REVIEW

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The effects of vitamin D on mood alteration in women's life: Focus on depression

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Vitamin D (VD) is a vital liposoluble neurosteroid micronutrient, particularly crucial for women's health. International literature strongly correlates sufficient VD levels with comprehensive mental well-being in women. This link is intricately related to neurobiological pathways and hormonal fluctuations, where low VD levels are notably associated with depression. This study comprehensively explores the neurobiological mechanisms that link VD and altered mood in women. Considering the increased susceptibility to hormonal shifts in women, our research investigates the intricate interplay between VD's neurobiology and mood regulation. Through the focused analysis of specific studies, we untangle the complex web of connections between VD and mood changes in women. Our approach takes into account the dynamic nature of hormonal changes, deepening our understanding of these mechanisms. Our study underscores VD's significant role as a neurosteroid micronutrient, especially in women's health. By examining the intricate relationships between VD's neurobiology and hormones, we propose strategies to improve mood regulation and psychological well-being in women. In addition, we recommend targeted measures to achieve optimal VD levels, helping to manage challenges arising from hormonal fluctuations. The present review highlights the multifaceted contribution of VD to women's health, particularly in mood regulation. Through the analysis of the interplay of neurobiology, hormones and VD, our study provides avenues for enhancing women's mental and emotional well-being through customized interventions.

Key words: vitamin D, women's mental health, depression, vitamin D insufficiency, vitamin D supplementation, 25-hydroxy vitamin D

INTRODUCTION

VD plays a significant role in mental health. In particular, incidents of depression that occur in the female population are remarkably affected by low serum levels of VD, which is mainly acquired *via* sun exposure, specifically from ultraviolet B-rays (UVB) (80–90% of VD acquisition) and as an exogenous form in foods (milk and derivatives and in fatty fish). In the kidney, VD's conversion to a hormonal form is linked with calcium homeostasis. Endothelial brain cells convert VD_3 into 25(OH)D3 and then to 1,25(OH)2D3 before it is transferred to astrocytes, promoting VDR binding and initiating gene transcription (Silva et al., 2021). The main metabolites of VD, which enter the body through sunlight *via* exposed skin and food and dietary supplement intake, are VD_2 and VD_3, with VD_3 available from more food sources than VD_2 (Vázquez-Lorente et al., 2020). VD_2 is available from fish oil/flesh, supplements, eggs, butter, liver and mushrooms (Morales-Suárez-Varela et al., 2022), with herbs and fruits also contributing to VD_2 levels and meat and fish also contributing to VD_3. Thus, VD levels are related to environment and lifestyle. Genetic factors and heritability also impact VD levels, but environmental factors are the primary VD determinants (sunlight, latitude, skin exposure), which emphasizes the relationship between VD levels and seasonality. VD deficiency (VDD) is more common in winter, at higher latitudes and in urban places due to lifestyle choices and lower sunlight exposure (Boulkrane et al., 2020), which negatively impacts neuropsychiatric dis-

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orders. To establish the basis of this review, we first investigate the roles and mechanisms of VD, then explore depression and its prevalence among women. Then, we delve into the correlation between VD and depression, followed by an exploration of the wider implications of VDD and its associated outcomes. Finally, we discuss the recommended dietary allowances for VD (VD RDA) and delve into strategies to address inadequate VD levels (VDI). This context is then followed by a section on comparative studies and an exposition of the findings of this narrative review.

METHODS

PubMed and Google Scholar databases were searched for articles published electronically in international journals using relevant keywords concerning the impact of VD on women's neurophysiology; the consequences of vitamin D supplementation (VDS)-VDI and their correlation were documented in several studies. As relevant data was extracted from international literature, only studies published in English were identified and included in the current review. The search strategy and research selection were based on the keywords vitamin D, women's mental health, depression, vitamin D insufficiency and 25-hydroxy vitamin D. The data collection methodology for selection criteria first included quality assessment; the full texts of research where data were extracted from were evaluated by omitting unrelated studies through screening the title, abstract and full texts and the research objectives were assessed to verify compatibility with relevant outcomes. As far as inclusion criteria were concerned, data were extracted based on selected international studies, taking into consideration the title, author, type of study, sample size and prevalence of VDD in the female population and divided into relative subgroups (pregnant women, patients, geographical areas) reporting the prevalence of VDD (variability in the VD dose administered was a factor affecting the results of the studies). Referring to exclusion criteria, apart from observational studies used to detect a link between VD and mood disorders, criteria were considered, such as sensory modulation disorder (SMD) and VDS and other studies were excluded (in vivo experimental studies and investigations, as well as case reports). As for eligibility criteria, the review included randomized-controlled trials (RCTs) and cohort studies that enrolled adults with depression reported as an outcome of VDD, compared with normal VD levels. The limitations were the range of under-studied populations with different characteristics, such as maternal depression combined with other depression forms (moderate and/or severe) that did not measure covariates such as stress and exercise; also excluded were studies with heterogeneous or uncertain depression history and variations in origin of depression, which were regarded as methodological biases.

