Review Article

Expanding non-calcaemic roles of vitamin D in therapeutics and their mechanisms

SAHIL KUMAR, ARUN GHOSH, IJASUL HAQUE, VANDANA TAYAL

ABSTRACT

Vitamin D is a fat-soluble secosteroid that has a major role in calcium homeostasis in humans. The non-calcaemic roles of vitamin D have been extensively studied in the past few decades, and it is associated with various diseases, including cardiovascular, central nervous system, respiratory, infectious, autoimmune, metabolic disorders, and carcinomas. This review aimed to analyse the available evidence on non-calcaemic roles of vitamin D. We found that most observational studies concluded that low levels of vitamin D are associated with the incidence of many diseases, and some of the interventional studies supported this by positive outcomes after vitamin D supple-mentation. However, most of the systematic reviews and meta-analyses concluded that vitamin D supplemen-tation has no therapeutic benefit, although these had limitations of heterogeneity of studies and inclusion of low-quality studies. We conclude that further high-quality randomized controlled trials with vitamin D supplemen-tation should be conducted in diseases where there is a strong association between low levels of vitamin D and disease incidence in large observation studies.

Natl Med J India Article in Press

INTRODUCTION

Vitamin D, also known as 1α,25-dihydroxyvitamin D3 ($1,25[OH]_2D3$), is a fat-soluble micronutrient recognized as the main calcitropic hormone regulating calcium phosphate homeostasis and bone mineral metabolism. The term 'D' was coined because it was the fourth vitamin to be discovered in the sequence.[1]

The major source of vitamin D is ultraviolet B (UVB) radiation (290–315 nm)—induced photochemical and thermal conversion of 7-dehydrocholesterol in the skin, resulting in the generation of vitamin D3 (cholecalciferol). It is then hydroxylated at 2 sites—one in the liver (calcidiol) and the other in the kidneys (calcitriol).[2] Calcitriol then enters target cells, where it binds to the vitamin D receptor (VDR) in the nucleus that regulates cellular function.[3] The discovery that VDR exists in cells beyond those found in the intestine, bone, kidney, and parathyroid gland highlighted the possibility of the non-calcaemic effects of vitamin D.

Vitamin D may be responsible for regulating up to 200 genes that may facilitate many of its pleiotropic health benefits.[4] Since several such actions of vitamin D are now known, numerous studies have been done to elucidate its potential role in the therapeutics of a wide spectrum of pathologies (Fig. 1). Hence, we collated the available data apart from the classical roles of skeletal homeostasis over the recent years.

CALCAEMIC USES OF VITAMIN D

The primary therapeutic applications of vitamin D include preventing and treating nutritional rickets, treating metabolic rickets and osteomalacia (especially in cases of chronic renal failure), managing hypoparathyroidism, treating hypophosphataemia linked to Fanconi's syndrome, and both preventing and treating osteoporosis.[5]

The recommended daily intake of vitamin D is 600 IU for adults aged 70 or younger and 800 IU for those over 70. The maximum safe intake is set at 4000 IU per day; exceeding this amount increases the risk of adverse effects.[6]

Several expert bodies such as Endocrine Society of Clinical Practice and the Institute of Medicine (IOM, USA) in their 'Dietary Reference Intakes' have defined 20 ng/ml (or 50 nmol/L) as 'vitamin D requirement of nearly all normal healthy persons,' by using bone health as the main basis.[7,8] According to the National Academy of Medicine, an estimated 97.5% of the population will have their vitamin D needs met at a serum level of 20 ng/ml and risk for deficiency, relative to bone health, begins to occur at levels less than 12 to 20 ng/ml.

NON-CALCAEMIC ROLES AND MECHANISMS OF VITAMIN D IN THERAPEUTICS

A number of studies have been done to investigate the therapeutic role of vitamin D in numerous diseases.

Cardiovascular diseases

Observational studies have consistently suggested an inverse

ESIC Medical College and Hospital, Academic Block, NH-3, NIT, Faridabad, Haryana 121001, India
SAHIL KUMAR Department of Pharmacology

Maulana Azad Medical College, First Floor, Pathology Block, New Delhi 110002, India
ARUN GHOSH, IJASUL HAQUE, VANDANA TAYAL Department of Pharmacology

Correspondence to VANDANA TAYAL; *vandana_tayal@yahoo.com*

[**To cite:** Kumar S, Ghosh A, Haque I, Tayal V. Expanding non-calcaemic roles of vitamin D in therapeutics and their mechanisms. *Natl Med J India* 2026. DOI: 10.25259/NMJI_420_2024]

© *The National Medical Journal of India 2026*

association between serum 25-hydroxyvitamin D levels and the risk of cardiovascular disease (CVD) events. Low vitamin D levels are linked to an elevated risk of myocardial infarction (MI), stroke,[9,10] CVD mortality,[11] and heart failure in case–control and prospective epidemiologic studies.[12–16]

Proposed mechanisms of vitamin D in CVDs. Vitamin D receptors in vascular tissues, myo-cardium, and smooth muscle impact calcium influx, muscle relaxation, and diastolic function.[17] It influences the renin–angiotensin–aldosterone (RAA) system, parathyroid hormone function, endothelial function, and arterial thrombogenesis.[17,18]

Its anti-inflammatory action in endothelial cells hinders the progression of atherosclerosis by inhibiting smooth muscle proliferation, suppressing vascular calcification, and regulating cytokines.[19–21] Additionally, it reduces blood pressure through renoprotective effects, suppressing the RAA system, and improving endothelial function.[22,23] Vitamin D regulates inflammation by inhibiting prostaglandins, mitogen-activated protein kinase, and nuclear factor kappa β pathways.[24]

Evidence related to vitamin D supplementation in CVDs. A meta-analysis of 4 studies with 307 patients with coronary artery disease (CAD) indicated that vitamin D supplementation in subjects with vitamin D deficiency had a favourable effect on diastolic blood pressure and parathyroid hormone concentrations. The study also suggested that vitamin D may be recommended to be used as an adjunct therapy to routine treatment in CAD patients with vitamin D deficiency (Table 1).[25,26]

However, in a meta-analysis of more than 83 000 individuals in 21 randomized controlled trials (RCTs), vitamin D supplementation was not found to be associated with reduced major adverse CVD events.[27] In the case of stroke, a meta-analysis also showed that vitamin D supplementation did not influence the risk of incident stroke.[28] Another meta-analysis concluded the reduction in systolic blood pressure with vitamin D supplementation was not found to be statistically significant compared to placebo, and there was no reduction in diastolic blood pressure.[29]

Altogether, in hypertension, supplementation of vitamin D has shown no significant effect on blood pressure.[30]

Disorders of the central nervous system (CNS)

Vitamin D plays a diverse role in the CNS and the integrity of CNS functioning. Various studies have shown that levels of vitamin D have been inversely related to the prevalence of many neurobehavioural disorders, including depression,[31] Alzheimer's disease,[32] Parkinson's disease[33] and multiple sclerosis.[34]

Proposed mechanism of vitamin D in CNS disorders. Vitamin D plays a role in maintaining the expression of the calcium pumps and buffers that reduce calcium levels, which is postulated to be a beneficial effect against the onset of depression.[35] Additionally, it controls the release of nerve growth factor (NGF), crucial for the survival of neurons in both the hippocampus and cortex.[36]

It also has neuroprotective action against the neuro-degenerative process associated with Alzheimer's disease and cognition through antioxidative mechanisms, neuronal calcium regulation, immunomodulation, enhanced nerve conduction, and detoxification mechanisms.[33,37]

Vitamin D has also been found to be related to the incidence of schizophrenia as it regulates tyrosine hydroxylase, the rate-limiting enzyme necessary for the production of catechola-mines, which act as a major neuromodulator in the brain.[38]

Evidence related to vitamin D supplementation in CNS disorders. A meta-analysis of the efficiency of vitamin D supplementation in major depression revealed that the supplementation favourably impacted the depression ratings in patients with major depression (Table 2).[39] Similarly, in an RCT, it was concluded that supple-mentation with high doses of vitamin D seems to improve the symptoms of depression in overweight subjects.[31]

However, in Alzheimer's disease, a meta-analysis involving 2345 participants has shown no significant difference in the mini-mental state examination, verbal fluency, verbal memory, and attention scores between the vitamin D intervention group and the comparison group of patients.[40] Similarly, in Parkinson's disease and multiple sclerosis, meta-analyses have concluded that vitamin D supplements resulted in no significant benefits in improving motor functions or annualized relapse rate, respectively.[41,42]

Overall, while vitamin D shows promise for depression, its efficacy varies across neurobehavioural disorders.[43]

Diabetes mellitus (DM)

An association between vitamin D deficiency and the onset and progression of type 2 DM, as well as future macro-vascular events, was observed in multiple observational studies.[44] Furthermore, it was noticed that low levels of vitamin D are associated with poor renal function in patients with diabetic nephropathy.[45]

Proposed mechanism of vitamin D in DM. In vivo and in vitro studies have suggested various potential functions of vitamin D in glucose metabolism. These include enhancing insulin secretion by interacting with the vitamin D receptor present on pancreatic β cells, regulating immune responses and decreasing overall inflammation, and mitigating peripheral insulin resistance through the activation of vitamin D receptors found in muscles and the liver.[46,47]

