Journal*, *8*(4), 313-325. https://doi.org/10.1007/s13167-017-0120-8

Kravietz, A., Kab, S., Wald, L., Dugravot, A., Singh-Manoux, A., Moisan, F., & Elbaz, A. (2017). Association of UV radiation with Parkinson disease incidence: A nationwide French ecologic study. *Environmental research*, *154*, 50-56. https://doi.org/10.1016/j.envres.2016.12.008

Kwon, E., Gallagher, L. G., Nielsen, S. S., Franklin, G. M., Littell, C. T., Longstreth Jr, W. T., ... & Checkoway, H. (2013). Parkinson's disease and history of outdoor occupation. *Parkinsonism & related disorders*, *19*(12), 1164-1166. https://doi.org/10.1016/j.parkreldis.2013.08.014

Kwon, K. Y., Jo, K. D., Lee, M. K., Oh, M., Kim, E. N., Park, J., ... & Jang, W. (2016). Low serum vitamin D levels may contribute to gastric dysmotility in de novo Parkinson's disease. *Neurodegenerative Diseases*, *16*(3-4), 199-205. https://doi.org/10.1159/000441917

Landel, V., Stephan, D., Cui, X., Eyles, D., & Feron, F. (2018). Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. *The Journal of steroid biochemistry and molecular biology*, *177*, 129-134. https://doi.org/10.1016/j.jsbmb.2017.09.008

Lang, Y., Gong, D., & Fan, Y. (2015). Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis. *Pharmacoepidemiology and drug safety*, *24*(6), 559-566. https://doi.org/10.1002/pds.3781

Langa, F., & Leibrockc, K. M. C. B. (2019). Brain function and neuropsychiatric disease. *Neurosignals*, *27*, 40-49. https://doi.org/10.33594/000000182

Lang, F., Ma, K., Leibrock, C. B., Salker, M. S., & Singh, Y. (2020). The Putative Role of 1, 25 (OH) 2 D 3 in the Association of Milk Consumption and Parkinson's Disease. *Neuro-signals*, *28*(1), 14-24. https://doi.org/10.33594/000000321

Liang, Q., Cai, C., Duan, D., Hu, X., Hua, W., Jiang, P., ... & Gao, Z. (2018). Postnatal vitamin D intake modulates hippocampal learning and memory in adult mice. *Frontiers in neuroscience*, *12*, 141. https://doi.org/10.3389/fnins.2018.00141

Llewellyn, D. J., Lang, I. A., Langa, K. M., Muniz-Terrera, G., Phillips, C. L., Cherubini, A., ... & Melzer, D. (2010). Vitamin D and risk of cognitive decline in elderly persons. Archives of internal medicine, 170(13), 1135-1141.

Littlejohns, T. J., Henley, W. E., Lang, I. A., Annweiler, C., Beauchet, O., Chaves, P. H., ... & Llewellyn, D. J. (2014). Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*, *83*(10), 920-928. https://doi.org/10.1212/WNL.0000000000000755

Lv, L., Tan, X., Peng, X., Bai, R., Xiao, Q., Zou, T., Wang, C. (2020). The relationships of vitamin D, vitamin D receptor gene polymorphisms, and vitamin D supplementation with Parkinson's disease. *Translational neurodegeneration*, *9*, 1-13. https://doi.org/10.1186/s40035-020-00213-2

Lubomski, M., Davis, R. L., & Sue, C. M. (2020). Gastrointestinal dysfunction in Parkinson's disease. *Journal of neurology*, *267*, 1377-1388. https://doi.org/10.1007/s00415-020-09723-5

Metta, V., Sanchez, T. C., & Padmakumar, C. (2017). Osteoporosis: a hidden nonmotor face of Parkinson's disease. *International review of neurobiology*, *134*, 877-890. https://doi.org/10.1016/bs.irn.2017.05.034

McCullough, P. J., Lehrer, D. S., & Amend, J. (2019). Daily oral dosing of vitamin D3 using 5000 TO 50,000 international units a day in long-term hospitalized patients: Insights from a seven year experience. *The Journal of steroid biochemistry and molecular biology*, *189*, 228-239. https://doi.org/10.1016/j.jsbmb.2018.12.010

Moghaddasi, M., Mamarabadi, M., & Aghaii, M. (2013). Serum 25-hydroxyvitamin D3 concentration in Iranian patients with Parkinson's disease. *Iranian journal of neurology*, *12*(2), 56.

