The critical involvement of vitamin D in bone and mineral metabolism is historically known\(^1\),\(^2\). The identification of the vitamin D receptor (VDR) in almost all human organs including the heart and the blood vessels, and observations that individuals deficient in vitamin D are at increased risk of various extraskeletal diseases, stimulated research on the role of vitamin D for overall and cardiovascular health\(^3\)–\(^6\). In this Review, we summarize the existing knowledge on the effects of vitamin D on cardiovascular diseases and associated risk factors, with a particular focus on meta-analyses of epidemiological studies and randomized, controlled trials (RCTs). First, we provide a short summary of vitamin D metabolism and current vitamin D guidelines, a historical perspective on vitamin D and cardiovascular diseases, and a brief overview on the mechanistic effects of VDR activation on cardiovascular risk factors, the blood vessels, and the heart. The principal aspect of this Review is an update on observational studies, Mendelian randomization studies, and RCTs on vitamin D and cardiovascular risk. Finally, we outline and discuss ongoing vitamin D research, including large RCTs, and present our conclusions on how to deal with the management of vitamin D deficiency from a public health and cardiovascular health perspective.

Vitamin D metabolism

Vitamin D, the fourth vitamin to be named, was first described by McCollum as a factor that was able to cure rickets, a disease that is characterized by impaired bone mineralization and skeletal deformities\(^1\). Although initially classified as a vitamin, vitamin D is now recognized as a precursor (a prohormone) of the steroid hormone 1,25-dihydroxyvitamin D (1,25(OH)\(_2\)D), also called calcitriol. The major source for vitamin D is endogenous synthesis in the skin (FIG. 1). When the skin is exposed to ultraviolet-B (UVB) or sunlight radiation, the liver-derived precursor 7-dehydrocholesterol is converted to pre-vitamin D, which in turn isomerizes to vitamin D\(_7\). Food intake is usually only a minor source of vitamin D. The two main isoforms of vitamin D are vitamin D\(_3\) (cholecalciferol), which is synthesized in the skin and is contained in animal foods such as fish, and vitamin D\(_2\) (ergocalciferol), which the human body cannot synthesize and is contained in fungi (for example, yeast and mushrooms). Vitamin D\(_3\) probably has a higher bioavailability than that of vitamin D\(_2\), but in this Review (unless otherwise stated), we do not distinguish between these two isoforms because they share the same metabolism\(^4\). In the circulation, vitamin D sterols

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Vitamin D and cardiovascular disease prevention

Stefan Pilz\(^1,2\)*, Nicolas Verheyen\(^3\)*, Martin R. Gruber\(^1,4\), Andreas Tomaschitz\(^5,5\) and Winfried Mraz\(^6,8\)

Abstract | Vitamin D is a precursor of the steroid hormone calcitriol that is crucial for bone and mineral metabolism. Both the high prevalence of vitamin D deficiency in the general population and the identification of the vitamin D receptor in the heart and blood vessels raised interest in the potential cardiovascular effects of vitamin D. Experimental studies have demonstrated various cardiovascular protective actions of vitamin D, but vitamin D intoxication in animals is known to induce vascular calcification. In meta-analyses of epidemiological studies, vitamin D deficiency is associated with an increased cardiovascular risk. Findings from Mendelian randomization studies and randomized, controlled trials (RCTs) do not indicate significant effects of a general vitamin D supplementation on cardiovascular outcomes. Previous RCTs, however, were not adequately designed to address extraskeletal events, and did not focus on vitamin D-deficient individuals. Therefore, currently available evidence does not support cardiovascular benefits or harms of vitamin D supplementation with the commonly used doses, and whether vitamin D has cardiovascular effects in individuals with overt vitamin D deficiency remains to be evaluated. Here, we provide an update on clinical studies on vitamin D and cardiovascular risk, discuss ongoing vitamin D research, and consider the management of vitamin D deficiency from a cardiovascular health perspective.
The vitamin D receptor (VDR) and enzymes for vitamin D metabolism are expressed throughout the cardiovascular system. VDR and 1α-hydroxylase knockout mice have hypertension with myocardial hypertrophy and increased activity of the renin–angiotensin–aldosterone system. The molecular effects of VDR activation indicate various antiatherosclerotic and protective effects on the heart and on common cardiovascular risk factors. Observational studies have shown that low 25-hydroxyvitamin D levels are associated with an adverse cardiovascular risk profile and significantly increased risk of cardiovascular events. Mendelian randomization studies and randomized clinical trials have not shown significant effects of vitamin D on cardiovascular events, but these trials were not designed to investigate cardiovascular outcomes in vitamin D-deficient individuals. Vitamin D supplementation is currently not indicated for the purpose of cardiovascular disease prevention, but treatment of vitamin D deficiency is critical for skeletal health.

are mainly transported by the vitamin D-binding protein (DBP), which is a serum glycoprotein secreted by the liver. Vitamin D itself is biologically inactive and is hydroxylated to 25-hydroxyvitamin D (25(OH)D) in the liver (Fig. 1). Serum 25(OH)D is measured to assess vitamin D status, because this is the major circulating vitamin D metabolite that best reflects vitamin D intake from all sources. Further 1α-hydroxylation of 25(OH)D occurs mainly in the kidney, and results in the formation of the active vitamin D hormone 1,25(OH)2D. The endocrine production of 1,25(OH)2D is tightly regulated by parameters of bone and mineral metabolism. For example, 1,25(OH)2D production is stimulated by the parathyroid hormone and inhibited by fibroblast growth factor 23 (FGF-23), with the main aim of maintaining an adequate serum calcium level through the effects of 1,25(OH)2D on the kidney, intestine, and bone. Therefore, serum 1,25(OH)2D concentrations are not a good measure of vitamin D supply or status.