There is experimental evidence that activation of vitamin D receptors have a protective action on the podocyte of nephrons, and limits activation of the RAA system, slowing renin production and has an antiproteinuric effect in case of nephropathy.[48]

Evidence related to vitamin D supplementation in DM. An analysis of the combined data from 3 trials showed that vitamin D supplementation reduced the risk of developing type 2 DM in individuals with prediabetes.[49] Similar findings were observed in another meta-analysis, which concluded that vitamin D supple-mentation in moderate to high doses ($\geq$1000 IU/day) significantly reduced the risk of type 2 DM compared with placebo.[50]

Another meta-analysis concluded that vitamin D supplementation resulted in a significant improvement in insulin resistance. However, there was no improvement in fasting blood sugar and HbA1c levels.[51] In a meta-analysis of 24 studies, vitamin D had a significant effect in reducing albuminuria.[45]

All meta-analyses show that vitamin D has diverse effects in people with prediabetes and DM, with the majority of them recommending the use of vitamin D supplementation for the treatment or prevention of DM or its complications (Table 3).[52–54]

TABLE 1. Studies of vitamin D supplementation in cardiovascular diseases (CVDs)

Author, year	Details of the study	Study outcome	Remarks
Cardiovascular disorders			
Martins *et al*.[14], 2007	Third National Health and Nutrition Examination Survey in 7186 male and 7902 female adults ≥20 years	Adjusted prevalence of hypertension (odds ratio [OR] 1.30, 95% CI [1.13–1.49]), diabetes mellitus (OR 1.98, CI 1.57–2.51), obesity (OR 2.29, CI 1.99–2.63), and high serum triglyceride levels (OR 1.47, CI 1.30–1.65) was significantly higher in the first than in the fourth quartile of serum 25-(OH) D levels (p<0.001 for all)	Significant association between low vitamin D levels and increased CVD risk factors
Wang *et al*.[25], 2012	Meta-analysis of 19 prospective studies with 6123 CVD cases in 65 994 participants that assessed the association of 25-OH vitamin D concentration with CVD risk	There is a generally linear, inverse association between circulating 25-OH vitamin D ranging from 20 to 60 nmol/L and risk of CVD	Low vitamin D levels are associated with an increased risk of CVD
Chowdhury *et al*.[11], 2014	Systematic review and meta-analysis of 73 cohort studies (849 412 participants) and 22 randomized controlled trials (vitamin D given alone versus placebo or no treatment; 30 716 participants) that reported associations between vitamin D and cause-specific mortality outcomes	Comparing the bottom versus the top thirds of baseline circulating 25-OH vitamin D distribution, the pooled relative risk was 1.35 (95% CI 1.13–1.61) for death from CVD	Low vitamin D levels are associated with increased risk of death from CVD
Barbarawi *et al*.[27], 2019	Vitamin D supplementation and CVD risks in more than 83 000 individuals in 21 randomized clinical trials: A meta-analysis	Vitamin D supplementation compared with placebo was not associated with reduced major adverse cardiovascular events (RR 1.00 [95% CI 0.95–1.06]; p=0.85) nor the secondary end points of myocardial infarction, stroke, CVD mortality (RR 0.98 [95% CI 0.90–1.07]; p=0.68), or all-cause mortality	Limitation: Most of the included trials had not prespecified CVD as the primary endpoint and were underpowered for CVD events
Coronary artery disease			
Giovannucci *et al*.[15], 2008	Cohort study analysing data from the Health Professionals Follow-up Study in 18 225 men aged 40–75 years	High cholesterol combined with a vitamin D deficiency increased the risk of myocardial infarction by about 2.4 times (95% CI 1.53–3.84; p<0.001 for trend), but a vitamin D deficiency alone accounted for 2 times that risk (95% CI 1.24–3.54; p=0.02 for trend), or 83% of the entire increased risk	Vitamin D deficiency may be more predictive of a future heart attack than cholesterol status and other risk factors
Bahrami *et al*.[26], 2020	Vitamin D supplementation effects on the clinical outcomes of patients with coronary artery disease: A systematic review and meta-analysis; included 4 randomized controlled trials (RCTs), 307 coronary artery disease (CAD) patients	Vitamin D supplementation had significant favourable effects on diastolic blood pressure (BP) (–2.96 [95% CI –5.49, –0.43], p=0.02) and parathyroid hormone (–14.05 [95% CI –19.87, –8.23], p<0.001). However, it had no significant effects on the hs-C-reactive protein mean difference, total cholesterol, triglyceride, low- and and high-density lipoprotein	All included studies had a small sample size and a short duration of intervention

contd.

Author, year	Details of the study	Study outcome	Remarks
Zhang *et al.*[16], 2022	Meta-analysis of 13 studies including 17 892 patients with CAD evaluating the value of 25-OH vitamin D level in predicting cardiovascular or all-cause mortality, and major adverse cardiovascular events (including death, non-fatal myocardial infarction, heart failure, revascularization, stroke, etc.)	The pooled adjusted risk ratio (RR) was 1.60 (95% CI 1.35–1.89) for all-cause mortality, 1.48 (95% CI 1.28–1.71) for cardiovascular mortality, and 1.33 (95% CI 1.18–1.49) for major adverse cardiovascular events	Low vitamin D levels are associated with increased all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events
Hypertension			
Pfeifer *et al.*[22], 2001	An 8-week study of 148 vitamin D-deficient older women. Supplemental vitamin D (800 IU) plus calcium (1200 mg) was given	9% decrease in systolic BP with supplemental vitamin D plus calcium compared with calcium alone was demonstrated	Vitamin D supplementation resulted in a decreased systolic BP
Beveridge *et al.*[30], 2015	A meta-analysis of 46 randomized placebo-controlled clinical trials that used vitamin D supplementation for a minimum of 4 weeks for any indication and reported BP data.	No effect of vitamin D supplementation was seen on systolic BP (effect size, 0.0 [95% CI –0.8 to 0.8] mmHg; p=0.97) or diastolic BP (effect size, –0.1 [95% CI –0.6 to 0.5] mmHg; p=0.84)	Vitamin D supplementation did not affect systolic BP
Qi *et al.*[29], 2017	The effect of vitamin D supplementation on hypertension in non-CKD populations: A systematic review and meta-analysis. Included 8 RCTs, 917 patients	Vitamin D supplementation slightly reduced the systolic BP by 1.964 mmHg (95% CI 0.362–3.566; p=0.016), but did not lower diastolic BP (standardized mean difference [SMD] –0.087, 95% CI –0.208–0.033; p=0.155)	Systolic BP reduction with vitamin D supplementation is not statistically significant compared to placebo
Stroke			
Manouchehri *et al.*[9], 2017	Case–control study	Vitamin D deficiency was associated with an increased risk of ischaemic stroke by nearly 7-fold compared to controls (p<0.001, OR 7.17, 95% CI 3.36–15.29). A 13-fold increase (p<0.001, 95% CI 5.03–36.02) in the risk of large vessel stroke, and a 4.37-fold increase (p=0.001, 95% CI: 1.8–10.4) for small vessel stroke was observed.	Deficiency of vitamin D is associated with increased risk of ischaemic stroke
Judd *et al.*[10], 2016	Case–control study, plasma 25-(OH) vitamin D was measured in 610 participants who developed incident stroke (cases) and in 937 stroke-free individuals from a stratified comparison cohort	Lower 25-OH vitamin D concentrations were associated with a higher risk of stroke (25-OH vitamin D >30 ng/ml reference; 25-OH vitamin D concentrations 20–30 ng/ml, hazard ratio 1.33, 95% CI 0.89–1.96; 25-OH vitamin D <20 ng/ml, hazard ratio 1.85, 95% CI 1.17–2.93)	Vitamin D deficiency is a risk factor for incident stroke, and the strength of this association does not appear to differ by race
Su *et al.*[28], 2021	Association between vitamin D and risk of stroke: A PRISMA-compliant systematic review and meta-analysis. Included 20 cohort studies (213 276 participants), a case–control analysis (13 642 participants). 15 RCTs (41 146 participants given vitamin D supplementation and 41 163 participants given a placebo)	Higher circulating levels of 25(OH) vitamin D were associated with a reduced risk of stroke (odds ratio/relative risk= 0.78, 95% CI: 0.70–0.86, I^2=41.5%, p=0.025). Vitamin D supplementation did not influence the risk of stroke (hazard ratio=1.05, 95% CI: 0.96-1.14, I^2=2.3%, p=0.425)	Risk of stroke is less in patients with higher levels of vitamin D, but the supplementation of vitamin D does not influence the risk of stroke

