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Vitamin D and depression in older adults: lessons learned from observational and clinical studies

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Abstract

Depression is a mental disorder triggered by the interaction of social, psychological and biological factors that have an important impact on an individual's life. Despite being a well-studied disease with several established forms of treatment, its prevalence is increasing, especially among older adults. New forms of treatment and prevention are encouraged, and some researchers have been discussing the effects of vitamin D (VitD) on depression; however, the exact mechanism by which VitD exerts its effects is not yet conclusive. In this study, we aimed to discuss the possible mechanisms underlying the association between VitD and depression in older adults. Therefore, we conducted a systematic search of databases for indexed articles published until 30 April 2021. The primary focus was on both observational studies documenting the association between VitD and depression/depressive symptoms, and clinical trials documenting the effects of VitD supplementation on depression/depressive symptoms, especially in older adults. Based on pre-clinical, clinical and observational studies, it is suggested that the maintenance of adequate VitD concentrations is an important issue, especially in older adults, which are a risk population for both VitD deficiency and depression. Nevertheless, it is necessary to carry out more studies using longitudinal approaches in low- and middle-income countries to develop a strong source of evidence to formulate guidelines and interventions.

Keywords: **Depression: 25-hydroxycholecalciferol: Vitamin D: Review: Observational studies: Clinical trials: Older adults: Ageing**

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Introduction

Depression is a mental disorder that causes clinically significant suffering and/or impairment in social, professional, economic and other important areas of an individual's life, and is the main cause of suicide in more severe cases[1–4]. The prevalence of depression in 2015 was estimated to be 4·4 % globally, with a higher prevalence among those between 55 and 77 years of age. Women appear to be more affected (7·5 %) than men (5·5 %)[5]. Among those over 60 years old, depression occurs in 7·0 % of the general older population[6]. According to the Global Burden of Disease, Injuries, and Risk Factors – GBD survey, depression is among the top three causes of disability[7]. There has been a significant increase in the global burden of disease in years lived with disabilities (YLDs) in the past 20 years due to depressive disorders. In 1990, depression occupied the fourth position, moving to the third in 2007 with an increase of 33·4 %, and remained in the third position between 2007 and 2017; however, it has increased by 14·3 %[8]. Moreover, as many people with depressive symptoms are undiagnosed, the prevalence of depressive disorders is probably higher than reported[4].

Mental disorders are among the main problems in public health, and mood disorders are diseases with higher costs to health systems worldwide[2,3,9,10]. According to the Mental Health Atlas of the World Health Organization (WHO), low- and middle-income countries spend less than $1 per year per capita in the treatment and prevention of mental disorders, compared with an average of >$80 in high-income countries, owing to socioeconomic issues[11]. Therefore, there is an urgent need to identify the modifiable risk factors associated with the aetiology of depression, helping with the treatment and prevention of this disorder, especially in low- and middle-income countries[12,13].

Depression is a complex disease triggered by the interaction between social, psychological and biological factors[4,14]. In older adults, depression can be triggered by a series of factors such as limitations in daily activities, cognition, mobility and

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social changes such as retirement, social isolation and relocation to long-term institutions[15]. Among the biological factors, genetic predisposition, neurotransmitter and neuroendocrine system imbalance, functional and structural brain anatomy, and cognition are the most studied mechanisms[16,17]. Recently, nutritional factors have shown an important relationship with the evolution, prevention and treatment of mental disorders[18]. The association between VitD and depression has emerged in scientific scenarios, and this nutrient seems to be relevant in the prevention of depressive symptom development. However, the mechanism by which VitD exerts its effects remains unclear[19,20].

Many clinical trials have been conducted to investigate the potential therapeutic effect of VitD on patients with depression, but the results remain inconclusive due to methodological issues[21]. VitD is a fat-soluble vitamin that is present in two forms: VitD2 (ergosterol) and VitD3 (cholecalciferol). It is obtained from diet, supplementation and sun exposure[22,23]. VitD has a well-established role in mineral bone metabolism, but its effects are not restricted to bone health and are also important in maintaining many biological processes, such as the regulation of gene expression, cell proliferation and differentiation, and immune system regulation[24–26]. In the central nervous system (CNS), the presence of nuclear (vitamin D receptor, VDR) and membrane (protein disulphide isomerase family A member 3, PDIA3) receptors for VitD and some enzymes (cytochrome P450 family enzymes CYP27a1, CYP27b1 and CYP24a1) responsible for converting its active form has raised the hypothesis that VitD may be involved in the pathophysiology of depression[27–31].

Low serum VitD concentrations [25-hydroxycholecalciferol, 25(OH)D] have been considered a public health problem worldwide, especially in the elderly[32]. For older adults, the prevalence of 25(OH)D deficiency (<50 nmol/l or <20 ng/ml) was 36 % in the United States[33], 19 % in Canada[34], 36 % in China(35 and 4–89 % in European countries[32]. In low- and middle-income countries, the prevalence was approximately 41 % for older adults in Brazil[36], 91 % in India[37] and 46 % in Guatemala[38]. However, different cut-off points have been suggested, and a single value to define VitD deficiency or insufficiency has been debated[39]. Moreover, the establishment of desirable serum VitD concentrations is based on bone health to maintain mineral and skeletal homoeostasis[39,40].

It is important to mention that VitD levels via skin synthesis and intestinal absorption are influenced by various factors such as skin pigmentation, latitude, season, age, obesity and inflammatory bowel diseases, among others[41–43]. Due to reduced sun exposure, decreased skin synthesis and dietary intake, and intestinal malabsorption, the elderly are among the top risk groups for VitD deficiency[41,44]. They also present significant complications related to low VitD concentrations (<20 ng/ml), such as the risk of fractures due to fragility and bone loss, which contribute to age-related muscle weakness and sarcopenia[28,43,45,46]. In addition, VitD concentrations <20 ng/ml have been associated with an increased risk of all-cause mortality[47].

In this review, we aimed to update the role of VitD in depression, discussing the metabolism of VitD, its mechanism of action in the brain and the main evidence of pre-clinical, clinical and observational studies, especially those involving older adults, a population risk for both conditions, in an attempt to highlight the potential preventive and therapeutic effects of this nutrient. Also, we aimed to suggest future directions for new studies. To this end, we conducted a systematic search for articles published until 30 April 30 2021. The databases used were PubMed, Scopus, Embase, Science Direct and Web of Science (details are presented in the supplementary material).

Vitamin D: synthesis and metabolism

The synthesis of VitD (Fig. 1) by epidermal epithelial cells begins when the exposure to ultraviolet B radiation (UVB, 290–315 nm) promotes the non-enzymatic transformation of 7-dehydrocholesterol (7-DHC or pro-VitD) in pre-VitD3[48,49]. A photolytic break forms a secosteroid molecule, which then undergoes an isomerisation reaction induced by heat to transform it into VitD3 (or cholecalciferol), a process that takes about 8 h[48–50]. Keratinocytes are the main cells of the epidermis that have the enzymatic machinery to metabolise VitD in its active form and express the vitamin D receptor (VDR)[22,51]. In contrast, the synthesis of the active form of VitD from either food or supplementation begins with incorporation into micelles and absorption through the enterocyte membrane by apical membrane transporters or by passive diffusion[52]. A fraction of VitD is incorporated into the chylomicrons, which are transported to the lymphatic system and then to the venous system by vitamin D binding protein (DBP)[50]. The other fraction is incorporated into adipose tissue and skeletal muscles[53].

Both VitD2 and VitD3 are transported in the blood by DBP and must undergo activation through two consecutive enzymatic hydroxylation reactions in the liver and kidneys. In the liver, VitD2 and VitD3 are converted into 25-hydroxyvitamin D (calcidiol or 25(OH)D) by the action of 25-hydroxylases (cytochrome P450 enzymes group, CYP2R1 or CYP27A1)[54–56]. The 25(OH)D coupled with DBP is transported to various tissues with cells containing the enzyme 1-α-hydroxylase (CYP27B1), as in the kidney, where it converts 25(OH)D to 1,25-dihydroxyvitamin D (calcitriol or $1,25(OH)_2D3$), the active form of VitD[54–56].

The conversion of $1,25(OH)_2D3$ in the kidney is regulated by several factors, including circulating concentrations of parathyroid hormone (PTH) in the parathyroid glands, serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23) in the bone and its self-regulation. $1,25(OH)_2D3$ decreases its own synthesis by negative feedback; it decreases the secretion of parathyroid hormone and increases the expression of 24-hydroxylase[57]. This self-regulation by the expression of 24-hydroxylase is found in most tissues and is essential for the catabolism of 25(OH)D and $1,25(OH)_2D3$[58].

