Rev Endocr Metab Disord (2017) 18:259–272
DOI 10.1007/s11154-017-9417-0

Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence

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Published online: 27 April 2017

Abstract Vitamin D has long been established as an elemental factor of bone physiology. Beyond mineral metabolism, the expression of the vitamin D receptor has been identified throughout the cardiovascular (CV) system. Experimental studies showed beneficial effects of vitamin D on heart and vessels, but vitamin D intoxication in animals also led to hypercalcemia and vascular calcification. Our knowledge has been extended by epidemiological studies that showed that 25-hydroxyvitamin D (25(OH)D) levels are inversely associated with an increased CV risk itself, but also with established CV risk factors, such as arterial hypertension, endothelial dysfunction and atherosclerosis. Conversely, randomized controlled trials could not document significant and consistent effects of vitamin D supplementation on CV risk or events. Potential explanations may lie in differences in reference ranges or the possibility that low vitamin D in CV disease is only an epiphenomenon. In the latter case, the key question is why low 25(OH)D levels are such a strong predictor of health. While we wait for new data, the current conclusion is that vitamin D is a strong risk marker for CV risk factors and for CV diseases itself.

Keywords Vitamin D · Cardiovascular · Mortality · Vitamin D receptor · Epidemiology · Cardiovascular risk · Review

1 Introduction

Vitamin D is a secosteroid hormone, synthesized mainly in the skin upon ultraviolet-B (UVB) radiation [1]. Its storage form is 25-hydroxyvitamin-D (25(OH)D) which has an approximate half-life of 2 to 3 weeks. The active metabolite, 1,25-dihydroxy-vitamin D ($1,25[OH]_2D$) is only active for a couple of hours (up to 27 h maximally). The assessment of the vitamin D status is therefore based on the measurement of 25(OH)D [1]. Recommendations for supplementation currently rely on the positive effects of vitamin D on bone health [1–3]. Dietary standards and recommendations for the general

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population in the EU and the USA therefore mainly apply to the prevention of rickets, osteomalacia and fractures [4–6]. However except for children, randomized trials (RCTs) regarding vitamin D effects on fractures are inconsistent [7–15]. Therefore a broadly accepted consensus neither exists on the vitamin D dose nor on target 25(OH)D levels that should be achieved in clinical practice for cardiovascular disease (CVD) prevention [16–19]. Nevertheless, vitamin D supplementation - also in form of food fortification programs - is increasingly implemented [1, 18, 19]. The main aim of food fortification programs is the prevention of vitamin D deficiency and its adverse consequences [1–6, 16–19]. Vitamin D deficiency can affect up to 50% of a population depending on the geographical region, season and definition [19–23]. The high prevalence rates of vitamin D deficiency may be attributable to several factors including increased age, nutrition and lifestyle but also ethnicity [1, 20, 21]. Independent of latitude a higher prevalence rate of 25(OH)D has been described in African Americans, people of Indian descent and others with darker skin color. Likely because vitamin D3 (cholecalciferol) production is limited by melanin, but socioeconomic differences and prevalence of obesity may be confounding factors. Furthermore, the overall influence of ethnic origin may be less than the influence of age [20, 21]. Children, adolescents and elderly are at similar high risk for vitamin D deficiency and insufficiency [1, 20, 21]. This is thought to be partly due to inadequate exposure to sunlight, reduced dietary intake of vitamin D and changes in the synthesis capacity in the skin [1, 4, 9]. Pregnancy and lactation are also conditions associated with a high risk of vitamin D deficiency [1, 4]. The aforementioned risk groups constitute a vast proportion of the population in developed society so that vitamin D deficiency may represent a public health issue [1–6]. A broad range of studies demonstrated that vitamin D deficiency is a risk marker for several pathologic conditions and that it is associated with all-cause and cardiovascular mortality [1, 10, 20–23]. The United States Institute of Medicine (IOM) has defined vitamin D deficiency at 25(OH)D concentration lower than ≤30 nmol/L, inadequacy lies between 30 and 50 nmol/L and sufficiency at 50–75 nmol/L. Concentrations between 75 and 125 nmol/L have been inconsistently associated with harm whereas potential toxicity is possible to occur at concentrations ≥125 nmol/L [4].