The effects of 1,25(OH)2D can be autocrine and paracrine because 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase) expression has been reported in several extrarenal cells, including cells of the cardiovascular system. This local tissue production of 1,25(OH)2D seems to be mainly dependent on the availability of circulating 25(OH)D, but 1,25(OH)2D production is also regulated by other factors such as cytokines. Finally, 1,25(OH)2D exerts its biological effects by binding to the intracellular vitamin D receptor housed in the cytosol. The tissue and cell-type specific distribution of the VDR throughout the body is still not fully resolved, however, and not all studies detected VDR expression in tissues such as skeletal, cardiac, or smooth muscle. After activation of the cytosolic VDR by ligand binding and translocation to the nucleus, the activated VDR interacts with vitamin D response elements in the promoter region of target genes and, thereby, regulates approximately 3% of the genome. Degradation of 1,25(OH)2D and other vitamin D metabolites is initiated by 24-hydroxylase, an enzymatic process that is induced, for example, by VDR activation itself, thereby preventing vitamin D intoxication as part of an autoregulatory loop.

Current vitamin D guidelines

Dietary reference intakes and dietary reference values for the general population in Europe and North America are based on beneficial vitamin D effects on skeletal health — that is, beneficial for the prevention of rickets, osteomalacia, and fractures. Overt vitamin D deficiency leads to reduced calcium absorption in the gut that can cause hypocalcaemia. Low serum calcium levels are detected by the extracellular calcium-sensing receptor (CaSR) in the parathyroid glands, which subsequently increases parathyroid hormone secretion in order to preserve physiological serum calcium levels by increasing calcium release from bones and increasing calcium reabsorption in the kidneys. High parathyroid hormone levels are, therefore, a hallmark of vitamin D deficiency.

Several cut-off values and target ranges for 25(OH)D have been proposed in the scientific literature. In a report published in 2011, the Institute of Medicine of the National Academies (USA) concluded that 25(OH)D concentrations of 50 nmol/l (20 ng/ml) are sufficient to meet the vitamin D requirements in 97.5% of the general population (Box 1). Under conditions of low sunlight exposure, such as during the winter in Europe, intake of 800 international units (IU) of vitamin D per day (1 μg is equivalent to 40 IU of vitamin D) is required to achieve 25(OH)D concentrations of 50 nmol/l (20 ng/ml) in almost all individuals. Therefore, a daily vitamin D (cholecalciferol or ergocalciferol) intake of 600–800 IU is recommended for the adult population when sunlight exposure is low or absent. However, epidemiological studies indicate that the actual vitamin D intake by nutrition and supplements is <200 IU per day in most individuals of the general population, which in turn results in a high prevalence of vitamin D deficiency.

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Meta-analyses of RCTs have shown that vitamin D supplementation can significantly reduce fractures, and Bischoff-Ferrari et al. reported that a daily vitamin D intake of approximately 800–2,000 IU per day is required to achieve this effect. Other meta-analyses have shown that the antifracture effects of vitamin D are restricted to studies with vitamin D plus calcium supplementation or to institutionalized individuals. Vitamin D supplementation is a standard treatment for patients with osteoporosis, but the pathways by which vitamin D reduces fractures are still not entirely clear because vitamin D supplementation has no significant effect on bone mineral density. Accumulating evidence suggests that the prevention of falls by vitamin D can be responsible, at least partially, for the antifracture effect. However, not all meta-analyses showed that vitamin D supplementation significantly reduced falls. Moreover, no general consensus exists on the vitamin D dose that should be used to treat patients with osteoporosis, and which 25(OH)D levels should be achieved. The main question of this debate is whether 50 nmol/l (20 ng/ml) or 75 nmol/l (30 ng/ml) should be the (minimum) target level, but several other cut-off values and target ranges for 25(OH)D have also been proposed.

Vitamin D (cholecalciferol or ergocalciferol) supplementation increases serum 25(OH)D levels in a dose-dependent manner — a rule of thumb suggests that 1,000 IU vitamin D per day increases the 25(OH)D level.

Figure 1 | Human metabolism of vitamin D. After endogenous synthesis in the skin — where 7-dehydrocholesterol is converted to pre-vitamin D₃ in response to ultraviolet-B exposure and then is isomerized to vitamin D₃ in the epidermal basal layers — or dietary intake of vitamin D₂/D₃, vitamin D binds to the vitamin D-binding protein (DBP) in the bloodstream and is transported to the liver, where vitamin D is hydroxylated to 25-hydroxyvitamin D₃. Production of the active secosteroid 1,25-dihydroxyvitamin D₃ upon 1α-hydroxylation in the kidney is tightly regulated, stimulated by the parathyroid hormone (PTH) and inhibited by fibroblast growth factor-23 (FGF-23) and 1,25-dihydroxyvitamin D₃ itself. The rate-limiting step in catabolism is the degradation of 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ to 24,25-hydroxyvitamin D₃ and 1,24,25-trihydroxyvitamin D₃, respectively, which are consequently metabolized to calcitriolic acid and excreted by the kidney. The biological effects of 1,25-dihydroxyvitamin D₃ are induced via binding to the almost ubiquitously expressed vitamin D receptor. Major endocrine actions include the regulation of calcium and phosphate homeostasis. In extrarenal tissues (for example, in cardiovascular tissues), 1,25-dihydroxyvitamin D₃ can also exert autocrine and paracrine effects.
by approximately 25 nmol/l (10 ng/ml). Another possibility is to treat patients with vitamin D deficiency with ‘active vitamin D’, that is, with calcitriol or its analogues (such as paricalcitol). However, active vitamin D treatment has a narrow therapeutic window with risk of hypercalcaemia and hyperphosphatemia; therefore, this treatment is mainly restricted to patients with chronic kidney disease or hypoparathyroidism. In this Review, we focus on the literature on vitamin D (cholecalciferol or ergocalciferol) supplementation and 25(OH)D concentrations, and provide only a few examples of studies on active vitamin D treatment or 1,25(OH)2D levels.

**Vitamin D and cardiovascular disease**

In the 1930s and 1940s, fortification of dairy products such as milk (but also beer, hot dogs, etc.) with vitamin D was widely introduced (for example, in the USA and UK) along with the promotion of sun or UVB exposure for the prevention and treatment of rickets. These interventions almost erased vitamin D deficiency in children and with the promotion of sun or UVB exposure for the prevention and treatment of rickets in children was suspected to result from the vitamin D food fortification. Therefore, vitamin D food fortification was subsequently banned in most countries for some decades. Although several of the case reports from the 1950s on hypercalcaemia in children were likely to be a result of the inherited disease Williams syndrome, the observation that pharmacological doses of vitamin D lead to hypercalcaemia with vascular calcification, in particular in the setting of chronic kidney disease, has been well documented in animal experiments. The perception of vitamin D as being harmful for the cardiovascular system was then challenged in the early 1980s by Robert Scragg, who raised the hypothesis that the increase in cardiovascular diseases in winter might be a result of low 25(OH)D levels as a consequence of reduced sunlight exposure during wintertime. This hypothesis stimulated research on the potential cardiovascular benefits of vitamin D, with an enormous increase in publications on this topic over the past 10 years.

