

Vitamin D in cardiovascular diseases

VITAMIN D

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INTRODUCTION

The role of vitamin D in calcium-phosphorus metabolism and its fundamental importance for growth and the maintenance of skeletal integrity throughout life have long been acknowledged. Furthermore, and for many years now, a considerable body of experimental, clinical and epidemiological evidence has shed light on other important functions of the vitamin D biological system in relation to cell differentiation and growth, modulation of the immune response, control of other hormonal system activity and, not least, its ability to interfere with major cardiometabolic risk factors and to influence the development and progression of many cardiovascular disorders¹. In a previous review published in this very journal in 2019, the composition and functions of the vitamin D biological system, the criteria for measuring and assessing the vitamin's nutritional status, and the results of multiple studies on the possible relationships between vitamin D's nutritional status and metabolic and cardiovascular alterations were discussed extensively, including an examination of possible pathophysiological connections vitamin D. In the years since that date, recent clinical and epidemiological research has been aimed at both obtaining further confirmation of what has been observed through previous clinical and observational studies, and above all at attempting to demonstrate the possible "causal" role of vitamin D deficiency in relation to the aforementioned disease conditions through controlled and randomised trials with high quality scientific criteria. This review therefore endeavours to selectively focus on the results of these latest studies and to discuss the scientific basis for the use of vitamin D supplementation for prophylactic or therapeutic purposes.

RESULTS OF THE MOST RECENT OBSERVATIONAL STUDIES

Table 1 summarises the essential data provided by the most recent publications

referring to observational studies. The data include a prospective study on a large American population sample, two Mendelian randomisation studies and a considerable number of meta-analyses of prospective studies, most of which focused on all-cause and cardiovascular mortality or other cardiovascular outcomes. Wan et al.'s prospective study³, performed on a rather large sample of diabetic patients drawn from the population of the National Health and Nutrition Examination Survey (NHANES), with long follow-ups and a considerable number of events, showed, as have many previous observational studies, a strong and statistically significant inverse association between baseline plasma 25(OH)D levels and the risk of death from cardiovascular and all causes. The studies by Heath et al.⁴, Gholami et al.⁵ and Jani et al.⁶ were all meta-analyses of prospective studies conducted mainly on samples from the general population. Of all of these, the study by Gholami et al. was the most selective, having excluded the many studies conducted on participants already affected at baseline by cardiometabolic or other disease conditions, which might favour the phenomenon of "reverse causation", whereby lower vitamin D levels were not the cause of the disease but a consequence of it due to less exposure to sunlight and/or nutritional deficiencies. In fact, in all three meta-analyses an inverse association was consistently found between baseline 25(OH)D values and the primary outcome of the study, which was total mortality for Heath et al.'s study, cardiovascular mortality for Gholami et al.'s study, and the incidence of a first or recurrent cardiovascular event for Jani et al.'s study. In contrast, the meta-analysis by Wang et al.⁷ focused on prospective studies conducted on samples of heart failure patients. Though the number of the studies examined was relatively small (n = 7), the total number of patients was quite large (approximately 6,000), with follow-ups occurring at between 1 and 5 years. This

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Conflict of interest

The Author declares no conflict of interest.

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TABLE I.
Vitamin D, cardiovascular outcomes and mortality: results from the most recent observational studies.