The mechanisms of VD synthesis were analyzed, with the help of studies that correlated its insufficient concentration with fluctuations in women's mood and neurophysiology, by comparing population groups with various characteristics (such as residence in different geographical areas, pregnancy and age differences) and using relevant indicators, such as those related to depression, life quality and sun exposure, without neglecting the factors of bone mineral density, body mass, sexual function and maternal morbidity.

VD functions and mechanisms

VD (D_2-ergocalciferol/D_3-cholecalciferol or both) is a neuroprotective factor with a role in brain development, cell growth and differentiation, facilitation of immunomodulation regulation, neurotransmission and anti-inflammatory effects (Boulkrane, 2020); it also affects neuromuscular function and calcium-phosphate homeostasis (Casseb et al., 2019). VDD decreases calcium intestinal absorption, reducing its status and triggering parathyroid hormone (PTH) release, whose levels are inversely proportional to 25(OH)D (optimal serum level is defined as the concentration suppressing PTH maximum release) (Vázquez-Lorente et al., 2020). *Via* neuroplasticity and neuroimmunomodulation, VD impacts mood and brain functional irregularities such as cognitive ability, depression, dementia, autism and schizophrenia (Al Anouti et al., 2022). As an essential nutrient, apart from its anti-inflammatory and immune effects, it also stimulates insulin release by pancreatic B-cells (Rajabi-Naeeni et al., 2019). It is mainly synthesized in the body *via* skin exposure, having a protective role in diseases such as influenza, respiratory tract infections, cancer, autoimmune and cardiovascular diseases, as well as in cognitive, behavioral and mood disorders, as VD and UVB exposure affect serotonin-melatonin regulation in the brain and peripheral tissues.

Analytically, in peripheral tissues, 25(OH)D binds to vitamin D response elements (VDREs) on tryptophan hydroxylase (TPH) genes and inhibits enzyme TPH1 expression, lowering serotonin production. 25(OH)D brain levels increase the expression of the enzyme TPH2, necessary for serotonin production, affecting mood, cognition, impulse control and social behavior.

Serotonin-melatonin synthesis is enhanced due to the effect of VD metabolism on circadian processes, suggesting VD in the serotonergic pathway may impact the role of VD in mental disorders. Sufficient 25(OH)D ensures adequate 1,25(OH)2D production, promoting TPH2 activation for serotonin production, which is beneficial for mood and cognitive functioning. VD synthesis *via* skin exposure is more effective at raising 25(OH)D levels than VD intake (Huiberts and Smolders, 2021).

VD also plays a role in functions related to metabolism, pregnancy and bone health (Morales-Suárez-Varela et al., 2022). VD_3 is additionally linked to gut microbiota, restoring intestinal barrier impairment, mucosal injury and vulnerability to infections, promoting the formation and growth of the gut microbial balance, preserving the inviolability of junction complexes and protecting the intestine, affecting the composition and function of the intestinal microbiome, altering the structure of gut microbiota, preventing gastrointestinal diseases, modulating inflammatory processes *via* molecular pathways, altering gut microbiota composition and promoting the attenuation of depression. The gut is an important route whereby stress triggers depression; VD variations interact with changes in the gut, and then the changes in gut microbiota promote neuropsychiatric diseases.

Mood disturbances in menopausal women result from changes in estradiol, VD_3 levels and neuroinflammation. Nuclear factor kB (NF-kB) controls proinflammatory cytokine expression (involved in neuroinflammatory diseases and triggered by stress) and its enhancement increases cytokine production. VDR is involved in blocking inflammation in immune functions of the gastrointestinal tract *via* NF-κB. Multiple neurobiological pathways are linked to activation of vitamin D receptors (VDRs). Stress triggers can induce an impairment in gut permeability mediated by corticotropin-releasing hormone (CRH), which acts on the gut and induces tumor necrosis factor-a (TNF-a), both increasing gut permeability. A decline in estrogen is involved in negative changes in normal gut microbiota in perimenopausal and menopausal women and is linked to risk affective-related disorders (such as depression), which reveals interactions between female gonadal hormones and gut microbiota. The impact of VD_3 on affective-related disorders in an estrogen imbalance is gut microbiota normalization and relief of neuro-inflammation. Females in menopause have a higher risk of VDD due to a VD-poor diet, restricted outdoor activity (less sun exposure) and decreased capacity to produce enough calcitriol due to an age-related decline in hydroxylation in the kidneys (Boulkrane et al., 2020).