The scientific rationale to study the role vitamin D in cardiovascular diseases is the identification of the vitamin D receptor (VDR) and vitamin D metabolizing enzymes in different parts of the CV system [3]. It is crucial to evaluate whether it indeed has clinically relevant effects on the CV system [24–30]. Besides, it must be addressed whether vitamin D supplementation with commonly used doses satisfies the safety assumptions.

In this umbrella review, we summarize the literature on vitamin D, CV risk factors and CVD. The main focus is on large cohort studies, meta-analyses and systematic reviews of epidemiological studies. We begin with a short historical perspective and then summarize the effects of VDR activation on cardiovascular risk factors in particular on arterial hypertension [27], on the vasculature and the heart. In the third part we review observational studies, including Mendelian randomization studies. Finally, we discuss the ongoing research on vitamin D and current hypotheses, excluding randomized controlled trials as they are discussed extensively elsewhere [1, 10, 16, 19, 21, 24–26].

2 Historical overview

Historically Vitamin D is known to cure rickets a (childhood) bone disease, which was [is] especially prevalent in first few life years. Consequently, vitamin D food fortification was installed in the 1930s and 1940s to eradicate or at least largely decrease the incidence rate of rickets [28, 29]. A major concern was the suspicion in the 1950's that vitamin D food fortification was leading to hypercalcemia or even supravalvular aortic stenosis. Indeed it has to be noted that animal studies have repeatedly shown that larger doses of vitamin D can cause vascular calcification and hypercalcemia [28–31]. The processes linking hypervitaminosis-D to vascular calcifications is likely to be related to deposition of calcium, phosphate and mineral complexes. The mechanism seems to be the induction of an osteochondrogenic phenotype in vascular smooth muscle cells [31]. However, clinical and epidemiologic data suggest that within broad ranges, vitamin D supplementation is safe. From a contemporary perspective, it is more likely that the children of the original cases-series with vitamin D intoxication actually suffered from Williams syndrome. This chromosomal anomaly is characterized by a disturbed calcium metabolism and such individuals are prone to adverse effects by vitamin D supplementation. Nevertheless vitamin D food fortification was subsequently largely banned due to fear of vitamin D overdosing and intoxication [28, 29]. After further progress in the field associations between higher vitamin D intake and increased cardiovascular risk were postulated in the middle of the 1970s. However, the majority of studies in the late 1970s could not detect any significant associations between 25(OH)D concentrations and cardiovascular events [32–35]. The view of vitamin D was radically changed by Robert Scragg in 1981 [36]. He raised the hypothesis that the increased incidence of CV events in winter months might be partly attributable to lower sunlight exposure and reduced vitamin D synthesis in the skin [36]. In 2008 publications from large community studies on an inverse association between 25(OH)D and CV events triggered an enormous rise in research activity on this topic over the last few years [4–6, 10, 16, 22–26, 28, 37–40].

3 Vitamin D receptor and key enzymes of vitamin D in the cardiovascular system

Experimental studies have identified the VDR and vitamin D metabolizing enzymes (i.e. 1-alpha hydroxylase and 24-hydroxylase) in cells of the CV system [3, 41–44]. This supports the hypothesis of a causal relationship between vitamin D and CVD. However, it has to be kept in mind that the contemporary literature is not fully consistent. There are – although in contrast to the vast majority - some studies published which were unable to detect VDR expression in cardiovascular tissues [41–44].