Newmark, H. L., & Newmark, J. (2007). Vitamin D and Parkinson's disease—a hypothesis. *Movement disorders*, *22*(4), 461-468. https://doi.org/10.1002/mds.21317

Ometto, F., Stubbs, B., Annweiler, C., Duval, G. T., Jang, W., Kim, H. T., ... & Veronese, N. (2016). Hypovitaminosis D and orthostatic hypotension: a systematic review and meta-analysis. *Journal of hypertension*, *34*(6), 1036-1043. https://doi.org/10.1097/HJH.0000000000000907

Park, S. B., Chung, C. K., Lee, J. Y., Lee, J. Y., & Kim, J. (2019). Risk factors for vertebral, hip, and femoral fractures among patients with Parkinson's disease: A 5-year follow-

up in Korea. *Journal of the American Medical Directors Association*, *20*(5), 617-623. https://doi.org/10.1016/j.jamda.2018.08.014

Pertile, R. A., Cui, X., & Eyles, D. W. (2016). Vitamin D signaling and the differentiation of developing dopamine systems. *Neuroscience*, *333*, 193-203. https://doi.org/10.1016/j.neuroscience.2016.07.020

Peterson, A. L., Mancini, M., & Horak, F. B. (2013). The relationship between balance control and vitamin D in Parkinson's disease—a pilot study. *Movement Disorders*, *28*(8), 1133-1137. https://doi.org/10.1002/mds.25405

Pignolo, A., Mastrilli, S., Davì, C., Arnao, V., Aridon, P., dos Santos Mendes, F. A., D'Amelio, M. (2022). Vitamin D and Parkinson's disease. *Nutrients*, *14*(6), 1220. https://doi.org/10.3390/nu14061220

Plantone, D., Primiano, G., Manco, C., Locci, S., Servidei, S., & De Stefano, N. (2022). Vitamin D in neurological diseases. *International Journal of Molecular Sciences*, *24*(1), 87. https://doi.org/10.3390/ijms24010087

Plum, L. A., & DeLuca, H. F. (2010). Vitamin D, disease and therapeutic opportunities. *Nature reviews Drug discovery*, *9*(12), 941-955. https://doi.org/10.1038/nrd3318

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., ... & Lang, A. E. (2017). Parkinson disease. *Nature reviews Disease primers*, *3*(1), 1-21. https://doi.org/10.1038/nrdp.2017.13

Rcom-H'cheo-Gauthier, A. N., Meedeniya, A. C., & Pountney, D. L. (2017). Calcipotriol inhibits α-synuclein aggregation in SH-SY 5Y neuroblastoma cells by a Calbindin-D28k-dependent mechanism. *Journal of Neurochemistry*, *141*(2), 263-274. https://doi.org/10.1111/jnc.13971

Reid, I. R. (2020). A broader strategy for osteoporosis interventions. *Nature Reviews Endocrinology*, *16*(6), 333-339. https://doi.org/10.1038/s41574-020-0339-7

Rimmelzwaan, L. M., van Schoor, N. M., Lips, P., Berendse, H. W., & Eekhoff, E. M. (2016). Systematic review of the relationship between vitamin D and Parkinson's disease. *Journal of Parkinson's disease*, *6*(1), 29-37. https://doi.org/10.3233/JPD-150615

Salamon, H., Bruiners, N., Lakehal, K., Shi, L., Ravi, J., Yamaguchi, K. D., ... & Gennaro, M. L. (2014). Cutting edge: vitamin D regulates lipid metabolism in Mycobacterium tuberculosis infection. *The Journal of Immunology*, *193*(1), 30-34. https://doi.org/10.4049/jimmunol.1400736

Sanchez, B., Lopez-Martin, E., Segura, C., Labandeira-Garcia, J. L., & Perez-Fernandez, R. (2002). 1, 25-Dihydroxyvitamin D3 increases striatal GDNF mRNA and protein expression in adult rats. *Molecular Brain Research*, *108*(1-2), 143-146. https://doi.org/10.1016/S0169-328X(02)00545-4

Sato, Y., Kikuyama, M., & Oizumi, K. (1997). High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease [RETRACTED]. *Neurology*, *49*(5), 1273-1278. https://doi.org/10.1212/WNL.49.5.1273

Sato, Y., Iwamoto, J., & Honda, Y. (2011). Vitamin D deficiency-induced vertebral fractures may cause stooped posture in Parkinson disease. *American Journal of Physical Medicine & Rehabilitation*, *90*(4), 281-286. https://doi.org/10.1097/PHM.0b013e3182063a42

Scherzer, C. R., Eklund, A. C., Morse, L. J., Liao, Z., Locascio, J. J., Fefer, D., ... & Gullans, S. R. (2007). Molecular markers of early Parkinson's disease based on gene expression in blood. *Proceedings of the National Academy of Sciences*, *104*(3), 955-960. https://doi.org/10.1073/pnas.0610204104