**Mechanistic studies**

From a cardiovascular perspective, mice with a systemic knockout of the Vdr or 1α-hydroxylase (Cyp27b1) genes are characterized by myocardial hypertrophy with overexpression of the renin–angiotensin–aldosterone system (RAAS), hypertension, increased thrombogenicity, and progression of atherosclerosis. Various molecular effects of vitamin D with relevance to the cardiovascular system have been described, which we have summarized according to the effects on cardiovascular risk factors, blood vessels, and the heart (FIG. 2).

**Cardiovascular risk factors.** Apart from modulating mineral metabolism, VDR activation also has a suppressive effect on parathyroid hormone synthesis. High parathyroid hormone serum concentrations are associated with cardiovascular risk factors such as chronic kidney disease and obesity, and with increased risk of cardiovascular events. Experimental studies indicate that parathyroid hormone exerts various effects on the cardiovascular system, including the promotion of intracellular calcium overloading of cardiomyocytes, generation of oxidative stress, proarrhythmic actions, and induction of myocardial hypertrophy, endothelial dysfunction, and aldosterone secretion.

The proposed antihypertensive properties of vitamin D might be mediated by suppression of the RAAS. VDR activation suppresses the transcription of the renin gene by blocking the activity of the cAMP response element in the renin gene promoter. Experimental studies suggest that, besides low calcium and high parathyroid hormone levels, vitamin D deficiency can also contribute to arterial hypertension by increasing vascular resistance and vasoconstriction.

Various molecular effects of VDR activation suggest antidiabetic properties of vitamin D, including increases in insulin secretion and insulin sensitivity as well as protection against cytokine induced β-cell dysfunction and β-cell death. Vitamin D might also prevent type 1 diabetes mellitus through anti-inflammatory actions and by increasing regulatory T cells that protect against autoimmune diseases (and atherosclerosis).

The effects of vitamin D on lipid metabolism are largely unclear and might be harmful or beneficial. VDR activation suppresses apolipoprotein A-I (apoA1) expression—the major constituent of HDL cholesterol—and might indirectly increase fat absorption in the gut because the increased calcium absorption induced by vitamin D might reduce the formation of the calcium-fatty acid soaps that are excreted in the faeces. By contrast, another hypothesis is that the increases in calcium absorption induced by vitamin D might even reduce serum triglyceride levels by decreasing hepatic triglyceride formation or secretion through an effect on hepatocellular calcium. Other potentially beneficial vitamin D effects on blood lipids might be mediated by lowering parathyroid hormone levels (which suppresses lipolysis) or by increasing insulin secretion and sensitivity.

Several other cardiovascular, protective, molecular effects of VDR activation have been described.
For example, VDR activation regulates inflammation by blocking nuclear factor κB (NF-κB) activation, which might prevent kidney diseases — through protective effects on podocytes and other antiproteinuric actions such as increased expression of LRP2 (which encodes megalin) — and anaemia (for example, through suppression of inflammation and hepcidin production, and by increasing erythropoiesis), regulates coagulation, and reduces oxidative stress.\textsuperscript{10,33,37–39,53}

**Vascular dysfunction.** The molecular effects of vitamin D on blood vessel cells have been extensively reviewed.\textsuperscript{54} Experimental studies suggest that vitamin D can protect against atherosclerosis by inhibiting the transformation of macrophages to foam cells and by increasing cholesterol efflux.\textsuperscript{54,55} Endothelial repair might be promoted by 1,25(OH)\textsubscript{2}D\textsubscript{3}-induced production of vascular endothelial growth factor (VEGF) in vascular smooth muscle cells.\textsuperscript{59} Upregulation of endothelin receptor type B (EDNRB) and downregulation of oxytocin receptor (OXTR) expression by VDR activation can lead to vessel relaxation.\textsuperscript{53} Other antithrombogenic properties of VDR activation include anti-inflammatory actions such as reduced TNF-α and IL-6 expression in endothelial cells, reduced thrombogenicity — through the downregulation of tissue factor (TF) and upregulation of thrombomodulin (THBD) expression in endothelial cells and macrophages — and increased endothelial nitric oxide production.\textsuperscript{53} Interestingly, in mice with endothelial-specific knockout of the Vdr gene, vascular function is significantly altered, with increased sensitivity to angiotensin-2 compared with control mice.\textsuperscript{50} Moreover, VDR activation has been shown to promote vascular repair by circulating angiogenic myeloid cells by inducing stromal cell-derived factor 1 (SDF-1).\textsuperscript{57} By contrast, a minority of experimental studies have indicated some potentially proatherosclerotic effects of vitamin D such as increased monocyte adhesion to endothelial cells.\textsuperscript{59}

**Cardiovascular effects of vitamin D receptor activation.** a | The biological actions of 1,25-dihydroxyvitamin D are mediated by binding to the nuclear high-affinity vitamin D receptor (VDR). The activated VDR heterodimerizes with the retinoid X receptor (RXR) and the ligand-bound VDR–RXR complex binds to vitamin-D response elements located in the promoter of target genes. This process causes the recruitment of co-activators or co-repressors, which leads to positive or negative transcriptional regulation of gene expression. b | On the basis of the major findings from experimental studies, the effects of vitamin D can be categorized into effects on the blood vessels, the heart, and on cardiovascular risk factors. While most studies indicate beneficial cardiovascular effects of vitamin D receptor activation, the effects of vitamin D on lipid metabolism and vascular calcification are unclear and might be harmful or beneficial. LRP2, low-density lipoprotein receptor-related protein 2; APOA1, apolipoprotein A-I (APOA1); THBD, thrombomodulin; VEGF, vascular endothelial growth factor (VEGF); SDF-1, stromal cell-derived factor 1; TF, tissue factor; MCP1, macrophage chemotactic protein 1; TNF, tumor necrosis factor; IL-6, interleukin-6; IL-1β, interleukin-1β; VSMC, vascular smooth muscle cells.
The effects of vitamin D on vascular calcification are a double-edged sword, with both deficiency and excess of vitamin D (in particular in the setting of end-stage renal disease) causing vascular calcification and transformation of vascular smooth muscle cells towards an osteoblastic phenotype. Phosphate overload, which stimulates vitamin D degradation by increasing 24-hydroxylase expression, is a pivotal component for vascular calcification. VDR activation increases phosphate absorption and phosphate levels, which in turn stimulate FGF-23 secretion by osteocytes. FGF-23 is a master regulator of phosphate homeostasis and increases renal phosphate excretion. The expression of klotho, which is encoded by the KL gene and is a co-receptor for FGF-23, is increased by VDR activation. This co-receptor has been shown to protect against vascular calcification, indicating that the interactions between vitamin D, klotho, and FGF-23 are critically involved in vascular calcification.