The biological effects of $1,25(OH)_2D3$ are largely mediated by VDR, which is expressed in almost all human cells[59,60]. The VDR belongs to a subfamily of nuclear receptors, which contains two sites for ligand binding called the genomic pocket (VDR-GP), which binds in a bowl-like configuration for gene transcription, and the alternative pocket (VDR-AP), which connects in a planar-like configuration for quick responses[60]. When VDR-GP binds to $1,25(OH)_2D3$, it enters the cell nucleus and

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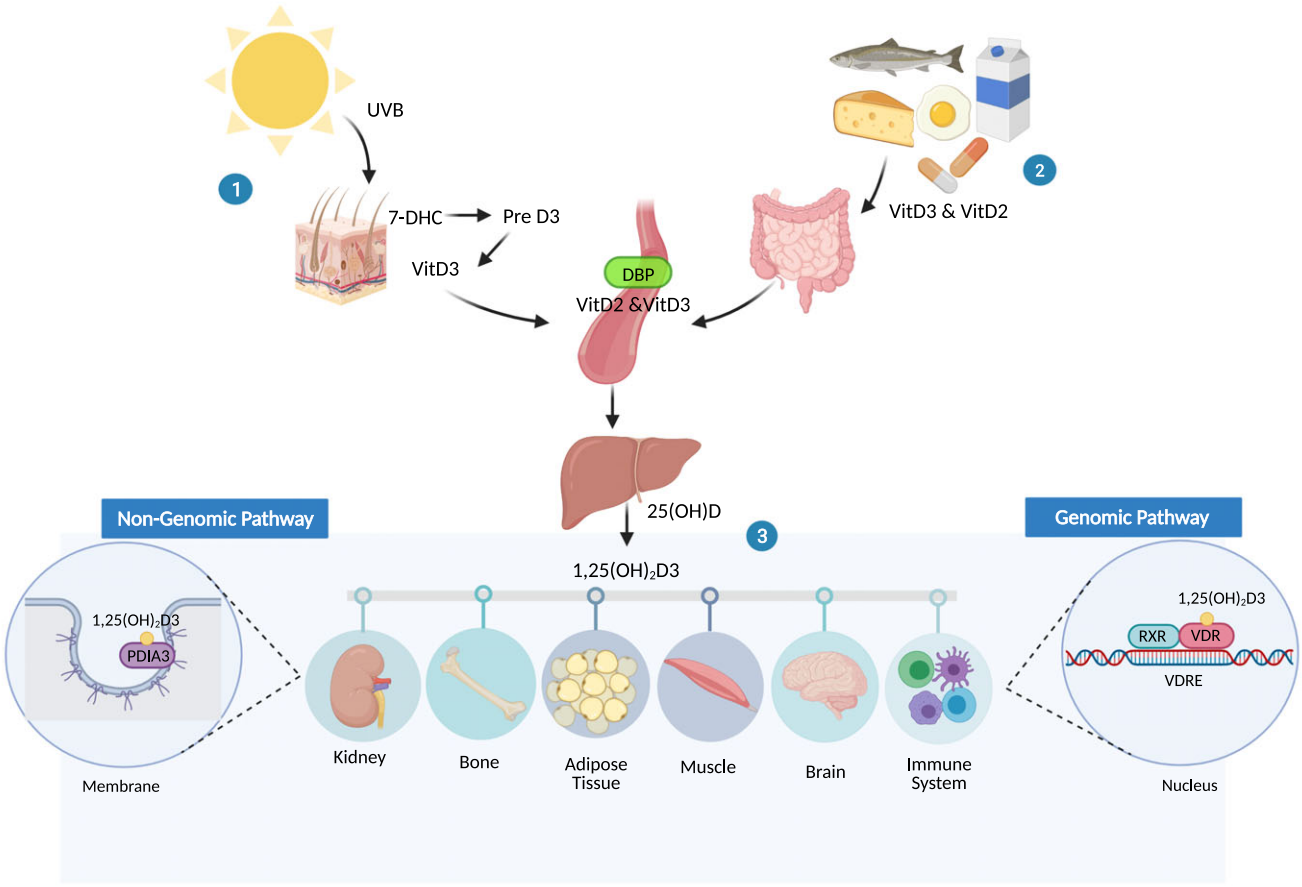

Fig. 1. Vitamin D synthesis, metabolism and target tissue actions. (1) The synthesis of VitD from sunlight initiates in the skin when 7-DHC is converted in pre-VitD3 and then VitD3 [25(OH)D3 or cholecalciferol] and is carried by DBP through blood circulation. (2) The VitD from dietary intake (VitD2/ergocalciferol and D3/cholecalciferol) is absorbed in the small intestine and packed into chylomicrons to reach the systemic circulation. Both VitD3 and VitD2 are also transported through blood circulation by DBP to the liver, where they are converted to 25-hydroxyvitamin D [calcidiol or 25(OH)D] by the action of 25-hydroxylases. (3) 25(OH)D coupled to DBP is transported to the target organs such as kidney, bones, adipose tissue, muscle and brain, and cells such as in the immune system containing the enzyme 1-α-hydroxylase, which convert 25(OH)D to 1,25-dihydroxyvitamin D [calcitriol or $1,25(OH)_2D3$], the active form of VitD. VitD act through both genomic and non-genomic pathways. In the genomic pathway, VitD active form enters the nucleus linked to the VDR where it binds to the RXR and then binds to the VDRE, resulting in modulation of target gene expression. In the non-genomic pathway, the VitD active form binds to the PDIA3 and starts signalling cascades, including the activation of phospholipase A2 activating protein (PLAA), phospholipase A2 (PLA2), phospholipase C (PLC) and opening Ca^{2+} channels that results in the activation of secondary messengers. This figure was made using BioRender (license: YN235V4QZA)

binds to the retinoid X receptor (RXR). This complex then binds to the vitamin D responsive element (VDRE) in the promoter regions of the target genes by recruiting co-activator or co-repressor complexes that regulate the transcription of genes either positively or negatively[53,60]. The other suggested VitD receptor is PDIA3, also known as endoplasmic reticulum protein (ERp60, ERp57 and Grp58) or VitD membrane-associated rapid-response steroid-binding protein (1,25-MARRS)[61]. PDIA3 is present in caveolae (lipid rafts) and is linked to the rapid responses of $1,25(OH)_2D3$ by activating signalling cascades, where it physically interacts with downstream mediators[61,62], including the activation of phospholipase A2 activating protein (PLAA), phospholipase A2 (PLA2), phospholipase C (PLC) and opening Ca^{2+} channels that result in the activation of secondary messengers[63]. PDIA3 is involved in the function of immune and musculoskeletal systems as well as mammary gland growth and development, and participates in the intestinal uptake of calcium and phosphate[63]. PDIA3 also mediates the effect of $1,25(OH)_2D3$ on the regulation of osteoblasts and chondrocytes[64].

Vitamin D: mechanism of action in the brain

The first evidence of the role of VitD in brain function began with autoradiographic findings of the presence of VDR in the brain tissue of laboratory animals[65]. VDR is found in neurons and glial cells in most regions of the brain, including the cortex (temporal, frontal, parietal and cingulate); deep grey matter (thalamus, basal ganglia, hypothalamus, hippocampus and amygdala); cerebellum, nuclei of the brain stem and substantia nigra (an area abundant in dopaminergic neurons); spinal cord; and ventricular system[66]. In addition, an alternative mechanism was observed in post-mortem human brain tissue samples. It was

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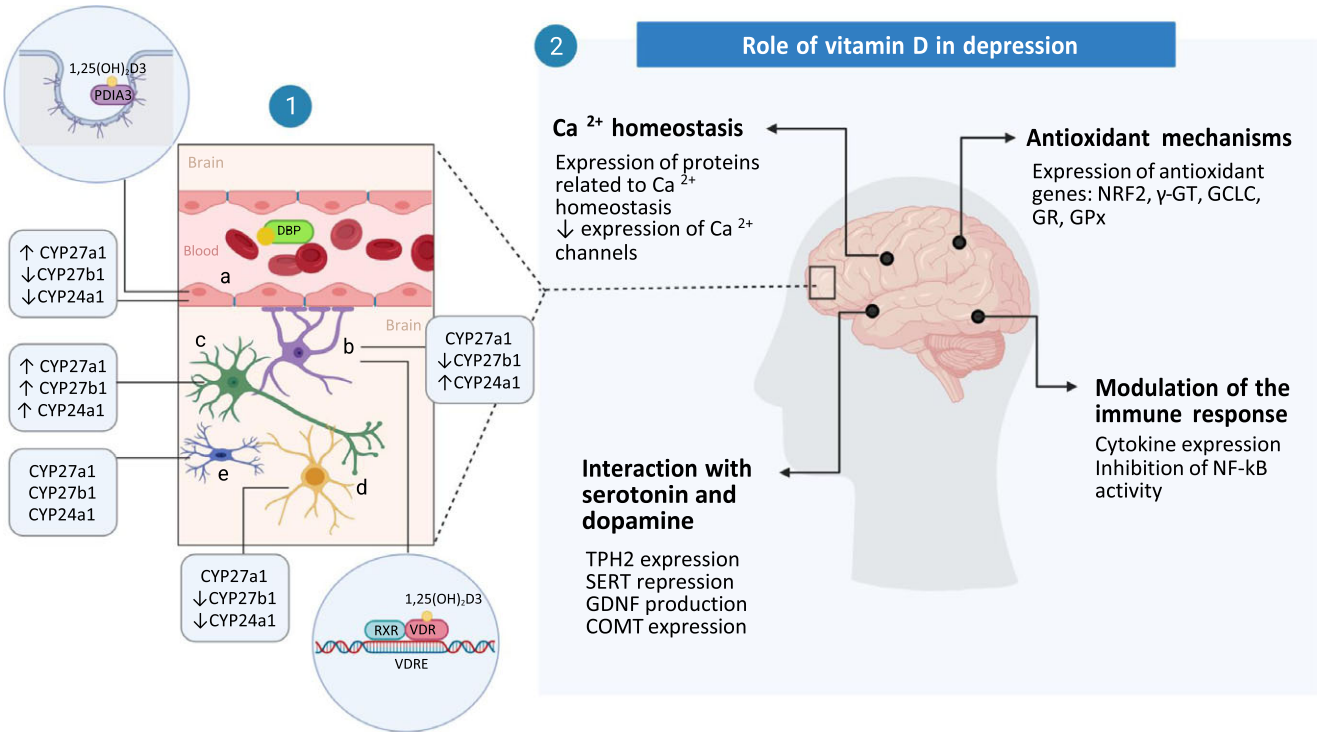