3.1 Knock out models

Mice with a systemic knock-out of the VDR or of 1-alpha hydroxylase develop cardiovascular anomalies. CVD in VDR knock-out animals is characterized by myocardial hypertrophy, increased activity of the renin-angiotensin-aldosterone system (RAAS), protein homeostasis, lipid metabolism, cellular stress response, arterial hypertension, increased thrombogenicity and changes in the vascular function [3, 41–46]. More so, it has been shown in mice models that a cardiomyocyte-specific knockout of the VDR causes myocardial hypertrophy largely independent of the effects on the RAAS and blood pressure [47]. An endothelial cell-specific VDR knock-out was associated with altered vascular function. This altered vascular function attended by increased sensitivity to angiotensin 2 of endothelial cells and a reduction in endothelial NO synthase expression [48, 49]. Interestingly, mice developed insulin resistance and glucose intolerance following a skeletal muscle-specific VDR knock-out [50]. Studies in LDL receptor knock-out mice found increased vascular calcification and atherosclerosis in the case of additional vitamin D deficiency. In detail the authors described for a reduction in 25(OH)D equal or above 50% that there was an increase by 50% in vascular calcifications [51]. Data from this animal model suggest that vitamin D deficiency may induce or promote a transdifferentiation of vascular cells into osteoblast-like cells what would then explain the excessive calcification. Interestingly, vitamin D treatment was able to reverse the changes [51, 52]. Independent of LDL diet-induced 25(OH)D deficiency was also associated with increased vascular calcification intensity in apolipoprotein E knockout mice [53]. In summary, the VDR knock-out models consistently indicated a causative role between vitamin D and vascular health.

3.2 Molecular and (patho-)physiologic effects

Based on the observations that animals with knock-outs of the VDR or 1-alpha hydroxylase suffer from cardiovascular disease, over one-hundred studies aimed to elucidate the mechanism behind this observation [29]. In view of the classic understanding of vitamin D as a master regulator of mineral metabolism, current evidence suggests that vitamin D affects mainly calcium and phosphate homeostasis in cells and the interstitial space [54]. Another additive explanation/mechanism would be the elevation of parathyroid hormone (PTH) occurring as a consequence of vitamin D deficiency [16]. It is well established that vitamin D is able to suppress PTH by direct effects on the parathyroid gland. Epidemiological evidence has indicated that PTH itself is a risk factor for CVD and predicts CV events [55]. The mechanism might be based on PTH-induced calcium overloading of cardiomyocytes with subsequent proarrhythmic actions, myocardial hypertrophy, but also aldosterone secretion [55–62]. This data suggests that to a certain point that both excess, as well as deficiency of vitamin D, can induce vascular calcification through a complex interplay with phosphate, calcium, and lipoproteins [63–69]. High serum phosphate levels even seem to be a prerequisite for vitamin D-induced vascular calcification, at least in animal (knock-out) models [68–76].

3.3 Vitamin D and fibrosis

Other experiments have raised the hypothesis that active vitamin D and phosphate is able to stimulate the secretion of fibroblast growth factor-23 (FGF-23) by osteocytes [39, 40, 44]. Though FGF-23 is an increasingly accepted marker of myocardial and renal fibrosis, the clinical relevance of the interaction between vitamin D and FGF-23 remains to be elucidated [71].

4 Observational studies

Observational studies have consistently reported an association between 25(OH)D concentrations and increased CV risk [39, 40]. More so, studies have described the association between 25(OH)D with traditional cardiovascular risk factors, such as arterial hypertension, hyperlipidaemia and diabetes mellitus (Table 1). However, even strong associations may, despite broad adjustments in statistical models, always be subject to residual confounding, collinearity and reverse causation [78]. The most commonly incriminated confounding factors – which are hard to measure and thus hard to adjust for - are limited physical activity, sun exposure and diet. Another possible confounding factor is Inflammation [79], as it lowers 25(OH)D concentrations by increasing 24-hydroxlyase expression and by decreasing vitamin D binding protein (DBP) [78, 79]. Therefore, some authors suggested that vitamin D deficiency may be just a general marker of poor health [78].

4.1 Rickets and cardiovascular diseases

There are four case reports of nutritional rickets and severe heart failure. Treatment of these children with vitamin D and

Table 1 Large meta-analyses and observational studies on associations between 25(OH)D and cardiovascular risk or events