Heart. VDR expression has been detected in cardiac myocytes and fibroblasts, and cardiomyocyte-specific knock out of the Vdr gene in mice is associated with myocardial hypertrophy. These knockout mice display activation of the fetal gene programme in cardiomyocytes — that is, increased atrial natriuretic peptide (Nppa) and actin, α1 skeletal muscle (Acta1) gene expression — and increased expression of Rcan1, which encodes MCIP1 (modulatory calcineurin inhibitor protein 1, also known as calcipressin-1), a downstream target of calcineurin/nuclear factor of activated T-cells (NFAT) signalling. Given that 1,25(OH)D treatment reduced Rcan1 expression in neonatal cardiomyocytes, the antihypertrophic effects of VDR activation have been hypothesized to be mediated by suppression of the calcineurin/NFAT/RCAN1 pathways. Accordingly, rats with vitamin D deficiency also develop cardiac hypertrophy along with interstitial fibrosis. Interestingly, myocardial hypertrophy in rats is accompanied by increased VDR gene and protein expression in the heart. In experimental studies, VDR activation in the myocardium regulates extracellular matrix turnover by modulating the expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases. Moreover, VDR activation modulates myocardial contractility, probably by regulating calcium flux. Mice with a systemic knockout of the Vdr gene in mice is associated with cardiovascular risk factors. In a meta-analysis of prospective cohort studies including a total of 283,537 participants and 55,816 incident cases of hypertension, the pooled risk of incident hypertension per 25 nmol/l (10 ng/ml) increment in baseline 25(OH)D was 0.88 (95% CI 0.81–0.97). Other meta-analyses of prospective studies have also indicated that low 25(OH)D levels are associated with an increased risk of developing type 2 diabetes and gestational diabetes, whereas results are inconsistent for metabolic syndrome and cardiovascular disease.

Cardiovascular risk factors. In a meta-analysis of observational studies, the odds ratio for developing type 1 diabetes comparing vitamin D supplementation with no supplementation during early life was 0.71 (95% CI 0.51–0.98). A significant association between vitamin D deficiency and obesity was reported in meta-analyses of mainly cross-sectional studies, but prospective data on this issue are insufficient. Significant cross-sectional associations between vitamin D deficiency and an atherogenic lipid profile have been described, in particular with low HDL-cholesterol and high triglyceride levels, but hardly any prospective data for these associations are available. Moreover, vitamin D deficiency is also associated with other cardiovascular risk factors such as inflammation, chronic kidney disease, and anemia. Interestingly, meta-analyses of observational studies indicate that low 25(OH)D levels are associated with myalgia in patients receiving statin therapy, and with diabetic peripheral neuropathy.

Cardiovascular diseases. Several meta-analyses of prospective studies have consistently shown that low 25(OH)D serum concentrations indicate an increased risk of overall cardiovascular events and cardiovascular mortality. A meta-analysis including 19 prospective studies showed that when 25(OH)D levels were below approximately 60 nmol/l (24 ng/ml), the risk of cardiovascular disease increased monotonically across decreasing 25(OH)D levels, with a relative risk.
of 1.03 (95% CI 1.00–1.06) per 25 nmol/l (10 ng/ml) decrement in 25(OH)D levels44 (FIG. 3). Although meta-analyses and most individual studies have detected an increased risk of cardiovascular events only in individuals with low 25(OH)D levels, a few studies report a U-shaped association, with an increased cardiovascular risk for low and high 25(OH)D levels44–97. Whether individuals with particularly high 25(OH)D levels and increased cardiovascular risk are the ones who started taking supplements or changed their lifestyle towards increased sun exposure as a consequence of a diagnosis of vitamin D deficiency or a clinical disease is an intriguing hypothesis that has to be further evaluated. Of note, large meta-analyses have not reported a significantly increased risk of cardiovascular events for individuals with high 25(OH)D concentrations, but the long-term outcome data on this topic are scarce. Therefore, in view of the existing literature, we can conclude that concentrations of 25(OH)D above approximately 125 nmol/l (50 ng/ml) are a reason for concern, not because they are proven to be harmful, but because of insufficient data on such high concentrations of 25(OH)D. Acute vitamin D intoxication with hypercalcaemia usually does not occur at 25(OH)D concentrations below approximately 375 nmol/l (150 ng/ml), and can be achieved only by extreme overdosing of vitamin D. In relation to specific cardiovascular diseases, low 25(OH)D has been associated with increased risk of ischaemic heart diseases and myocardial infarctions85,96. While vitamin D deficiency is associated with cardiovascular events and mortality, the majority of epidemiological studies do not show a significant association with the presence of angiographic coronary artery disease or carotid atherosclerosis99–103. By contrast, a meta-analysis of cross-sectional studies reported that a low 25(OH)D level is associated with peripheral artery disease94. Low 25(OH)D levels have also been associated with endothelial dysfunction, but this association has not been consistently found in all studies97–99. Some studies have shown that low 25(OH)D levels are associated with the incidence of heart failure, but associations between 25(OH)D and left ventricular systolic and diastolic function have not been consistently observed99,100–108. Interestingly, several studies reported that vitamin D deficiency is associated with significantly increased risk of sudden cardiac death106–112. Moreover, meta-analyses of prospective studies have shown that low 25(OH)D serum concentrations are associated with an increased risk of cerebrovascular events and strokes113–116. By contrast, data on the association between 25(OH)D and venous thromboembolism, as well as atrial fibrillation, are inconsistent117–120.