Fig. 2. The role of vitamin D in depression. (1) In the brain, both active and inactive VitD is carried through blood circulation binding to DBP and can permeate the blood–brain barrier. All brain cells (endothelial cells (A), astrocytes (B), neurons (C), oligodendrocytes (D) and microglia (E)) have the machinery to transform VitD. VitD is turned into 25(OH)D by CYP27a1 in endothelial cells and neurons, and it is metabolized to $1,25(OH)_2D3$ by CYP27b1 in neurons or microglia. All brain cells can express VDR, but it is highly expressed by astrocytes. When it enters the cell, $1,25(OH)_2D3$ can bind to VDR, and then to the RXR in the nucleus. The complex VDR–RXR binds to the VDRE and initiates gene transcription or can be inactivated when in excess by CYP24a1. All brain cells can express PDIA3, but it is highly expressed in endothelial cells where $1,25(OH)_2D3$ can bind it, and PDIA3 physically interacts with downstream mediators to initiate rapid responses and induce signalling cascades. (**2**) VitD regulates the expression of many processes related to depression. It maintains Ca^{2+} homoeostasis, activates the expression of many antioxidant genes, regulates the formation of serotonin and dopamine, and reduces inflammation by reducing the expression of inflammatory cytokines. TPH2, tryptophan hydroxylase 2; SERT, serotonin reuptake transporter; GDNF, glial cell-derived neurotrophic factor; COMT, catechol-*O*-methyltransferase; NRF2, nuclear factor-erythroid-2-related factor 2; γ-GT, γ-glutamyl transpeptidase; GCLC, glutamate-cysteine ligase; GR, glutathione reductase; GPx, glutathione peroxidase; NF-κB, nuclear factor-kappa B. This figure was made using BioRender (license: FB235V4MBD)

demonstrated that $1,25(OH)_2D3$ can be activated locally through the expression of the enzyme 1α-hydroxylase, which is classically expressed in the kidney and is responsible for catalysing the conversion of 25(OH)D into $1,25(OH)_2D3$, showing that both forms (VitD and 25(OH)D) can pass through the blood–brain barrier[67,68].

It has been proposed that within the neurovascular unit, the machinery for conversion of both VitD forms involves the cytochrome P450 family enzymes CYP27a1, CYP27b1 and CYP24a1 which are expressed in neurons, and CYP27a1 which is expressed in all neural cell types and is highly expressed in endothelial cells[31]. The active form of VitD triggers genomic actions associated with VDR or non-genomic actions related to PDIA3, which is expressed in small amounts in extra-cerebral tissues such as the liver and kidney. On the other hand, PDIA3 is highly expressed in the brain and appears to be the main brain receptor for VitD in neural tissue (Fig. 2).

VitD is known as a neurosteroid because of its important role in the CNS in processes related to cell differentiation, production and release of neurotrophic factors, synthesis of neurotransmitters, intracellular calcium homoeostasis, influence on the redox state, function and metabolism of neuronal cells and cognition (Fig. 2)[29,69]. The active form of VitD stimulates the synthesis of nerve growth factor (NGF) which acts on cholinergic neurons, and positively regulates the synthesis of neurotrophic factors derived from the glial cell line (GDNF), which acts on dopaminergic neurons, and neurotrophin 3 (NT-3), which is key to neuronal promotion, survival, differentiation and plasticity[66]. Due to its involvement in several brain functions, observational studies in humans subjects have linked low serum VitD concentrations with some brain disorders such as schizophrenia, failure in synaptic plasticity related to learning and memory, cognitive decline and mood disorders[27,29,70].

Vitamin D and depressive symptoms: evidence from pre-clinical and clinical studies

Pre-clinical studies

Depression is a multifactorial disease, which makes it challenging to identify the precise biological mechanisms that link VitD to depression. However, some hypotheses have been proposed based on the experimental research data. Calcium homoeostasis, glutamatergic/GABAergic and monoaminergic system

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modulation, influence on circadian rhythm, anti-inflammatory properties and redox balance modulation are among the most investigated mechanisms.

The homoeostasis of intracellular and extracellular calcium (Ca^{2+}) is an important factor responsible for driving the onset of depression, which links VitD with the development of depressive symptoms because of its interaction with excitatory synapses[27]. The imbalance in intracellular Ca^{2+} is caused by an elevation in glutamate and by activation of the phosphoinositide signalling pathway that generates inositol triphosphate (IP3) which releases Ca^{2+} from internal stores[27,71,72]. The elevation of Ca^{2+} can affect both ionotropic (*N*-methyl-D-aspartate) and metabotropic (mGluR) receptors[73]. This change in neural activity drives excitatory neurons and is responsible for the decline in the activity and the number of GABAergic inhibitory neurons, as well as modulation of the activity of other neurotransmitter systems, including the inhibition of the serotonergic system and the release of norepinephrine and dopamine[74]. However, $1,25(OH)_2D$ can act in this pathway by inducing the expression of proteins related to the maintenance of Ca^{2+} homoeostasis, such as calbindin, parvalbumin, Na^+/Ca^{2+} exchanger (NCX1) and pump Ca^{2+}-ATPase (PMCA). It also regulates Ca^{2+} concentrations by reducing the expression of the CaV1·2 calcium channel[27,75].

Concerning other neurotransmitter systems, it has been proposed that depression could result from a deficiency of serotonin (5-HT) in the synaptic cleft[76–78]. 5-HT is derived from the essential amino acid tryptophan. To produce 5-HT in the brain, tryptophan must first be transported across the blood–brain barrier and then metabolised by the enzyme tryptophan hydroxylase 2 (TPH2). VDR activation by $1,25(OH)_2D3$ can induce the expression of the TPH2 gene in serotonergic neurons[79,80]. In addition, $1,25(OH)_2D3$ could act in the repression of the serotonin reuptake transporter (SERT or 5-HTT), and the mitochondrial enzyme responsible for 5-HT catabolism, monoamine oxidase-A, resulting in potentiated serotonergic transmission[81].

In the dopaminergic system, VitD is involved in the maturation of dopaminergic neurons. VDR is present in the nucleus of positive neurons for tyrosine hydroxylase (TH), and can stimulate glial cell line-derived neurotrophic factor (GDNF) in dopaminergic neurons[82]. VDR also modulates metabolism through the genomic regulation of catechol-*O*-methyl transferase (COMT) expression, a key enzyme involved in dopamine turnover[82,83]. In addition, in a rat model of depression, VitD appears to produce therapeutic effects comparable to antidepressant drugs such as fluoxetine, improving anhedonia-like symptoms, probably by regulating the effect of dopamine-related actions on the nucleus accumbens[84].

From a chronobiological perspective, a growing body of evidence suggests that VitD participates in the mechanisms orchestrating the circadian rhythm, suggesting that hypovitaminosis D might play a role in sleep disorders[85]. VitD has been associated with the regulation and maintenance of optimal sleep[86]. The mediating role of VitD in the circadian rhythm is supported by studies demonstrating the association between lower concentrations of VitD and sleep[87,88]. In addition, a circadian oscillation pattern can be equally observed in plasma $1,25(OH)_2D3$ concentration and DBP, which corroborates the association between VitD and the circadian system[87].

Because sunlight partially regulates the synthesis of VitD and is the main zeitgeber in the regulation of the circadian rhythm, it is conceivable that VitD might contribute to the transduction of signs regulating it[89,90]. The suprachiasmatic nucleus (SCN) is a hypothalamic structure found directly above the optic chiasm, and its strategic anatomical position allows prompt central response to sunlight stimuli through the retina. SCN is the main oscillator, which accounts for the control of circadian rhythms by regulating several body functions during a 24-h cycle, sending peripheral signals through neurohumoral mechanisms[91]. For this reason, the authors postulated that VitD is likely involved in the regulation of the sleep/wake rhythm[90].

Melatonin is a neurohormone involved in the regulation of mammalian circadian rhythms and sleep. It is released in response to darkness and is synthesised by the pineal gland[92]. Its synthesis occurs from the metabolism of serotonin[93], which, in turn, is also regulated by VitD. Along with VDR, $1,25(OH)_2D$ triggers the central expression of *TPH2*, the gene responsible for encoding the enzyme catalysing the conversion of tryptophan into 5-hydroxytryptophan, which is then metabolised into serotonin and subsequently as melatonin[67,79]. Therefore, it is thought that the combination of deficits in serum VitD levels and circadian rhythm impairments could induce a robust increase in depressive symptoms and/or act as an interplay variable in the pathophysiology of major depressive disorder.

Regarding anti-inflammatory pathways, it is also relevant to point out that both melatonin and VitD mediate the mitochondrial function in homoeostasis, such as down-regulating mechanistic target of rapamycin (mTOR), inducible nitric oxide synthase (iNOS) and nuclear factor kappa B (NF-κB) pathways, and up-regulating Sirtuin-1 (SIRT-1) and adenosine monophosphate-activated protein kinase (AMPK) pathways, which are critical mechanisms to avoid anomalous inflammatory responses related to oxidative stress and apoptosis[94].

Pro-inflammatory cytokines, interleukins and other inflammatory markers, such as prostaglandins and acute-phase C-reactive protein, have been implicated to play role in the pathophysiology of depression[95–97]. Inflammation leads to increased blood–brain barrier permeability, allowing easier entry of inflammatory molecules into the CNS[98]. At a cellular level, it has been observed that tumour necrosis factor α (TNF-α) can induce glutamate release by activated microglia *in vitro*, leading to excitotoxic damage to neurons[99]. Some cytokines can directly increase enzymatic activity for converting tryptophan to kynurenine and decreasing the production of serotonin[100–102]. Considering that macrophages, dendritic cells and activated B and T lymphocytes express 1α-hydroxylase and VDR, VitD could act by modulating the immune response and regulating cytokine expression[97,103]. Moreover, it was demonstrated that the activity of NF-κB, a transcription factor involved in the synthesis of pro-inflammatory cytokines, was inhibited by $1,25(OH)_2D3$, which helps to maintain the balance of T-helper (Th) cells, inhibiting the production of Th1 and Th17 cytokines and increasing Th2 cytokine synthesis[75].

