



Original article



EMAS position statement: Vitamin D and menopausal health

Panagiotis Anagnostis^{a,*}, Sarantis Livadas^b, Dimitrios G. Goulis^a, Silvia Bretz^c, Iuliana Ceausu^d, Fatih Durmusoglu^e, Risto Erkkola^f, Ivan Fistonic^g, Marco Gambacciani^h, Marije Geukesⁱ, Haitham Hamoda^j, Caoimhe Hartley^k, Angelica Lindén Hirschberg^l, Blazej Meczekalski^m, Nicolas Mendozaⁿ, Alfred Mueck^{o,p}, Antonina Smetnik^q, Petra Stute^r, Mick van Trotsenburg^s, Margaret Rees^t, Irene Lambrinoudaki^u

^a Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece

^b Endocrine Unit, Athens Medical Center, Athens, Greece

^c Clinica Silvia Bretz, Rio de Janeiro, Brazil

^d Department of Obstetrics and Gynecology I, "Carol Davila" University of Medicine and Pharmacy, "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania

^e Istanbul Medipol International School of Medicine, Istanbul, Turkey

^f Department of Obstetrics and Gynecology, University Central Hospital, Turku, Finland

^g Institute for Women's Health, Zagreb, Croatia

^h Menopause and Osteoporosis Unit, San Rossore Clinical Center, Pisa, Italy

ⁱ Department of Obstetrics and Gynecology, Ziekenhuisgroep Twente (Hospital Group Twente), Post box 7600, 7600 SZ Almelo, the Netherlands

^j Department Gynaecology, King's College Hospital, Denmark Hill, London SE5 9RS, UK

^k Menopause Health Clinic and The Rotunda Hospital, Dublin, Ireland

^l Department of Women's and Children's Health, Karolinska Institutet and Department of Gynecology and Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden

^m Department of Gynecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland

ⁿ Department of Obstetrics and Gynecology, University of Granada, Spain

^o Department of Women's Health, University Hospital Tuebingen, Germany

^p Beijing OB/GYN Hospital, Capital Medical University, China

^q Department of Gynecological Endocrinology, National Medical Research Centre for Obstetrics, Gynecology and Perinatology, Ministry of Healthcare of the Russian Federation, Moscow, Russia

^r Department of Obstetrics and Gynecology, University Clinic Inselspital, Bern, Switzerland

^s Sigmund Freud University, Vienna, Austria and Consultancy genderPRO, Vienna, Austria

^t Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

^u Second Department of Obstetrics and Gynecology, Aretaieio Hospital, Medical School, National and Kapodistrian University of Athens, Greece

ARTICLE INFO

Keywords:

Vitamin D
Menopause
Postmenopausal women
Vasomotor symptomatology
Cardiovascular disease
Cancer
COVID-19

ABSTRACT

Introduction: There is increasing evidence that vitamin D has widespread tissue effects. In addition to osteoporosis, vitamin D deficiency has been associated with cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease. However, the effect of vitamin D supplementation on non-skeletal outcomes requires clarification, especially in postmenopausal women.

Aim: This position statement provides an evidence-based overview of the role of vitamin D in the health of postmenopausal women based on observational and interventional studies.

Materials and methods: Literature review and consensus of expert opinion.

Results and conclusions: Vitamin D status is determined by measuring serum 25-hydroxyvitamin D levels. Concentrations <20 ng/ml (<50 nmol/l) and <10 ng/ml (<25 nmol/l) are considered to constitute vitamin D deficiency and severe deficiency, respectively. Observational data suggest an association between vitamin D deficiency and adverse health outcomes in postmenopausal women, although they cannot establish causality. The evidence from randomized controlled trials concerning vitamin D supplementation is not robust, since many studies did not consider whether people were deficient at baseline. Moreover, high heterogeneity exists in terms of the population studied, vitamin D dosage, calcium co-administration and duration of intervention.

* Corresponding author.

E-mail address: pan.anagnostis@gmail.com (P. Anagnostis).

<https://doi.org/10.1016/j.maturitas.2022.12.006>

Concerning skeletal health, vitamin D deficiency is associated with low bone mass and an increased risk of fractures. Vitamin D supplementation at maintenance doses of 800–2000 IU/day (20–50 µg/day), after repletion of vitamin D status with higher weekly or daily doses, may be of benefit only when co-administered with calcium (1000–1200 mg/day), especially in the elderly populations and those with severe vitamin D deficiency.

Concerning cardiovascular disease, vitamin D deficiency is associated with an increased prevalence of cardiovascular risk factors, mainly metabolic syndrome, type 2 diabetes mellitus and dyslipidemia. Vitamin D deficiency, especially its severe form, is associated with an increased risk of cardiovascular events (coronary heart disease, stroke, mortality), independently of traditional risk factors. Vitamin D supplementation may have a modestly beneficial effect on lipid profile and glucose homeostasis, especially in obese individuals or those ≥60 years old and at doses of ≥2000 IU/day (≥50 µg/day). However, it has no effect on the incidence of cardiovascular events.

Concerning cancer, vitamin D deficiency is associated with increased incidence of and mortality from several types of cancer, such as colorectal, lung and breast cancer. However, the data on other types of gynecological cancer are inconsistent. Vitamin D supplementation has no effect on cancer incidence, although a modest reduction in cancer-related mortality has been observed.

Concerning infections, vitamin D deficiency has been associated with acute respiratory tract infections, including coronavirus disease 2019 (COVID-19). Vitamin D supplementation may decrease the risk of acute respiratory tract infections and the severity of COVID-19 (not the risk of infection).

Concerning menopausal symptomatology, vitamin D deficiency may have a negative impact on some aspects, such as sleep disturbances, depression, sexual function and joint pains. However, vitamin D supplementation has no effect on these, except for vulvovaginal atrophy, at relatively high doses, i.e., 40,000–60,000 IU/week (1000–1500 IU/week) orally or 1000 IU/day (25 µg/day) as a vaginal suppository.

1. Introduction

Vitamin D comprises a group of lipophilic hormones that regulates calcium homeostasis through its actions on the kidney, gastrointestinal tract, skeleton and parathyroid glands. It is pivotal in maintaining skeletal health [1,2]. The two major forms are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₂ is produced from ergosterol by several organisms: phytoplankton, invertebrates and fungi in response to ultraviolet (UV) irradiation [1,2]. The major natural source of vitamin D₃ is cutaneous synthesis from 7-dehydrocholesterol through exposure to sunlight, though a small amount is obtained from the diet, specifically animal-based foods such as fatty fish, eggs and milk [1,2]. There are wide individual variations in both cutaneous synthesis and gastrointestinal absorption of vitamin D. Two hydroxylations are needed to obtain the bioactive hormone 1,25-dihydroxyvitamin D, or calcitriol. In the liver, the first hydroxylation metabolizes vitamin D into 25-hydroxyvitamin D [3], or calcidiol; in the kidneys and other tissues, the second hydroxylation produces calcitriol. Both vitamin D₃ and vitamin D₂ are synthesized commercially and found in dietary supplements or fortified foods [1,2].

Calcitriol stimulates calcium and phosphate absorption and regulates the transcription of many genes. In humans, locally synthesized calcitriol is involved in a wide range of non-calcitropic functions, including, among others: insulin production, myocardial contraction, immunomodulation, monocyte antimicrobial action, innate immunity, cell proliferation and apoptosis [2]. Calcitriol exerts its biological actions primarily through the vitamin D receptor (VDR), a nuclear receptor, although non-genomic actions have also been described [2,4]. VDRs and 1α-hydroxylase are expressed in many tissues, such as immune cells (macrophages, monocytes), cardiomyocytes, vascular smooth muscle cells, and β-cells in the pancreas and reproductive tract tissues [2,5].