Depression and women

Approximately 840 million people are affected by depression (women:men, 2:1), with genetic and epigenetic factors playing a role in the disease, which is characterized by at least two weeks of symptoms (low mood, worthlessness and/or hopelessness feeling, loss of pleasure and interest in daily activities, decreased energy levels, appetite loss, sleep disturbance, changes in psychomotor function and suicidal ideation) and linked to neurotransmitter function. Impairments in the functioning of monoamines affect depression, which occurs in individuals with a disorder history when levels of neurotransmitter substrates are depleted; serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors and tricyclic antidepressants are prescribed for affective-related disorders and reduce brain levels of biogenic monoamines involved in mood disorders. Another hypothesis suggests that the onset of depression is partly explained by stress impact; stress factors activate CRH release in the hypothalamus, producing secretion of adrenocotricotropic hormone (ACTH), leading to cortisol release from adrenal glands. Reduced function of the hypothalamic-pituitary-adrenal (HPA) axis affects mood disorders (depression-anxiety).

The prevalence of depression ranges between 6% and 17% (Boulkrane et al., 2020) and middle-aged women experience more stress, leading to a decrease in immunity (Park et al., 2020). It is significant that, among health determinant factors mapped to a widely used model (Dahlgren-Whitehead's), participation in social and community networks and health risk factors are related to the broader social determinant of a population's health; psycho-social theory should also be taken into account, which highlights the interaction of social disorganization, marginalization, and harmful decisions causing a neuroendocrine response and stress (Mentis, 2022). Women have a greater risk of depression, with females experiencing higher depression scores compared to males. This gender divergence starts at 11–14 and the greater likelihood of girls developing depression compared to boys becomes obvious by the age of 12 and continues throughout the lifespan.

Gonadal hormones (progesterone-estrogen) have a predominant role in depression scores. The interplay between the HPA axis and sex-specific hormones also affects depression onset. Affective-related disorders are linked with modifications of sex hormone levels for menopause. Gonadal steroid receptors act as transcription factors and affect brain function, modulating gene expression. An imbalance or abnormal functioning of steroid receptors changes the monoamine balance in

the brain (serotonin-noradrenalin levels). An estrogen imbalance contributes to vulnerability to depression and response to pharmacotherapy. Gender differences in depression occur initially during adolescence, with greater score differences in adulthood, explaining why adult women have higher depression rates. Genes interact with the environment, affecting hormonal balance. Another period of risk for depression period is during pregnancy or after childbirth (10–16% for pregnancy).

Depression is linked with estrogen deficiency in menopause due to factors present that increase the depression risk. Perimenopause is characterized by estrogen deficits, accompanied by affective-related disorders. Normal cyclic deteriorations in female hormones intensify the risk of depression during the menopausal transition. Female hormone imbalances also drive postpartum depression. A history of depression is often linked to a previous deficit in ovarian functioning, indicating a link between female steroids and mood disorders. Post-menopause depression levels are more comparable to men's, showing that female gonadal hormones' negative effects are lessened. A woman's endocrine status, especially after menopause, leads to depression vulnerability (63.4% of women *versus* 34.7% of men) (Boulkrane et al., 2020).

VD and depression

Mental disorders have roots in fetal life related to deficiencies in micronutrients, including VD. In pregnancy, VD is influenced by an increase in levels of maternal calcitriol and vitamin D binding protein (VDBP). In early life, VD mediates brain processes and the maternal VD balance, determining the fetal origins or mental health and is linked with inflammatory responses to stress and mental disorders in adult life (Lisi et al., 2020). Depression is the most common psychiatric disease with mechanisms related to neural function. Results concerning whether VDI is a causal factor in depression or secondary are conflicting (Geng et al., 2019). VDD's link to depression is related to several mechanisms: a) VD receptors are distributed throughout the brain-limbic system, cerebellum and cortex - which control behaviors involved in emotional processing and affective-related disorders; b) lower levels of VD are present in persons diagnosed with depression; c) VD regulates serotonin synthesis *via* the modulation of tryptophan hydroxylase 2 gene expression and d) VD has a modulatory role in immuno-inflammatory pathways relevant to depression by activating the stress response.

In pregnancy, Edinburgh Postnatal Depression Scale (EPDS) scores and 25(OH)D_3 levels were inversely correlated with higher depression, which was related to lower 25(OH)D_3 levels. Elevated VD food intake is related to lower depression levels in pregnancy. VDD influences pathways associated with depression, indicating a causal link between depression and hypovitaminosis VD, a depression risk factor. The literature underlines a potential link between VD levels and depression and gut microbiota. A lack of VD in early life may trigger depression at a later period in a woman's life, as VD at non-optimal levels is no longer neuroprotective, making one more vulnerable to affective-related disorders. VDD is associated with poorer mental health, depression, psychotic disorders and chronic problems. Evidence that VD is potentially a cause rather than a consequence of depression is sparse, although VDD during development may be relevant to psychosis risk.