Table 1 | Meta-analyses on the association between vitamin D and cardiovascular events and mortality

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of studies</th>
<th>Participants/events</th>
<th>Metric</th>
<th>Pooled risk (95% CI)</th>
<th>Tests for heterogeneity</th>
<th>Egger test, P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>Schwéttker et al. (2014)93</td>
<td>8</td>
<td>23,081/1,886</td>
<td>RR (Q1 versus Q5)</td>
<td>1.41 (1.18–1.68)</td>
<td>I² = 13%</td>
<td>NR</td>
</tr>
<tr>
<td>Grandi et al. (2010)97</td>
<td>5</td>
<td>24,387/2,007</td>
<td>HR (lowest versus highest category)</td>
<td>1.83 (1.19–2.80)</td>
<td>Q = 2.10; P = 0.0003</td>
<td>NR</td>
</tr>
<tr>
<td>Wang et al. (2012)114</td>
<td>NR</td>
<td>NR</td>
<td>RR (lowest versus highest category)</td>
<td>1.42 (1.19–1.71)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chowdhury et al. (2014)91</td>
<td>29</td>
<td>101,649/10,203</td>
<td>RR (T1 versus T3)</td>
<td>1.43 (1.25–1.64)</td>
<td>I² = 83.9%</td>
<td>0.96</td>
</tr>
<tr>
<td>Afzal et al. (2014)115</td>
<td>NR</td>
<td>NR</td>
<td>RR (Q1 versus Q4)</td>
<td>0.79 (0.72–0.87)</td>
<td>I² = 47.8%</td>
<td>0.331</td>
</tr>
<tr>
<td>Fan et al. (2014)116</td>
<td>7</td>
<td>23,481/2,265</td>
<td>RR (lowest versus highest category)</td>
<td>1.57 (1.24–2.00)</td>
<td>I² = 47.8%</td>
<td>0.331</td>
</tr>
<tr>
<td>Tomson et al. (2013)107</td>
<td>12</td>
<td>42,565/4,632</td>
<td>HR (Q4 versus Q1)</td>
<td>0.79 (0.72–0.87)</td>
<td>I² = 0%</td>
<td>0.12</td>
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<tr>
<td><strong>Cardiovascular events (fatal and nonfatal)</strong></td>
<td></td>
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<tr>
<td>Grandi et al. (2010)97</td>
<td>4</td>
<td>5,253/756</td>
<td>HR (lowest versus highest category)</td>
<td>1.54 (1.22–1.95)</td>
<td>Q = 2.55; P = 0.47</td>
<td>NR</td>
</tr>
<tr>
<td>Sokol et al. (2011)98</td>
<td>7</td>
<td>27,620/2,530</td>
<td>RR (lowest versus highest category)</td>
<td>1.68 (1.23–2.28)</td>
<td>I² = 63.8%</td>
<td>0.11</td>
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<tr>
<td>Wang et al. (2012)114</td>
<td>19</td>
<td>65,994/6,123</td>
<td>RR (lowest versus highest category)</td>
<td>1.52 (1.30–1.77)</td>
<td>I² = 61%</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
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<tr>
<td>Brandm-Jacobsen et al. (2012)95</td>
<td>18</td>
<td>82,982/8,376</td>
<td>HR (Q1 versus Q4)</td>
<td>1.39 (1.25–1.54)</td>
<td>I² = 81%</td>
<td>0.12</td>
</tr>
<tr>
<td>Brandm-Jacobsen et al. (2015)117</td>
<td>2*</td>
<td>10,170/1,625</td>
<td>HR (Q1 versus Q4)</td>
<td>1.83 (1.30–2.57)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
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<tr>
<td>Brandm-Jacobsen et al. (2013)118</td>
<td>10</td>
<td>58,384/2,644</td>
<td>HR (Q1 versus Q4)</td>
<td>1.52 (1.26–1.84)</td>
<td>I² = 59%</td>
<td>0.008</td>
</tr>
<tr>
<td>Sun et al. (2012)119</td>
<td>7</td>
<td>39,095/1,214</td>
<td>RR (lowest versus highest category)</td>
<td>1.52 (1.20–1.85)</td>
<td>I² = 0%</td>
<td>NR</td>
</tr>
<tr>
<td>Chowdhury et al. (2012)115</td>
<td>27</td>
<td>47,809/926</td>
<td>RR (Q3 versus Q1)</td>
<td>0.36 (0.28–0.47)</td>
<td>I² = 0%</td>
<td>0.7</td>
</tr>
<tr>
<td>Wang et al. (2012)114</td>
<td>7</td>
<td>10,170/1,625</td>
<td>HR (Q1 versus Q4)</td>
<td>1.42 (1.19–1.71)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Heterogeneity was assessed by the Cochran Q or I². Probability of publication bias was expressed by Egger test. All meta-analyses used study-level data as source data, except for Schöttker et al. (2014), Afzal et al. (2014), and Brondum-Jacobsen et al. (2015), which used individual patient data. NR, not reported; Q, quartile; Q4, quintile; RR, relative risk; T, tertile. *Meta-analyses by Afzal et al. (2014) and Brondum-Jacobsen et al. (2015) were not based on a systematic literature search. †Brondum-Jacobsen et al. (2012) used a composite outcome of myocardial infarction and ischaemic heart disease.
Figure 3 | **Dose–response association between circulating 25-hydroxyvitamin D and risk of cardiovascular disease.** Meta-analysis of 16 independent studies conducted using a fractional polynomial spline regression. Circles indicate the relative risk (RR) in each study and the circle size is proportional to the precision of the RR (inverse of its variance). The linear trend from the correlated RRs and 95% CIs (shown in purple around the regression line) across categories of 25-hydroxyvitamin D was calculated with the method described by Greenland and Longnecker\(^{112}\) for the dose–response analysis. Permission obtained from Wolters Kluwer Health © 2016 Macmillan Publishers Limited. All rights reserved.