Interestingly, Boontanrart *et al.* (2016) reported that activated microglia were associated with an increased expression of VitD

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receptor and Cyp27b1, which encodes the 1α-hydroxylase enzyme for converting 25(OH)D into its active form, thereby enhancing their responsiveness to 25(OH)D. Moreover, activated microglia exposed to 25(OH)D had reduced expression of pro-inflammatory cytokines, interleukin (IL)-6, IL-12 and TNF-α, and increased expression of IL-10. The decrease in pro-inflammatory cytokines was dependent on IL-10 induction of suppressor of cytokine signalling-3 (SOCS3). Therefore, 25(OH)D increases the expression of IL-10, creating a feedback loop via SOCS3 which reduces the pro-inflammatory immune response by activated microglia and probably protects the CNS from damage[104]. In agreement with these findings, Lee *et al.* (2020) showed that VitD signalling in neurons elicits an anti-inflammatory state in microglia. Moreover, the partial deletion of VDR in neurons during early life exacerbates CNS autoimmunity in adult mice. Therefore, by changing the immune response of microglia, VitD may be an interesting mechanism for avoiding a prolonged inflammatory state in the CNS[105].

In addition, VDR activation stimulates the expression of many antioxidant genes, such as the nuclear factor erythroid-2 (NRF2), γ-glutamyl transpeptidase (γ-GT), glutamate-cysteine ligase (GCLC), glutathione reductase (GR) and glutathione peroxidase (GPx)[27]. VitD negatively regulates the expression of iNOS in monocyte-derived cells, and increases the activity of γ-GT, an important enzyme in the glutathione pathway[106,107]. Reinforcing the modulation of oxidative stress as a mechanism associated with the antidepressant-like effect of VitD, repeated administration of this compound (2·5, 7·5 and 25 μg/kg for 7 d) prevented depressive-like behavior and brain oxidative stress induced by chronic administration of corticosterone (21 d) in male and female mice[108,109]. It has been demonstrated that reactive oxygen species (ROS) trigger a variety of molecular cascades that increase the permeability of the blood–brain barrier, allowing inflammatory cytokines to enter the CNS[110]. Moreover, it has been well established that inflammation and oxidative stress, which mutually amplify each other, play an important role in the pathophysiology of depression and can be a target for therapeutic strategies[111].

Clinical studies

Nineteen randomised clinical trials using VitD supplementation for depressive symptoms in adults were published up to 2020 (Table 1). Nine studies were double-blinded, and twelve included individuals aged >65 years. Most of the studies were conducted in high-income countries (13/19). Seven studies were conducted with community-dwelling, healthy volunteers or individuals with no specification, and three studies only with VitD-deficient individuals[112–114]. Six included only individuals with the diagnosis of depression, and two with individuals with VitD deficiency and diagnosed depression[115,116]. Considering only the studies that included individuals with a diagnosis of depression (with or without VitD deficiency), 4/8 presented improvement in depressive symptoms after VitD supplementation.

Seven (7/19) studies reported an improvement in depressive symptoms after VitD supplementation, eleven reported no improvement and one study lacked the power to assess due to sampling size[123]. Considering the studies that observed depressive symptom improvement, five of seven were conducted with individuals with depression, and one of these (1/7) reported individuals with concomitant depression and VitD deficiency. VitD doses ranged from 600 to 300 000 IU, and the majority (6/7) used VitD doses above the dietary reference intake (DRI) (> 4000 IU/d). VitD doses of 600–4000 IU were used on a daily basis; 20 000–50 000 IU were used weekly; and the effect of a single dose of 150 000–300 000 IU was evaluated.

Compared with the seven studies with positive results, the eleven studies that did not report improvements tended to use lower VitD doses (<4000 IU) and longer periods (from 6 months to 5 years of supplementation). Of the eleven negative studies, only four used higher doses: Sanders *et al.* (2011) used a single dose of 500 000 IU in the winter for 3–5 years; Dean *et al.* (2011) used 5000 IU/d for 6 weeks; Kjægaard *et al.* (2012) used 20 000 IU/week for 6 months; and Gugger *et al.* (2019) used 24 000 IU or 60 000 IU for 12 months[113,120,128,129]. The age range was higher in the studies that did not observe any improvement in depressive symptoms (individuals >70 years).

Two meta-analyses have shown controversial results in clinical trials with VitD supplementation. Spedding *et al.* (2014) showed that VitD supplementation (daily doses of ≥800 IU) could have an effect comparable to that of antidepressants in depressive symptoms[21]. Due to the methodological variability of the studies, the other meta-analysis conducted by Gowda *et al.* (2015) showed results that did not support this hypothesis[131]. In addition, a 5-year follow-up study found no potential effect of VitD on the incidence of depression[117]. Comparing the findings of the published meta-analysis with the studies searched in the present review, we observed that studies that did not observe improvements in depressive symptoms were conducted with older people with no diagnosis of depression, with lower VitD doses and for longer periods of follow-up. On the contrary, studies with positive results were conducted with younger populations with a diagnosis of depression and higher VitD doses for short periods of follow-up.

Key points of pre-clinical and clinical studies

Pre-clinical studies have pointed to the potential and possible effect of vitD on depression. However, despite a considerable number of clinical studies, it has not yet been possible to prove whether VitD can prevent or be used as an adjuvant treatment in depression. The data remain controversial. In addition, it is not possible yet to define which doses/amount of vitamin D would be most appropriate for depression.

Vitamin D and depressive symptoms: evidence from observational studies

Table 2 summarises the information from forty-four observational studies that investigated the relationship between VitD and depression/depressive symptoms in both adults and older adults since 2006.

From over 15 years of research published, we observed that most studies included a mixed population with adults and older

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Table 1 Vitamin D supplementation and depression/depressive symptoms: clinical trials with older adults

Authors (country)	Classification	Age range	Vitamin D supplementation	Depressive symptoms assessment	25(OH)D assessment	Main results
Okereke *et al.*, 2020[117] (USA)	RCT $n = 9181$ VitD, $n = 9172$ placebo	≥50	2000 IU/d of cholecalciferol for 5·3 years (interquartile range, 5·0–5·7 years)	PHQ-8	NA	No improvement.
Zhu *et al.*, 2020[112] (China)	RCT $n = 62$ VitD, $n = 44$ placebo	18–60 years (individuals with serum 25(OH) D levels ≤75 nmol/l)	1600 mg VD daily supplementation for 6 months	MINI HAMD-17 RSAS RPAS HAMA-14	Radioimmunoassay	No improvement.
Vellekkatt *et al.*, 2020[115] (India)	Double-blind RCT $n = 23$ VitD, $n = 23$ placebo	18–65 years (diagnosed with depression and individuals with serum 25(OH) D levels <20 mg/ml)	One single 300,000 IU of cholecalciferol (Arachitol) injection (intervention) intramuscularly. Follow-up in 12 weeks	DSM-5 MINI HDRS-17	Automated chemiluminescent immunoassay	Improvement in supplemented group. Depression score at baseline 3·0 (2·0–4·0); 12 weeks 5·0 (3·2–8·0); $p = 0·001$ for VitD group. No effects on placebo group.
Alghamdi *et al.*, 2020[118] (Saudi Arabia)	RCT $n = 49$ SOC + VitD, $n = 13$ SOC	18–65 years (diagnosed with MDD)	50,000 IU of vitamin D (calciferol) for 3 months	DSM-5 BDI	Automated chemiluminescent immunoassay	Mildly depressed men → no significant changes in BDI scores after VitD supplementation. Moderate, severe and extreme depression showed significant decreases in BDI scores after vitamin D supplementation ($p < 0·05$). Women → moderate, severe and extreme depression had lower BDI scores after VitD supplementation ($p < 0·05$). Moderate depression changed from 28 ± 1·2 to 23 ± 1·4 ($p < 0·05$); severe depression improved from 36 ± 0·9 to 27 ± 3·6 ($p < 0·05$); extreme depression improved from 44 ± 1·5 to 34 ± 2·5 ($p < 0·05$).
Zajac *et al.*, 2020[119] (Australia)	Double-blinded, four-armed parallel-group RCT $n = 91$ VitD; $n = 94$ standard mushroom $n = 147$ VitD2-enriched mushroom $n = 92$ placebo	60–90 years	Daily 600 IU of either D2 or D3 for 24 weeks	PANAS DASS−21 General Happiness Scale	High-throughput liquid chromatography tandem mass spectroscopy (LC-MSMS)	No improvement.
De Ing *et al.*, 2019[116] (the	RCT $n = 77$ VitD, $n = 78$ placebo	60–80 years (clinically relevant depressive symptoms, ≥1 functional limitation, and	1200 IU/d vitamin D3 for 12 months	CES-D	Liquid chromatography followed by tandem mass spectrometry method	No improvement.