Due to darker skin's absorption of sunlight, Blacks and Asians are more prone to having lower VD levels. In most parts of the world, in sunny months, optimal VD levels (approx. 1.000 IU/day) are achieved by minimal sun exposure. The liver transports VD_2-VD_3 with chylomicrons. It binds to proteins in plasma that, in turn, carry VD_3 produced from sunlight exposure. In the skin, ultraviolet (UV) light transforms proVD to pre-VD, isomerized to VD_3. Approximately 10% of body VD is obtained orally, transported to the liver, hydroxylated to 1,25VD and acts *via* VDR, as detected in human organs. 1,25VD binds to VDR, and the complex forms a heterodimer with retinoid X receptor (RXR). The 1,25VD-VDR-RXR complex binds to VD-reacting elements, modulating gene expression (Boulkrane et al., 2020). Low levels of VD contribute to depression. There are brain receptors for VD involved in emotional processing and affective disorders, which regulate serotonin synthesis and impact immunity and production of pro-inflammatory cytokines with an impact on mood due to activation of the stress response. Depression has been related to VDD in young adults in the United States of America (USA). Non-summer meteorological/behavioral factors limit skin exposure to sunlight, leading to a decrease in VD_3 and a depletion of the body's reserves. People from a range of climates often have VDI in winter and do not regain sufficiency for months. This reveals the seasonality of VD levels and explains seasonal affective disorder (SAD), the models for which emphasize that a disruption in vulnerable individual's circadian rhythms, following day length changes and confounded with other factors (intensity of solar radiation, cloud cover, clothing), account for seasonal variations in depression (Kerr et al., 2015), which, like general mood disorders, are highly correlated with an organism's balance, with particular reference to female hormonal variations.

Wider VDD-VDI consequences

VDD plays a role in the etiology of psychotic disorders. Prenatal VDD is related to changes in brain structure, neurochemistry and behavior and it has been shown that low VD levels reduce cognitive function and increase cancer risk, diabetes, cardiovascular disease and premature death. It is also interesting that low and high sun exposure is related to an increase in psychotic experiences (PEs). Moreover, studies strongly link VDD with an increased risk for schizophrenia and mental symptoms. VD modulates dopamine neurotransmission, with an association found between early-life VDD and later psychotic disorder. PEs share risk factors with psychotic disorders, including social adversity and cognitive impairment. PEs in early life are related to an increased risk of later psychotic disorders and are related to anxiety, depression, substance misuse, suicide risk and self-harm (Pilecka et al., 2017).

Hypovitaminosis D is related to lifestyle habits, as well as outdoor activities and food intake. Studies have shown a link between VD status and anxiety symptoms. VD levels are especially low in Middle Eastern countries such as the United Arab Emirates (UAE), mainly due to sun avoidance, due to traditional coverings of most of the skin and a lack of VD-fortified food. There are benefits of adequate VD levels, ranging from calcium metabolism to immune modulation and health of nervous system (NS). VDI is linked to an increased risk of disease and VDD affects psychiatric and mental disorders, including anxiety disorders and generalized anxiety disorder (GAD) (Al Anouti et al., 2022), fractures, osteoporosis, metabolic syndrome, diabetes, cardiovascular disease, cancer and depression (Park et al., 2020) and results in higher fasting glucose levels (Rajabi-Naeeni et al., 2019) and major depressive disorder (MDD) risk (Casseb et al., 2019). In the West, VDI in the form of 25(OH) (< 30 ng/ml) affects 75% of people. Studies have addressed the role of VD in serotonin-melatonin regulation and in improving mood and sleep. In addition to increased time spent indoors, wearing clothes covering most of the skin's surface and/or using sunscreen contribute to low VD levels. At higher latitudes and during winter, VD synthesis through sunlight exposure is almost impossible due to a large solar zenith angle, leading to the absorption of UVB radiation from the ozone layer (Huiberts and Smolders, 2021), affecting calcium homeostasis, cognition, emotions, stress, anxiety, depression and sleep quality and having neuropsychophysiological implications. Hypovitaminosis D is found in children, adolescents, adults and the elderly.

VDD is related to brain volume reductions in addition to lower amounts of white matter, highlighting how a decrease in plasma VD levels acts as an indicator of brain health. 25(OH)D low levels have been related to depression, showing that hypovitaminosis D represents a vulnerability for depression onset (as VD has neuroprotective effects *via* inhibition of inflammatory cytokines), followed by obsessive-compulsive and panic disorders and/or anxiety. Studies have shown a link between decreased levels of VD and higher anxiety and depression (Silva et al., 2021). Other studies have shown an improved glycemic status in patients with new-onset type 1 diabetes mellitus (T1DM) and in women with gestational diabetes mellitus (GDM) with the use of omega3-VD, as well as effects on prediabetes, glycemic status, serum lipids and psychological distress in women of reproductive age with prediabetes and hypovitaminosis D, detecting potential effects of these two supplements in decreasing type 2 DM (T2DM) risk factors (Rajabi-Naeeni et al., 2019).