Author	Study type	Features	Main results
Wan et al., 2021 ³	Prospective	6,329 diabetic adults (NHANES III and NHANES 2001-2014), 55,126 person-years of follow-up, 2,056 events	Inverse association between baseline 25(OH)D concentration, all-cause mortality and CV mortality. Multivariate-adjusted HR for 25(OH)D values respectively < 25.0, 25.0-49.9, 50.0-74.9, ≥ 75.0 nmol/L = 1.00 (ref.), 0.70, 0.56, 0.59 for all-cause mortality (p-trend 0.003) and 1.00 (ref.), 0.62, 0.46, 0.50 for CV mortality (p-trend 0.02)
Heath et al., 2019 ⁴	Meta-analysis of prospective studies	54 studies (n = 812,646)	Inverse association between baseline 25(OH)D levels and all-cause mortality, non-linear type with a plateau for values between 75 and 90 nmol/L
Gholami et al., 2019 ⁵	Meta-analysis of prospective studies	25 studies (n = 98,171), 10,099 CV events	Inverse association between baseline 25(OH)D levels and CV risk. When comparing values < 30 and values > 50 nmol/L: RR = 1.54 (95% CI: 1.29-1.84) for mortality and RR = 1.18 (95% CI: 1-1.39) for incidence
Jani et al., 2021 ⁶	Meta-analysis of prospective studies	79 studies (n = 1,397,831), 46,713 CV events	Inverse linear association between baseline 25(OH)D levels and CV risk. When comparing the lowest and highest category of 25(OH)D: RR = 1.34 (95% CI: 1.26-1.43, p < 0.001) for the incidence of a new event and RR = 1.86 (95% CI: 1.46-2.36, p < 0.001) for recurrent events
Wang X et al., 2022 ⁷	Meta-analysis of prospective or retrospective studies	7 studies (n = 5,941 patients with heart failure), follow-up 1-5 years	When comparing the lowest and highest category of 25(OH)D: RR = 1.37 (95% CI: 1.13-1.66) for all-cause mortality and RR = 1.38 (95% CI: 0.87-2.19) for frequency of re-hospitalisation
Kong et al., 2023 ⁸	Meta-analysis of prospective studies	19 studies (n = 41,916), 3,015 fatal CV events and sudden deaths, follow-up 2-14 years	Inverse association between baseline circulating vitamin D levels and risk of CV death or sudden death in the range of 10-100 nmol/L. When comparing the lowest and highest category of 25(OH)D: HR (95% CI) 1.75 (1.49-2.06)
Javedi et al., 2023 ⁹	Meta-analysis of prospective studies	21 studies of diabetic patients	In comparison with the highest category (> 50 nmol/L) of 25(OH)D: RR = 1.36 (95% CI: 1.23, 1.49) for category 25 - < 50 nmol/L and RR = 1.58 (1.33-1.83) for category < 25 nmol/L, for all-cause mortality. Similar results for CV morbidity and mortality. Dose-response analysis indicates a non-linear inverse association, with lowest risk value at 25(OH)D ~60 nmol/L for all-cause mortality and CV mortality
Vergatti et al., 2023 ¹⁰	Meta-analysis of prospective studies	4 studies (n = 7,717 stroke patients), 496 cases of new stroke episode, follow-up 3-86 months	Non-linear inverse association between 25(OH)D levels at first stroke and incidence of new stroke episode with lowest risk at 28 ng/mL. In the comparison with the lowest category of 25(OH)D: RR = 0.20 (95% CI: 0.10-0.67, p < 0.001) for the highest category
Sutherland et al., 2022 ¹¹	Mendelian randomisation study	N = 307,601 UK Biobank participants (age 37-73 years) with 25(OH)D values measured and predicted on the basis of 35 genetic variants, 14-year follow-up and 18,700 fatal events	L-shaped inverse association between genetically predicted 25(OH)D and all-cause and CV mortality (p = 0.033) with steep decline in risk of death for increasing concentrations up to 50 nmol/L Increase in all-cause mortality in genetic analysis of 25% (95% CI = 16-35) for participants with 25(OH)D measured at 25 nmol/L compared to those with 50 nmol/L
Zhou et al., 2022 ¹²	Mendelian randomisation study	N = 295,788 UK Biobank participants with measured and predicted 25(OH)D values based on 35 genetic variants, 14-year follow-up and 44,519 incident cases of CV disease	L-shaped inverse association between genetically predicted 25(OH)D and incidence of CV events, with steep initial drop in risk for increasing vitamin D concentrations and plateau at around 50 nmol/L

CV: cardiovascolare; IC: intervallo di confidenza; RR: rischio relativo; HR: *hazard ratio*.