Summarizing the observational data, we can conclude that low 25(OH)D concentrations (below approximately 50 nmol/l or 20 ng/ml; Box 1) are a significant marker for an increased cardiovascular risk. Apart from data on 25(OH)D, several studies, in particular in patients with chronic kidney disease, showed that low 1,25(OH)\(_2\)D serum concentration is also associated with an increased risk of death and cardiovascular events, and that prescription of active vitamin D treatment (with calcitriol or its analogues) is associated with improved survival\(^{121}\).

**Mendelian randomization studies**

Several studies have examined the associations between single nucleotide polymorphisms (SNPs) of the VDR gene and clinical outcomes and cardiovascular risk factors\(^{122-129}\). The results of these investigations are mixed and still do not conclusively show a clinically relevant effect of VDR SNPs on cardiovascular risk\(^{122-129}\). In the context of genetics, the association between serum 25(OH)D levels and cardiovascular risk seems to be modified by ethnicity and by particular SNPs of the DBP gene\(^{130}\).

Genome-wide association studies (GWAS) identified four genetic loci that are associated with 25(OH)D serum concentrations and indicated that a small percentage (approximately 1–4%) of the variation in serum 25(OH)D concentrations is genetically determined\(^{131,132}\). The proteins encoded by the identified genes are involved in vitamin D production, such as the synthesis of vitamin D precursors (DHCR7) and vitamin D 25-hydroxylation (CYP2R1), as well as in vitamin D metabolism, for example, in vitamin D transport by DBP (GC) and 24-hydroxylation (CYP24A1)\(^{133-135}\). These SNPs can be used to perform Mendelian randomization studies and evaluate whether the genetically determined variation in 25(OH)D levels is associated with cardiovascular risk\(^{136}\). However, these studies might be limited because <5% of the variation in 25(OH)D serum levels can be explained by the above mentioned SNPs. Conversely, Mendelian randomization studies are considered to have a high-evidence level because the genetically determined variation in 25(OH)D serum concentration is, in general, not associated with confounding factors and indicates a lifelong exposure. By contrast, RCTs are performed for only a short period of time.

In relation to cardiovascular risk factors, Mendelian randomization studies do not support a causal relationship between 25(OH)D serum levels and obesity and C-reactive protein concentration\(^{137-139}\). A Mendelian randomization study reported that genetic variants associated with low serum concentrations of 25(OH)D are associated with an increased risk of type 2 diabetes\(^{140}\), but this finding could not be replicated in another publication\(^{141}\). Similarly, another Mendelian randomization study suggested an association between high 25(OH)D levels and a favourable lipid profile\(^{142}\), but a larger study did not confirm a causal association between genetically determined 25(OH)D serum concentrations and HDL or LDL cholesterol\(^{143}\). In the context of hypertension, one Mendelian randomization study did not find an association between 25(OH)D levels and mean arterial blood pressure\(^{143}\). However, a large consortium reported that a 10% increase in genetically determined 25(OH)D concentration was associated with a change of −0.29 mm Hg in diastolic blood pressure (95% CI −0.52 to −0.07), a change of −0.37 mm Hg in systolic blood pressure (95% CI −0.73 to 0.003), and 8.1% decreased risk of hypertension (OR 0.92, 95% CI 0.87–0.97)\(^{144}\). Moreover, a fairly small (n<1,000) Mendelian randomization study indicated that high serum concentrations of 25(OH)D might be causally related to high serum adiponectin, which is considered to protect against cardiovascular diseases\(^{145}\).

Importantly, Mendelian randomization studies have not demonstrated that genetically determined 25(OH)D serum concentration is associated with coronary artery disease, myocardial infarction, stroke, or cardiovascular mortality\(^{138,146-148}\). In a large, Mendelian randomization study, a 20 nmol/l (8 ng/ml) reduction in 25(OH)D plasma concentration was associated with an increased risk of cardiovascular death (OR 1.13, 95% CI 1.03–1.24), but genetically determined 25(OH)D was not associated with cardiovascular mortality (OR 0.77, 95% CI 0.55–1.08)\(^{149}\). Therefore, Mendelian randomization studies confirm that ‘measured’ plasma 25(OH)D is inversely associated with risk of cardiovascular diseases, but genetically determined (and likewise unconfounded) 25(OH)D is not.

**Randomized, controlled trials**

**Cardiovascular risk factors.** Vitamin D supplementation is effective in decreasing parathyroid hormone levels, and some small RCTs and meta-analyses of...
RCTs have suggested blood-pressure-lowering effects of vitamin D\textsuperscript{149,150}. However, a meta-analysis published in 2015 that included 4,541 participants reported no significant effect of vitamin D supplementation on systolic and diastolic blood pressure\textsuperscript{151}. These data have been confirmed in an RCT of 200 patients with hypertension that also showed no significant effect of vitamin D supplementation on ambulatory blood pressure\textsuperscript{152}. Notably, one small meta-analysis in adults with obesity indicated that vitamin D supplementation was associated with a slight, but significant, increase in systolic blood pressure\textsuperscript{153}. However, this meta-analysis was limited by the small number of studies included and by a high heterogeneity between the trials\textsuperscript{154}.

In a meta-analysis of RCTs including a total of 43,407 participants, vitamin D supplementation had no significant effect on parameters of glucose homeostasis (insulin resistance, insulin secretion, and HbA1c) or diabetes prevention\textsuperscript{155}. Similar results have been reported by meta-analyses in specific patient groups and pregnant women\textsuperscript{156–158}.

Vitamin D supplementation had no effect on measures of obesity in meta-analyses of RCTs\textsuperscript{159–161}. The vast majority of RCTs reported no relevant effect of vitamin D supplementation on blood lipids\textsuperscript{160,161}. A slight increase in LDL-cholesterol level was noted in two meta-analyses, but these findings should be interpreted with caution when considering the small samples sizes and the high heterogeneity between the studies\textsuperscript{160,161}. Importantly, the largest meta-analysis on this topic reported no effect of vitamin D supplementation on total cholesterol, triglycerides, and LDL-cholesterol or HDL-cholesterol levels\textsuperscript{162}. The conclusion of a systematic review was that the relationship between vitamin D and blood lipids is a topic that has not been adequately investigated and reliable evidence does not yet exist\textsuperscript{160}.