Outcome	First author (year; reference no.)	Number of studies	Participants/ events	Type of included studies	25(OH)D cut-offs	Pooled risk (95% CI)
Acute coronary syndrome*	Dror Y; 2013 [130]	1	422,822 / 3933	Single cohort including Clalit Health Services members aged >45 between July 2007 and December 2011	24,96 nmol/L 24,96–49,92 nmol/L >89,856 nmol/L	1.88 (95% CI, 1.80–1.96) 1.25 (95% CI, 1.21–1.30) 1.13 (95% CI, 1.04–1.22)
Fatal and non-fatal ischemic heart disease, myocardial infarction, early death	Brøndum-Jacobsen P; 2012 [110]	18 (17)	82,982 / 8376	peer-reviewed population-based prospective studies	 < 25 nmol/L 25.0–49.9 nmol/L 49.9–74.9 nmol/L >75.0 nmol/L	HR (95% CI) 1.5 (1.2–2.0) 1.2 (1.0–1.6) 1.2 (0.9–1.5) 1.0 [reference]
Risk of cardiovascular diseases	Wang L; 2012 [109]	19	65,994 / 6123	Prospective study Observational study	20 to 60 nmol/L 25-nmol/L	1.03(95% CI, 1.00–1.06) 1.07 (95% CI, 1.03–1.12).
Myocardial infarction	Giovannucci E; 2008 [37]	9	18,225 / 454	Prospective Studies	37,44 nmol/L	2.09 (95% CI, 1.24–3.54)
Difference in systolic and diastolic blood pressure (BP)	Beveridge LA [77]	27	4541 / -	Randomized placebo-controlled clinical trials with vitamin D supplementation and associated baseline 25(OH)D level that predicted response	Systolic BP: < 24.96 nmol/L 24.96–49.92 nmol/L >49.92 nmol/L Diastolic BP: < 24.96 nmol/L 24.96–49.92 nmol/L >49.92 nmol/L	-0.4(95%CI, -0.3-2.3) -0.7(95%CI, -2.0-0.6) -0.2(95% CI, -1.8-1.3) -1.2(95% CI, -2.4-0.0) -0.2(95% CI, −1.0-0.6) -0.2(95% CI, -0.5-0.9)

calcium lead to a recovery of myocardial function [80, 81]. Pathologic insights come from one report of an autopsy from a similar case. It showed a dilated hypertrophic heart, with an increase in interstitial fibrosis in the subendocardial regions [80]. Somehow contradicting evidence comes from patients with hereditary $1,25(OH)_2D$ resistant rickets who do not experience major cardiovascular problems (at least not under adequate treatment) [82, 83].

4.2 Hypertension

The idea that vitamin D affects blood pressure (BP) has been derived from observations that low UVB exposure is associated with increased risk of arterial hypertension [36, 84]. This is supported by reports that BP is lower during the summer compared to winter, although heat and UVA exposure could be obvious confounders. Other authors demonstrated that the prevalence of arterial hypertension increases with increasing distance from the earth's equator, but ethnic and genetic differences also limit the interpretation of these results [26, 85, 86]. In the meta-analysis by Kunutsor et al. [84] comprising 283,537 participants, the relative risk (RR) for incidence of hypertension with 95% confidence interval (95% CI) in the top versus the bottom tertile of 25(OH)D was 0.70 (0.58 to 0.86). Although there was no significant association between vitamin D intake and presence of hypertension [84]. Nevertheless, it is of interest that in 2006 the American Heart Association issued a scientific statement regarding the effects of diet and dietary supplements on high blood pressure that did not include vitamin D as a relevant supplement to reduce BP [87]. In the very same statement, though, dietary calcium up to two grams *per day* was indicated to induce a minimal reduction on systolic and diastolic blood pressure, below 1 and 2 mmHg, respectively. These recommendation are based on the current lack of proof for a causal relationship between vitamin D alone and hypertension [20, 26].

4.3 Other cardiovascular risk factors

Several meta-analyses confirmed that 25(OH)D deficiency is an independent risk factor for developing type 2 diabetes mellitus, whether it is not clear if there is an association between vitamin D and metabolic syndrome [88–93]. Vitamin D deficiency has also been discussed as a risk factor for type 1 diabetes, but the data has been inconclusive [92, 94, 95]. Obesity is strongly associated with lower vitamin D concentrations [96, 97]. This might be explained by the studies describing that vitamin D is sequestered in adipose tissue, but other factors such inactivity, inflammation or simply volumetric dilution may be alternative explanations [98, 99]. In regard to the lipid profile, observational studies described a clear association, in particular with high triglycerides and low high-density lipoprotein (HDL) cholesterol [98, 99]. Other cardiovascular risk factors such as inflammation and chronic kidney disease are also associated with vitamin D deficiency [100–107].