meta-analysis found a significant inverse relationship between basal 25(OH)D levels and mortality or risk of re-hospitalisation for heart failure and/or its complications. The meta-analysis by Kong et al.⁸ assessed the relationship between baseline 25(OH)D levels and risk of fatal cardiovascular events

or sudden death in 19 studies, with over 40,000 participants and over 3,000 events over a period of 2-14 years. Once again, the relationship found in this study was inverse, over a wide range of 25(OH)D concentrations, with a 75% increase in risk when comparing levels at < 10 nmol/L and

those at > 100 nmol/L. Instead, the meta-analysis by Javedi et al.⁹, which considered only prospective studies conducted on diabetic patients, demonstrated an inverse association between baseline 25(OH)D levels and all-cause mortality in this patient category as well, with a plateau at around

60 nmol/L and an increased risk of 36% for values between 25 and 50 nmol/L and of 56% for values at < 25 nmol/L. The results were similar for cardiovascular morbidity and mortality. Finally, the meta-analysis by Vergatti et al.¹⁰ reviewed four studies, which included approximately 8,000 patients who had suffered stroke, with follow-ups occurring at between 3 and 86 months, and 496 cases of new stroke episodes. This study showed that higher basal 25(OH)D levels had a protective effect with an 80% reduction in the risk of recurrence in the highest category (> 28 nmol/L) compared to the lowest vitamin D category.

The last two publications included in Table I in the list of "observational" studies are two Mendelian randomisation studies, conducted, moreover, by two independent groups of authors on one single population. It should be premised that Mendelian randomisation is a method that in some way acts as a bridge between the category of observational studies and that of interventional randomised controlled trials. Through the use of allelic variants of one or more genes involved in the coding of a certain protein, it makes it possible to acquire robust elements of evidence regarding the possibility of causal relationships between certain risk factors and clinical outcomes of interest. The main advantage of the Mendelian randomisation method is its ability to neutralise to a good extent the effect of confounding factors that plague classic observational studies and, in particular, reduce the risk of "reverse causality". In practice, by contrasting subjects, in a population observed and followed over time, with one or more gene variants, which respectively result in higher or lower levels of a certain substance (in our case 25(OH)D), it became possible to compare the incidence of certain events in the two groups in the same way as can be achieved in an RCT, but with a much lower cost and far less effort. The studies by Sutherland et al.¹¹ and Zhou et al.¹² targeted the same population of approximately 300,000 participants from the UK Biobank, with 25(OH)D values measured and predicted on the basis of 35 genetic variants and a follow-up of 14 years.

The main difference between the two studies was in the outcomes, consisting in the former of all-cause and cardiovascular mortality and in the latter of incident cases of cardiovascular disease. In both of these

studies, a significant L-shaped (non-linear) inverse association was found between genetically predicted 25(OH)D levels and the respective outcomes, with a steep decline in the risk of mortality and morbidity for increasing concentrations up to 50 nmol/L, where a plateau was observed, not unlike in traditional observational studies.

RESULTS OF THE MOST RECENT INTERVENTIONAL TRIALS

Table II shows the essential data from interventional randomised controlled trials that have tested the efficacy of vitamin D supplementation in various population types. The table includes a single RCT and a series of meta-analyses of RCTs predominantly, but not exclusively, oriented towards evaluating the effects of supplementation on cardiovascular mortality and morbidity.

The study by Virtanen et al.¹³, which tested the efficacy of 1,600 or 3,200 IU of vitamin D₃/day versus placebo in a sample drawn from the general population of Finland, who were free of cardiovascular disease at baseline, recorded 119 major cardiovascular events over 5 years. The supplementation conferred no significant protection compared to placebo with regard to the incidence of total or specific CV events. The study's significant limitations concerned a majority of the sample subjects' high baseline 25(OH)D levels and low cardiovascular risk, which resulted in a low number of events.