Table 1 (*Continued*)

Authors (country)	Classification	Age range	Vitamin D supplementation	Depressive symptoms assessment	25(OH)D assessment	Main results
Netherlands)		serum 25(OH)D concentrations of 15–50/70 nmol/l (depending on the season))				
Gugger *et al.*, 2019[120] (Switzerland)	RCT $n = 67$ 24 000 IU VitD3; $n = 67$ 60 000 IU VitD3; $n = 66$ 24 000 IU VitD3 plus 300 μg calcifediol	≥70 years (community-dwelling adult with a prior fall event)	Monthly 24 000 IU vitamin D as the conventional treatment; monthly 60 000 IU vitamin D3 as the high doses; monthly 24 000 IU vitamin D3 plus 300 μg calcifediol during 12 months	GDS-15	NA	No improvement.
Alavi *et al.*, 2019[121] (Iran)	RCT $n = 39$ VitD, $n = 39$ placebo	>60 years (outpatients with depression)	50 000 IU of VitD3 weekly for 8 weeks	GDS-15	Chemiluminescent immunoassay	The depression score decreased from 9·25 (DP 2·4) to 7·48 (DP 1·66) in vitamin D group ($p = 0·0001$), while there was a non-significant increase in the depression score in the placebo group. Vitamin D could explain the 81·8 % of the depression score after intervention.
Hansen *et al.*, 2019[122] (Denmark)	RCT $n = 26$ VitD, $n = 19$ placebo	18–65 years (individuals diagnosed with mild to severe depression)	2800 IU/d VitD3 for 12 weeks	HAMD-17 MDI	High-performance liquid chromatography followed by tandem mass spectrometry	No improvement.
Aucoin *et al.*, 2018[123] (Canada)	Double-blinded RCT, $n = 125$	18–75 years (patients with non-remitted depression)	Weekly (bolus) doses of 28 000 IU of vitamin D3 or placebo for 8 weeks	BDI-II FCPS	NA	The sample size of enrolled participants (7/125, 5·6 %) lacks power to conduct a full assessment of findings.
Yalamanchili & Gallagher, 2018[124] (USA)	Double-blind, multi-doses RCT, $n = 273$ (VIDOS study)	57–90 years (older Caucasian and African-American women)	Low (400–800 IU), medium (1600–3200 IU) and high (4000–4800 IU) doses of VitD3 for 1 year	GDS-LF30	Radioimmunoassay	No improvement.
Mozaffari-Khosravi *et al.*, 2013[125] (Iran)	RCT $n = 39$ G300, $n = 36$ G150, $n = 34$ no injection	20–60 years (depression symptoms for at least 2 weeks)	A single dose of 300 000 or 150 000 IU of vitamin D intramuscularly, and the NTG (non-test group) received no injection for 3 months	BDI-II	ELISA	Significant difference in mean of Beck Depression Inventory II test score between G300 and NTG after treatment (17·4 ± 9·8 *v.* 24·3 ± 6·2 BDI score, respectively; $P = 0·001$).
Khoraminya *et al.*, 2013[126] (Iran)	Double-blind, placebo-controlled RCT. $n = 20$ fluoxetine, $n = 20$ fluoxetine+VitD3	18–65 years (outpatients, diagnosis of major depressive disorder)	1500 IU of VitD3 + one capsule (20 mg) fluoxetine or VitD3 placebo plus 20 mg fluoxetine for 8 weeks	HDRS-24 BDI-21	ELISA	Analysis of covariance for depression severity adjusted for baseline values at weeks 2, 4, 6 and 8 showed that the vitamin D–fluoxetine combination was significantly better than fluoxetine alone from the fourth week of treatment.
Kjægaard *et al.*,	RCT $n = 120$ VitD3, n	30–75 years (participants with low serum 25(OH)D)	20 000 IU VitD3 per week or placebo for 6 months	BDI-II HADS-14	Liquid chromatography followed by tandem mass spectrometry method	No improvement.

Table 1 (*Continued*)

Authors (country)	Classification	Age range	Vitamin D supplementation	Depressive symptoms assessment	25(OH)D assessment	Main results
2012[113] (Norway)	= 110 placebo (Tromsø study)			The Seasonal Pattern Assessment Scale MADRS		
Bertone-Johnson *et al.*, 2012[127] (USA)	Double-blinded, placebo-controlled RCT *n* = 18 176 VitD3 + Ca, *n* = 18 106 placebo (Women's Health Initiative study)	50–79 years (postmenopausal women)	400 IU daily supplementation with of VitD3 + 1000 mg of elemental calcium for 1 and 3 years	Burnam scale	Not described	No improvement.
Dean *et al.*, 2011[128] (Australia)	Parallel-arm, double-blind, placebo-controlled RCT *n* = 63 VitD3, *n* = 65 placebo.	≥18 years (healthy volunteers)	5000 IU/d VitD3 or placebo for 6 weeks	BDI	High-performance liquid chromatography followed by tandem mass spectrometry	No improvement.
Sanders *et al.*, 2011[129] (Australia)	Double-blind, placebo-controlled RCT *n* = 1001 VitD3, *n* = 1011 placebo	≥70 years (community-dwelling women)	500 000 IU VitD3 orally or placebo every autumn/winter for 3–5 consecutive years	General Health Questionnaire, the 12-item Short Form Health Survey, the Patient Global Impression–Improvement scale and the WHO Well-Being Index 500	Radioimmunoassay	No improvement.
Jorde *et al.*, 2008[130] (Norway)	Double-blinded, placebo-controlled RCT *n* = 116, 40 000 IU (DD); *n* = 106 20 000 IU (DP); *n* = 112, placebo (PP)	21–70 years (BMI 28·0–47·0 kg/m^2)	20 000 (DP) or 40 000 IU (DD) VitD3 per week *v.* placebo (PP) for 1 year	BDI	Immunometry (electrochemiluminescence)	There was a significant reduction (improvement) in the total BDI and the BDI subscale scores in the DD group, a significant reduction in the BDI 14–21 subscale score in the DP group, but no significant change in the PP group.
Vieth *et al.*, 2004[114] (Canada)	Single-blinded RT Study I, *n* = 64. Study II, *n* = 66	Study I: 39–67 years (if summer 2001 25(OH)D <61 nmol/l). Study II: 39–67 years (if summer 2001 25(OH)D was <51 nmol/l)	Study I: 4000 IU/d or 600 IU/d December 2001 and February 2002. Study II: 4000 IU/d or 600 IU/d December 2002 and February 2003	Brief questionnaire, based on conventional depression-screening tools, and incorporating questions relating to energy and mood	Radioimmunoassay	Study I: Wellbeing score improved more for the 100 μg/d group than for the lower-dosed group (one-tail Mann–Whitney $p = 0{\cdot}036$). Study II: Wellbeing scores improved with both doses of vitamin D (two-tail $p < 0{\cdot}001$)

NA, not assessed; RCT, randomised controlled trial; VitD, vitamin D; PHQ-8, patient health questionnaire depression scale; MINI, mini-international neuropsychiatric interview; HAMD-17, Hamilton depression rating scale-17; RSAS, revised social anhedonia scale; RPAS, revised physical anhedonia scale; HAMA-14, Hamilton anxiety rating scale-14; HDRS-17, Hamilton depression rating scale-17; BDI, Beck depression inventory; PANAS, positive and negative affect schedule; DASS-21, 21-item depression; CES-D, Center for Epidemiological Studies Depression; GDS-15, 15-item geriatric depression scale; MDI, major depression inventory; BDI-II, Beck depression inventory-II; FCPS, Fawcett–Clark pleasure capacity scale; GDS-LF30, long form 30-item GDS; HDRS-24, Hamilton depression rating scale-24; BDI-21, Beck depression inventory-21; HADS-14, hospital anxiety and depression scale; MADRS, Montgomery–sberg depression rating scale.

Table 2. Vitamin D supplementation and depression/depressive symptoms: observational studies with older adults