With reference to inflammation, meta-analyses of vitamin D RCTs have reported inconsistent results, indicating either no effect or, for example, a decrease in C-reactive protein and tumour necrosis factor concentrations after vitamin D supplementation\textsuperscript{163–165}. Some RCTs indicate that vitamin D can exert immunomodulatory effects, for instance, by increasing regulatory T cells, but further studies are warranted to address this topic\textsuperscript{165}. Summarizing currently available RCT data on vitamin D supplementation and cardiovascular risk factors, we conclude that, apart from a well-established effect on parathyroid hormone concentrations, no consistent and significant effects on other cardiovascular risk factors have been demonstrated\textsuperscript{165,166}.

**Cardiovascular diseases.** Meta-analyses of RCTs of vitamin D supplementation have shown no significant effects on endothelial dysfunction\textsuperscript{160–168}. In a meta-analysis including eight studies with a total of 529 participants, vitamin D treatment had no overall effect on flow-mediated dilatation (a method used to estimate endothelial function), but the heterogeneity between the included RCTs was very high\textsuperscript{168}. Another meta-analysis showed that vitamin D supplementation had no significant effect on pulse wave velocity and/or the augmentation index as indicators of arterial stiffness\textsuperscript{169}. In a meta-analysis of seven RCTs with a total of 573 patients with congestive heart failure, vitamin D supplementation had no significant effect on left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide level, or 6-min walking distance\textsuperscript{164}. The VINDICATE study\textsuperscript{171}, published in 2016, was designed to evaluate whether 4,000 IU of vitamin D\textsubscript{3} per day during 1 year had any effect on the 6-min walking distance (primary end point) and on left ventricular structure and function (secondary end points) in 229 patients with chronic heart failure secondary to left ventricular systolic dysfunction and with 25(OH)D level <50 nmol/l (20 ng/ml). No significant effects were found for the 6-min walking distance, but vitamin D\textsubscript{3} supplementation was associated with a 6.07% increase in left ventricular ejection fraction compared with placebo (95% CI 3.20–8.95, P < 0.0001) and a reversal of left ventricular remodelling with improvements in left ventricular end-diastolic diameter (mean change −2.49 mm, 95% CI −4.09 to −0.90, P = 0.002) and left ventricular end-systolic diameter (mean change −2.09 mm, 95% CI −4.1 to −0.06, P = 0.043)\textsuperscript{171}.

In RCTs that were mainly designed to investigate skeletal outcomes in elderly individuals, vitamin D supplementation had no significant effect on overall cardiovascular events and cardiovascular mortality\textsuperscript{162,166,172–175}. These findings are important because calcium supplements per se have been associated with an increased risk of myocardial infarction in some studies\textsuperscript{176}. In analyses of specific cardiovascular events, a meta-analysis that included 21 RCTs of vitamin D and a total of 13,033 participants, the hazard ratios for heart failure, myocardial infarction, and stroke were 0.82 (95% CI 0.58–1.15), 0.96 (95% CI 0.83–1.10), and 1.07 (95% CI 0.91–1.29), respectively\textsuperscript{177}.

In this meta-analysis, RCTs with either vitamin D (cholecalciferol or ergocalciferol) or active vitamin D (for example, calcitriol) were included, and RCTs with coadministration of calcium were included only if the comparator group received the same medication. In another meta-analysis that included only RCTs with vitamin D (cholecalciferol or ergocalciferol) supplementation with or without calcium, the analysis of nine of these trials, with a total of 48,647 participants and 1,489 events, showed that vitamin D had no effect on the incidence of myocardial infarction and ischaemic heart disease (relative risk 1.02, 95% CI 0.93–1.13)\textsuperscript{178}. The analysis of eight of the trials, with a total of 46,431 participants and 1,213 events, showed that vitamin D had no effect on stroke or cerebrovascular disease (relative risk 1.01, 95% CI 0.90–1.13)\textsuperscript{179}. These results remained similar and nonsignificant when the RCTs with or without calcium supplementation were analysed separately\textsuperscript{22}. A Cochrane review showed that vitamin D\textsubscript{3} supplementation significantly reduced all-cause mortality compared with placebo or no intervention (risk ratio 0.94, 95% CI 0.91–0.98; n = 75,927), but vitamin D\textsubscript{3} had no significant effect on cardiovascular mortality (risk ratio 0.98, 95% CI 0.90–1.07; n = 47,267)\textsuperscript{172}.
A major limitation of many large RCTs of vitamin D is that serum 25(OH)D concentrations at baseline and after intervention are not available. Moreover, previous vitamin D RCTs were heterogeneous in terms of doses and dosing intervals, and sensitivity analyses (with limited statistical power) suggested no major differences between different vitamin D doses. Overall, the results from vitamin D RCTs show that the findings from observational studies could not be replicated in interventional studies. These data suggest that vitamin D deficiency can be just a marker of ill health, and that the association between vitamin D deficiency and cardiovascular risk could be explained by confounding and/or reverse causation. In epidemiological studies, however, a significantly increased risk of cardiovascular events was observed only in a minor part of the study population at the lower end of the 25(OH)D distribution, with some indication of a U-shaped or reverse J-shaped curve. Therefore, findings from previous RCTs of vitamin D that enrolled patients regardless of their 25(OH)D serum concentration might have missed the detection of significant effects in study participants with vitamin D deficiency. Nevertheless, we also conclude from the existing literature that if vitamin D has clinically relevant effects on the cardiovascular system, the effect sizes are likely to be small compared with those of treatments such as angiotensin-converting-enzyme inhibitors or statins, therefore requiring adequately designed and well-powered RCTs to test the cardiovascular effects of vitamin D.

**Future perspectives**

Current classifications of vitamin D status are based on 'total' serum 25(OH)D concentrations, where approximately 90% of 25(OH)D is bound to DBP. However, accumulating evidence suggests that free (unbound) 25(OH)D or bioavailable 25(OH)D (free plus albumin-bound 25(OH)D) could be of relevance, in particular in conditions with low DBP concentrations (such as liver cirrhosis or nephritic syndrome) or high DBP concentrations (such as in pregnancy). Investigations on this topic, as well as on the underlying reasons for the ethnic differences in the association between vitamin D status and cardiovascular diseases, are warranted.