The meta-analyses by Zhang¹⁴, Pei¹⁵, Ruiz-García¹⁶ and Mattumpuram¹⁷, and their respective colleagues, all involved studies conducted on sample subjects drawn from the general population. Three of these studies^{14,15,17} showed that vitamin D supplementation had no effect on mortality or cardiovascular morbidity. On the other hand, the meta-analysis by Ruiz-García et al., which differed in that it only included trials lasting > 1 year and with at least 50 participants, demonstrated a reduction in all-cause mortality, especially in relation to the higher-quality trials, i.e. with a lower risk of bias. Nevertheless, although lacking a positive result for the main outcome, the meta-analysis by Zhang et al. showed a more favourable trend for trials of longer duration and supplementation with vitamin D₃ rather than vitamin D₂. The meta-analysis performed by Jayedi et al.⁹, which included trials conducted only on diabetic patients, did not show any protective

efficacy of supplementation against cardiovascular morbidity and mortality; however, a rather low level of evidence was indicated. In its turn, the study by Khan et al.,¹⁸ which included trials conducted on pre-diabetic subjects, found no efficacy of supplementation in reducing the incidence of diabetes or in improving insulin resistance. The meta-analysis by Yeung et al.¹⁹, which included trials conducted in nephropathic patients, similarly showed no efficacy in reducing all-cause or cardiovascular mortality, albeit with the limitations found in trials with very short durations, low numbers of subjects and low quality. The meta-analysis by Pincombe et al.,²⁰ which was characterised by an evaluation of trials that examined the effects of vitamin D supplementation on endothelial function and by its inclusion of 42% of patients with baseline vitamin D insufficiency or deficiency, found no significant benefit on any of the main parameters of endothelial function, except for a positive trend in flow-mediated vasodilation.

Finally, the systematic review by Zittermann et al.²¹, who evaluated 22 studies that reported on the possible adverse effects of vitamin D administration in doses from 3,200 to 4,400 IU/day versus placebo for at least 6 months, showed that with these doses there was an increased risk of hypercalcaemia (albeit this was contained in just 4 cases out of 1,000 subjects treated), but not of hypercalciuria, nephrolithiasis or total mortality.

DISCUSSION

The overall analysis of the different types of recent studies that assessed the impact of vitamin D deficiency and its possible supplementation on the main cardiovascular outcomes confirmed what had emerged previously: there is a strong discrepancy between the outcomes of observational studies and those of interventional trials. The former, also corroborated by the results of the most recent Mendelian randomisation studies, highlighted with internal clarity and consistency the negative impact of a condition of vitamin D insufficiency and even more so of vitamin D deficiency. On the contrary, albeit with a few exceptions, the latter did not support the potential benefit derived from vitamin supplementation and, therefore, would not suggest that there is a causal role of vitamin Deficiency in determining metabolic and cardiovascular

TABLE II.
Vitamin D supplementation, cardiovascular outcomes and mortality: results from recent trials.