This position statement sets out the best evidence regarding the association between vitamin D deficiency and skeletal and non-skeletal aspects of menopausal health. The effect of vitamin D supplementation in this regard is also discussed.

2. Methodology

PubMed for English-language publications was searched to provide an update on the previous European Menopause and Andropause Society (EMAS) statement [6]. The evidence-based medicine pyramid was followed, with priority given to data deriving from meta-analyses or

randomized controlled trials (RCTs). Further references were identified by a manual search of key journals in the field of reproductive endocrinology.

3. Evidence from epidemiological and interventional studies

The role of vitamin D in bone metabolism is well established [6]. Risk factors for hypovitaminosis D after menopause include low UV-induced vitamin D synthesis in the skin, low exposure to sunlight, dark skin, skin aging, poor dietary intake, reduced ability to synthesize calcitriol in the kidneys, obesity, malabsorption, and certain medications (e.g., anti-convulsants, antiretrovirals) [6].

The prevalence of vitamin D deficiency in postmenopausal women may reach up to 80% according to a European study (n = 8532) which used a threshold of 30 ng/ml (75 nmol/l) for 25(OH)D concentrations to designate deficiency [7]. This finding has been corroborated in further studies, emphasizing the global nature of vitamin D deficiency. In particular, Valladares et al., in their analysis of 21,236 women that also applied the 30 ng/ml (75 nmol/l) threshold, reported prevalence rates for hypovitaminosis D of 73.6%, 78.6%, 86.1%, 81.5%, and 90.4% in Europe, North America, Africa, Middle East, and Asia, respectively [8]. Furthermore, older women are at even higher risk of vitamin D deficiency, as shown in a cohort study of 2000 women aged over 80 years from nine European countries; 88.6% and 53.4% of them suffered from vitamin D deficiency, applying the 30 ng/ml (75 nmol/l) and 20 ng/ml (50 nmol/l) thresholds, respectively [9].

3.1. Skeletal health

3.1.1. Epidemiological studies

The negative association between 25(OH)D and fracture risk in the general population has been shown in several meta-analyses. In one that included 15 prospective cohort studies (51,239 participants; 3386 hip fracture cases), the adjusted relative risk (RR) was 1.58 [95% confidence interval (CI) 1.41–1.77] for the lowest compared with the highest 25(OH)D concentrations' categories. Notably, this association was statistically significant only in subjects with 25(OH)D <24ng/ml (<60 nmol/l) [10]. Concerning postmenopausal women, almost 50% with a fracture history or osteoporosis have 25(OH)D concentrations <15 ng/ml (37.5 nmol/l) [11]. A similar finding was observed in the Women's Health Initiative (WHI) study, where the association was independent of the number of falls, physical function, frailty, renal function, and sex-steroid

hormone concentrations. Moreover, for each 10 ng/ml (25 nmol/l) decrease in 25(OH)D concentration, the fracture risk increased by 33% [12]. Moreover, vitamin D deficiency is also associated with decreased bone mineral density (BMD) in postmenopausal women, independently of ethnic origin [13,14].

3.1.2. *Interventional studies*

Evidence from RCTs suggests that vitamin D supplementation may reduce fracture risk only when combined with calcium [15]. An umbrella review of meta-analyses of RCTs showed that calcium at doses of 500–1200 mg/day, combined with vitamin D at doses of 400–1600 IU/day (10–40 µg/day), reduced the risk of hip fractures in eight of 12 meta-analyses (RR from 0.61 to 0.84) and the risk of any fractures in seven of 11 meta-analyses (RR from 0.74 to 0.95) with a follow-up of 1–7 years. However, no fracture risk reduction was noted in meta-analyses evaluating community-dwelling individuals exclusively [16]. This was also confirmed in the recent Vitamin D and Omega-3 Trial (VITAL), the largest and most holistic RCT so far in this context, in which vitamin D monotherapy, at a dose of 2000 IU/day, had no effect on fracture risk, in men >50 and women >55 years of age [17]. In any case, the anti-fracture benefit of the combination of vitamin D with calcium is most evident in the elderly populations [15].

A U-shaped effect of vitamin D supplementation on fracture risk should also be considered, since high vitamin D doses, at monthly (60,000–100,000 IU) or daily intervals (>4000 IU), tend to increase fracture risk, mainly in individuals without vitamin D deficiency [15]. This may be attributed to the functional decline of lower extremities and increased risk of falls [18]. On the other hand, a meta-analysis of 11 RCTs for the primary prevention of fractures in adults without vitamin D deficiency, osteoporosis or prior fracture did not find any benefit of vitamin D supplementation, in doses ranging between 300 IU/day and 100,000 IU/month [19].

Calcium can also be provided through the consumption of dairy products (a supplement of 500 mg is equivalent to eating 2–3 portions of dairy products). Interestingly, increased consumption of dairy products is associated with a reduced risk of hip fractures [20]. Calcium supplementation at daily doses of up to 1000 mg/day is safe regarding cardiovascular risk [21,22]. However, excessive calcium supplementation (>1000 mg) may be associated with gastrointestinal complaints and urinary calculi [19].

Studies have been inconsistent in the findings concerning an association between vitamin D and BMD [23,24]. Nevertheless, vitamin D (100–1600 IU/day), when combined with protein (10–44 g/day), may improve muscle strength in patients with sarcopenia, according to a recent meta-analysis of eight RCTs. This effect was pronounced in patients with severe vitamin D deficiency (<12 ng/ml (<30 nmol/l)) [25].

3.1.3. *Summary recommendations*

There is no evidence for an anti-fracture benefit of vitamin D supplementation in postmenopausal women without vitamin D deficiency or at low fracture risk. In contrast, vitamin D supplementation combined with calcium should be considered in postmenopausal women of any age with low serum 25(OH)D concentrations (<20 ng/ml or <50 nmol/l) suffering from osteoporosis and/or at high fracture risk, according to the FRAX model. A tailor-made approach that takes account of BMI, adherence and compliance with treatment is recommended, with regular assessment (3–6 monthly intervals) to check that 25(OH)D concentrations exceed the threshold of 20 ng/ml (50 nmol/l) and maintain it. This is usually achieved by daily doses of 2000–4000 IU (4000–6000 IU in obese patients) [4]. In parallel, 1000–1200 mg of calcium, either from dietary sources or from supplements, should be encouraged for at least 3–5 years to obtain the optimal benefit for skeletal health. This daily allowance of calcium does not increase the risk of cardiovascular disease or nephrolithiasis.

3.2. *Cardiovascular disease*

3.2.1. *Epidemiological studies*

Cross-sectional and cohort studies support an association between vitamin D deficiency and the prevalence of cardiovascular risk factors, such as hypertension, dyslipidemia, hyperglycemia and metabolic syndrome in the general population [26]. A meta-analysis of 10 prospective (n = 58,262) and 19 cross-sectional studies (n = 90,535) showed a lower risk of hypertension with 25(OH)D concentrations in the highest compared with the lowest category [RR 0.76 (95% CI 0.63–0.90) and 0.79 (95% CI 0.73–0.87), for prospective and cross-sectional studies, respectively]. However, this was evident for women ≤55 years, but not for older ages [27]. This finding was replicated in a cross-sectional analysis of the National Health and Nutrition Examination Surveys (NHANES) 2007–2010, where no association was observed in postmenopausal women [28]. A meta-analysis of 57 cross-sectional (n = 210,575) and two cohort studies (n = 8494) confirmed the protective effect of highest vs. lowest 25(OH)D concentrations on triglycerides [odds ratio (OR) 0.81, 95% CI 0.74–0.89], irrespective of age. This was also the case for high-density lipoprotein cholesterol (HDL-C) (OR 0.82, 95% CI 0.76–0.89). There was no association between 25(OH)D concentrations and total (TC) or low-density lipoprotein cholesterol (LDL-C) [29]. Concerning glucose metabolism, an inverse association exists between vitamin D status and insulin resistance [30]. Meta-analyses have also demonstrated an increased risk of type 2 diabetes in patients with vitamin D deficiency compared with those with sufficiency [31,32]. Furthermore, vitamin D deficiency is also associated with an increased risk of metabolic syndrome in postmenopausal women, irrespective of estradiol concentrations [33].