TABLE 2. Studies of vitamin D supplementation in disorders of the nervous system

Author, year	Details of the study	Study outcome	Additional remarks
Multiple sclerosis (MS)			
Jagannath *et al*.[42], 2018	Meta-analysis: To evaluate the benefit and safety of vitamin D supplementation for reducing disease activity in people with MS; included 12 RCTs, 933 patients	Vitamin D did not affect the annualized relapse rate at 52 weeks' follow-up; on the Expanded Disability Status Scale at 52 weeks' follow-up; and on MRI gadolinium-enhancing T1 lesions at 52 weeks' follow-up	Vitamin D has no beneficial effects in improving the annualized relapse rate
Depression			
Jorde *et al*.[43], 2008	Cross-sectional study and randomized double blind controlled trial of 20 000 or 40 000 IU vitamin D per week versus placebo for 1 year in 441 subjects	Those receiving a high dose of vitamin D had a significant improvement in depressive symptom scale scores after 1 year, versus those receiving a placebo	Supplementation of vitamin D resulted in improvement of depressive symptoms
Jhee *et al*.[31], 2017	533 CKD patients included. The association between vitamin D deficiency and depression was evaluated by multivariate logistic regression analysis	Prevalence of depression was significantly higher in CKD patients with (vs. without) vitamin D deficiency. Regression analysis showed that vitamin D deficiency was a significant independent predictor of depression after adjusting for confounding factors	Vitamin D deficiency is a significant predictor of depression
Vellekkatt *et al*.[39], 2019	Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. Included 4 RCTs, 948 patients	Vitamin D supplementation favourably impacted depression ratings in major depression. Pooled mean effect size for vitamin D supplementation on depressive symptom ratings in major depression was 0.58 (95% CI, 0.45–0.72)	Supplementation of vitamin D resulted in improvement of depressive symptoms Limitations: Limited number of trials available and inherent methodological bias noted in a few of them
Alzheimer's disease			
Oudshoorn *et al*.[32], 2008	Cross-sectional study of patients with Alzheimer's disease	An association was found between Mini-Mental Status Exam (MMSE) test scores and serum 25-OH vitamin D levels, with a beta-coefficient of 0.05 (p=0.01). Vitamin D-sufficient patients had significantly higher MMSE scores as compared to vitamin D-in sufficient ones	Those with sufficient vitamin D levels had significantly higher MMSE scores than those with insufficient vitamin D levels
Du *et al*.[40], 2020	Vitamin D supplement for prevention of Alzheimer's disease: A systematic review and meta-analysis. Included 9 RCTs, 2345 participants	No significant difference in the MMSE, verbal fluency, verbal memory, visual ability, and attention cores between the intervention and comparison groups (Standardized mean difference [SMD]=–0.05, 95% CI=–0.51 to 0.41; SMD=–0.01, 95% CI=–0.13 to 0.11; SMD=0.12, 95% CI=–0.45 to 0.69; SMD=0.42, 95% CI=–0.15 to 1.00; and SMD=0.01, 95% CI=–0.24 to 0.27, respectively).	The current evidence does not support a beneficial effect of vitamin D supplements in preventing Alzheimer's disease

contd.

Cancer

In vitro studies have proposed a possible anticancer effect of vitamin D, as it may influence multiple cellular processes such as proliferation, differentiation, angiogenesis, and apoptosis.[55]

Proposed mechanisms of vitamin D in gynaecological cancers. Vitamin D receptor genes, which are influenced by vitamin D, play important roles in the mammary gland by regulating calcium transport during lactation, hormone

Author, year	Details of the study	Study outcome	Additional remarks
Parkinson's disease			
Knekt *et al.*[33], 2010	3173 men and women; 29-year follow-up period. Estimates of the relationship between serum vitamin D concentration and Parkinson's disease incidence were calculated using Cox's model	Individuals with higher serum vitamin D concentrations showed a reduced risk of Parkinson's disease. The relative risk between the highest and lowest quartiles was 0.33 (95% CI 0.14–0.80) after adjustment for sex, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index, and month of blood draw	High vitamin D status protects against Parkinson's disease
Zhou *et al.*[41], 2019	The association between vitamin D status, vitamin D supplementation, sunlight exposure, and Parkinson's disease: A systematic review and meta-analysis. Included 5 case–control studies (n=2075), 1 cohort study (n=199), and 2 RCTs (n=144)	Insufficiency and deficiency of 25-(OH) vitamin D and reduced exposure to sunlight were significantly associated with an increased risk of Parkinson's disease. However, vitamin D supplements resulted in no significant benefits in improving motor function for patients with Parkinson's disease.	Vitamin D supplementation does not improve motor function in patients with Parkinson's disease

differentiation, and milk production. It has been reported that variations in the vitamin D receptor (VDR) genes may increase the risk of breast cancer.[56]

It was found that polymorphism in the vitamin D receptor (FokI gene) is associated with an increased risk of ovarian cancer and that the VDR can be a preventive target for ovarian cancer.[57] Significantly increased 24-hydroxylase mRNA levels were found in endometrial cancer tissue compared to tissues from healthy controls.[58] The 24-hydroxylase enzyme is responsible for the catabolism of vitamin D and, potentially, its increase may reduce the cellular effects of calcitriol.[59]

Evidence related to vitamin D supplementation in gynaecological cancers. A recent meta-analysis suggests a protective relationship between circulating vitamin D and breast cancer development in premenopausal women.[60] But another meta-analysis concluded that there is insufficient evidence to support the efficacy of vitamin D supplementation in breast cancer risk and change of mammography density.[61]

In a meta-analysis, it was concluded that the supplementation of vitamin D could not decrease the risk of ovarian cancer.[62] A previous population-based case–control study done in African American women also revealed that vitamin D supplementation alone was not associated with a decreased risk of ovarian cancer.[63] In a prospective cohort analysis, it was concluded that there was no significant association between total dietary vitamin D and endometrial cancer incidence.[64]

The overall evidence does not suggest a correlation between vitamin D supplementation and the incidence of gynaecological malignancies.

Proposed mechanisms of vitamin D in other cancers. Vitamin D exerts an anticancer mechanism by inhibiting tumour cell growth and inducing apoptosis. These alternative pathways involve improving DNA repair, providing antioxidant protection, and modulating the immune system. Additionally, 1,25-dihydroxyvitamin D may regulate various cell types, such as stromal cells, endothelial cells, and immune system cells, potentially contributing to the prevention of cancer through vitamin D mediation.[65]

Evidence related to vitamin D supplementation in other cancers. A meta-analysis of 9 studies has revealed that vitamin D intake and blood 25-(OH) D levels were inversely associated with the risk of colorectal cancer (Table 4).[66] In a post hoc subgroup analysis, vitamin D supplementation reduced the risk of relapse or death in patients with digestive tract cancer.[67] However, a previous randomized placebo-controlled trial involving 36 282 postmenopausal women had concluded that daily supplementation of calcium with vitamin D did not affect the incidence of colorectal cancer.[68] Another meta-analysis suggests that vitamin D taken from diet and/or supplements has no association with the incidence of skin cancer.[69]

In prostate cancer, a meta-analysis also found that vitamin D supplementation does not provide any beneficial effects to patients.[70] An updated meta-analysis of RCTs also concluded that vitamin D supplementation did not reduce total cancer incidence.[71]

The overall evidence on the relationship between vitamin D and various types of cancers remains inconclusive, with mixed findings from meta-analyses and studies, indicating the need for further research to establish a clearer under-standing of the potential associations.

Autoimmune diseases

Observational studies have identified a connection between deficient vitamin D levels and increased risk of autoimmune disorders like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and autoimmune thyroiditis.[72]

Proposed mechanisms of vitamin D in autoimmune diseases. Molecular studies propose that vitamin D deficiency in RA intensifies inflammatory responses and encourages osteoclast-mediated bone resorption. Vitamin D treatment in RA exhibits anti-inflammatory effects by downregulating

TABLE 3. Studies of vitamin D supplementation in diabetes mellitus

Author, year	Details of the study	Study outcome	Remarks
Diabetes mellitus			
Hypponen *et al*.[52], 2001	A study on 10 366 children in Finland over 31 years	2000 IU of vitamin D per day during their first year of life can reduce the risk of type 1 diabetes by approximately 80% (95% CI 0.05–0.89)	Vitamin D supplementation in high doses is associated with reduced risk of type 1 diabetes
Pittas *et al*.[49], 2006	An interventional study of 83 779 women with no history of diabetes over 2–4 years	Combined daily intake of >1200 mg calcium and >800 IU vitamin D was associated with 33% (RR=0.67, 95% CI 0.49–0.90) lower risk of type 2 diabetes as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D	Supplementation with high doses of vitamin D is associated with decreased risk of type 2 diabetes
Jamilian *et al*.[53], 2016	Prospective randomized, double-blind, placebo-controlled trial, 60 participants with gestational diabetes mellitus were divided into 2 groups of either 1000 IU vitamin D3 and 1000 mg evening primrose oil (EPO) or placebo for 6 weeks	After 6 weeks of intervention, changes in fasting plasma glucose (–3.6±7.5 vs. 1.5± 11.4 mg/dl, p=0.04), serum insulin concentrations (–2.0±5.3 vs. +4.6±10.7 μIU/ml, p=0.004), homeostasis model of assessment (HOMA) insulin resistance (–0.5±1.1 vs. 1.1± 2.5, p=0.003), HOMA-B cell function (–7.7±23.3 vs. 17.4± 42.9, p=0.007) and the quantitative insulin sensitivity check index (0.01±0.02 vs. –0.01±0.02, p=0.007) in the vitamin D plus EPO group were significantly different from the placebo group	Significant decrease in fasting blood sugar and serum insulin concentration in the vitamin D plus EPO group compared to the placebo group
Zhang *et al*.[45], 2017	Efficacy of vitamin D3 in patients with diabetic nephropathy: An updated meta-analysis of 24 studies including 1978 patients	Pooled results indicated that vitamin D3 had a significant effect in reducing albuminuria (SMD=–0.23, 95% CI: –0.30, –0.15) and that the vitamin D3 group had a lower ratio of urinary microalbumin to creatinine than the control group (SMD=–0.49, 95% CI: –0.90, –0.08).	Based on the evidence of this study, vitamin D3 could be suggested as a recommended drug for patients with diabetic nephropathy in clinical practice
Li *et al*.[51], 2018	The effect of vitamin D supplementation on glycaemic control in Type 2 diabetes patients: A systematic review and meta-analysis included 20 studies (*n*=2703)	Vitamin D supplementation resulted in a significant improvement in insulin resistance, i.e. reduction in HOMA-IR (SMD=–0.57; 95% CI: –1.09 to –0.04). No improvement in fasting blood sugar and HbA1c levels	Vitamin D supplementation improves insulin resistance, but not the fasting blood sugar and HbA1c levels
Pittas *et al*.[54], 2020	A meta-analysis of longitudinal observational studies that report on the association between blood 25-(OH) vitamin D level and incident diabetes.	In the 3 large trials that were specifically designed and conducted for the prevention of diabetes, vitamin D supplementation, when compared with placebo, reduced the risk of developing diabetes by 10% to 13% (hazard ratio 0.87; 95% CI: 0.68–1.09) in persons with prediabetes not selected for vitamin D deficiency	Supplementation of vitamin D reduces the risk of diabetes in the prediabetic population