4.4 Cardiovascular diseases

Meta-analyses of observational studies have consistently found that 25(OH)D deficiency (and insufficiency) is associated with an increased risk of cardiovascular mortality (Table 2) and cardiovascular events (i.e. myocardial infarction, heart failure and stroke) [107–119]. One meta-analysis including 65,994 patients reported a RR of 1.03 (95%CI 1.00–1.06) per 25 nmol/L decrement in 25(OH)D levels for CVD [109]. But specific for atherosclerotic coronary artery diseases (CAD) there are less consistent data so far [40, 120, 121]. Degerud et al. and Alsancak et al. did not observe any correlation of 25(OH)D and percent lumen loss as assessed with coronary angiography, although their sample size might have been too small [122, 123]. In 2014 Verdoia and co-workers reported an association in 1045 patients between 25(OH)D deficiency with CAD [124]. In line a Korean study reported an association between obstructive coronary artery disease (as assessed by CT angiography) and Vitamin D insufficiency [125]. In a cohort of typ 2 diabetic patients from Denmark Joergensen et al. reported that severe vitamin D deficiency (defined as 25(OH)D < 12.5 nmol/L, $n = 19$) was associated with increased coronary artery diseases, unfortunately this study suffers from inconsistent application of varying imaging techniques and sample size problems [126]. Even though some authors have claimed certainty about the role of 25(OH)D in CAD development [127], the absence of clinical trials make such allegations currently groundless. Nevertheless, existing evidence points to a possible role of vitamin D deficiency in CAD, raising the necessity of a randomized controlled trial in such a cohort of patients. In summary, the majority of studies concluded that an increased risk of CVD exists in participants with vitamin D deficiency (< 50 nmol/L), only a minority of studies reported on a U-shaped association [128–132]. Zittermann et al. observed that those with the highest 25(OH)D levels had actually low $1,25(OH)_2D$. They hypothesized that a reduced metabolism of 25(OH)D might explain this observation and that is could be responsible for the increased risk seen at high 25(OH)D concentrations [128]. Although extremely high 25(OH)D concentrations are considered toxic [132], epidemiologic studies did not detect an increased cardiovascular risk at these supranormal 25(OH)D levels. However, such high concentrations of 25(OH)D remain of concern and should to be avoided.

4.5 Myocardial infarction and stroke:

The majority of studies has proposed an association between 25(OH)D and myocardial infarction, stroke and sudden

Table 2 Large meta-analyses on vitamin D and cardiovascular mortality

Outcome	First author (year;reference no.)	Number of RCTs	Participants/ events	Follow-up in years	Main Hypothesis	Included studies	25(OH)D cut-offs	Pooled risk (95% CI)
Cardiovascular mortality	B. Schöttker [118]	8	26,018 / 2626	11 14.2 15.9 8.3 7.9 7.5 7 4.2	Masuring of 25-hydroxyvitamin D [25(OH)D] concentrations and evaluate cardiovascular mortality.	ESTHER Tromsø MONICA/ KORA SENECA HAPIEE Czech Republic HAPIEE Poland HAPIEE Lithuania NHANES III	24–62 nmol/L	1.38(CI95% 0.95–2.01) 1.16 (CI 95%, 0.95–2.01) 2.32 (CI95% 1.24–4.34) 0.98(CI95% 0.40–2.38) 1.32 (CI 95%, 1.25–4.30) 1.75 (CI95% 0.82–3.74) 1.26 (CI95% 0.82–3.74) 1.41(CI95% 0.97–1.63)
Cardiovascular disease mortality	Durup D; 2015 [129]	27	247,574 / 5454	7	Determine the association between cardiovascular events, stroke, and acute myocardial infarction mortality and serum levels of 25(OH)D.	Copenhagen vitamin D study (an observational cohort study)	12.5 nmol/L 12.5 nmol/L 125 nmol/L	2.5 for men (95% CI 2.2–2.9) 1.7 for women (95% CI 1.5–1.9) 1.3 (95% CI 1.2–1.4)
Cardiovascular and overall mortality	Zittermann A; 2012 [108]	14	62,548 / 5562	1.3–27	Measuring of 25-hydroxyvitamin D [25(OH)D] serum concentrations and evaluate mortality in observational studies among general populations.	MHFS study Women's Health and Aging Study (WHAS) Tromsø study Population-based cohort study	12.5 nmol/L 25 nmol/L 50 nmol/L	0.86 (95% CI 0.82, 0.91) 0.77 (95% CI 0.70, 0.84) 0.69 (95% CI 0.60, 0.78)
Vascular mortality	Tomson J; 2013 [114]	12	42,565 / 4632	13 (mean)	To examine the independent relevance of 25(OH)D for vascular and non-vascular mortality	Hoorn study Kuopio study ULSAM InCHIANTI Framingham offspring cohort MrOS Rancho Bernardo Cardiovascular health study NHANES III Tromso Mini finland health study Whitehall resurvey	>80 nmol/L	Per double of 25(OH)D RR 0.80 (95% CI, 0.70–0.91)
Cardiovascular death	Chowdhury, 2014 [116]	73	849,412 / 10,203	Mean 6.0 Range: 0.5–27	To evaluate the extent to which circulating vitamin D is associated with cardiovascular mortality	-	52.4–72.4 nmol/L 25.0–49.9 nmol/L <25.0 nmol/L Delta 25 nmol/L	1.07 (1.01–1.15) 1.20 (1.12–1.27) 1.50 (1.21–1.87) 1.16 (1.08–1.23)