Several large RCTs to address whether vitamin D supplementation has an effect on cardiovascular outcomes are currently ongoing (Table 3). However, these RCTs are limited by the inclusion of participants regardless of their vitamin D status. This lack of restriction in baseline vitamin D status is of concern because even subgroup analyses with the vitamin D-deficient individuals included in these RCTs — who should be the target population for vitamin D treatment — will not change the general conclusions based on neutral trial results. This concern is well exemplified by a recent RCT involving patients in the intensive care unit that showed no overall effect on all-cause mortality, but a significantly reduced risk of death with vitamin D supplementation in patients with 25(OH)D concentrations <30 nmol/l (12 ng/ml).

Apart from the RCTs on hard clinical end points, several ongoing projects, such as the European Union
**Conclusions**

Currently available evidence does not support significant benefits or harms of vitamin D supplementation — with the commonly used doses — on cardiovascular risk. The main knowledge gaps that remain to be investigated in future trials are the potential cardiovascular effects of vitamin D treatment in patients with overt vitamin D deficiency and to elucidate the adequate vitamin D doses and 25(OH)D concentrations that are associated with a risk of adverse or even toxic effects. From a public-health perspective, underscoring the cardiovascular safety of vitamin D — with the commonly used doses — is of great importance when considering the efforts to improve vitamin D status in the general population in order to meet the vitamin D requirements for skeletal health. Public-health authorities are responsible for ensuring the recommended daily vitamin D intake of 600–800 IU in the general population (under circumstances of limited or no sun exposure), and several countries have already introduced vitamin D food fortification, although with limited success. With regard to patient care, the antifracture effects of vitamin D have been documented for daily vitamin D doses of 800–2,000 IU, whereas daily vitamin D doses of up to 4,000 IU (and probably even 10,000 IU) are considered to be safe with regard to acute vitamin D toxic effects leading to hypercalcaemia. With caution is warranted when using intermittent high-dose vitamin D supplementation, which might even increase the risk of falls. The indication for 25(OH)D measurement is controversial, with some researchers arguing against widespread testing, whereas others consider routine measurements of 25(OH)D concentrations justified in patients with conditions or diseases associated with high risk of vitamin D deficiency (such as chronic kidney disease or obesity). Finally, a wide consensus exists that 25(OH)D levels <50 nmol/l (20 ng/ml) should be avoided and treated by increasing the vitamin D supply. This recommendation also applies to patients with and at high risk of cardiovascular diseases when considering the overall beneficial effects on skeletal health along with the cardiovascular safety of vitamin D.

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Table 3 | Large, randomized, placebo-controlled trials on vitamin D treatment effect on cardiovascular outcomes

<table>
<thead>
<tr>
<th>Randomized, controlled trial</th>
<th>Location</th>
<th>Sample size/ recruitment status</th>
<th>Mean active study period (years)</th>
<th>Study end</th>
<th>Main inclusion criteria</th>
<th>Intervention doses</th>
<th>Cardiovascular end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>VITAL* (Pradhan et al.183,203)</td>
<td>USA</td>
<td>25,875/ completed</td>
<td>5</td>
<td>2017*</td>
<td>≥50 years (men), ≥55 years (women)</td>
<td>2,000 IU per day</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>ViDaD (Scragg et al.184,204)</td>
<td>New Zealand</td>
<td>5,110/ completed</td>
<td>4</td>
<td>2016</td>
<td>50–84 years</td>
<td>100,000 IU per month</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>FIND* (Tuomainen et al.205)</td>
<td>Finland</td>
<td>2,500/ completed</td>
<td>5</td>
<td>2018</td>
<td>≥60 years (men), ≥65 years (women)</td>
<td>1,600 IU per day</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DO-HEALTH* (Bischoff-Ferrari et al.206)</td>
<td>Western Europe</td>
<td>2,152/ completed</td>
<td>3</td>
<td>2017</td>
<td>≥70 years</td>
<td>2,000 IU per day</td>
<td>Cardiovascular events, cardiovascular mortality</td>
</tr>
<tr>
<td>VIDALI feasibility study (Peto et al.207)</td>
<td>UK</td>
<td>1,600/ completed</td>
<td>2</td>
<td>2017</td>
<td>65–84 years</td>
<td>100,000 IU per month</td>
<td>Cause-specific mortality</td>
</tr>
<tr>
<td>EVITA* (Zittermann et al.208)</td>
<td>Germany</td>
<td>400/ completed</td>
<td>3</td>
<td>2016</td>
<td>18–79 years, 25(OH)D ≤75 nmol/l, congestive heart failure</td>
<td>4,000 IU per day</td>
<td>Event-free survival‡</td>
</tr>
</tbody>
</table>

Only trials with n ≥ 400 patients are shown and only the cardiovascular end points are provided. Study end was approximated from data available at the respective clinical trial registry. 25(OH)D, 25-hydroxyvitamin D; IU, international units. *Registered at ClinicalTrials.gov. †Registered at Australian New Zealand Clinical Trials Registry. £Registered at ISRCTN registry. §Sample size was reduced from 18,000 to 2,500, according to clinical trial registry. ¶Events are defined as cardiac transplantation, high urgent listing for cardiac transplantation, resuscitation, hospitalization, and ventricular assist device implantation. *The VITAL trial might end later than 2017 because randomization was completed in March 2014.

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92. Theodoratou, E., Tzoulaki, I., Zgaga, L. & Ioannidis, J. P. Vitamin D and mortality: meta-analysis and all-cause mortality of participants from a large consortium of cohort studies from Europe and the United States. BMJ 348, g5566 (2014).


Author contributions
All the authors contributed to researching data, discussions on content, writing the article, and to reviewing and editing of the manuscript before submission.

Competing interests statement
The authors declare no competing interests.

Review criteria
References for this Review were retrieved from a PubMed-MEDLINE literature search up to 30 January 2016 using the search terms ‘vitamin D’ plus ‘cardiovascular’, ‘heart’, ‘Mendelian randomisation’, ‘randomised controlled trial’ or ‘meta-analysis’. Articles were limited to the English language, and references from selected papers were used to expand the search. All retrieved manuscripts were considered for inclusion in this Review. Some articles were not cited because of space restrictions.

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