contd.

Author, year	Details of the study	Study outcome	Remarks
Barbarawi *et al.*[50], 2020	Meta-analysis of RCTs testing vitamin D supplementation in the prevention of type 2 diabetes	The RR for vitamin D compared with placebo was 0.96 (95% CI 0.90–1.03); p=0.3. In trials testing moderate to high doses of supplementation (≤1000 IU/day), all conducted among participants with prediabetes, the RR for vitamin D compared with placebo was 0.88 (95% CI, 0.79–0.99). In contrast, the trials testing lower doses, which were conducted in general population samples, showed no risk reduction (RR, 1.02; 95% CI, 0.94–1.10; p value, interaction by dose=0.04)	In patients with prediabetes, vitamin D supplementation at moderate to high doses (≤1000 IU/day) significantly reduced the incidence of type 2 diabetes, compared with placebo

TABLE 4. Studies of vitamin D supplementation in cancers

Author, year	Details of the study	Study outcome	Remarks
Breast cancer			
Estébanez *et al.*[60], 2018	Meta-analysis examining the effects of vitamin D intake on breast cancer risk. 68 studies published between 1998 and 2018 were analysed	Protective effect of 25-(OH) vitamin D and breast cancer in both cohort (RR=0.85, 95% CI 0.74–0.98) and case–control studies (OR=0.65, 95% CI 0.56–0.76). However, analysing by menopausal status, the protective vitamin D–breast cancer association persisted only in the premenopausal group (OR=0.67, 95% CI 0.49–0.92) when restricting the analysis to nested case–control studies	High serum levels of 25-(OH) vitamin D have a protective effect on breast cancer risk in premenopausal women
Li *et al.* [61], 2021	Systematic review and meta-analysis to clarify the efficacy of vitamin D supplementation on the risk of breast cancer. 7 RCTs were identified for the effect of vitamin D on the risk of breast cancer, with 19 137 females included in the meta-analysis	No statistically significant effect of vitamin D on risk of breast cancer was found in classical random-effects meta-analysis (RR=1.04, 95% CI: 0.84–1.28, p=0.71). There was no statistically significant effect of vitamin D on mammography density observed: mean difference =0.46, 95% CI: –2.06 to 2.98, p=0.72	Vitamin D supplementation has no association with the risk of breast cancer
Ovarian cancer			
Qin *et al.*[63], 2016	490 ovarian cancer cases and 656 women of African–American descent were recruited, in a population-based case–control study. Multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% CIs	Calcium intake was associated with a decreased risk of ovarian cancer (OR=0.51, 95 CI: 0.30–0.86; p-trend: 0.009), but vitamin D intake was not. Longer sun exposure in summer months was found to predict a lower risk (OR=0.71, 95% CI: 0.51–0.99; p-trend: 0.049)	Vitamin D supplementation alone was not found to be associated with a decreased risk of ovarian cancer in African–American women
Xu *et al.*[62], 2021	A dose-response relationship meta-analysis to analyse the association between vitamin D/calcium intake and 25-(OH) vitamin D and risk of ovarian cancer. 21 studies involving 980 008 participants were included	No significant association was observed between total vitamin D intake and ovarian cancer risk (RR: 1.02; 95% CI, 0.89–1.16, p=0.81). Further subgroup analysis suggested that neither dietary vitamin D intake (RR: 0.80; 95% CI, 0.62–1.03, p=0.09) nor supplementary vitamin D intake (RR: 0.98; 95% CI, 0.85–1.13, p=0.80) was associated with the risk of ovarian cancer	Vitamin D intake is not associated with the risk of ovarian cancer

contd.

Author, year	Details of the study	Study outcome	Remarks
Endometrial cancer			
Liu *et al*.[64], 2013	The prospective cohort analysis of predicted 25-(OH) vitamin D and total dietary vitamin D intake used the Cox proportional hazards model and involved 644 incident endometrial cancer events from 1986 to 2006 in the Nurses' Health Study	There was no significant association between predicted 25-(OH) vitamin D and endometrial cancer incidences, with hazard ratio for the highest (versus the lowest) quintile of predicted 25-(OH) vitamin D as 1.00 (95% CI 0.73–1.36; p-trend=0.33)	No significant association between the incidence of endometrial cancer and vitamin D intake
Other cancers			
Wactawski-Wende *et al*.[68], 2006	Randomized, double-blind, placebo-controlled trial; 18 176 post-menopausal women received 1000 mg calcium carbonate and 400 IU of vitamin D3, and 18 106 received a matching placebo for an average of 7 years.	Daily supplementation of calcium with vitamin D for 7 years had no effect on the incidence of colorectal cancer among post-menopausal women. (Hazard ratio, 1.08; 95% CI 0.86–1.34; p=0.51)	The long latency associated with the development of colorectal cancer, along with the 7-year duration of the trial, may have contributed to this null finding
Ma *et al*.[66], 2011	Systematic review and meta-analysis of prospective studies assessing the association of vitamin D intake or blood levels of 25-(OH) vitamin D with the risk of colorectal cancer. Nine studies on vitamin D intake and 9 studies on blood 25-(OH) vitamin D levels were included in the meta-analysis	The pooled RRs of colorectal cancer for the highest versus lowest categories of vitamin D intake and blood 25-(OH) vitamin D levels were 0.88 (95% CI 0.80–0.96) and 0.67 (95% CI 0.54–0.80), respectively. There was no heterogeneity among studies of vitamin D intake (p=0.19) or among studies of blood 25-(OH) vitamin D levels (p=0.96). A 10 ng/ml increment in blood 25-(OH) vitamin D level conferred a RR of 0.74 (95% CI 0.63–0.89)	Vitamin D intake and blood 25-(OH) vitamin D levels were inversely associated with the risk of colorectal cancer
Caini *et al*.[69], 2014	A meta-analysis to evaluate the association of vitamin D serum levels and dietary intake with cutaneous melanoma (CM) and non-melanoma skin cancer (NMSC) risk and melanoma prognostic factors; 20 papers were included for an overall 1420 CM and 2317 NMSC	The summary relative risks (SRRs) from random effects models for the association of highest versus lowest vitamin D serum levels were l1.46 (95% CI 0.60–3.53) and 1.64 (95% CI 1.02–2.65) for CM and NMSC, respectively. The SRR for the highest versus lowest quintile of vitamin D intake was 0.86 (95% CI 0.63–1.13) for CM and 1.03 (95% CI 0.95–1.13) for NMSC	Vitamin D taken from diet and/or supplements is not associated with the incidence of skin cancer
Shahvazi *et al*.[70], 2019	A systematic review and meta-analysis of clinical trials on the effect of vitamin D supplementation on prostate cancer	The analysis of controlled clinical trials revealed that the prostate specific antigen (PSA) change from baseline (weighted mean difference= –1.66 ng/ml, 95% CI –0.69–0.36, p=0.54), PSA response proportion (RR=1.18, 95% CI 0.97–1.45, p=0.14) and mortality rate (risk ratio=1.05, 95% CI 0.81–1.36; p=0.71) were not significantly different between vitamin D supplementation and placebo groups. Single-arm trials revealed that vitamin D supplementation had a modest effect on PSA response proportion: 19% of those enrolled had at least a 50% reduction in PSA by the end of treatment (95% CI 7%–31%; p=0.002)	High-dose vitamin D supplementation does not appear to provide any advantages for patients with prostate cancer and thus should not be advised as a treatment option

contd.