VDD (25(OH)D<20 ng/mL) is prevalent in pregnancy (60%). Levels of 30-50 ng/mL are recommended to achieve VD benefits. Low levels of VD in pregnancy result in the production of less bone mineral content in the fetal skeleton and evidence points to the role of VD in maternal mortality and morbidity. VDD in pregnancy causes maternal-fetal side effects, increasing the risk of preeclampsia, glucose intolerance, gestational diabetes, preterm birth and hypocalcemia crisis in the mother. Along with poor skeletal development, the risk increased for dysfunction in the mother and newborn and a small child for gestational age (SGA) birth. Also, VDD in the fetus has been related to an inadequate immune system, wheezing and eczema and respiratory infections in infants. VDD is related to increased risks of morbidity and mortality in terms of cardiovascular, malignant and autoimmune diseases. VDI is common in pregnancy, with VDD increasing the prevalence of adverse outcomes (Morales-Suárez-Varela et al., 2022).

PMS affects 50% of reproductive women and is characterized by physical and psychological symptoms (breast tenderness, headaches, bloating, irritability, anxiety, depression, mood swings), ranging in severity and affecting productivity and interpersonal relationships. Non-pharmaceutical therapies for premenstrual syndrome (PMS) related to dietary intake offer potential low-cost treatment strategies. VD is one such treatment, improving dysmenorrhea and related to calcium homeostasis, as low calcium intake is related to higher PMS risk. Low 25(OH)D levels are related to higher rates of mood disorders, specifically depression, linked with PMS (Alkhalaf et al., 2021).

VD has anti-inflammatory activities. Increased activation of the HPA and inflammation in gestation influences maternal health and fetal neurodevelopment during and beyond pregnancy. VDD influences the immune system's efficacy. VDD during gestation

is related to a reduction in fetal brain development and correlated with altered brain-derived neurotrophic factor production. Low maternal VD in gestation is related to a greater risk of mental illness (Lisi et al., 2020). VDD is also related to skeletal and non-skeletal problems due to nutritional deficits, liver and/or kidney failure, VD action resistance, low sunlight exposure and sunscreen use. VDD affects overweight people who have lower sun exposure and reduced skin biosynthesis/intrinsic factors related to obesity. Low VD levels were related to a higher frequency of fractures and low bone mass, in addition to osteoporosis, having an inverse relationship with VD and body mass index (BMI) (Vázquez-Lorente et al., 2020). VDD and mood disorders are prevalent in the elderly, and VD intake is related to mental quality of life (QoL) in elderly women (Motsinger et al., 2012).

VD RDA–VDS

VD RDA differs worldwide. VD status is evaluated by 25(OH)VD serum levels due to the longer half-life, compared to metabolite 1,25(OH)VD levels (Boulkrane et al., 2020). VDS is useful for achieving sufficient blood levels, which affect cognitive and affective processes, as VDI is linked with mental disorders. Studies have shown an increased risk of depression with lower 25(OH)D and an effect of VDS on symptoms in depressed people. Individuals with VDI were more likely to have a sleep disorder, poorer sleep quality, shorter sleep duration and/or excessive daytime sleepiness, and there is a potential relationship between VDS and sleep and mood (Huiberts and Smolders, 2021). VDS was also investigated in the prevention and treatment of depression and anxiety, particularly when VDS was carried out in MDD (Casseb et al., 2019).

Obesity is also considered in VD RDAs, as it is linked with reduced VD levels. VD and sex hormones in postmenopausal women are related, where a reduction in estrogen levels reduces VD levels, affecting musculoskeletal, metabolic and cardiovascular conditions and mental health. In menopause, women are prone to the consequences of VDD, as decrease in bone mineral density (BMD) and lean mass and increase in fat mass, resulting from an estrogen level decrease; additionally, 25(OH)D levels are inversely related to BMI in postmenopausal women. VD is transformed as 1,25-(OH)-2VD by cytochrome P450 family 27 subfamily B member 1 (CYP27B1), mainly located in the kidney and also expressed in the placenta, a major site of VD metabolism in pregnancy. Additionally, VD is related to maternal morbidity-related outcomes. As pregnant women have higher VD needs, it also affects fetus growth and VDS reduces the risk of gestational diabetes, hypertension, preeclampsia and early labor. The VD RDA during pregnancy ranges worldwide from 200 to 4000 IU/day, which is reflected in Table 1, where daily recommendations for adequate VD levels for different subgroups and countries are presented (Morales-Suárez-Varela et al., 2022), highlighting VDS as a beneficial, cost-effective way of coping with mental disorders.

Comparative studies

Thirty-six studies examined the effects of 25(OH)D on depression in healthy people, with 26 revealing

Table 1. Vitamin D reference daily allowance.