cardiac death [34, 133–138]. Some studies claimed that there is an association between low 25(OH)D and a higher risk of atrial fibrillation and venous thromboembolism [139, 140]. Overall the data on the topic is not consistent [141, 142]. Evidence on carotid atherosclerosis and endothelial dysfunction is also sparse [143–148]. Nevertheless a recent subgroup analysis of our own randomized controlled trial raised the awareness of a possible improvement of endothelial function in patients with arterial hypertension and vitamin deficiency [149].

4.6 Heart failure

The first clinical observations raising the possibility of a link between vitamin D and heart failure were case reports of children with rickets and heart failure, which resolved after Vitamin D substitution [80, 81]. This launched research into potential CV interaction of vitamin D, but until recently only a few studies have claimed that there is an associations between 25(OH)D and ventricular function [133–136, 150–155]. The observational data coming from the MESA cohort showed no association between 25(OH)D and parameters of LV function as assessed by MRI [150]. The findings were reproduced by a sub-study of AGES [151]. Similarly, LV mass index by echocardiography was also not associated with 25(OH)D in the Hoorn study [152]. It may be interpreted that this further refutes a large influence of vitamin D on blood pressure [26, 36, 84, 87]. Nevertheless all three studies confirmed an association between PTH and parameters of systolic LV function and/or LV mass [150, 151, 153]. In regard to interventional data, two meta-analysis aimed to assess the existing trial evidence. Ford and co-workers published the results of the RECORD trial together with a meta-analyis of existing RCT's [137]. The overall results of meta-analysis that included 21 trials with a total of 13,033 patients were negative, although the trial itself found a statistically significant reduction in heart failure (adjusted HR: 0.75; 95% CI: 0.58, 0.97; $P = 0.027$) in 5292 patients [137]. The differences between included trials hamper conclusions in regard to heart failure. Especially as dose (between 400 IU and 500,000 IU of vitamin D per dose) and concomitant calcium supplementation vary heavily between the included studies. Another difference is the baseline 25(OH)D values and the age, but no specific analysis was conducted in such subgroups. A secondary analysis from the women's health initiative of vitamin D plus calcium effects on heart failure incidence report a beneficial effect in the subgroup of women without diabetes, hypertension or coronary artery diseases [156]. In a very small (23 patients) RCT Dalbeni et al. described an improvement of LVEF with 4000 IU/daily vitamin D [157]. The recently published VINDICATE trial reported in 229 patients with chronic heart failure and vitamin D deficiency (< 50 nmol/L) improvement of LV function and dimension by vitamin D treatment (4000 IU/day) [158]. Although the primary endpoint (6 min walk test) was missed, the results support a causal role of vitamin D and heart failure. In summary, epidemiologic evidence did not find a consistent association of vitamin D deficiency and heart failure in adults, although some trials have indicated a possible effect.