Shrestha, S., Lutsey, P. L., Alonso, A., Huang, X., Mosley Jr, T. H., & Chen, H. (2016). S erum 25-hydroxyvitamin D concentrations in Mid-adulthood and P arkinson's disease risk. *Movement Disorders*, *31*(7), 972-978. https://doi.org/10.1002/mds.26573

Shirvani, A., Kalajian, T. A., Song, A., Allen, R., Charoenngam, N., Lewanczuk, R., & Holick, M. F. (2020). Variable genomic and metabolomic responses to varying doses of vitamin D supplementation. *Anticancer Research*, *40*(1), 535-543. https://doi.org/10.21873/anticanres.13982

Sleeman, I., Aspray, T., Lawson, R., Coleman, S., Duncan, G., Khoo, T. K., ... & Yarnall, A. (2017). The role of vitamin D in disease progression in early Parkinson's disease. *Journal of Parkinson's disease*, *7*(4), 669-675. https://doi.org/10.3233/JPD-171122

Sosa Henríquez, M., & Gómez de Tejada Romero, M. J. (2020). Cholecalciferol or calcifediol in the management of vitamin D deficiency. *Nutrients*, *12*(6), 1617. https://doi.org/10.3390/nu12061617

Suzuki, M., Yoshioka, M., Hashimoto, M., Murakami, M., Kawasaki, K., Noya, M., ... & Urashima, M. (2012). 25-hydroxyvitamin D, vitamin D receptor gene polymorphisms, and severity of Parkinson's disease. *Movement Disorders*, *27*(2), 264-271. https://doi.org/10.1002/mds.24016

Suzuki, M., Yoshioka, M., Hashimoto, M., Murakami, M., Noya, M., Takahashi, D., & Urashima, M. (2013). Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. *The American journal of clinical nutrition*, *97*(5), 1004-1013. https://doi.org/10.3945/ajcn.112.051664

Tanaka, K., Miyake, Y., Fukushima, W., Kiyohara, C., Sasaki, S., Tsuboi, Y., ... & Fukuoka Kinki Parkinson's Disease Study Group. (2017). Vitamin D receptor gene polymorphisms, smoking, and risk of sporadic Parkinson's disease in Japan. *Neuroscience Letters*, *643*, 97-102. https://doi.org/10.1016/j.neulet.2017.02.037

Tolosa, E., Garrido, A., Scholz, S. W., & Poewe, W. (2021). Challenges in the diagnosis of Parkinson's disease. *The Lancet Neurology*, *20*(5), 385-397. https://doi.org/10.1016/S1474-4422(21)00030-2

Topal, K., Paker, N., Bugdayci, D., Ozer, F., & Tekdos, D. (2010, May). Bone mineral density and vitamin D status with idiopathic Parkinson's disease. In *Osteoporosis International* (Vol. 21, pp. 141-142). Springer.

Wang, J. Y., Wu, J. N., Cherng, T. L., Hoffer, B. J., Chen, H. H., Borlongan, C. V., & Wang, Y. (2001). Vitamin D3 attenuates 6-hydroxydopamine-induced neurotoxicity in rats. *Brain research*, *904*(1), 67-75. https://doi.org/10.1016/S0006-8993(01)02450-7

Wang, L., Evatt, M. L., Maldonado, L. G., Perry, W. R., Ritchie, J. C., Beecham, G. W., ... & Scott, W. K. (2015). Vitamin D from different sources is inversely associated with Parkinson disease. *Movement disorders*, *30*(4), 560-566. https://doi.org/10.1002/mds.26117

Wrzosek, M., Łukaszkiewicz, J., Wrzosek, M., Jakubczyk, A., Matsumoto, H., Piątkiewicz, P., ... & Nowicka, G. (2013). Vitamin D and the central nervous system. *Pharmacological reports*, *65*(2), 271-278. https://doi.org/10.1016/s1734-1140(13)71003-x

Yilmazer, S., Dursun, E., & Gezen-Ak, D. (2013). Vitamin D inquiry in hippocampal neurons: consequences of vitamin D-VDR pathway disruption on calcium channel and the vitamin D requirement. Neurology Science. 34, 1453–1458. https://doi.org/10.1007/s10072-012-1268-6

Zhou, Z., Zhou, R., Zhang, Z., & Li, K. (2019). The association between vitamin D status, vitamin D supplementation, sunlight exposure, and Parkinson's disease: a systematic review and meta-analysis. *Medical science monitor: International medical journal of experimental and clinical research*, *25*, 666-674. https://doi.org/10.12659/MSM.912840