WHO	200 IU/day for pregnant women with VDD
US	600 IU/day aged 19–50 (including pregnancy) to levels > 50 nmol/L in minimal sunlight exposure. 1,000–1,600 IU (25–40 g/day) in pregnancy for highest VD3 level. VD maximal production (at least 32 ng/mL) with VDS 4,000 IU/day until delivery
American Pregnancy Association	100 µg/day, 10 µg/day for women
China	600 IU/day during pregnancy
UK	maternal intake of 400 IU/day; the health department provides free VDS to pregnant women and newborn children
Switzerland	1,500–2,000 IU/day for those at risk of VDD and 600 IU for women without such risk
Canada	400–600 IU/day for pregnant women
Turkey	free VDS (1,200 IU/day) provided from early pregnancy to 6 months after delivery
New Zealand	400 IU/day for pregnant women with VDD risk; for women not at risk, 200 IU/day
Researchers at Medical University of South Carolina College of Medicine	4,000 IU/day for pregnant women, starting at 12–16 weeks of gestation, VDS 4,000 IU/day is most effective in pregnancy; treatment (< 37 weeks) goal > 40 ng/mL related to preterm birth risk reduction

a negative correlation between 25(OH)D and depression. People reporting mood and/or sleep complaints are more likely to stay indoors, with lower 25(OH)D due to decreased UVB exposure. Considering the VD serotonergic pathway (as VD is key regulator of serotonin production, by activating TPH2 – inhibiting TPH1's expression and influencing brain structure and neural wiring) and the time-dependent (circadian) variations of naturally occurring 25(OH)D (high serum levels in daytime-reduced in night and following these light-dark cycles, cholecalciferol's levels increase by UVB exposure, resulting to sufficient serotonin-melatonin synthesis), the recording time of VD's levels is important for assessing its impact on mood and sleep (Huiberts and Smolders, 2021).

VD_3 was used to examine depression in 1 trial with 50 females with type 2 DM and depression, using an everyday VD treatment (VD2, 50,000 IU) administered for a period of six months. A reduction in depression and anxiety and an increased mental health level were reported with VD treatment. In another study, among 47 women with VD level problems, 16 took VD at 4,000 IU/day for six months and 31 with VDI were divided into two groups: 17 received VD at 2,000 IU/day and 14 went without VD treatment. The female sexual function index (FSFI) score was decreased with VD treatment and the Beck's Depression Inventory (BDI) II score increased in women with VDD compared to women with VDI. VD enhanced sexual parameters in both groups, with VDD and VDI and diminished the BDI-II score in women with VDD. Administration of VD affected mood and female sexual functioning in those with low VD levels.

Eighty perimenopausal women with a score ≥13 on EPDS and ≥20 on fatigue identification form (FIF) were divided into groups after giving birth. One group was given VD_3 1000 international units (IU) over six months and the control group received a placebo. VD treatment reduced depression-fatigue scores in depressed women, suggesting that, for those with high depression trigger factors in the postpartum period, there are benefits to affective disorder (Boulkrane et al., 2020). 11,020 postmenopausal women in the US were examined for psycho-social stress in relation to BMD changes. The link between social stress and greater bone loss over six years of follow-up suggested that poor social relationships may be related to bone loss in postmenopausal women (Follis et al., 2019).

A study conducted on postpartum women used BDI and hospital anxiety and depression scale (HADS) to trace depression. A 25(OH)D level of less than 20 ng/mL is considered VDD, while 25(OH)D levels between 21-29 ng/mL are considered insufficient. There is controversy on the ideal 25(OH)D range. VDD is defined as a 25(OH)D level of <20 ng/ml (Silva et al., 2021). Women experience more stress in middle age, influencing QoL in old age. The effects of a forest therapy program on 53 middle-aged women living in the city were examined. Differences in VD levels were verified before and after the forest (experimental group) and urban (control group) programs. Forest therapy programs promoted the middle-aged women's health, preventing disease and improving QoL. The study verified the forest therapy programs' benefits on women aged 40 to 64. VD levels were measured before and after participation in the programs in the forest and in the city. The VD levels were a measure for evaluating physiological changes in the forest and urban environments. VD levels increased from 17.81 ng/mL before therapy to 18.11 ng/mL after therapy in the forest group. In the urban group, the average VD level decreased from 17.62 ng/mL before therapy to 16.95 ng/mL after therapy. In the experimental group (forest environment), participation did not affect body levels of VD, but it decreased with participation in the urban group (Park et al., 2020).