A growing body of evidence shows an inverse association between 25 (OH)D concentrations and the prevalence of CVD, including coronary heart disease and stroke, and CVD mortality. This is most evident in the case of severe vitamin D deficiency [25(OH)D <10 ng/ml (<25 nmol/l)] [34]. A meta-analysis confirmed a higher incidence of major adverse cardiovascular events (OR 1.92, 95% CI 1.24–2.98) for patients with vitamin D deficiency [35]. Severe vitamin D deficiency is associated with increased cardiovascular mortality in older adults, according to another meta-analysis (RR 1.47, 95% CI 1.15–1.81) [36]. This was confirmed in a prospective study from the UK Biobank, which examined 307,601 participants of White European ancestry (aged 37–73 years at enrolment) [37].

3.2.2. *Interventional studies*

Vitamin D supplementation may have a modestly beneficial effect on lipid profiles in postmenopausal women. A meta-analysis of RCTs showed a decrease in triglyceride concentrations [weighted mean difference (WMD) -3.55 mg/dl, 95% CI -5.34 to -1.76] with vitamin D supplementation (300–4000 IU/day). HDL-C increased when the treatment duration was <26 weeks (WMD 2.67 mg/dl, 95% CI 0.66–4.68), as did TC (WMD 6.56 mg/dl, 95% CI 0.78–12.35). Moreover, vitamin D decreased LDL-C when the dose was >400 IU/day (WMD -1.89 mg/dl, 95% CI -2.47 to -1.31) [38]. Vitamin D supplementation has no effect on systolic or diastolic blood pressure, independent of age, baseline vitamin D status or vitamin D dose [39]. On the other hand, vitamin D supplementation may improve the metabolic syndrome profile in postmenopausal women, especially triglycerides and insulin resistance [40], although it has no effect on body composition and weight [41]. It may also reduce the incidence of type 2 diabetes in patients with prediabetes by 11% (RR 0.89, 95% CI 0.80–0.99), according to another meta-analysis [42], especially in non-obese patients and with daily doses ≥2000 IU [42]. However, vitamin D supplementation (from 400 to 100,000 IU/month) does not reduce the risk of total cardiovascular events, myocardial infarction, stroke, and cardiovascular or all-cause mortality, according to several meta-analyses [43–45] and the VITAL study [17].

3.2.3. Summary recommendations

Vitamin D deficiency is associated with increased prevalence of cardiovascular risk factors, mainly metabolic syndrome, type 2 diabetes and atherogenic dyslipidemia, and increased incidence of CVD events, independently of these risk factors. However, vitamin D supplementation does not decrease this risk, despite a modestly beneficial effect on glucose metabolism, triglyceride and HDL-C concentrations.

3.3. Cancer

3.3.1. Epidemiological studies

Evidence from case-control and prospective cohort studies supports an association between vitamin D deficiency and cancer. In particular, 25(OH)D concentrations in the highest category [>25 – 30 ng/ml (62.5 – 75 nmol/l)] are associated with a reduced risk of colorectal and lung cancer by 48% and 84%, respectively, compared with the lowest category [46,47]. Concerning breast cancer, according to a meta-analysis, women with 25(OH)D concentrations in the highest category (>20 ng/ml or >30 ng/ml; >50 nmol/l or >75 nmol/l) are at 15% and 35% lower risk compared to those with 25(OH)D in the lowest category (<10 ng/ml or <20 ng/ml; <25 nmol/l or <50 nmol/l) [48]. Interestingly, the overall and cancer-specific mortality rates are increased in postmenopausal women with 25(OH)D concentrations in the lowest compared with the highest tertile [HR 1.52 (95% CI 1.22–1.88) and 1.74 (95% CI 1.23–2.40), respectively], according to a meta-analysis [49]. Nevertheless, vitamin D deficiency is not associated with an increased risk of ovarian cancer [50] and no firm conclusions can be drawn concerning other gynecological cancers [51–53]. In the prospective UK Biobank study, severe vitamin D deficiency was associated with increased all-cause and cancer-related mortality compared with 25(OH)D concentrations >20 ng/ml (50 nmol/l) [37].

3.3.2. Interventional studies

Heterogeneity among studies exists concerning the effect of vitamin D supplementation on the incidence of cancer and cancer-related mortality. Vitamin D supplementation (400 IU/day to 100,000 IU/4 months, mostly 2000 IU/day) may reduce the incidence of colorectal cancer (OR 0.87, 95% CI 0.82–0.92) and prolong the survival of patients with the condition [54,55]. Furthermore, it has no effect on the incidence of lung [56,57], breast or ovarian cancer [58]. However, the updated systematic review by the US Preventive Services Task Force did not show any beneficial effect of vitamin D on cancer incidence (vitamin D dosage ranging from 400 IU/day to 100,000 IU/month or 150,000 IU/3 months) [45]. A Cochrane meta-analysis reported a slight decrease in cancer-related mortality (RR 0.88, 95% CI 0.78–0.98), although this was not demonstrated in studies conducted solely in female populations [44]. An updated meta-analysis confirmed this reduction in cancer-related mortality [59]. This was also demonstrated in the VITAL study, where vitamin D supplementation at a dose of 2000 IU/day tended to decrease cancer-related mortality after 5.3 years of follow-up (HR 0.83, 95% CI 0.67–1.02), and this effect became significant if the first two years of follow-up were excluded (HR 0.75, 95% CI 0.59–0.96) [60].

3.3.3. Summary recommendations

Vitamin D deficiency may be associated with increased incidence and mortality of several types of cancer, such as colorectal, lung and breast cancer. No effect on cancer outcomes has been shown with vitamin D supplementation, except for a modest decrease in cancer-related mortality.

3.4. Infections - inflammation

3.4.1. Epidemiological studies

Vitamin D deficiency may adversely affect the immune system and increase the risk of infections, including acute respiratory tract

infections [61,62], and many autoimmune diseases, including rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease and autoimmune thyroid disease [63]. According to the study mentioned above from the UK Biobank [37], severe vitamin D deficiency is associated with increased mortality from respiratory diseases.

Numerous studies have been conducted to assess the association between vitamin D status and the severity of coronavirus disease 2019 (COVID-19) infection. Evidence from meta-analyses suggests higher mortality and hospitalization rates for people with vitamin D deficiency compared with those with sufficiency [64], although without any effect on the risk of COVID-19 infection [65].

3.4.2. Interventional studies

The data on the effect of vitamin D supplementation on the risk of acute respiratory infections are inconsistent. A meta-analysis showed a modest benefit (OR 0.92, 95% CI 0.86–0.99), independent of baseline 25(OH)D concentrations, but only with doses of 400–1000 IU/day and for a duration of ≤ 12 months and among participants aged <16 years at enrolment [66]. Another recent meta-analysis failed to show such a benefit [67].

Regarding autoimmune diseases, a reduced risk was demonstrated with a dose of 2000 IU/day (VITAL study; HR 0.78, 95% CI 0.61–0.99). However, there was no effect on individual autoimmune diseases, including rheumatoid arthritis, polymyalgia rheumatica, psoriasis and autoimmune thyroid disease [68].

Concerning COVID-19, vitamin D supplementation may decrease the risk of admission to the intensive care unit by 54–65% (bolus dose of 50,000–200,000 IU and maintenance dose ranging from 800 IU/day to 10,000 IU/week or 50,000 IU/month) [69–71]. Evidence on the risk of infection and COVID-19-associated mortality is inconsistent [69–71]. An ongoing RCT evaluating the effect of vitamin D supplementation (3200 IU/day) or placebo on COVID-19 severity and/or mortality will shed light on this [72].