5 Mendelian randomization studies

The inherent weakness of observational studies is their inability to demonstrate a causal interference between two factors. This limitation might be overcome by Mendelian randomization studies. In a nutshell, the presence or absence of certain genetic polymorphisms of a particular gene should be distributed randomly in the community and therefore their association with CV phenotypes allow implicitly assumptions on causality. A detailed discussion of advances and limitations of Mendelian randomization studies can be found elsewhere [159, 169]. Several genetic studies investigating single nucleotide polymorphisms (SNPs) of the VDR gene and cardiovascular outcomes, unfortunately, failed to provide evidence for a causal role of vitamin D for CV risk [160–168]. Genome-wide association studies (GWAS) identified four genetic loci that are associated with serum 25(OH)D levels [166–168]. The identified loci are involved in the biosynthesis of vitamin D at all major steps, and include synthesis of the precursor 7-dehydrocholesterol reductase (*DHCR7*), 25-hydroxylation of vitamin D (25-hydroxylase), transport (DBP) and in the degradation (i.e. 24-hydroxylase) [167–172]. As 25(OH)D is largely produced in the skin by sunlight exposure and to some degree determined by dietary intake, all known genetic polymorphisms explain only ~1–4% of the variation in serum 25(OH)D concentrations [167]. Results from so far published Mendelian randomization studies refute the hypothesis of vitamin D deficiency as a causal risk factor for obesity and high C-reactive protein (CRP) concentrations [172]. Less consistent data exist in regard to type 2 diabetes and lipid levels [173–179]. Studies on blood pressure are also not settling. The largest study in this field reported that a 10% increase in genetically determined 25(OH)D levels was associated with a change of < 1 mmHg in systolic and diastolic BP, and an 8.1% decreased odds ratio of hypertension [177]. Though this should not be mistakenly interpreted as effect size in individual patients with vitamin D deficiency, RCTs already supported the assumption of small effects of vitamin D supplementation on BP [25, 26, 178].

Mendelian randomization studies were unable to uniformly link vitamin D associated loci with coronary artery disease, myocardial infarction, stroke or cardiovascular mortality [40, 180–182]. These results, provisionally argue against a causal effect of vitamin D deficiency on cardiovascular diseases.

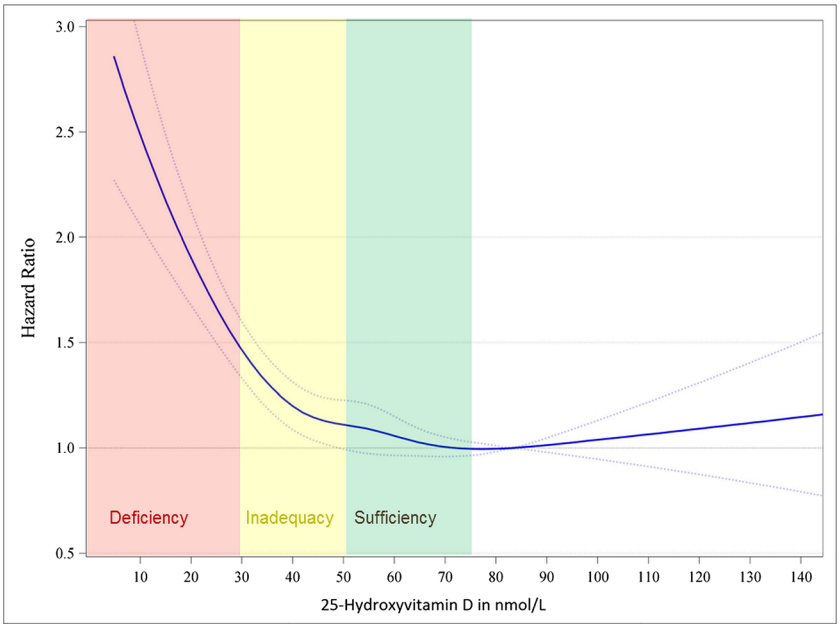

Fig. 1 Dose-response trend of hazard ratios of death from all causes by standardized 25-hydroxyvitamin D concentrations. Colours referring to the IOM definition of vitamin D deficiency, inadequacy and sufficiency [4]. Hazard ratios [*blue line* with 95% confidence interval as the *dotted blue lines*] are referring to the 25-hydroxyvitamin D concentration of 83.4 nmol/L. Reproduced with permission from reference under the Creative Commons CC0 licensing [193].