Low VD levels also contribute to MDD (neuropsychiatric disease leading to social functioning impairment and increased morbidity-mortality) and the BDI scale was used to assess MDD severity. Females showed the greatest improvements in depression after three months of VDS. Depressed persons had lower BDI scores after VD treatment. VDS increased serotonin levels, ameliorating MDD symptoms (Alghamdi et al., 2020). Intake of VD-rich foods and supplements and a link with sun avoidance/exposure and anxiety were also examined in 386 women over 18. Sun avoidance was related to an elevated risk of anxiety in adult females in the UAE. In several studies (Ethiopia and India), more than 80% and 60% of pregnant women, respectively, suffered from VDD.

Severe maternal morbidity (SMM) in pregnancy has been reported, affecting 50,000 women/year in the USA (0.5–1.3% of pregnancies). In pregnancy, phosphate-calcium metabolism changes and the fetus relies on the maternal VD supply received across the placenta. A review described mean VDD prevalence rates in pregnant women and newborns. In the postpartum period, VDD prevalence was 63%. VD status in pregnancy varies due to maternal sunlight exposure, skin pigmentation, latitude, lifestyle, BMI and VDS. Darker skin and less sunlight exposure led to greater VDD risk (Morales-Suárez-Varela et al., 2022).

Furthermore, VDS benefits dementia. The effect of VD exposure was greater in women, explained by links between estrogen and VD as estrogen declines in aged women, contributing to VDD. VDS has a greater impact on elderly females due to the lower activated VD levels

that are related to peri- and postmenopausal changes. Estrogen deficiency contributes to postmenopausal osteoporosis. RCTs showed a positive effect of VD on BMD. A higher risk of osteoporosis in peri- and postmenopausal women compared to males is shown by the greater VDS rate among older women (Ghahremani et al., 2023).

Sun exposure and PEs were examined in Swedish women. Community assessment of PEs (CAPEs) was administered to establish PEs. Sun exposure was measured by sunbathing holidays and sunburn history. 34,297 women were included. Those with 0 sunbathing holidays and ≥2 sunbathing holiday weeks scored higher on the CAPE scale than those with 1 week. Compared to women with 1 sunburn, women with 0 or ≥2 sunburns showed higher scores on the CAPE scale. In middle-aged women, low and high sun exposure is related to increased PEs. Schizophrenia and psychotic disorders affect 2–3% of people. This study demonstrates sun exposure's link with PEs (Pilecka et al., 2017).

Higher VD intake and 25(OH)D levels were related to a lower risk of PMS. In two female cohorts (18–44), 25(OH)DS was shown to possibly be associated with improved dysmenorrhea. There is a link between 25(OH) DI and PMS in women with regular cycles. 25(OH)D was related to breast tenderness and aches and pains and related to inflammatory pathways, increased pain signaling and improved dysmenorrhea *via* proinflammatory cytokine reduction. VD treats aromatase inhibitor musculoskeletal symptoms caused by estrogen dysregulation with symptomatology similar to PMS, suggesting similar mechanisms (Alkhalaf et al., 2021); 950 women were included (18–60 years) in the study. VD levels and psychophysiological aspects were evaluated. The study used HADS and BDI to examine anxiety and depression (Silva et al., 2021).

According to World Health Organization (WHO) (2017), 3.6% of people (approximately 264 million) suffer from anxiety. Females (4.6%) are more affected than males (2.6%). A correlation between anxiety and age, VDD, diet and VDS, along with sun exposure, was examined in female UAE college students. The sun avoidance inventory (SAI) assesses sun avoidance attitudes. In adult females at Abu Dhabi universities, there was a high rate of VDD (65%) and pattern of sun avoidance and inadequate VD-rich food intake. These data are concordant with findings among female UAE university students with limited VD intake and minimal sun exposure. Anxiety was related to decreased VD intake and sun exposure, as well as higher SAI with VDD and greater GAD risk. These data are in concordance with a correlation between VDD and anxiety, where patients with VDD had higher HADS. Higher measured sun avoidance habits related to higher GAD risk. Outdoor activities were avoided and female clothes covered most of the body for cultural reasons, reducing sun exposure.

Another study examined the VDD-depression link in UAE college students *via* sun avoidance habits. Students with low VD dietary intake had a greater risk of depression with a higher VDD prevalence, as most of the body was concealed and VDS was shown to alleviate GAD symptoms (Al Anouti et al., 2022). Women with a BMI >27 kg/m^2 had lower VD status (Geng et al., 2019).

Female undergraduates in the Pacific Northwest completed the scale of center for epidemiologic studies depression (CES D) (weeks W1–W5). VDI (<30 ng/mL) was common at W1 (42%) and W5 (46%) and depression rates (CES-D ≥16) of 34–42% at W1-W5 were observed. Low levels of VD and depression were linked (depression prevalence was 25% in American women). A study of 30-year-old women showed a rate of 63.4%. Norwegian participants (185 women, 18–25, enrolled at a USA university) showed seasonality scores (34–42% depression). VD_3 was negatively correlated over five weekly assessments (Kerr et al., 2015). In IWHS (in postmenopausal women), VD intake of <400 IU/day was related to poorer QoL compared to those with ≥400 IU/day. Women with VD <400 IU/day had lower mental QoL, indicating that VD raised the elderly women's QoL (Motsinger et al., 2012).