3.4.3. Summary recommendations

Vitamin D deficiency is associated with an increased risk of infections, including COVID-19. Vitamin D supplementation may modestly decrease this risk, particularly the risk of admission to an intensive care unit. However, the high heterogeneity in design, duration, population and vitamin D dosage among studies must be underscored.

3.5. Menopausal symptoms

3.5.1. Epidemiological studies

Few studies have focused on the association between vitamin D deficiency and menopausal (i.e., vasomotor) symptoms. A cross-sectional analysis of 530 women (mean age 66.2 ± 6.8 years) from the WHI Calcium and Vitamin D (CaD) trial showed no association between 25(OH)D concentrations and menopausal symptoms, including hot flashes, night sweats, racing heart, sleep disorders, emotional well-being and energy/fatigue, after adjustment for age [73]. Another cross-sectional study in postmenopausal women ($n = 210$) showed a higher prevalence of vitamin D deficiency in women with hot flashes compared with those without, after adjustment for age and menopause duration [74]. Vitamin D deficiency in postmenopausal women has also been associated with an increased prevalence of sleep disturbances (including poor sleep quality, short sleep duration and sleepiness) [75], depression (especially for women aged ≤ 60 years) [76] and sexual dysfunction [77].

3.5.2. Interventional studies

Few studies have examined the effect of vitamin D supplementation on menopausal symptoms (vasomotor, neurocognitive, psychological, sexual, and genitourinary). Data from the WHI CaD trial, in which 17,101 postmenopausal women (50–79 years old) were randomized to calcium carbonate 1000 mg plus vitamin D 400 IU daily and 17,056 to

placebo, did not show any difference between groups in terms of postmenopausal symptoms, either overall or individually, such as sleep disturbances, emotional well-being, energy/fatigue, hot flashes or night sweats [78]. A more recent RCT showed an improvement in the vasomotor, sexual and physical domain scores of women taking a combination of isoflavones (40 mg/day), calcium (500 mg/day), vitamin D (300 IU/day) and inulin (3 g/day) compared with placebo after 12 months of treatment [79]. Furthermore, no effect of vitamin D supplementation on depression has been shown, either in general or specifically among postmenopausal women (dosage ranging from 400 IU/day to 500,000 IU/year) [80,81]. Concerning sleep quality, RCT data have also shown no improvement with vitamin D supplementation [82,83]. Moreover, the VITAL study found that vitamin D at 2000 IU/day had no effect on cognitive decline [84]. However, vitamin D supplementation can benefit postmenopausal genitourinary syndrome, in comparison with placebo, either as a vaginal suppository at daily doses of 1000 IU or orally at 60,000 IU weekly doses (data from the two RCTs). [85]. This favorable effect on vulvovaginal atrophy symptoms was also shown in an RCT after 12 weeks of oral ergocalciferol at 40,000 IU/week [86].

3.5.3. Summary recommendations

Vitamin D deficiency may be associated with an increased risk of menopausal symptoms (hot flashes, sleep disorders, depression, sexual dysfunction), but the evidence is not robust. It does not derive from studies conducted exclusively in postmenopausal women or those with documented deficiency. Vitamin D supplementation has no effect on menopausal symptoms, either as a whole or as individual symptoms, except for a modest effect on vulvovaginal atrophy.

A summary of the effect of vitamin D deficiency on skeletal and non-skeletal menopausal health is presented in Table 1.

4. Critical appraisal of the literature and future perspectives

Explanations for the apparent discrepancy between RCTs and observational studies include the following:

- The vast majority of RCTs were conducted in individuals who were not vitamin D deficient, but were generally of good health and at relatively low cardiovascular and fracture risk.
- The duration of studies demonstrating a beneficial effect on outcomes, such as CVD and cancer, was relatively short.
- The role of potential fluctuations in 25(OH)D and parathyroid hormone concentrations in studies that gave high intermittent doses cannot be estimated.
- The association between vitamin D deficiency and adverse health outcomes may have been driven by confounding or reverse causality: chronic conditions or conditions at a preclinical stage or other factors may have contributed to vitamin D deficiency rather than vice versa (e.g., physical inactivity due to illness or obesity could reduce sunlight exposure) [87–89].

25(OH)D concentrations ≥ 20 ng/ml (≥ 50 nmol/l) are essential for the maintenance of optimal skeletal health. However, the evidence suggests a modest anti-fracture and anti-fall efficacy of vitamin D supplementation at doses of 800–2000 IU/day, and only when it is co-administered with calcium (1000–1200 mg/day) in the elderly with severe vitamin D deficiency [25(OH)D < 10 – 12 ng/ml (< 25 – 30 nmol/l)] [15]. High compliance and a duration of > 3 years are required for such a benefit [15]. There is no firm evidence for the benefits of vitamin D supplementation in postmenopausal women with 25(OH)D concentrations > 20 ng/ml (> 50 nmol/l) and at low risk of fracture.

Higher 25(OH)D concentrations [> 30 ng/ml (> 75 nmol/l)] may be needed for non-skeletal effects, although the evidence from RCTs is weak. Vitamin D supplementation is not recommended for managing postmenopausal symptoms (i.e., hot flashes, night sweats, depression, sleep disorders, sexual dysfunction), CVD or cancer prevention.

Table 1

Effect of vitamin D deficiency and vitamin D supplementation on skeletal and non-skeletal postmenopausal health.

Outcome	Association with 25 (OH)D concentrations	Effect of vitamin D supplementation
Fracture risk	Negative	↓ only with calcium, evidence for a U-shaped effect
BMD	Negative	↑/↔
Postmenopausal symptoms (as a whole)	No association	↔ ^a
Individual menopause-related symptoms (hot flashes, night sweats, heart racing, emotional well-being, energy/fatigue)	No association	↔
Joint pain	Negative	↔ ^a
Sleep disorders	Inconsistent results	↔
Depression	Negative	↔
Sexual dysfunction	Negative	↔
Vulvovaginal atrophy	No association	↓
Arterial hypertension	No association	↔
Triglycerides	Negative	↓
HDL-cholesterol	Positive	↓
Total cholesterol	No association	↔
LDL-cholesterol	No association	↔
Metabolic syndrome	Negative	↓
Blood glucose	Negative	↓
Insulin resistance	Negative	↓
T2DM/prediabetes	Negative	↓ ^b
CHD	Negative	↔
Stroke	Negative	↔
CVD mortality	Negative	↔
Colorectal cancer	Negative	↔
Lung cancer	Negative	↔
Breast cancer	Negative (?)	↔
Ovarian, endometrial or cervical cancer	No association	↔
Cancer mortality	Negative	↓
ARIs	Negative	↓/↔
Autoimmune diseases	Negative	↓/↔
COVID-19	Negative	↓ ^c

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; ARIs; acute respiratory tract infections; BMD: bone mineral density; CHD: coronary heart disease; COVID-19: coronavirus disease 2019; CVD: cardiovascular disease; HDL: high-density lipoprotein; LDL: low-density lipoprotein; T2DM: type 2 diabetes mellitus; ↓: decrease; ↔: no effect.

^a Benefit with vitamin D₃ 18,400 IU/day in combination with lycopene, astaxanthin and citrus bioflavonoids.

^b Evidence for a favorable effect exists for those with BMI < 30 kg/m² or ≥ 60 years old and with a vitamin D dose of ≥ 1000 – 2000 IU/day.

^c Vitamin D supplementation may reduce the risk of hospitalization but not the risk of infection or mortality from COVID-19.