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Di Gessa *et al.*, 2021[132] (England)	≥50	Cohort population-based longitudinal analysis ($n = 3365$)	CES-D-8	Sufficient ≥50 nmol/l Insufficient <50 nmol/l	Those with insufficient levels were more likely to report elevated depressive symptoms at follow-up (OR 1·39, 95 CI 1·00–1·93)
Mulugeta *et al.*, 2021[133] (United Kingdom)	37–73	Cohort (Biobank) Cross-sectional analysis ($n = 307\,618$)	Hospital diagnosed depression and self-reported depression	Quartiles: >75 nmol/l ≥50 and <75 nmol/l ≥25 and <50 nmol/l <25 nmol/l	In observational analysis, the odds of depression decreased with higher 25(OH)D concentrations (adjusted OR per 50 % increase 0·95; 95 % CI 0·94, 0·96)
Van Den Berg *et al.*, 2021[134] (Netherlands)	≥60	Cohort of depressed people Longitudinal analysis ($n = 232$)	DSM-IV CIDI IDS-SR	Mean nmol/l	An increase in vitamin D of 0·22 nmol/l was associated with a decrease with each point of the IDS score (SE 0·11, $p = 0·049$, ES 0·12)
Ceolin *et al.*, 2020[135] (Brazil)	≥60	Cohort population-based cross-sectional analysis ($n = 557$)	GDS-15	Sufficiency ≥30 ng/ml Insufficiency 21–29 ng/ml Deficiency ≤20 ng/ml	Found a significant association between 25(OH)D and depressive symptoms with OR 2·27; 95 % CI 1·05, 4·94 for deficient compared with sufficient
Sahasrabudhe *et al.*, 2020[136] (United States)	45–75	Cohort of Puerto Rican people Cross-sectional and longitudinal analysis ($n = 1434$)	CES-D	Sufficient ≥20 ng/ml Insufficient 12 to >20 ng/ml Deficient <12 ng/ml	No association between serum 25(OH)D and depressive symptomatology
Köhnke *et al.*, 2020[137] (Germany)	35–65	Cohort cross-sectional analysis ($n = 1169$)	IDS DSM-IV HAM-D-17	Adequate ≥20 ng/ml Insufficient 12 to <20 ng/ml Deficient <12 ng/ml	Compared with non-depressed, patients with MDD had OR 1·91 (95 % CI 1·39, 2·62) to insufficiency and OR 2·10 (95 % CI 1·46, 3·02) to deficiency in 25(OH)D
Granlund *et al.*, 2020[138] (Sweden)	25–64	Population-based cross-sectional analysis ($n = 195$)	HAD	< 25 nmol/l (<10 ng/ml) <50 nmol/l(<20 ng/ml) ≥ 50 nmol/l (≥20 ng/ml)	No association between depression and 25(OH)D
Rhee *et al.*, 2020[139] (South Korea)	19–76	Nationally representative population Cross-sectional analysis ($n = 1736$)	PHQ-9	Mean ng/ml	The association between serum 25(OH)D concentrations and total PHQ-9 scores was statistically significant (IRR 0·74; 95 % CI 0·59, 0·93) only in men
Bigman, 2020[140] (United States)	20–80	Nationally representative population Cross-sectional analysis ($n = 11\,471$)	PHQ-9	25(OH)D3: Sufficiency <30 ng/ml Inadequacy 20–30 ng/ml Deficiency <20 ng/ml 25(OH)D2: Presence >0·6 ng/ml Nearly no presence ≤0·6 ng/ml	Participants with deficiency in 25(OH)D3 presented OR 1·19 (95 % CI 1·03, 1·37) to report symptoms of depression compared with sufficient Participants with presence of 25(OH)D2 presented OR 1·35 (95 % CI 1·18, 1·55) to report symptoms of depression compared with nearly no presence
Ronaldson *et al.*, 2020[141] (United Kingdom)	40–69	Cohort (Biobank)	PHQ-2	Sufficient >50 nmol/l Insufficient 20–50 nmol/l	Participants with no depression at baseline with insufficiency (OR 1·14; 95 % CI 1·07, 1·22) and with deficiency (OR 1·24; 95 % CI 1·13, 1·36) were more likely to develop new-onset depression at follow-up
		Cross-sectional and longitudinal analysis ($n = 139\,128$)	PHQ-9	Deficient <20 nmol/l	Similar prospective associations were reported for those with depression at baseline with insufficiency (OR 1·11; 95 % CI 1·00, 1·23) and deficiency (OR 1·30; 95 % CI 1·13, 1·50)
Briggs *et al.*, 2019[142] (Ireland)	≥50	Cohort population-based longitudinal analysis ($n = 3965$)	CES-D-20 CES-D-8 CES-D-20	Sufficiency >50 nmol/l Insufficiency 30–50 nmol/l Deficiency <30 nmol/l Mean nmol/l	Only participants with vitamin D deficiency had a significantly higher likelihood of incident depression (OR 1·56; 95 % CI 1·07, 2·26)

Table 2. (*Continued*)

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Elstgeest *et al.*, 2018[143] (Netherlands)	Two cohorts: 55–65 65–88	Cohort population-based longitudinal analysis ($n = 173$, $n = 450$)			The older cohort → change in 25(OH)D was not associated with the change in CES-D score (follow-up, 13 years)
				Tertiles	The younger cohort → increase in 25(OH)D was associated with a decrease in CES-D score (adjusted *B* per 10 nmol/l 25(OH)D increase: −0·62 (95 % CI −1·17, −0·07) (follow-up, 6 years))
De koning *et al.*, 2018[143] (the Netherlands)	Two cohorts: 55–65	Cohort population-based	CES-D-20	Sufficiency 50–75 nmol/l and >75 nmol/l	On cross-sectional analysis, no associations were significant
		Cross-sectional and longitudinal analysis ($n = 1282$, $n = 737$)		Insufficiency 30–50 nmol/l	On longitudinal analysis, women in the older cohort with baseline 25(OH)D concentrations up to 75 nmol/l presented 17–24 % more depressive symptoms (follow-up 6 years) compared with those with >75 nmol/l
	>65			Deficiency <30 nmol/l	In men and in the younger-old cohort, no significant associations were observed.
Sherchand *et al.*, 2018[144] (Nepal)	≥18	Cross-sectional analysis ($n = 300$)	BDI	Sufficient 30–100 ng/ml Insufficient 20–29 ng/ml Deficient <20 ng/ml	The association presented OR 3·5 (95 % CI 1·1, 11·9) for clinically significant depression in the vitamin D deficient category when compared with sufficient
Vidgren *et al.*, 2018)[145] (Finland)	53–73	Cohort population-based Cross-sectional analysis ($n = 1602$)	DSM-III	Tertiles: T1 8·5–34·4 nmol/l T2 34·4–50·7 nmol/l T3 50·8–112·8 nmol/l	Lower serum 25(OH)D concentrations (<34·4 nmol/l) were associated with depression (OR 1·64; 95 % CI 1·03, 2·59) compared with those with higher serum 25(OH)D concentrations
Yao *et al.*, 2018[146] (China)	≥100	Cohort of centenarian people Cross-sectional analysis ($n = 940$)	GDS-15	Deficiency < 20 ng/ml or 50 nmol/l	Vitamin D deficiency was an independent risk factor for depression (OR 1·47; 95 % CI 1·08, 2·00). The multivariate analysis showed OR 1·73 (95 % CI 1·10, 2·72) of depressive symptoms for the lowest *v.* highest quartiles of vitamin D levels and the adjusted OR 1·10 (95 % CI 1·01, 1·19) for 5 ng/ml decrement of serum 25(OH)D levels
De Oliveira, Hirani & Biddulph, 2018[147] (England)	≥50	Cohort population-based	CES-D	Mean nmol/l	Low 25OHD presented an association with elevated depressive symptoms (OR 1·58; 95 % CI 1·20, 2·07) for the lowest quartile; for <30 nmol/l (OR 1·45; 95 % CI 1·15, 1·83); and for ≤50 nmol/l (OR 1·34; 95 % CI 1·10, 1·62)
		Cross-sectional analysis ($n = 5607$)		Quartiles (≤30; 30·01–46·00; 46·01–64·00; >64·01 nmol/l) >50 nmol/l 30–50 nmol/l <30 nmol/l ≤50 nmol/l >50 nmol/l	Women→ the lowest (OR 1·67; 95 % CI 1·20, 2·34) and second-lowest (OR 1·68; 95 % CI 1·20, 2·35) quartiles as well as those with levels <30 nmol/l (OR 1·40; 95 % CI 1·06, 1·86) and ≤50 nmol/l (OR 1·35; 95 % CI 1·07, 1·72) were more likely to report elevated depressive symptoms Men → the association only remained significant for those with <30 nmol/l (OR 1·60,; 95 % CI 1·06, 2·42)
Jovanova *et al.*, 2017[148] (Netherlands)	≥55	Cohort population-based cross-sectional and longitudinal analysis ($n = 3251$)	CES-D DSM-IV	Mean nmol/l Cut-off: <37·5 *v.* >37·5; <50 *v.* >50; <75 *v.* >75 nmol/l	Cross-sectionally → low 25(OH)D were associated with more depressive symptoms ($B = -0·27$; 95 % CI , 0·51, −0·04) A serum ≤37·5 nmol/l was associated with depressive symptoms ($B = 0·48$; 95 % CI 0·01, 0·95) compared with >37·5 nmol/l

Table 2. (*Continued*)

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
				Quartiles <28·57; 28·58–43·81; 43·82–63·21; >63·21 nmol/l	Longitudinally → low 25(OH)D were not associated with change of depressive symptoms or incident MDD
				Sufficiency (>50 nmol/l) Deficiency (<50 nmol/l)	
Collin *et al.*, 2017[149] (France)	≥40	Cohort case–control study from a randomised double-blind, placebo-controlled (vitamin D was not part of the supplementation) longitudinal analysis ($n = 1196$)	CES-D	Cut-off: <30 *v.* ≥30; <20 *v.* ≥20; <10 *v.* ≥10 ng/ml	25(OH)D above 10 ng/ml was related to a lower probability of recurrent depressive symptoms (PR 0·48; 95 % CI 0·33, 0·69)
				Based on: suboptimal status 20–29 ng/ml Insufficiency 10–19 ng/ml Deficiency <10 ng/ml	When comparing individuals with concentrations <20 *v.* ≥20 or <30 *v.* ≥30 ng/mL, no significant results were obtained
Lee *et al.*, 2017[150] (South Korea)	20–88	Population-based cross-sectional analysis ($n = 7198$)	Self-reporting	No deficiency ≥20 ng/ml Deficiency <20 ng/ml	Positive association between vitamin D deficiency and depressive symptoms (OR 1·54; 95 % CI 1·20, 1·98) was found
Shin *et al.*, 2016[151] (Japan)	20–70	Cross-sectional analysis Medical record data ($n = 52\,228$)	CES-D	Sufficiency ≥20 ng/ml Insufficiency 10–19·99 ng/ml Deficiency <10 ng/ml	The presence of depressive symptoms was significantly increased in participants with vitamin D deficiency after adjusting for potentially confounding factors (OR 1·158; 95 % CI 1·003, 1·336)
Rabenberg *et al.*, 2016[152] (Germany)	18–79	Nationwide representative population-based cross-sectional analysis ($n = 6331$)	PHQ-9	Quartiles: 9–27, 28–42, 43–59 and 60–347 nmol/l	A significant association with severity of depressive symptoms remained in summer, with 0·73 (95 % CI −1·31, −0·14; $p = 0·02$) indicating lower PHQ-9 scores in the highest *v.* lowest quartile
					In the logistic regression, the association did not remain significant in fully adjusted models
Van Den Berg *et al.*, 2016[153] (Netherlands)	≥60	Cohort of depressed people longitudinal analysis ($n = 367$)	CIDI IDS-SR	Sufficient ≥ 75 nmol/l Hypovitaminosis D 50–75 nmol/L Insufficient 25–50 nmol/l Deficient 10–25 nmol/l Severely deficient <10 nmol/l	Vitamin D had no effect on the course of depression or remission
Song *et al.*, 2016[154] (South Korea)	≥65	Cohort cross-sectional analysis ($n = 2853$)	GDS-15	≥30·0 ng/ml 20·0–29·9 ng/ml	Men → compared with those with ≥30·0 ng/ml People with 10·0–19·9 ng/mL presented OR 2·50 (95 % CI 1·20, 5·18) and those with <10·0 ng/ml presented OR 2·81 (95 % CI 1·15, 6·83) to depressive symptoms
				10·0–19·9 ng/ml <10·0 ng/ml	Women → the associations between 25(OH)D and depressive symptoms were not significant
Brouwer-Brolsma *et al.*, 2016[155] (Netherlands)	≥65	Cohort randomised, double-blind, placebo-controlled Cross-sectional analysis (baseline) ($n = 2839$)	GDS-15	Quartiles: <36·7, 36·7–53·4, 53·4–71·7 and >71·7 nmol/l	Fully adjusted models indicated a 22 % (RR 0·78; 95 % CI 0·68, 0·89), 21 % (RR 0·79; 95 % CI 0·68, 0·90) and 18 % (RR 0·82; 95 % CI 0·71, 0·95) lower score of depressive symptoms in people in the second (36·7–53·4 nmol/l), third (53·4–71·7 nmol/l) and fourth (>71·7 nmol/l) quartiles, when compared with people in the first quartile (<36·7 nmol/l)
Rocha-Lima *et al.*, 2016[156] (Brazil)	≥80	Cohort of free-living independent elderly	GDS-15	Sufficiency >30 ng/ml Insufficiency 10–30 ng/ml	Found a difference between GDS score comparing the groups: deficiency ($U = 144,50$; $z = -3,126$; $p = 0,002$) and insufficiency groups ($U = 975,50$; $z = -2,793$; $p = 0·005$) are different from sufficiency group
		Cross-sectional analysis ($n = 182$)		Deficiency <10 ng/ml	