Author, year	Details of the study	Study outcome	Remarks
Kanno *et al*.[67], 2023	Post hoc subgroup analysis of the AMATERASU randomized, double-blind, placebo-controlled clinical trial (Vitamin D3 2000 IU/day) supplementation or placebo)	In the p53-immunoreactive subgroup (80 patients), relapse or death occurred in 9 of 54 patients (16.7%) in the vitamin D group and 14 of 26 patients (53.8%) in the placebo group; 5-year relapse-free survival (RFS) was significantly higher in the vitamin D group (13 patients [80.9%]) than the placebo group (1 patient [30.6%]; hazard ratio [HR], 0.27; 95% CI 0.11–0.61; p=0.002). This was significantly different from 272 patients in the non–p53 immunoreactive subgroup, in which vitamin D did not affect 5-year RFS (vitamin D: 35 of 158 patients [22.2%] vs placebo 24 of 114 patients [21.1%]; HR 1.09; 95% CI 0.65–1.84; p for interaction=0.005)	Vitamin D supplementation reduced the risk of relapse or death in the subgroup of patients with digestive tract cancer who were p53 immunoreactive

IL-6 and TNF-β, as well as enhancing the differentiation of regulatory T and B cells.[2]

Regarding SLE, vitamin D's positive impact may stem from its ability to expand regulatory T cells and reduce frequencies of Th1 cells, Th17 cells, memory B cells, and auto-antibodies, with lower vitamin D levels correlating with increased SLE severity and higher disease activity.[73,74]

Evidence related to vitamin D supplementation in autoimmune diseases. A meta-analysis of 7 studies concluded that vitamin D supplementation reduced anti-ds DNA positivity in SLE and could reduce RA recurrence (Table 5).[75] Similar findings were obtained in a previous study in which supplementation of vitamin D was found to improve the inflammatory and haemostatic marker levels and reduce disease activity in patients with SLE.[76]

A previous study done in 30 000 women had suggested an inverse association between greater intake of vitamin D and the risk of RA.[77] A meta-analysis of more than 130 studies demonstrated an inverse association between vitamin D and the development of several autoimmune diseases, such as SLE, thyrotoxicosis, type 1 diabetes, multiple sclerosis, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive RA, and polymyalgia rheumatica.[72]

To conclude, vitamin D supplementation has been shown to consistently reduce anti-ds DNA in SLE, lower recurrence of RA, and is inversely associated with various autoimmune diseases.

Respiratory disorders

A correlation between a deficiency of vitamin D and an increased susceptibility to respiratory ailments such as asthma, chronic obstructive pulmonary disease (COPD), and tuberculosis (TB) has been revealed in different epidemiological and observational investigations.[78] Also, various observational studies reported that reduced vitamin D levels resulted in a higher infection risk, mortality, and severity in Covid-19 infection.[79]

Proposed mechanisms of vitamin D in diseases of the respiratory system. Vitamin D exerts a significant influence on the respiratory system by impacting both pulmonary cell biology and immunity. This concept is substantiated by the elevated expression of CYP27B1, responsible for activating vitamin D, observed in lung epithelial cells.[80] Additionally, research underscores the notable association between vitamin D receptor (VDR) polymorphism and a heightened susceptibility to lower respiratory tract infections.[81]

Activation of monocytes via TLR2/1 results in the vitamin D-dependent synthesis of cathelicidin, which exhibits antimicrobial activity against intracellular *Mycobacterium tuberculosis*.[82] Additionally, vitamin D positively influences various immunological pathways across different asthma subtypes, regulating the functions of lymphocytes, mast cells, antigen-presenting cells, and structural cells to dampen excessive inflammatory reactions.[83]

Evidence related to vitamin D supplementation in diseases of the respiratory system. In few clinical trials, vitamin D supplementation provided some protective effects against TB and influenza.[84,85] A meta-analysis of 7 studies has shown that vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (Table 6).[86] Another meta-analysis concluded that vitamin D supplementation showed no influence on the improvement of sputum smear-negative conversion rates and body mass index (BMI), as well as the decrease in ESR in patients with pulmonary TB.[87]

A recent meta-analysis on Covid-19 patients suggested that vitamin D supplementation does not have a significant impact on reducing mortality, intensive care unit (ICU) admission, and the rates of mechanical ventilation or intubation among Covid-19 patients.[88] Analysing the 8 included RCTs, a meta-analysis concluded that there were no significant differences found in the quantitative synthesis of clinical outcomes in patients with cystic fibrosis.[89]

Overall, while vitamin D supplementation appears beneficial for reducing asthma exacerbation requiring corticosteroids, it shows no significant impact on clinical outcomes of TB, Covid-19, or cystic fibrosis based on various meta-analyses.

Pregnancy and foetal outcomes

In addition to improving the mother's vitamin D level, vitamin D supplementation during pregnancy may lower the risk of

TABLE 5. Studies of vitamin D supplementation in autoimmune diseases

Author, year	Details of the study	Study outcome	Remarks
Autoimmune disorders			
Merlino *et al.*[77], 2004	A study of 30 000 women aged 55 to 69 over 11 years	Inverse association between greater intake of vitamin D and RA risk. Vitamin D from supplements showed a stronger influence in RA development than did dietary vitamin D. (RR 0.67, 95% CI 0.44–1.00, p for trend=0.05)	Vitamin D intake reduces the risk of RA
Abou-Raya *et al.*[76], 2013	Vitamin D intake (2000 IU/day for 12 months) in SLE patients	The overall prevalence of sub-optimal and deficient 25-(OH) vitamin D serum levels among patients with SLE at baseline was 69% and 39%, respectively. Lower 25-(OH) vitamin D levels correlated significantly with higher SLE disease activity. At 12 months of therapy, there was a significant improvement in levels of inflammatory and haemostatic markers as well as disease activity in the treatment group compared to the placebo group	Intake improved the inflammatory and haemostatic marker levels and reduced disease activity
Lima *et al.*[75], 2016	In juvenile SLE, cholecalciferol supplementation (50 000 IU/ week) was administered for 24 weeks. A randomized, double-blind, placebo-controlled trial	At the end of the intervention, a significant improvement in SLEDAI (SLE Disease Activity Index) (p=0.01) and in ECLAM (European Consensus Lupus Activity Measurement) was observed in the juvenile-onset SLE-Vit D group compared to the juvenile-onset SLE-PL group. A reduction of fatigue related to social life score was found in the juvenile-onset SLE-Vit D group compared to the juvenile-onset SLE-PL group (p=0.008)	Cholecalciferol supplementation is effective in decreasing disease activity and improving fatigue in juvenile-onset SLE patients
Franco *et al.*[74], 2017	A systematic review and meta-analysis of 7 studies on vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases	After vitamin D supplementation, RA recurrence decreased; however, not significantly (risk difference= –0.10, 95% CI=–0.21, 0.00, p=0.05). No statistical significance was observed regarding visual analog scale (mean difference= 2.79, 95% CI=–1.87, 7.44, p=0.24) and disease activity score 28 (mean difference=–0.31, 95% CI=–0.86, 0.25, p=0.28). Regarding systemic lupus erythematosus, anti-ds DNA positivity was significantly reduced (risk difference=–0.10, 95% CI=–0.18, –0.03; p=0.005)	Vitamin D supplementation reduced anti-ds DNA positivity in SLE and could possibly reduce RA recurrence

preterm birth, low birthweight, and pre-eclampsia. Nevertheless, there is not much data on the advantages and disadvantages of using vitamin D supplements alone to improve the health of expectant mothers and infants.[90,91]

Proposed mechanisms of vitamin D in pregnancy. Pre-eclampsia and vitamin D deficiency are directly and indirectly associated through biologic mechanisms, including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, and hypertension. Vitamin D may influence early placental development and thus, the development of pre-eclampsia through its role in gene regulation and expression; yet, more studies are needed to confirm this.[92]

Vitamin D supplementation promotes good foetal growth and favourable maternal–foetal outcomes, and this might be due to the physiological effects of vitamin D on gestation (greater angiogenesis, effects on renin gene expression, and immunomodulation of inflammatory reactions).[93]

The evidence related to vitamin D supplementation in diseases of the respiratory system is given in Table 7.

RECENT FINDINGS FROM MEGATRIALS

Many extra-skeletal effects are still unknown to have a clear

TABLE 6. Studies of vitamin D supplementation in diseases of the respiratory system