Author	Study type	Features	Main results
Virtanen et al., 2022 ¹³	RCT	RCT with 2,495 participants \geq 60 years from Finnish general population, free of CVD at baseline, stratified into 3 groups: placebo, 1,600 IU vitamin D ₃ /day and 3,200 IU vitamin D ₃ /day, 5-year follow-up with 119 major CV events	Vitamin D ₃ supplementation was not associated with a reduction in the incidence of major CV events (4.9%, 5.0% and 4.3% in the placebo, vitamin D 1,600 IU vitamin D ₃ /day and vitamin D 3,200 IU vitamin D ₃ /day groups, respectively), nor in the incidence of myocardial infarction, stroke or CV death. Major limitations of the study: high baseline 25(OH)D levels in study participants on average and low number of events
Zhang et al., 2019 ¹⁴	Meta-analyses of RCTs	52 trials (n = 75,454) with 7,993 total deaths of which 1,331 CV, median follow-up 1 year (only for 12/52 trials: duration > 3 years)	Vitamin D ₂ /D ₃ supplementation was not associated with a reduction in all-cause mortality (R-ratio = 0.98, 95% CI: 0.95-1.02) or CV (R-ratio = 0.98, 95% CI: 0.88-1.08). Other study considerations and limitations: vitamin D ₃ is more effective than D ₂ , longer trials, greater efficacy, many studies allowed spontaneous supplementation in the control group, mean baseline vitamin D levels were high
Pei et al., 2022 ¹⁵	Meta-analyses of RCTs	18 trials (n = 70,278), 1,495 CV, follow-up 1-6 years	Vitamin D ₂ /D ₃ supplementation was not associated with a reduction in total CV mortality (RR = 0.96, 95% CI: 0.88-1.06), stroke incidence (RR = 1.05, 95% CI: 0.92-1.20) myocardial infarct, (RR = 0.97, 95% CI: 0.87-1.09 and total CV events = 0.97, 95% CI: 0.91-1.04). Main limitations of the study: baseline mean vitamin D levels were high, baseline CV risk rather low, relatively short follow-up
Ruiz-García et al., 2023 ¹⁶	Meta-analyses of RCTs	80 studies (n = 163,131) of which 35 were low risk, 34 medium risk and 11 high risk of bias. Trials with less than 50 participants and < 1 year duration were excluded. Median follow-up 2 years	Vitamin D ₂ /D ₃ supplementation reduced all-cause mortality (OR 0.95, 95% CI: 0.93-0.99; p < 0.02) This effect is confirmed for the trials with a lower risk of bias, whereas it is not confirmed for those with lower quality. Vice versa, there was no association between vitamin D supplementation and total CV mortality from heart attack, stroke or heart failure. Major limitations of the study: lack of 25(OH)D levels at baseline
Mattumpuram et al., 2024 ¹⁷	Meta-analyses of RCTs	36 trials (n = 493,389)	Vitamin D supplementation had no effect on CV mortality (RR = 1.01, 95% CI: 0.94-1.08), on stroke risk (RR = 1.03, 95% CI: 0.95-1.11) and myocardial infarct, (RR = 0.98, 95% CI: 0.91- 1.06; p = 0.65)
Jayedi et al., 2023 ⁹	Meta-analyses of RCTs	6 trials (n = 7,316 diabetic patients)	Vitamin D ₂ /D ₃ supplementation did not reduce all-cause mortality (RR 0.96, 95% CI: 0.79-1.16) nor CV morbidity and mortality. Main limitations of the study: for CV morbidity and mortality very low degree of evidence
Khan et al., 2023 ¹⁸	Meta-analyses of RCTs	7 trials (n = 6,775 pre-diabetic patients), follow-up from 3 months to 5 years with 1,385 events	In all but 1 trial vitamin D supplementation did not reduce the incidence of diabetes (20.0% vitamin D vs 23.3% placebo). Even the HOMA-index values were not significantly different during treatment
Yeung et al., 2023 ¹⁹	Meta-analyses of RCTs	128 studies (n = 11,270 nephropathic patients)	Vitamin D supplementation did not reduce all-cause mortality (RR = 1.04, 95% CI: 0.84-1.24) or cardiovascular mortality (RR = 0.73, 95% CI: 0.31-1.71). Main limitations of the study: inclusion of trials of very short duration, low numbers and poor quality
Pincombe et al., 2023 ²⁰	Meta-analyses of RCTs	26 studies (n = 2,808), with 42% of participants suffering from vitamin D deficiency or insufficiency, to assess the effect of supplementation on endothelial function	None of the three endothelial function parameters measured improved as a result of supplementation: flow-mediated vasodilation, FMD% (+1.17%, 95% CI: -0.20-2.54, p = 0.095), pulse wave velocity, PWV (-0.09 m/s, 95% CI: -0.24 - 0.07, p = 0.275), incrementation index, Alx (+0.05%, 95% CI: -0.1 - 0.19, p = 0.52)
Zittermann et al., 2023 ²¹	Meta-analyses of RCTs	22 studies (n = 12,952) reporting safety data with vitamin D supplementation at doses of 3,200 to 4,400 IU/day for at least 6 months	Vitamin D supplementation at the doses used was found to be associated with an increased risk of hypercalcaemia (RR = 2.21, 95% CI: 1.26-3.87), albeit limited to 4 cases per 1,000 patients treated. Vice versa, no effect on the risk of hypercalciuria, nephrolithiasis or total mortality