The vehicle substance combined with the vitamin D in tablet formulations may affect vitamin D bioavailability. According to a systematic review, an oil vehicle induces higher 25(OH)D concentrations (> 4 -fold) compared with a powder or an ethanol vehicle [90]. Furthermore, the effect of the gut microbiome on vitamin D bioavailability should be considered [91]. Finally, the potential interaction of seasonal changes in 25(OH)D concentrations with skeletal and non-skeletal outcomes may be another confounder [92].

Future studies should elucidate unresolved issues, such as:

- The need for universal screening for vitamin D deficiency in postmenopausal women
- The optimal 25(OH)D threshold at which to initiate vitamin D supplementation [< 10 ng/ml (< 25 nmol/l), < 20 ng/ml (< 50 nmol/l) or < 30 ng/ml (< 75 nmol/l)]
- The discrimination between vitamin D replacement and vitamin D supplementation

- The optimal dosage (weekly or daily) and duration
- The distinct benefit of the combination of calcium and vitamin D
- The optimal 25(OH)D range (lower and upper thresholds) to obtain skeletal and non-skeletal benefit.

5. Summary key points

- Vitamin D deficiency, especially the severe form, compromises menopausal skeletal health, and is associated with low BMD and increased risk of fractures.
- Vitamin D deficiency may worsen menopausal symptoms, although the evidence is not robust and does not derive from studies conducted exclusively in postmenopausal women.
- Vitamin D deficiency is associated with increased cardiovascular risk factors, mainly metabolic syndrome, type 2 diabetes and dyslipidemia.
- Vitamin D deficiency, especially the severe form, is independently associated with increased risk of cardiovascular events (coronary heart disease, stroke, mortality), cancer (i.e., colorectal, lung and breast) and infections, including COVID-19.
- Concerning vitamin D supplementation, heterogeneity exists among studies in terms of the population studied, baseline vitamin D status, the dose of vitamin D, the co-administration of calcium and the duration of intervention.
- Vitamin D doses of 800–2000 IU/day (20–50 µg/day) may provide anti-fracture benefits only when co-administered with calcium (1000–1200 mg/day), especially in the elderly populations and those with severe vitamin D deficiency.
- No effect of vitamin D supplementation on menopausal symptoms has been shown by RCTs, except for vulvovaginal atrophy.
- Vitamin D supplementation may have a modestly beneficial effect on lipid profile and glucose homeostasis.
- No effect of vitamin D supplementation has been shown on the risk of CVD events or cancer outcomes, except for a modest decrease in overall cancer-related mortality.
- Vitamin D supplementation may decrease the severity of COVID-19 infection (inconsistency exists regarding the risk of infection and mortality).

Contributors

Panagiotis Anagnostis, Sarantis Livadas, Dimitrios G. Goulis and Irene Lambrinouadaki prepared the initial draft and circulated it to all other named authors (EMAS board members and advisors) for comments and approval; Irene Lambrinouadaki and Margaret Rees coordinated production.

Funding

No funding was sought or secured for the preparation of this position statement.

Provenance and peer review

This article is an EMAS position statement and was not externally peer reviewed.

Declaration of competing interest

1. Panagiotis Anagnostis: none declared.
2. Sarantis Livadas: none declared.
3. Dimitrios G. Goulis: none declared.
4. Silvia Bretz: none declared.
5. Iuliana Ceausu: none declared.
6. Fatih Durmusoglu: none declared.
7. Risto Erkkola: none declared.

8. Ivan Fistonc: none declared.
9. Marco Gambacciani: none declared.
10. Marije Geukes: none declared.
11. Haitham Hamoda: none declared.
12. Caiomhe Hartley: none declared.
13. Angelica Lindén Hirschberg, in the past three years, has received grant support from ITF Research Pharma for the Blissafe study.
14. Blazej Meczekalski: none declared.
15. Nicolas Mendoza: none declared.
16. Alfred Mueck: none declared.
17. Antonina Smetnik: none declared.
18. Petra Stute: none declared.
19. Mick van Trotsenburg: none declared.
20. Margaret Rees: none declared.
21. Irene Lambrinouadaki: none declared.

References

- [1] M.F. Holick, T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences, *Am. J. Clin. Nutr.* 87 (4) (2008) 1080S–1086S.
- [2] F. Saponaro, A. Saba, R. Zucchi, An update on vitamin D metabolism, *Int. J. Mol. Sci.* 21 (18) (2020).
- [3] T. Akiba, T. Morikawa, M. Odaka, T. Nakada, N. Kamiya, M. Yamashita, M. Yabe, T. Inagaki, H. Asano, S. Mori, Y. Tsukamoto, M. Urashima, Vitamin D supplementation and survival of patients with non-small cell lung cancer: a randomized, double-blind, placebo-controlled trial, *Clin. Cancer Res.* 24 (17) (2018) 4089–4097.
- [4] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R. P. Heaney, M.H. Murad, C.M. Weaver, S. Endocrine, Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, *J. Clin. Endocrinol. Metab.* 96 (7) (2011) 1911–1930.
- [5] P. Anagnostis, S. Karras, D.G. Goulis, Vitamin D in human reproduction: a narrative review, *Int. J. Clin. Pract.* 67 (3) (2013) 225–235.
- [6] F.R. Perez-Lopez, M. Brincat, C.T. Erel, F. Tremollieres, M. Gambacciani, I. Lambrinouadaki, M.H. Moen, K. Schenck-Gustafsson, S. Vujovic, S. Rozenberg, M. Rees, EMAS position statement: vitamin D and postmenopausal health, *Maturitas* 71 (1) (2012) 83–88.
- [7] O. Bruyere, O. Malaise, A. Neuprez, J. Collette, J.Y. Reginster, Prevalence of vitamin D inadequacy in European postmenopausal women, *Curr. Med. Res. Opin.* 23 (8) (2007) 1939–1944.
- [8] T. Valladares, R. Simoes, W. Bernardo, A.C.B. Schmitt, M.R.A. Cardoso, J. M. Aldrighi, Prevalence of hypovitaminosis D in postmenopausal women: a systematic review, *Rev. Assoc. Med. Bras.* (1992) 65 (5) (2019) 691–698.
- [9] O. Bruyere, J. Slomian, C. Beaudart, F. Buckinx, E. Cavalier, S. Gillain, J. Petermans, J.Y. Reginster, Prevalence of vitamin D inadequacy in European women aged over 80 years, *Arch. Gerontol. Geriatr.* 59 (1) (2014) 78–82.
- [10] Q.B. Lv, X. Gao, X. Liu, Z.X. Shao, Q.H. Xu, L. Tang, Y.L. Chi, A.M. Wu, The serum 25-hydroxyvitamin D levels and hip fracture risk: a meta-analysis of prospective cohort studies, *Oncotarget* 8 (24) (2017) 39849–39858.
- [11] S. Gaugris, R.P. Heaney, S. Boonen, H. Kurth, J.D. Bentkover, S.S. Sen, Vitamin D inadequacy among postmenopausal women: a systematic review, *QJM* 98 (9) (2005) 667–676.
- [12] J.A. Cauley, A.Z. Lacroix, L. Wu, M. Horwitz, M.E. Danielson, D.C. Bauer, J.S. Lee, R.D. Jackson, J.A. Robbins, C. Wu, F.Z. Stanczyk, M.S. LeBoff, J. Wactawski-Wende, G. Sarto, J. Ockene, S.R. Cummings, Serum 25-hydroxyvitamin D concentrations and risk for hip fractures, *Ann. Intern. Med.* 149 (4) (2008) 242–250.
- [13] N.O. Kuchuk, N.M. van Schoor, S.M. Pluijm, A. Chines, P. Lips, Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: global perspective, *J. Bone Miner. Res.* 24 (4) (2009) 693–701.
- [14] D.Y. Lee, J.H. Jee, Y.Y. Cho, J.Y. Jang, T.Y. Yu, T.H. Kim, Y.J. Hong, W.J. Hong, S. M. Jin, K.Y. Hur, J.H. Kim, S.W. Kim, J.H. Chung, M.K. Lee, Y.K. Min, Serum 25-hydroxyvitamin D cutoffs for functional bone measures in postmenopausal osteoporosis, *Osteoporos. Int.* 28 (4) (2017) 1377–1384.
- [15] P. Anagnostis, J.K. Bosdrou, E. Kenanidis, M. Potoupnis, E. Tsidiris, D.G. Goulis, Vitamin D supplementation and fracture risk: evidence for a U-shaped effect, *Maturitas* 141 (2020) 63–70.
- [16] M. Chakhtoura, D.S. Bacha, C. Gharios, S. Ajjour, M. Assaad, Y. Jabbour, F. Kahale, A. Bassatne, S. Antoun, E.A. Akl, R. Bouillon, P. Lips, P.R. Ebeling, G. El-Hajj Fuleihan, Vitamin D supplementation and fractures in adults: a systematic umbrella review of meta-analyses of controlled trials, *J. Clin. Endocrinol. Metab.* 107 (3) (2022) 882–898.
- [17] S.R. Cummings, C. Rosen, VITAL findings - a decisive verdict on vitamin D supplementation, *N. Engl. J. Med.* 387 (4) (2022) 368–370.
- [18] H.A. Bischoff-Ferrari, B. Dawson-Hughes, E.J. Orav, H.B. Staehelin, O.W. Meyer, R. Theiler, W. Dick, W.C. Willett, A. Egli, Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial, *JAMA Intern. Med.* 176 (2) (2016) 175–183.