Table 2. (*Continued*)

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Husemoen, *et al.*, 2016[157] (Denmark)	18–64	Nationwide representative Cross-sectional and longitudinal analysis ($n = 5308$)	SCL	Mean nmol/l	Low serum 25(OH)D is not associated with self-reported symptoms/diagnosis of depression
Jääskeläinen, *et al.*, 2015[158] (Finland)	30–79	Nationwide representative Population-based cross-sectional analysis ($n = 5371$)	BDI Munich-Composite International Diagnostic Interview	Deficiency <50 nmol/l Quartiles: 7–33, 34–43, 44–55 and 56–134 nmol/l	Inverse association between serum 25(OH)D concentration and depressive disorder comparing the highest and lowest quartiles (OR 0·65; 95 % CI 0·46, 0·93)
Almeida *et al.*, 2015[159] (Australia)	71–88	Cohort of men	GDS-15	Sufficient ≥50 nmol/l Mild deficiency 30–49 nmol/l	Vitamin D concentration <50 nmol/l was associated with current depression (OR 1·65; 95 % CI 1·13, 2·42) but not past or future depression
		Cross-sectional and longitudinal analysis ($n = 3105$)	PHQ-9	Moderate to severe deficiency <30 nmol/l	
Williams *et al.*, 2015[160] (United States)	70–79	Cohort cross-sectional and longitudinal analysis ($n = 2598$)	CES-D-10	Sufficiency ≥30 ng/ml	Serum 25(OH)D was not associated with CES-D scores at baseline and 1-year follow-up
				Insufficiency 20–<30 ng/ml Deficiency <20 ng/ml	Participants with <20 ng/ml were at greater risk of developing depression (HR 1·65; 95 % CI 1·23, 2·22) over 4 years of follow-up compared with those with ≥30 ng/ml
Imai *et al.*, 2015[161] (Iceland)	66–96	Cohort population-based	GDS-15	Adequate ≥50 nmol/l Inadequate 30–49·9 nmol/l Deficient <30 nmol/l	Men → deficient status were more likely to have current major depressive disorder (OR 2·51; 95 % CI 1·03, 6·13) compared with adequate
		Cross-sectional analysis ($n = 5006$)	DSM-IV		Women → associations were not significant
Józefowicz *et al.*, 2014[162] (Poland)	18–65	Cross-sectional analysis ($n = 180$)	HDRS	Recommended 30–80 ng/ml Insufficiency 21–29 ng/ml Deficiency <20 ng/ml	HDRS scores were negatively correlated with levels of vitamin D ($p < 0·02$), however, did not differ significantly between the groups of classification
Toffanello *et al.*, 2014[163] (Italy)	≥65	Cohort population-based cross-sectional and longitudinal analysis ($n = 1675$)	GDS	Sufficiency ≥75 nmol/l	Women → deficiency had higher GDS scores than those with sufficiency in mean (SE) GDS scores: 9·57 (0·37) *v.* 8·31 (0·31), respectively, $p = 0·02$
				Insufficiency ≥50 to <75 nmol/l	Men → no significance
				Deficiency <50 nmol/l	25OHD deficiency and insufficiency were not associated with a higher probability of developing depressed mood during the follow-up
Milaneschi *et al.*, 2014[164] (the Netherlands)	18–65	Cohort cross-sectional and longitudinal analysis ($n = 2386$)	DSM-IV CIDI	Mean nmol/l	Lower 25(OH)D levels were found in participants with current depression ($p = 0·001$, Cohen's $d = 0·21$), particularly in those with the most severe symptoms ($p = 0·001$, Cohen's $d = 0·44$)
			IDS		In currently depressed persons, 25(OH)D was inversely associated with symptom severity ($\beta = -0·19$, SE 0·07, $p = 0·003$) suggesting a dose–response and risk (RR 0·90; 95 % CI 0·82, 0·99) of having a depressive disorder at 2-year follow-up
Lapid *et al.*, 2013[165] (United States)	≥60	Cross-sectional analysis ($n = 1618$)	HICDA	Optimal range ≥25 ng/ml Mild to moderate deficiency 10–24 ng/ml Severe deficiency <10 ng/ml	25(OH)D was correlated with depression (OR 0·990; 95 % CI 0·983, 0·998). Those with severe vitamin D deficiency were twice as likely to have depression (OR 2·093; 95 % CI 1·092, 4·011)

Table 2. (*Continued*)

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Jaddou *et al.*, 2012[166] (Jordan)	≥25	Nationwide representative population-based cross-sectional analysis ($n = 4002$)	DASS21	Cut-off: <30 and ≥30 ng/ml Quartiles: >63·22, 42·31–63·22, 27·61–42·30 and ≤27·60 ng/ml	Depression was significantly higher in the level <30 ng/ml compared to those with ≥30 ng/ml (OR 1·38, $p = 0·00$) In the quartiles, the lowest (OR 1·48, $p = 0·00$) and the second-lowest (OR 1·24, $p = 0·03$) showed higher depression compared with the highest quartile
Chan *et al.*, 2011[167] (Hong Kong/China)	≥65	Cohort of men	GDS-15	Mean nmol/l	An inverse association was observed, with the highest (≥92 nmol/l) compared with lowest (≤ 63 nmol/l) quartile of serum 25OHD had an OR = 0·46 (95 % CI 0·22, 0·98) for depression.
		Cross-sectional and longitudinal analysis ($n = 939$)		Quartiles: ≤63, 64–76, 77–91 and ≥92 nmol/l	No association was observed between serum 25OHD and incident depression at 4 years
Lee *et al.*, 2011[168] (Italy, Belgium, Poland, Sweden, United Kingdom, Spain, Hungary, Estonia)	40–79	Cohort of men Cross-sectional analysis ($n = 3369$)	BDI-II	Mean nmol/l	A 10 nmol/l decrease in 25(OH)D was associated with an average increase of 3·2 % (95 % CI 1·1, 5·5; $p = 0·05$) in the BDI-II score
				Quartiles: >78·4, 57·0–78·4, 39·0–56·9 and <39·0	In the quartiles, the association between depression and 25(OH)D quartiles only just remained significant for the lowest *v.* highest quartile (OR 1·74; 95 % CI 1·00, 3·00)
				Sufficient ≥75 nmol/l Sub-optimum 50–74·9 nmol/l	
				Insufficient 25–49·9 nmol/l Deficient <25 nmol/l	In the categories, the deficiency (OR 1·73; 95 % CI 1·03, 2·93) and insufficiency remained significant (OR 1·80; 95 % CI 1·09, 2·98)
Milaneschi *et al.*, 2010[169] (Italy)	≥65	Cohort population-based longitudinal analysis ($n = 954$)	CES-D	Optimal levels ≥50 nmol/l	Women → the 3- and 6-year average in CES-D scores increased, respectively 2·1 (SE = 0·9; $p = 0·02$) and 2·2 (SE = 1·1; $p = 0·04$) points higher in <50 nmol/L compared to ≥50 nmol/L
				Insufficiency <50 nmol/l	Low vitamin D had significantly higher risk of developing depressive mood over the follow-up (HR 2·0; 95 % CI 1·2, 3·2) Men → the 3-year average were 1·9 (SE = 0·8; $p = 0·01$) points higher in <50 nmol/L compared with ≥50 nmol/L The risk of developing a depressed mood was not significant by HR
Stewart; Hirani, 2010[170] (England)	≥65	Population-based cross-sectional analysis ($n = 2070$)	GDS-10	Mean ng/ml Severe deficiency <10 ng/ml	Only the most severe deficiency (<10 ng/ml) remained associated with depression (OR 1·46; 95 % CI 1·02, 2·04)
				Deficiency <20 ng/ml Optimal ≥30 ng/ml	Dose–response association between 25(OH)D and depressive symptoms was shown strongly significance ($B = -1·94$; 95 % CI −2·67, −1·20)
Nanri *et al.*, 2009[171] (Japan)	21–67	Cross-sectional analysis ($n = 527$)	CES-D	Mean ng/ml Quartiles (median)	Depressive symptoms were not associated with serum 25-hydroxyvitamin D concentrations
Pan *et al.*, 2009[172] (China)	50–70	Population-based Cross-sectional analysis ($n = 3262$)	CES-D	Tertiles (mean/SD)	Depressive symptoms were not associated with serum 25-hydroxyvitamin D concentrations after adjustments
Hoogendijk *et al.*, 2008[173] (the Netherlands)	≥65	Cohort cross-sectional analysis ($n = 1282$)	CES-D Diagnostic Interview Schedule	Mean ng/ml Quartiles: ≤14·7, 14·7–20·4, 20·4–27·4 and >27·4 ng/ml	Depression severity was significantly associated with decreased serum 25(OH)D levels ($B = 8·0$; 95 % CI 15·2, 0·8; $p = 0·03$)