Author, year	Details of the study	Study outcome	Remarks
Diseases of the Respiratory System			
Asthma			
Jolliffe *et al*.[86], 2017	Systematic review and meta-analysis of individual participant data from randomized controlled trials of vitamin D3 or vitamin D2 supplementation in people with asthma that reported incidence of asthma exacerbation.	Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0.74, 95% CI 0.56–0.97; p=0.03; 955 participants in 7 studies; high-quality evidence).	Supplementing with vitamin D decreased the rate of asthma exacerbations.
Tuberculosis (TB)			
Martineau *et al*.[84], 2007	A double-blind randomized controlled trial in which 192 healthy adult TB contacts were given a single oral dose of 2.5 mg vitamin D. BCG-lux luminescence was measured *in vitro*.	Significantly enhanced participants' whole blood ability to restrict functional whole blood (BCG-lux) luminescence *in vitro*. (mean BCG-lux luminescence ratio at follow-up: 0.57 vs. 0.71, respectively; 95% CI for difference 0.01–0.25; p=0.03)	Vitamin D enhances TB contacts' immunity to mycobacteria.
Wang *et al*.[87],2018	A systematic review and meta-analysis on the efficacy and safety of vitamin D supplementation for pulmonary TB. Five studies were included in this meta-analysis.	Overall, compared with placebo intervention, vitamin D supplementation was found to have no significant effect on sputum smear negative conversion rates (RR=0.99; 95% CI=0.91 to 1.07; p=0.77), BMI (MD=0.11; 95% CI=–0.85 to 1.07; p=0.82), and ESR (MD=–2.29; 95% CI=–8.87 to 4.30; p=0.50).	Supplementation of vitamin D has no effect on sputum conversion rates in patients with TB.
Influenza			
Urashima *et al*.[85], 2010	Japanese randomized, controlled trial, children were given a daily vitamin D supplement of 1200 IU.	40% lower rate of influenza type A compared with those given a placebo; there was no significant difference in rates of influenza type B.	Vitamin D supplementation during the winter may reduce the incidence of influenza A, especially in specific subgroups of schoolchildren.
Covid-19			
Zhang *et al*.[88], 2023	A systematic review and meta-analysis of randomized controlled trials and cohort studies that examined the relationship between vitamin D supplementation and mortality, ICU admission, and mechanical ventilation or intubation rates among Covid-19 patients.	Pooled analysis of randomized controlled trials showed that vitamin D supplementation did not have a significant effect on reducing mortality (RR=0.94, 95% CI 0.69–1.29, p=0.7), while the results of cohort studies indicated that vitamin D indicated that vitamin D supplementation had a positive impact on reducing mortality among Covid-19 patients (RR=0.33, 95% CI 0.23–0.47, p<0.001). There was no statistically significant difference in the rates of ICU admission (RCTs: RR=0.64, 95% CI 0.38–1.08, p=0.10; cohort studies: RR=0.32, 95% CI 0.08–1.29, p=0.109) or rates of mechanical ventilation or intubation (RCTs: RR=0.77, 95% CI 0.58–1.02, p=0.07; cohort studies: RR=0.93, 95% CI 0.55–1.58, p=0.789).	Vitamin D supplementation does not have a significant impact on reducing mortality, ICU admission, rates of mechanical ventilation or intubation among Covid-19 patients.

contd.

causal relationship with vitamin D. Based on the combined data in the VITAL, ViDA, and D2d randomized clinical trials (>30 000 participants), vitamin D supplementation does not prevent falls, cancer, cardiovascular events, or the development of type 2 diabetes mellitus in adults with normal vitamin D levels (baseline serum 25-(OH) vitamin D >50 nmol/l). Some extra-skeletal benefits have been suggested for those with vitamin D deficiency in post hoc analysis. The effects

Author, year	Details of the study	Study outcome	Remarks
Cystic fibrosis			
Juhász *et al.*[89], 2021	Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis. Eight randomized controlled trials were included.	Analysing the 8 included RCTs, the intervention group had significantly higher serum 25-(OH) vitamin D levels, but there were no significant differences found in the quantitative synthesis of clinical outcomes, including bone disease, respiratory status, and immunological status-related outcomes.	Supplementation of vitamin D does not affect the clinical outcomes in patients with cystic fibrosis.

TABLE 7. Studies of vitamin D supplementation in pregnancy

Author, year	Details of the study	Study outcome	Remarks
De-Regil[91], 2016 (Up-date in 2019)	The authors searched the Cochrane pregnancy and childbirth group's trials register (23 February 2015), the international clinical trials registry platform (31 January 2015), the networked digital library of theses and dissertations (28 January 2015), and also contacted relevant organizations	Women who received vitamin D with calcium had a lower risk of pre-eclampsia than those not receiving any intervention (RR 0.51; 95% CI 0.32–0.80; 3 trials; 1114 women, moderate quality) vitamin D supplementation during pregnancy reduces the risk of preterm birth compared to no intervention or placebo (8.9% *v.* 15.5%; RR 0.36; 95% CI 0.14–0.93; 3 trials; 477 women, moderate quality). Vitamin D supplementation during pregnancy less frequently led to birthweight <2500 g than no intervention or placebo (RR 0.40; 95% CI 0.24–0.67; 3 trials; 493 women, moderate quality)	Supplementing pregnant women with vitamin D in a single or continued dose may reduce the risk of pre-eclampsia, low birthweight, and preterm birth
Asemi *et al.*[92], 2015	46 pregnant women randomly received either the multi-mineral-vitamin D supplements (n=23) or a placebo (n=23) for 9 weeks. Multi-mineral-vitamin D supplements: 800 mg calcium, 200 mg magnesium, 8 mg zinc, and 400 IU vitamin D3	Mean newborns' length (51.3± 1.7 vs. 50.3±1.2 cm, p=0.03) was significantly higher in multi-mineral-vitamin D group than in the placebo group. Multi-mineral-vitamin D supplements favourably influenced maternal SBP (–1.08 vs. 6.08 mmHg, p=0.001) and DBP (–0.44 vs. 3.05 mmHg, p=0.02)	Multi-mineral-vitamin D supplementation for 9 weeks in pregnant women at risk for pre-eclampsia resulted in increased newborn's length, increased circulating levels of maternal serum calcium, magnesium, zinc, and vitamin D, and led to decreased maternal SBP and DBP
Kabuyanga[93], 2024	1300 primigravid women <16 weeks of gestation were randomised with a 1:1 ratio to either the supplemented group (single monthly dose of cholecalciferol (60 000 IU) orally for 6 months or the control (B) group (no vitamin D or placebo)	Significant reduction in the risk of preeclampsia [RR=0.36 (0.19–0.69); p=0.001] and preterm delivery [RR=0.5 (0.32–0.78); p=0.002] observed in the intervention group. RR of 0.43 [(0.27–0.67); p<0.001] was found for low birth weight. The RR for caesarean section was 0.63 [(0.52–0.75); p<0.001]. The APGAR score at the 5th minute (p=0.021) and the size of the newborn were significantly higher in the supplemented group (p=0.005)	Single monthly dose (60 000 IU) of vitamin D supplementation, started in early pregnancy, significantly reduced the incidence of preeclampsia and its maternal and foetal complications

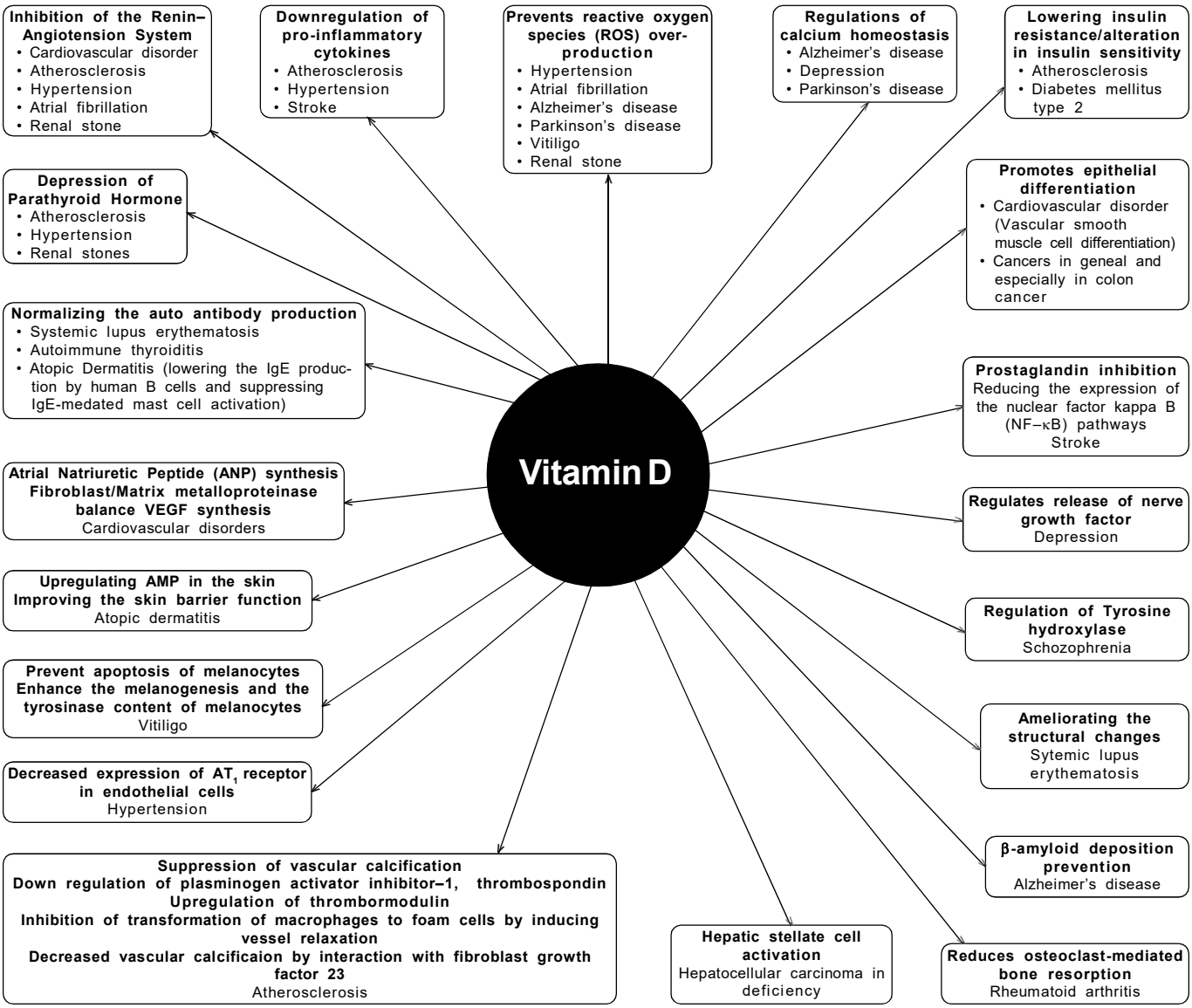


FIG 1. Non-calcaemic roles of vitamin D and its potential therapeutic applications

of consistently reduced serum 25-(OH) vitamin D concentrations on a range of outcomes have been examined in more than 60 Mendelian randomization trials, which are intended to reduce confounding bias. The majority of these studies have reported null effects. People with genetically reduced serum 25-(OH) vitamin D concentrations had a higher incidence of multiple sclerosis, according to four Mendelian randomization trials. A large number of intervention studies (and most probably Mendelian randomization studies) are still ongoing, and these might help provide a better understanding of who would benefit from vitamin D supplementation.[94]

CONCLUSION

Vitamin D deficiency is a global epidemic in the present era. Varied mechanisms of action and associations are available in the literature; however, translation into an evident clinical effect is still inconclusive. Multiple observational studies have suggested an association between deficiency of vitamin D and disorders of different systems, including cardiovascular, neurological, respiratory systems, and also in autoimmune disease, diabetes mellitus, and cancers.