CVD: cardiovascular disease; CV: cardiovascular; RCT: randomised controlled trial; CI: confidence interval; RR: relative risk; HR: hazard ratio; OR: odds ratio; FMD: flow-mediated vasodilation; PWV: pulse wave velocity; Alx: augmentation index.

alterations. The impossibility of demonstrating the expected protective effect of correcting vitamin Deficiency is likely to generate, and indeed has to some extent already generated, a paralysis in decision-making with regard to future implementation of vitamin supplementation.

To make a contribution to overcoming this impasse, which is potentially harmful or even very harmful to patients' health, three orders of considerations are offered for consideration below. The first concerns the quality and scientific validity of randomised controlled trials for the purpose of demonstrating a "causal" relationship between vitamin Deficiency and cardiovascular risk. In this regard, it should be acknowledged that large trials such as the VIDA (Vitamin D Assessment Study), the VITAL (Vitamin D and Omega-3 Trial) and the D2D (The Vitamin D and Type 2 Diabetes Study) had already provided evidence that vitamin D supplementation, for preventive purposes and not supported by documented insufficiency or deficiency, provided no convincing benefits. On the other hand, these same studies, precisely by virtue of their experimental design, were not able to demonstrate whether or not appropriately conducted supplementation, among patients who were certainly deficient and with monitoring over time of their 25(OH)D levels achieved through supplementation, exerted any protective action. Nor has this type of demonstration been produced by any of the more recent interventional studies considered in this review, as they were also affected by the same type of limitation with the addition, in many cases, of excessively short follow-ups and insufficient sample size. This notwithstanding, the meta-analyses by Ruiz-Garcia et al. and Zhang et al. were able to show a possible benefit through the selection of trials of longer duration and with a higher number of participants.

The second order of consideration concerns how an assessment can be made on whether or not there is a causal relationship between a certain risk factor (in our case vitamin D deficiency) and one or more predefined outcomes. In this connection, it has been authoritatively suggested by some, similarly to what has been done in connection with other important applications of preventive medicine, that the analysis of the results of randomised controlled trials should not be the sole tool used for assessment and that these trials should be accompanied by a

comprehensive analysis of all available knowledge. Specifically, reference was made to Hill's criteria²², which called into question, in addition to the results of the trials, the value of observational studies, taking due account of the strength of any associations observed, their consistency, the dose-response relationship, biological plausibility and consistency with data from laboratory studies and animal models. In the case of vitamin D deficiency, the critical analysis of all these factors argues in favour of a causal relationship with the cardiovascular outcomes examined, and it would be unreasonable not to take this into account, especially in light of the awareness of the great economic and practical difficulty of designing other interventional trials in the future that could overcome the methodological limitations of those already available.

The third and final consideration concerns the practical conduct to be followed by physicians in light of what has been discussed above and of current knowledge. Where it is clear that vitamin D supplementation is not to be considered irrespective of the assessment of nutritional status, having proved ineffective for the outcomes considered in already vitamin D-replete subjects, the currently available knowledge suggests that there is indeed a need to assess whether or not a condition of vitamin D deficiency actually exists, at least in that part of the population that is at greater risk of deficiency (elderly subjects, especially those who are housebound or in nursing homes and in any case all those who spend little time outdoors), also in relation to chronic morbid, cardiovascular, oncological or other conditions. In all these individuals, in the case of a documented vitamin D deficiency, i.e. 25(OH)D < 20 ng/mL or 50 nmol/L or even in a condition of marked insufficiency, supplementation should be carried out taking into account the results of the recent analysis by Zittermann et al., who documented the absence of risk of adverse effects at least up to a dose of 4,000 IU/day²¹. Of course, the indication for supplementation remains especially valid for patients with documented osteoporosis requiring treatment with bisphosphonates as well as for osteopenic patients who are unable to obtain normal values of the vitamin through diet and exposure to sunlight alone.

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