DISCUSSION

The studies demonstrated a strong relationship between VD and depression and the fact that the prevalence of VDD was significantly different in various geographical areas revealed regional risk factors. From the aforementioned, it is clear that mechanisms of VD synthesis are multifactorial and the effects of its deficiency, due to a variety of factors (sun exposure, geographical parameters, living conditions, insufficient intake of foods rich in VD) concern a wide range of symptoms in the female body. The impact of VD on female neurophysiology is evident (self-mentioned testimonies, assessment of indicators such as BDI, BMD, CAPE, FSFI, QoL, SAI, and SMM) and there is a clear interaction between VD blood concentrations and mood modification and fluctuations relating to emotional changes in women, with an emphasis on depression symptoms. Furthermore, findings showed reduced VD levels in people with depression (SMD) compared with control subgroups and that females had higher VDD prevalence compared to males. This was explained partially by female cultural factors such as clothing habits (and

subsequent extent of sun exposure), highlighting the risk factors for women's VDD, regardless of sunlight, in areas such as the UAE. The benefits of VDS in addressing mood disorders and depression were also confirmed, considering the inverse relationship between higher VD serum levels and depression and indicating, in parallel, the benefits of VDS in tackling depression symptoms.

VD's importance for the wider population's health should not be ignored, as VDD/VDI is a major health problem. In addition to changing individual habits (such as more frequent exposure to sun and dietary alterations relating to the intake of foods rich in VD), which is more necessary for women (whose psychological health is more vulnerable to VD serum fluctuations), national health policies should include measures aimed at adopting targets for the maintenance of VD concentrations at needed levels. Furthermore, as the outcomes revealed that VDD is a crucial risk factor increasing the already established burden of female depression, more data are needed to determine the impact of VD in preventing depression (Okereke and Singh, 2016). Additionally, as approximately 30% of depressed persons do not respond to pharmacotherapy, VDS showed benefits in mood disorder treatment in postmenopausal women with low VD levels. Hence, the current VD RDA (200–600 IU/day) must be revised (as, for low sunlight exposure, it should range between 800–1,000 IU/day) in order to achieve the preferred range (30-40 ng/ml) (Boulkrane et al., 2020) and subsequently QoL maximization. Also, a nutritional approach and VD_3S policies are related to improved VD status and should be considered so as to optimize QoL (Vázquez-Lorente et al., 2020).

Furthermore, application of health technology assessment (HTA) is considered a useful tool for tackling health services' rising costs with consumer demands (such as ensuring VD adequate levels), saving health system resources and providing a high level of health care (preventing/handling depression symptoms *via* VDS policies); thus, considering the clinical effectiveness, the evaluation of VD strategies and their budget impact/economic efficiency is important in ensuring that policymakers transparently focus on value-economic efficiency and real data integration (Mentis, 2022).

Considering prevention as a cornerstone measure, appropriate governmental interventions are demanded, including acute detection of the extent of female VDD and identification of risk factors, by urgently conducting RCTs and longitudinal studies focusing on high-risk groups (i.e., pregnant women). They should aim to minimize VDD's prevalence and its negative impact on mood through comprehensive planning and targeted healthcare decisions, including citizens' awareness and enhancing healthier lifestyles and increase the practical concern about women maintaining adequate VD threshold levels, preventing serum changes.

In summary and based on the findings derived from this review, the indicated measures proposed to safeguard the worldwide well-being of the female population are directly related to targeted public information by institutional bodies about the advantages of frequent exposure to sunlight and encouragement in this direction, annual governmental VDS purchase subsidy programs, especially for the female population having increased needs (advanced age, pregnancy), encouragement of more frequent interactions by the female population with nature and the forest environment—through a persistent pursuit of individual/group tourist excursions, totally or partially subsidized by the state and scaled according to the official assessment of personalized VD needs, with special considerations when occasional or permanent changes in clothing preferences is difficult or considered prohibitive (for reasons such as cultural and religious habits).

CONCLUSION

There is a remarkable prevalence of VDD and the research demonstrated the high rate of VDD among various female age groups (in particular, pregnant women prone to VDD) due to multiple factors (geographical location, clothing, diets poor in VD, limited outdoor activities, exposure to sunlight, reduced physical activity). The role of VD in the neurophysiological and mental health of the general population and especially in women's health, is indisputable. This highlights, on the one hand, the need for RCTs to further clarify the extent of the causation of VDD in depression and secondly, the need to maintain the required VD serum concentrations at acceptable levels through the implementation of specific healthcare measures, in order to achieve maximum health benefit, in particular, to prevent or successfully treat mental disorders and depressive incidents, the frequency of which is significantly higher in the female population.

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