- [19] L.C. Kahwati, R.P. Weber, H. Pan, M. Gourlay, E. LeBlanc, M. Coker-Schwimmer, M. Viswanathan, Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: evidence report and systematic review for the US Preventive Services Task Force, *JAMA* 319 (15) (2018) 1600–1612.
- [20] K. Hidayat, X. Du, B.M. Shi, L.Q. Qin, Systematic review and meta-analysis of the association between dairy consumption and the risk of hip fracture: critical interpretation of the currently available evidence, *Osteoporos. Int.* 31 (8) (2020) 1411–1425.
- [21] A. Cano, P. Chedraui, D.G. Goulis, P. Lopes, G. Mishra, A. Mueck, L.M. Senturk, T. Simoncini, J.C. Stevenson, P. Stute, P. Tuomikoski, M. Rees, I. Lambrinoudaki, Calcium in the prevention of postmenopausal osteoporosis: EMAS clinical guide, *Maturitas* 107 (2018) 7–12.
- [22] K. Michaëlsson, H. Melhus, E. Warensjö Lemming, A. Wolk, L. Byberg, Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study, *BMJ* 346 (2013), f228.
- [23] K.E. Hansen, R.E. Johnson, K.R. Chambers, M.G. Johnson, C.C. Lemon, T.N. Vo, S. Marvdashti, Treatment of vitamin D insufficiency in postmenopausal women: a randomized clinical trial, *JAMA Intern. Med.* 175 (10) (2015) 1612–1621.
- [24] M.J. Bolland, A. Grey, A. Avenell, Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis, *Lancet Diabetes Endocrinol.* 6 (11) (2018) 847–858.
- [25] N.K. Gkekas, P. Anagnostis, V. Paraschou, D. Stamiris, S. Dellis, E. Kenanidis, M. Potoupnis, E. Tsiridis, D.G. Goulis, The effect of vitamin D plus protein supplementation on sarcopenia: a systematic review and meta-analysis of randomized controlled trials, *Maturitas* 145 (2021) 56–63.
- [26] P. Anagnostis, V.G. Athyros, F. Adamidou, M. Florentin, A. Karagiannis, Vitamin D and cardiovascular disease: a novel agent for reducing cardiovascular risk? *Curr. Vasc. Pharmacol.* 8 (5) (2010) 720–730.
- [27] L. Ke, R.S. Mason, M. Kariuki, E. Mpofo, K.E. Brock, Vitamin D status and hypertension: a review, *Integr. Blood Press Control* 8 (2015) 13–35.
- [28] J.H. Kwak, Y.C. Hong, Y.H. Choi, Serum 25-hydroxyvitamin D and hypertension in premenopausal and postmenopausal women: National Health and Nutrition Examination Surveys 2007–2010, *Public Health Nutr.* 23 (7) (2020) 1236–1246.
- [29] S. Bahadorpour, Z. Hajhashemy, P. Saneei, Serum 25-hydroxyvitamin D levels and dyslipidemia: a systematic review and dose-response meta-analysis of epidemiologic studies, *Nutr. Rev.* 81 (1) (2022) 1–25.
- [30] S. Rafiq, P.B. Jeppesen, Vitamin D deficiency is inversely associated with homeostatic model assessment of insulin resistance, *Nutrients* 13 (12) (2021).
- [31] S. Mohammadi, Z. Hajhashemy, P. Saneei, Serum vitamin D levels in relation to type-2 diabetes and prediabetes in adults: a systematic review and dose-response meta-analysis of epidemiologic studies, *Crit. Rev. Food Sci. Nutr.* (2021) 1–21.
- [32] A.G. Pittas, J. Lau, F.B. Hu, B. Dawson-Hughes, The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis, *J. Clin. Endocrinol. Metab.* 92 (6) (2007) 2017–2029.
- [33] E.B. Schmitt, J. Nahas-Neto, F. Bueloni-Dias, P.F. Poloni, C.L. Orsatti, E.A. Petri Nahas, Vitamin D deficiency is associated with metabolic syndrome in postmenopausal women, *Maturitas* 107 (2018) 97–102.
- [34] P. Brondom-Jacobsen, M. Benn, G.B. Jensen, B.G. Nordestgaard, 25-hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies, *Arterioscler. Thromb. Vasc. Biol.* 32 (11) (2012) 2794–2802.
- [35] V. Jaiswal, A. Ishak, S. Peng Ang, N. Babu Pokhrel, N. Shama, K. Lnu, J. Susan Varghese, T. Storozhenko, J. Ee Chia, S. Naz, P. Sharma, A. Jaiswal, Hypovitaminosis D and cardiovascular outcomes: a systematic review and meta-analysis, *Int. J. Cardiol. Heart Vasc.* 40 (2022), 101019.
- [36] J. Yang, J. Ou-Yang, J. Huang, Low serum vitamin D levels increase the mortality of cardiovascular disease in older adults: a dose-response meta-analysis of prospective studies, *Medicine (Baltimore)* 98 (34) (2019), e16733.
- [37] J.P. Sutherland, A. Zhou, E. Hypponen, Vitamin D deficiency increases mortality risk in the UK biobank: a nonlinear Mendelian randomization study, *Ann. Intern. Med.* 175 (11) (2022) 1552–1559.
- [38] W. Zhang, J. Yi, D. Liu, Y. Wang, P. Jamilian, M.A. Gaman, K. Prabahar, J. Fan, The effect of vitamin D on the lipid profile as a risk factor for coronary heart disease in postmenopausal women: a meta-analysis and systematic review of randomized controlled trials, *Exp. Gerontol.* 161 (2022), 111709.
- [39] D. Zhang, C. Cheng, Y. Wang, H. Sun, S. Yu, Y. Xue, Y. Liu, W. Li, X. Li, Effect of vitamin D on blood pressure and hypertension in the general population: an update meta-analysis of cohort studies and randomized controlled trials, *Prev. Chronic Dis.* 17 (2020) E03.
- [40] P.P. Ferreira, L. Cangussu, F.N. Bueloni-Dias, C.L. Orsatti, E.B. Schmitt, J. Nahas-Neto, E.A.P. Nahas, Vitamin D supplementation improves the metabolic syndrome risk profile in postmenopausal women, *Climacteric* 23 (1) (2020) 24–31.
- [41] S.H. Chou, E.M. Murata, C. Yu, J. Danik, G. Kotler, N.R. Cook, V. Bubes, S. Mora, P. D. Chandler, D.K. Tobias, T. Copeland, J.E. Buring, J.E. Manson, M.S. LeBoff, Effects of vitamin D3 supplementation on body composition in the VITamin D and Omega-3 Trial (VITAL), *J. Clin. Endocrinol. Metab.* 106 (5) (2021) 1377–1388.
- [42] Y. Zhang, H. Tan, J. Tang, J. Li, W. Chong, Y. Hai, Y. Feng, L.D. Lunsford, P. Xu, D. Jia, F. Fang, Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis, *Diabetes Care* 43 (7) (2020) 1650–1658.
- [43] M. Barbarawi, B. Kheiri, Y. Zayed, O. Barbarawi, H. Dhillon, B. Swaid, A. Yelangi, S. Sundus, G. Bachuwa, M.L. Alkotob, J.E. Manson, Vitamin D supplementation and cardiovascular disease risks in more than 83000 individuals in 21 randomized clinical trials: a meta-analysis, *JAMA Cardiol.* 4 (8) (2019) 765–776.