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Table 2. (*Continued*)

Authors (country)	Age range (years)	Classification	Depression assessment	25(OH)D Classification	Main results
Wilkins *et al.*, 2006[174] (United States)	≥60	Cross-sectional analysis ($n = 80$)	Depressive Symptoms Inventory	Sufficient ≥20 ng/ml Insufficient 10–19·9 ng/ml Deficient <10 ng/ml	Vitamin D deficiency (OR 11·69; 95 % CI 2·04, 66·86) and insufficient (OR 2·54; 95 % CI 0·63, 10·51) were more likely to have a mood disorder compared with those with sufficient vitamin D

95 % CI, 95% confidence interval; OR, odds ratio; SE, standard error; ES, effect size; IRR, incidence rate ratio; *B*, unstandardised beta; RR, relative risk; 25(OH)D, 25-hydroxycholecalciferol; 25(OH)D2, 25-hydroxyvitamin D2; 25(OH)D2, 25-hydroxyvitamin D3; DSM-IV, diagnostic and statistical manual of mental disorders; CIDI, composite international diagnostic interview; IDS-SR, self-report version of the inventory of depressive symptoms; GDS-15, geriatric depression scale with 15 items; CES-D, Center for Epidemiologic Studies Depression scale; HAM-D-17, Hamilton depression rating scale-17 items; HAD, hospital anxiety and depression scale; PHQ-9, patient health questionnaire-9; BDI, Beck depression inventory; CIDI, composite international diagnostic interview; IDS-SR, inventory of depressive symptoms – self-report; SCL, symptom checklist; HDRS, Hamilton depression rating scale; HICDA, hospital international classification of disease adaptation; DASS21, depression anxiety stress scale.

adults (27/44), were composed of people from cohort studies (27/44) and high-income economies countries (38/44), and used screening scales of depressive symptoms (37/44). The majority of studies performed a cross-sectional (27/44), followed by both a cross-sectional and longitudinal (10/44), and, finally, a longitudinal analysis (7/44). Considering the studies that included only older adults (≥60 years, 17/44), most were composed of people from a cohort (14/17) and performed a cross-sectional (10/17), followed by both a cross-sectional and longitudinal (4/17) and, finally, a longitudinal analysis (3/17). Moreover, only three studies were performed in low- or middle-income countries. This is an important issue because, according to the Mental Health Action Plan 2013–2030, there is an imbalance between research in high- and low/middle-income countries that needs to be corrected to ensure that they have appropriate cultural and economic strategies to respond to mental health needs and priorities[13]. One of their main goals is to strengthen information systems, evidence and research on mental health, and it suggests the development of more studies from low/middle-income countries.

It is difficult to compare the main differences between the studies because each study was different in terms of the method used to analyse data, the cut-off point for the classification of serum VitD concentrations and the screening for depressive symptoms or diagnosis for depression. However, an increasing number of studies have found an association between VitD and both depressive symptoms (32/44) and depression (7/44), specifically in those with cross-sectional analyses (24/44 and 7/44, respectively). Considering the studies in which researchers stratified the analysis by sex (7/44), the association was divergent because some authors[147,169] found an association in both sexes, while other studies found an association for women[163,175] or men[139,154,161]. In studies that included both adults and older adults, only five (5/27) reported no association[136,138,157,171,172].

Among the studies that exclusively analysed data of older adults, those that performed a cross-sectional analysis (10/17) found an association between VitD and either depression[161,173] or depressive symptoms[135,146,154–156,165,170,174], but two studies that stratified the analysis by sex found an association only for men[154,161]. In studies that performed either longitudinal or cross-sectional and longitudinal analyses combined, the results are controversial. In the longitudinal analysis, one[153] did not find any effect of VitD on the course of depression or remission, while another found a decrease in the score of depression with an increase in VitD[134], and another[169] found an increase in depression score for a low level of VitD at 3 and 6 years follow-up in women and 3 years follow-up for men. In the cross-sectional and longitudinal combined analysis, some found a cross-sectional but not longitudinal association[159,167], another study[160] did not find an association at baseline and 1 year follow-up, just one found an association at 4 years follow-up and another found a cross-sectional association only for women and not in the follow-up[163]. Nevertheless, most of these studies found a higher risk for depression when considering VitD concentrations below 20 ng/ml or 50 nmol/l[135,146,154,159,160,163,169,174]. Other studies found higher risk when concentrations were below 10 ng/ml or 30 nmol/l[156,161,165,170],

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and two studies found a lower risk for depression in concentrations >36·7 nmol/l[176] and 92 nmol/l[167]. Moreover, a meta-analysis with a mixed population showed that an increase of 10 ng/ml in individuals with low serum concentrations of 25(OH)D had a protective effect against depression, with a decrease of 4 % in the risk of depression in cross-sectional studies, and a decrease of 8 % in the incidence of depression in cohort studies[177]. In studies involving only the elderly population, the same 10 ng/ml increase in serum 25(OH)D level was associated with a 12 % reduction in the risk of depression[178].

Key points of observational studies

Despite the controversial results from observational studies, the majority have pointed to a higher risk of depression with low levels of VitD (20 ng/ml or 50 nmol/l). However, the variability in methodology between studies is important to note. At this moment, it is not possible to suggest a possible VitD cut-off point specific for depression. Few studies were carried out with only older adults, as well as in low- and middle-income countries. Few longitudinal studies were carried out to demonstrate causality of depression due to low levels.

Future perspective

Older adults are considered a risk group for both depression and vitamin D deficiency, which justifies further studies to focus on this population. The ageing process is associated with a reduced ability to sustain homoeostasis, which could make elderly people more susceptible to pathological alterations, including neuropsychiatric disorders[179,180]. Also, women in menopausal transition are at risk of depression due to a lot of changes (i.e. hormone-related context, stressful events in life)[181]. Moreover, older adults with depression present a higher risk of mortality[182], especially in low- and middle-income countries, and have difficulties accessing treatment[4,183]. Another important factor is related to the adverse effects caused by antidepressant medications and the polypharmacy common in the elderly owing to the concomitance of several pathologies, which can facilitate the discontinuation of treatment[184–186].

Facing the urgency to identify the modifiable risk factors associated with the aetiology of depression, helping with the treatment and prevention of this disorder, it is important to carry out more studies following a proper methodology since we have an important background related to pre-clinical studies. As highlighted by the WHO, these studies need to be developed especially in low- and middle-income countries, since these places have higher prevalence of depression[12,13]. Further, observational studies have pointed to the preventive effect of adequate serum vitamin D concentrations on the development of depressive symptoms. More longitudinal studies have been suggested[178,187] to better elucidate the preventive effects of VitD on depression/depressive symptoms.

Besides, the variability in the diagnosis of depression, differences in VitD cut-off reference values and methods for serum VitD analysis could influence those findings that are still controversial[21,188,189]. Recently, the use of the standardised measurement of VitD proposed by the VitD Standardization Program (VDSP) has been recommended to improve clinical and public health practice, and it is important for future studies to apply this in their methodology[190,191]. Considering the randomised control trial (RCT) that included the elderly population (>65 years), most of them did not present any improvements in depressive symptoms after VitD supplementation. This could be due to the lower VitD doses used in those studies, and because they were not performed in older individuals diagnosed with depression. This is an important aspect to be addressed in future RCTs.

Conclusion

Overall, this updated review suggests that the monitoring and maintenance of adequate VitD concentrations is crucial, especially in older adults, a population at risk for both VitD deficiency and depression. Several pre-clinical, clinical and observational studies have suggested that VitD could have a beneficial effect on depression/depressive symptoms due to its genomic and non-genomic actions in many pathways involved in the pathophysiology of depression.

Although studies presented controversial results, clinical studies have shown that older adults with depression/depressive symptoms could benefit from higher doses of VitD supplementation for short periods. However, more RCTs are needed to confirm which doses and for how long the treatment is needed to achieve the greatest benefit. From the observational studies, the results are still controversial, but the majority have reported an association between low serum concentrations of VitD and high risk for depression/depressive symptoms in older adults, pointing to a possible preventive effect of VitD. Additional studies with prospective designs, especially in low- and middle-income countries, will possibly help to better elucidate the impact of deficient VitD status for mental health in adulthood and, consequently, for the elderly.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0954422422000026

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Conflict of interest

None.

Authorship

All authors contributed to conception of this study. Material was prepared and the first draft of the manuscript was written by G.C.

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