6 Future perspective

Though some large RCTs will soon be concluded and will expand existing knowledge, unfortunately, most of the ongoing vitamin D RCTs are limited by the inclusion of participants regardless of their 25(OH)D serum levels and some allow vitamin D supplement intake in the placebo group. This is a major limitation because the effects of vitamin D supplementation may be profoundly stronger in participants with very low starting 25(OH)D levels (Fig. 1) [193]. More so, in some trials the used immuno-assays for the determination of 25(OH)D may be of concern [183]. Some studies including critically ill patients even reported a mortality reduction of up to 50% (relative risk) but limited to the patients with 25(OH)D level < 30 nmol/L [184]. Similar subgroup analyses of individuals with vitamin D deficiency are expected to be reported in upcoming trials, but have important limitations, such as loss of power and more so they are usually not accepted by regulatory agencies. From a physiological point of view, the routine supplementation of a hormone without deficiency is at best unlikely to exert beneficial effect (in the worst case, harm might even be done) [15, 185–194]. Finally, we like to point out that if at the end we have to conclude that vitamin D is not causally responsible to CVD, we still would have to identify the confounding factors that are responsible for the strong association between vitamin D and CVD. This should be then a valuable clinical-therapeutic target, given the strong epidemiologic association.

7 Conclusions

Severe vitamin D deficiency is a major risk factor for osteomalacia and fractures, but might also adversely affect the cardiovascular system. It is not completely clear whether and at which concentrations vitamin D, as it is present in community-dwelling adults, is relevant for cardiovascular outcomes. In general, observational studies reported strong associations between low 25(OH)D concentrations and increased cardiovascular risk, arterial hypertension, dyslipidemia and endothelial dysfunction. Some RCTs have detected effects in patients with low (< 50 nmol/L) and very low vitamin D levels (< 30 nmol/L) [40, 184]. Even though supported by the large majority of cell-based models and VDR knockout animals, data from Mendelian randomization studies and larger RCTs, do not consistently support the assumption of a causal relationship between vitamin D and CVD. Interestingly the vitamin D trials often aim to focus und the hardest clinical endpoints, such as all-cause or organ specific mortality [11, 58, 84, 188, 189]. This may be an overambitious goal. Bone health or even small reductions in cardiovascular endpoints ought to be enough to support the introduction of preventive measures in the general population and high-risk subgroups. Beside, often the increase in 25(OH)D is commonly used as an surrogate for the successful supplementation of vitamin D. Unfortunately there is little evidence to discuss potential other approaches such as the reduction in PTH or time within "normal range". It is unclear if these variables would correlate

better with physiologic effects [24]. Therefore, before final conclusion can be drawn, there is an unmet need for adequately powered RCTs focussing on patients with low to very low 25(OH)D levels. In the case of neutral findings in future RCTs, the question remains which unidentified factor confounded the epidemiological results and if this factor would then turn into a therapeutic target to reduce the burden of CVD.

Compliance with ethical standards

Funding For the present review there was no funding.

Conflict of interest M.R.G. received partial travel support by Amgen Switzerland AG and Synlab Holding Deutschland Germany, GmbH. WM reports grants and personal fees from AMGEN, BASF, Sanofi, Siemens Diagnostics, Aegerion Pharmaceuticals, Astrazeneca, Danone Research, Numares, Pfizer, Hoffmann LaRoche: personal fees from MSD, Alexion; grants from Abbott Diagnostics, all outside the submitted work. W.M. is employed with synlab Holding Deutschland GmbH. Other authors report no potential conflicts of interest in regard to the present work.

Ethical approval All studies cited in the current manuscript that were performed by the authors and include procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. That includes that informed consent was obtained from all individual participants included in the studies cited hat where performed by any of the authors.

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