- [44] G. Bjelakovic, L.L. Gluud, D. Nikolova, K. Whitfield, J. Wetterslev, R.G. Simonetti, M. Bjelakovic, C. Gluud, Vitamin D supplementation for prevention of mortality in adults, *Cochrane Database Syst. Rev.* 1 (2014), CD007470.
- [45] E.A. O'Connor, C.V. Evans, I. Ivliv, M.C. Rushkin, R.G. Thomas, A. Martin, J.S. Lin, Vitamin and mineral supplements for the primary prevention of cardiovascular disease and cancer: updated evidence report and systematic review for the US Preventive Services Task Force, *JAMA* 327 (23) (2022) 2334–2347.
- [46] Q. Feng, H. Zhang, Z. Dong, Y. Zhou, J. Ma, Circulating 25-hydroxyvitamin D and lung cancer risk and survival: a dose-response meta-analysis of prospective cohort studies, *Medicine (Baltimore)* 96 (45) (2017), e8613.
- [47] P. Hernandez-Alonso, H. Boughanem, S. Canudas, N. Becerra-Tomas, M. Fernandez de la Puente, N. Babio, M. Macias-Gonzalez, J. Salas-Salvado, Circulating vitamin D levels and colorectal cancer risk: a meta-analysis and systematic review of case-control and prospective cohort studies, *Crit. Rev. Food Sci. Nutr.* (2021) 1–17.
- [48] N. Estebanez, I. Gomez-Acebo, C. Palazuelos, J. Llorca, T. Dierssen-Sotos, Vitamin D exposure and risk of breast cancer: a meta-analysis, *Sci. Rep.* 8 (1) (2018) 9039.
- [49] A. Vrieling, P. Seibold, T.S. Johnson, J. Heinz, N. Obi, R. Kaaks, D. Flesch-Janys, J. Chang-Claude, Circulating 25-hydroxyvitamin D and postmenopausal breast cancer survival: influence of tumor characteristics and lifestyle factors? *Int. J. Cancer* 134 (12) (2014) 2972–2983.
- [50] L. Yin, N. Grandi, E. Raum, U. Haug, V. Arndt, H. Brenner, Meta-analysis: circulating vitamin D and ovarian cancer risk, *Gynecol. Oncol.* 121 (2) (2011) 369–375.
- [51] L. Yan, Y. Gu, T. Luan, M. Miao, L. Jiang, Y. Liu, P. Li, X. Zeng, Associations between serum vitamin D and the risk of female reproductive tumors: a meta-analysis with trial sequential analysis, *Medicine (Baltimore)* 97 (15) (2018), e0360.
- [52] L. Kolnsberg, M. Riffelmann, M. Friedrich, Comparison of serum 25-hydroxyvitamin D levels in patients with malignant and benign gynaecological disease, *Anticancer Res.* 40 (1) (2020) 545–550.
- [53] J.J. Liu, K.A. Bertrand, S. Karageorgi, E. Giovannucci, S.E. Hankinson, B. Rosner, L. Maxwell, G. Rodriguez, I. De Vivo, Prospective analysis of vitamin D and endometrial cancer risk, *Ann. Oncol.* 24 (3) (2013) 687–692.
- [54] P.G. Vaughan-Shaw, L.F. Buijs, J.P. Blackmur, E. Theodoratou, L. Zgaga, F.V. N. Din, S.M. Farrington, M.G. Dunlop, The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials, *Br. J. Cancer* 123 (11) (2020) 1705–1712.
- [55] Y. Xu, M. Qian, J. Hong, D.M. Ng, T. Yang, L. Xu, X. Ye, The effect of vitamin D on the occurrence and development of colorectal cancer: a systematic review and meta-analysis, *Int. J. Color. Dis.* 36 (7) (2021) 1329–1344.
- [56] Z. Li, L. Wu, J. Zhang, X. Huang, L. Thabane, G. Li, Effect of vitamin D supplementation on risk of breast cancer: a systematic review and meta-analysis of randomized controlled trials, *Front. Nutr.* 8 (2021), 655727.
- [57] L. Zhou, B. Chen, L. Sheng, A. Turner, The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis, *Breast Cancer Res. Treat.* 182 (1) (2020) 1–8.
- [58] J. Xu, K. Chen, F. Zhao, D. Huang, H. Zhang, Z. Fu, J. Xu, Y. Wu, H. Lin, Y. Zhou, W. Lu, Y. Wu, D. Xia, 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.* 75 (3) (2021) 417–429.
- [59] Y. Zhang, F. Fang, J. Tang, L. Jia, Y. Feng, P. Xu, A. Faramand, Association between vitamin D supplementation and mortality: systematic review and meta-analysis, *BMJ* 366 (2019), 14673.
- [60] J.E. Manson, N.R. Cook, I.M. Lee, W. Christen, S.S. Bassuk, S. Mora, H. Gibson, D. Gordon, T. Copeland, D. D'Agostino, G. Friedenberg, C. Ridge, V. Bubes, E. L. Giovannucci, W.C. Willett, J.E. Buring, V.R. Group, Vitamin D supplements and prevention of cancer and cardiovascular disease, *N. Engl. J. Med.* 380 (1) (2019) 33–44.
- [61] Y.F. Zhou, B.A. Luo, L.L. Qin, The association between vitamin D deficiency and community-acquired pneumonia: a meta-analysis of observational studies, *Medicine (Baltimore)* 98 (38) (2019), e17252.
- [62] H. Pham, A. Rahman, A. Majidi, M. Waterhouse, R.E. Neale, Acute respiratory tract infection and 25-hydroxyvitamin D concentration: a systematic review and meta-analysis, *Int. J. Environ. Res. Public Health* 16 (17) (2019).
- [63] C. Sirbe, S. Rednic, A. Grama, T.L. Pop, An update on the effects of vitamin D on the immune system and autoimmune diseases, *Int. J. Mol. Sci.* 23 (17) (2022).
- [64] Z. Wang, A. Joshi, K. Leopold, S. Jackson, S. Christensen, T. Nayfeh, K. Mohammed, A. Creo, P. Tebben, S. Kumar, Association of vitamin D deficiency with COVID-19 infection severity: systematic review and meta-analysis, *Clin. Endocrinol.* 96 (3) (2022) 281–287.
- [65] M. Pereira, A. Dantas Damascena, L.M. Galvao Azevedo, T. de Almeida Oliveira, J. da Mota Santana, Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis, *Crit. Rev. Food Sci. Nutr.* 62 (5) (2022) 1308–1316.
- [66] D.A. Jolliffe, C.A. Camargo Jr., J.D. Sluyter, M. Aglipay, J.F. Aloia, D. Ganmaa, P. Bergman, H.A. Bischoff-Ferrari, A. Borzutzky, C.T. Damsgaard, G. Dubnov-Raz, S. Esposito, C. Gilham, A.A. Ginde, I. Golan-Tripto, E.C. Goodall, C.C. Grant, C. J. Griffiths, A.M. Hibbs, W. Janssens, A.V. Khadilkar, I. Laaksi, M.T. Lee, M. Loeb, J.L. Maguire, P. Majak, D.T. Mauer, S. Manaseki-Holland, D.R. Murdoch, A. Nakashima, R.E. Neale, H. Pham, C. Rake, J.R. Rees, J. Rosendahl, R. Scragg, D. Shah, Y. Shimizu, S. Simpson-Yap, G. Trilok-Kumar, M. Urashima, A. R. Martineau, Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials, *Lancet Diabetes Endocrinol.* 9 (5) (2021) 276–292.
- [67] H.E. Cho, S.K. Myung, H. Cho, Efficacy of vitamin D supplements in prevention of acute respiratory infection: a meta-analysis for randomized controlled trials, *Nutrients* 14 (4) (2022).