However, the supplementation of vitamin D is not found to provide beneficial effects in most of these disorders. The heterogeneity of results and the opposing nature of evidence and opinions limit the use of vitamin D therapeutically. In most diseases, a preventive or adjuvant role of vitamin D may be of greater importance. Vitamin D level testing may also become routine. Vitamin D food fortification and differentiation of nutrient trials from drug trials may come into focus in the future.

Conflicts of interest. None declared

REFERENCES

1 Wolf G. The discovery of vitamin D: The contribution of Adolf Windaus. *J Nutr* 2004;**134:**1299–302.
2 Umar M, Sastry KS, Chouchane AI. Role of vitamin D beyond the skeletal function: A review of the molecular and clinical studies. *Int J Mol Sci* 2018;

19:1618.
3 Holick MF. Vitamin D and health: Evolution, biologic functions, and recommended dietary intakes for vitamin D. *Clin Rev Bone Miner Metab* 2009; **7:**2–19.
4 Nair R, Maseeh A. Vitamin D: The 'sunshine' vitamin. *J Pharmacol Pharmacother* 2012;**3:**118–26.
5 Friedman PA. Agents affecting mineral ion homeostasis and bone turnover. Chapter 44 In: Brunton L, editor. *Goodman & Gilman's The Pharmacological Basis of therapeutics*. 12th edition. McGraw Hill 2011:1275–1306.
6 Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 international units daily, 1999–2014. *JAMA* 2017;**317:**2448–50.
7 Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, *et al*. Vitamin D deficiency 2.0: An update on the current status worldwide. *Eur J Clin Nutr* 2020;**74:**1498–513.
8 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;**96:**1911–30.
9 Manouchehri N, Vakil-Asadollahi M, Zandifar A, Rasmani F, Saadatnia M. Vitamin D status in small vessel and large vessel ischemic stroke patients: A case–control study. *Adv Biomed Res* 2017;**6:**146.
10 Judd SE, Nanes MS, Ziegler TR, Wilson PWF, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: Results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr* 2008;**87:**136–41.
11 Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, *et al*. Vitamin D and risk of cause-specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;**348:**g1903.
12 Al Mheid I, Quyyumi AA. Vitamin D and cardiovascular disease: Controversy unresolved. *J Am Coll Cardiol* 2017;**70:**89–100.
13 Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, *et al*. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117:**503–11.
14 Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, *et al*. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: Data from the third national health and nutrition examination survey. *Arch Intern Med* 2007;**167:**1159.
15 Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: A prospective study. *Arch Intern Med* 2008; **168:**1174–80.
16 Zhang H, Wang P, Jie Y, Sun Y, Wang X, Fan Y. Predictive value of 25-hydroxyvitamin D level in patients with coronary artery disease: A meta-analysis. *Front Nutr* 2022;**9:**984–87.
17 Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, *et al*. Vitamin D supplements and the prevention of cancer and cardiovascular disease. *N Engl J Med* 2019;**380:**33–44.
18 Martinez-Moreno JM, Herencia C, Oca AM de, Muñoz-Castañeda JR, Rodríguez-Ortiz ME, Díaz-Tocados JM, *et al*. Vitamin D modulates tissue factor and proteaseactivated receptor 2 expression in vascular smooth muscle cells. *FASEB J* 2016;**30:**1367–76.
19 Zittermann A, Koerfer R. Protective and toxic effects of vitamin D on vascular calcification: Clinical implications. *Mol Aspects Med* 2008;**29:**423–32.
20 Molinari C, Uberti F, Grossini E, Vacca G, Carda S, Invernizzi M, *et al*. 1α,25-dihydroxycholecalciferol induces nitric oxide production in cultured endothelial cells. *Cell Physiol Biochem* 2011;**27:**661–8.
21 Bozic M, Álvarez Á, de Pablo C, Sanchez-Niño M-D, Ortiz A, Dolcet X, *et al*. Impaired vitamin D signaling in endothelial cells leads to an enhanced leukocyte-endothelium interplay: Implications for atherosclerosis development. *PLoS One* 2015;**10:**e0136863.
22 Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86:**1633–7.
23 Dong J, Wong SL, Lau CW, Lee HK, Ng CF, Zhang L, *et al*. Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. *Eur Heart J* 2012;**33:**2980–90.
24 Liu X, Nelson A, Wang X, Farid M, Gunji Y, Ikari J, *et al*. Vitamin D modulates prostaglandin E2 synthesis and degradation in human lung fibroblasts. *Am J Respir Cell Mol Biol* 2014;**50:**40–50.
25 Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, *et al*. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012;**5:**819–29.
26 Bahrami LS, Ranjbar G, Norouzy A, Arabi SM. Vitamin D supplementation effects on the clinical outcomes of patients with coronary artery disease: A systematic review and meta-analysis. *Sci Rep* 2020;**10:**12923.
27 Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, *et al*. Vitamin D supplementation and cardiovascular disease risks in more than 83,000 individuals in 21 randomized clinical trials: A meta-analysis. *JAMA Cardiol* 2019;**4:**765–76.
28 Su C, Jin B, Xia H, Zhao K. Association between vitamin D and risk of stroke: A PRISMA-compliant systematic review and meta-analysis. *Eur Neurol* 2021; **84:**399–408.
29 Qi D, Nie X, Cai J. The effect of vitamin D supplementation on hypertension in non-CKD populations: A systematic review and meta-analysis. *Int J Cardiol* 2017;**227:**177–86.
30 Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, *et al*. Effect of vitamin D supplementation on blood pressure: A systematic review and meta-analysis incorporating individual patient data. *JAMA Intern Med* 2015;**175:**745–54.
31 Jhee JH, Kim H, Park S, Yun H-R, Jung S-Y, Kee YK, *et al*. Vitamin D deficiency is significantly associated with depression in patients with chronic kidney disease. *PLoS One* 2017;**12:**e0171009.
32 Oudshoorn C, Mattace-Raso FUS, van der Velde N, Colin EM, van der Cammen TJM. Higher serum vitamin D3 levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2008;**25:**539–43.
33 Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Sääksjärvi K, Heliövaara M. Serum vitamin D and the risk of Parkinson disease. *Arch Neurol* 2010;**67:**808–11.
34 Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC, *et al*. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;**62:**60–5
35 Berridge MJ. Vitamin D and depression: Cellular and regulatory mechanisms. *Pharmacol Rev* 2017;**69:**80–92.
36 Gezen-Ak D, Dursun E, Yilmazer S. The effect of vitamin D treatment on nerve growth factor (NGF) release from hippocampal neurons. *Noro Psikiyatr Ars* 2014;**51:**157–162.
37 Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Herrmann FR, *et al*. Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: A 7-year follow-up. *J Gerontol A Biol Sci Med Sci* 2012;**67:**1205–11.
38 Cui X, McGrath JJ, Burne THJ, Eyles DW. Vitamin D and schizophrenia: 20 years on. *Mol Psychiatry* 2021;**26:**2708–20.
39 Vellekkatt F, Menon V. Efficacy of vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. *J Postgrad Med* 2019;**65:**74–80.
40 Du Y, Liang F, Zhang L, Liu J, Dou H. Vitamin D supplement for prevention of Alzheimer's disease: A systematic review and meta-analysis: A systematic review and meta-analysis. *Am J Ther* 2021;**28:**e638–48.
41 Zhou Z, Zhou R, Zhang Z, Li K. The association between vitamin D status, vitamin D supplementation, sunlight exposure, and Parkinson's disease: A systematic review and meta-analysis. *Med Sci Monit* 2019;**25:**666–74.
42 Jagannath VA, Filippini G, Di Pietrantonj C, Asokan GV, Robak EW, Whamond L, *et al*. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev* 2018;**9:**CD008422.
43 Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: Randomized double blind trial. *J Intern Med* 2008;**264:**599–609.
44 Mitri J, Muraru, Pittas AG. Vitamin D and type 2 diabetes: A systematic review. *Eur J Clin Nutr* 2011;**65:**1005–15.
45 Zhang M, Liu T, Li W, Gong W, Yang X, Xi J. Efficacy of vitamin D3 in patients with diabetic nephropathy: An updated meta-analysis. *Iran Red Crescent Med J* 2017;**19:**e64275.
46 Gysemans CA, Cardozo AK, Callewaert H, Giulietti A, Hulshagen L, Bouillon R, *et al*. 1,25-dihydroxyvitamin D3 modulates expression of chemokines and cytokines in pancreatic islets: Implications for prevention of diabetes in nonobese diabetic mice. *Endocrinology* 2005;**146:**1956–64.
47 Park S, Kim DS, Kang S. Vitamin D deficiency impairs glucose-stimulated insulin secretion and increases insulin resistance by reducing PPAR-α expression in nonobese type 2 diabetic rats. *J Nutr Biochem* 2016;**27:**257–65.
48 Pérez-Gómez MV, Ortiz-Arduán A, Lorenzo-Sellares V. Vitamin D and proteinuria: A critical review of molecular bases and clinical experience. *Nefrologia* 2013;**33:**716–26.
49 Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, *et al*. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006;**29:**650–6.
50 Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, Gakhal I, *et al*. Effect of vitamin D supplementation on the incidence of diabetes mellitus. *J Clin Endocrinol Metab* 2020;**105:**2857–68.
51 Li X, Liu Y, Zheng Y, Wang P, Zhang Y. The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. *Nutrients* 2018;**10:**375.
52 Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. *Lancet* 2001;**358:**1500–3.
53 Jamilian M, Karamali M, Taghizadeh M, Sharifi N, Jafari Z, Memarzadeh MR, *et al*. Vitamin D and evening primrose oil administration improve glycemia and lipid profiles in women with gestational diabetes. *Lipids* 2016;**51:**349–56.
54 Pittas AG, Jorde R, Kawahara T, Dawson-Hughes B. Vitamin D supplementation for prevention of type 2 diabetes mellitus: To D or not to D? *J Clin Endocrinol Metab* 2020;**105:**3721–33.
55 Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin

D to prevent cancer. *Curr Med Res Opin* 2008;**24:**139–49.
56. Atoum M, Alzoughool F. Vitamin D and breast cancer: Latest evidence and future steps. Breast Cancer (Auckl) 2017;**11:**1178223417749816.
57 Liu Y, Li C, Chen P, Li X, Li M, Guo H, *et al*. Polymorphisms in the vitamin D receptor (VDR) and the risk of ovarian cancer: A meta-analysis. *PLoS One* 2013;**8:**e66716.
58 Agic A, Xu H, Altgassen C, Noack F, Wolfler MM, Diedrich K, *et al*. Relative expression of 1,25-dihydroxyvitamin D3 receptor, vitamin D 1 alpha-hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers. *Reprod Sci* 2007;**14:**486–97.
59 Bokhari AA, Lee LR, Raboteau D, Turbov J, Rodriguez IV, Pike JW, *et al*. Progesterone potentiates the growth inhibitory effects of calcitriol in endometrial cancer via suppression of CYP24A1. *Oncotarget* 2016;**7:**77576–90.
60 Estébanez N, Gómez-Acebo I, Palazuelos C, Llorca J, Dierssen-Sotos T. Vitamin D exposure and risk of breast cancer: A meta-analysis. *Sci Rep* 2018;**8:**9039.
61 Li Z, Wu L, Zhang J, Huang X, Thabane L, Li G. Effect of vitamin D supplementation on risk of breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Front Nutr* 2021;**8:**655727.
62 Xu J, Chen K, Zhao F, Huang D, Zhang H, Fu Z, *et al*. Association between vitamin D/calcium intake and 25-hydroxyvitamin D and risk of ovarian cancer: A dose-response relationship meta-analysis. *Eur J Clin Nutr* 2021;**75:**417–29.
63 Qin B, Moorman PG, Alberg AJ, Barnholtz-Sloan JS, Bondy M, Cote ML, *et al*. Dairy, calcium, vitamin D and ovarian cancer risk in African–American women. *Br J Cancer* 2016;**115:**1122–30.
64 Liu JJ, Bertrand KA, Karageorgi S, Giovannucci E, Hankinson SE, Rosner B, *et al*. Prospective analysis of vitamin D and endometrial cancer risk. *Ann Oncol* 2013;**24:**687–92.
65 Fleet JC, DeSmet M, Johnson R, Li Y. Vitamin D and cancer: A review of molecular mechanisms. *Biochem J* 2012;**441:**61–76.
66 Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: A systematic review of prospective studies. *J Clin Oncol* 2011;**29:**3775–82.
67 Kanno K, Akutsu T, Ohdaira H, Suzuki Y, Urashima M. Effect of vitamin D supplements on relapse or death in a p53-immunoreactive subgroup with digestive tract cancer: Post hoc analysis of the Amaterasu randomized clinical trial. *JAMA Netw Open* 2023;**1:**6:e2328886.
68 Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, *et al*. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;**354:**684–96.
69 Caini S, Boniol M, Tosti G, Magi S, Medri M, Stanganelli I, *et al*. Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: A comprehensive review and meta-analysis. *Eur J Cancer* 2014;**50:**2649–58.
70 Shahvazi S, Soltani S, Ahmadi SM, de Souza RJ, Salehi-Abargouei A. The effect of vitamin D supplementation on prostate cancer: A systematic review and meta-analysis of clinical trials. *Horm Metab Res* 2019;**51:**11–21.
71 Keum N, Lee DH, Greenwood DC, Manson JE, Giovannucci E. Vitamin D supplementation and total cancer incidence and mortality: A meta-analysis of randomized controlled trials. *Ann Oncol* 2019;**30:**733–43.
72 Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F, *et al*. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. *Autoimmun Rev* 2019;**18:**1023–50.
73 Terrier B, Derian N, Schoindre Y, Chaara W, Geri G, Zahr N, *et al*. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. *Arthritis Res Ther* 2012;**14:**R221.
74 Franco AS, Freitas TQ, Bernardo WM, Pereira RMR. Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases: A systematic review and meta-analysis: *Medicine (Baltimore)* 2017;**96:**e7024.
75 Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E, Pereira RMR. Vitamin D supplementation in adolescents and young adults with juvenile systemic lupus erythematosus for improvement in disease activity and fatigue scores: A randomized, double-blind, placebo-controlled trial. *Arthritis Care Res (Hoboken)* 2016;**68:**91–8.
76 Abou-Raya A, Abou-Raya S, Helmii M. The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: A randomized placebo-controlled trial. *J Rheumatol* 2018;**45:**171–3.
77 Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG, *et al*. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. *Arthritis Rheum* 2004;**50:**72–7.
78 Hejazi ME, Modarresi-Ghazani F, Entezari-Maleki T. A review of vitamin D effects on common respiratory diseases: Asthma, chronic obstructive pulmonary disease, and tuberculosis. *J Res Pharm Pract* 2016;**5:**7–15.
79 Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A. Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies. *J Steroid Biochem Mol Biol* 2021;**211:**105883.
80 Hansdottir S, Monick MM. Vitamin D effects on lung immunity and respiratory diseases. *Vitam Horm* 2011;**86:**217–37.
81 Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. *J Infect Dis* 2008;**197:**676–80.
82 Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: Vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J Immunol* 2007;**179:**2060–3.
83 Pfeffer PE, Hawrylowicz CM. Vitamin D in asthma: Mechanisms of action and considerations for clinical trials. *Chest* 2018;**153:**1229–39.
84 Martineau AR, Wilkinson RJ, Wilkinson KA, Newton SM, Kampmann B, Hall BM, *et al*. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007;**176:**208–13.
85 Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;**91:**1255–60.
86 Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, *et al*. Vitamin D supplementation to prevent asthma exacerbations: A systematic review and meta-analysis of individual participant data. *Lancet Respir Med* 2017;**5:**881–90.
87 Wang J, Feng M, Ying S, Zhou J, Li X. Efficacy and safety of vitamin D supplementation for pulmonary tuberculosis: A systematic review and meta-analysis. *Iran J Public Health* 2018;**47:**466–72.
88 Zhang Y, Li J, Yang M, Wang Q. Effect of vitamin D supplementation on COVID-19 patients: A systematic review and meta-analysis. *Front Nutr* 2023;**10:**1131103.
89 Juhász MF, Varannai O, Németh D, Szakács Z, Kiss S, Izsák VD, *et al*. Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis. *J Cyst Fibros* 2021;**20:**729–36.
90 World Health Organization. Vitamin D supplementation during pregnancy. Available at *www.who.int/tools/elena/interventions/vitamind-supp-pregnancy* (accessed on 05 June 2024)
91 De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2016;**1:**CD008873.
92 Asemi Z, Esmaillzadeh A. The effect of multi mineral-vitamin D supplementation on pregnancy outcomes in pregnant women at risk for pre-eclampsia. *Int J Prev Med* 2015;**6:**62.
93 Kabuyanga RK, Tugirimana PL, Sifa B, Balezi M, Dikete ME, Mitangala PN, *et al*. Effect of early vitamin D supplementation on the incidence of preeclampsia in primigravid women: A randomised clinical trial in Eastern Democratic Republic of the Congo. *BMC Pregnancy Childbirth* 2024;**24:**107.
94 Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The health effects of vitamin D supplementation: Evidence from human studies. *Nat Rev Endocrinol* 2022;**18:**96–110.