- [68] J. Hahn, N.R. Cook, E.K. Alexander, S. Friedman, J. Walter, V. Bubes, G. Kotler, I. M. Lee, J.E. Manson, K.H. Costenbader, Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial, *BMJ* 376 (2022), e066452.
- [69] B. Hosseini, A. El Abd, F.M. Ducharme, Effects of vitamin D supplementation on COVID-19 related outcomes: a systematic review and meta-analysis, *Nutrients* 14 (10) (2022).
- [70] N. Tentolouris, G. Samakidou, I. Eleftheriadou, A. Tentolouris, E.B. Jude, The effect of vitamin D supplementation on mortality and intensive care unit admission of COVID-19 patients. A systematic review, meta-analysis and meta-regression, *Diabetes Metab. Res. Rev.* 38 (4) (2022), e3517.
- [71] S.R. Varikasuvu, B. Thangappazham, A. Vykunta, P. Duggina, M. Manne, H. Raj, S. Aloori, COVID-19 and vitamin D (Co-VIVID study): a systematic review and meta-analysis of randomized controlled trials, *Expert Rev. Anti-Infect. Ther.* 20 (6) (2022) 907–913.
- [72] R. Wang, V. DeGruttola, Q. Lei, K.H. Mayer, S. Redline, A. Hazra, S. Mora, W. C. Willett, D. Ganmaa, J.E. Manson, The vitamin D for COVID-19 (VIVID) trial: a pragmatic cluster-randomized design, *Contemp. Clin. Trials* 100 (2021), 106176.
- [73] E.S. LeBlanc, M. Desai, N. Perrin, J. Wactawski-Wende, J.E. Manson, J.A. Cauley, Y.L. Michael, J. Tang, C. Womack, Y. Song, K.C. Johnson, M.J. O'Sullivan, N. Woods, M.L. Stefanick, Vitamin D levels and menopause-related symptoms, *Menopause* 21 (11) (2014) 1197–1203.
- [74] T. Arslanica, H. Korkmaz, S.B. Arslanica, B. Pehlivanoglu, O. Celikel, The relationship between vitamin D and vasomotor symptoms during the postmenopausal period, *Clin. Lab.* 66 (7) (2020).
- [75] Q. Gao, T. Kou, B. Zhuang, Y. Ren, X. Dong, Q. Wang, The association between vitamin D deficiency and sleep disorders: a systematic review and meta-analysis, *Nutrients* 10 (10) (2018).
- [76] S.Y. Ju, Y.J. Lee, S.N. Jeong, Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis, *J. Nutr. Health Aging* 17 (5) (2013) 447–455.
- [77] M. Askin, E.M. Koc, M. Soyoz, S. Aksun, S. Aydogmus, K. Sozmen, Relationship between postmenopausal vitamin D level, menopausal symptoms and sexual functions, *J. Coll. Physicians Surg. Pak.* 29 (9) (2019) 823–827.
- [78] E.S. LeBlanc, H. Hedlin, F. Qin, M. Desai, J. Wactawski-Wende, N. Perrin, J. E. Manson, K.C. Johnson, K. Masaki, F.A. Tylavsky, M.L. Stefanick, Calcium and vitamin D supplementation do not influence menopause-related symptoms: results of the Women's Health Initiative Trial, *Maturitas* 81 (3) (2015) 377–383.
- [79] S.G. Vitale, S. Caruso, A.M.C. Rapisarda, S. Cianci, A. Cianci, Isoflavones, calcium, vitamin D and inulin improve quality of life, sexual function, body composition and metabolic parameters in menopausal women: result from a prospective, randomized, placebo-controlled, parallel-group study, *Prz Menopauzalny* 17 (1) (2018) 32–38.
- [80] U. Gowda, M.P. Mutowo, B.J. Smith, A.E. Wluka, A.M. Renzaho, Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials, *Nutrition* 31 (3) (2015) 421–429.
- [81] S. Spedding, Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws, *Nutrients* 6 (4) (2014) 1501–1518.
- [82] C. Mason, J. de Dieu Tapsoba, C. Duggan, C.Y. Wang, L. Korde, A. McTiernan, Repletion of vitamin D associated with deterioration of sleep quality among postmenopausal women, *Prev. Med.* 93 (2016) 166–170.
- [83] A.U. Larsen, L.A. Hopstock, R. Jorde, G. Grimnes, No improvement of sleep from vitamin D supplementation: insights from a randomized controlled trial, *Sleep Med. X* 3 (2021), 100040.
- [84] J.H. Kang, C.M. Vyas, O.I. Okereke, S. Ogata, M. Albert, I.M. Lee, D. D'Agostino, J. E. Buring, N.R. Cook, F. Grodstein, J.E. Manson, Effect of vitamin D on cognitive decline: results from two ancillary studies of the VITAL randomized trial, *Sci. Rep.* 11 (1) (2021) 23253.
- [85] H. Riazi, M. Ghazanfarpour, M. Taebi, S. Abdollahian, Effect of vitamin D on the vaginal health of menopausal women: a systematic review, *J. Menopausal Med.* 25 (3) (2019) 109–116.
- [86] T. Kamronrithisorn, J. Manonai, S.A. Vallibhakara, A. Sophonsritsuk, O. Vallibhakara, Effect of vitamin D supplement on vulvovaginal atrophy of the menopause, *Nutrients* 12 (9) (2020).
- [87] P. Anagnostis, S.A. Paschou, D.G. Goulis, Vitamin D supplementation and cardiovascular disease risk, *JAMA Cardiol.* 2 (11) (2017) 1281–1282.
- [88] M.J. Bolland, A. Grey, A. Avenell, Assessment of research waste part 2: wrong study populations— an exemplar of baseline vitamin D status of participants in trials of vitamin D supplementation, *BMC Med. Res. Methodol.* 18 (1) (2018) 101.
- [89] A. Lucas, M. Wolf, Vitamin D and health outcomes: then came the randomized clinical trials, *JAMA* 322 (19) (2019) 1866–1868.
- [90] R.E. Grossmann, V. Tangpricha, Evaluation of vehicle substances on vitamin D bioavailability: a systematic review, *Mol. Nutr. Food Res.* 54 (8) (2010) 1055–1061.
- [91] R.K. Weersma, A. Zhernakova, J. Fu, Interaction between drugs and the gut microbiome, *Gut* 69 (8) (2020) 1510–1519.
- [92] E. Klingberg, G. Olerod, J. Konar, M. Petzold, O. Hammarsten, Seasonal variations in serum 25-hydroxy vitamin D levels in a Swedish cohort, *Endocrine* 49 (3) (2015) 800–808.