Journal of the Saudi Heart Association

Manuscript 1432

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Abstract

Introduction: **Cardiovascular events are the most common cause of mortality worldwide. Various studies have shown the relationship between serum 25-hydroxyvitamin D [25(OH)Vit D] levels and cardiovascular events. The purpose of this study is to investigate the meta-analysis of the relationship between serum 25(OH)Vit D levels and the risk of cardiovascular diseases (CVD), including stroke, coronary heart disease, peripheral arterial disease, and aortic disease in the population.**

Method: **Using valid keywords and searching the Medline, Science Direct, Scopus, and Web of Science databases, 22 papers were compiled. Data analysis was performed in the group of people with low serum 25(OH)Vit D levels (<75 nmol/L). The data were analyzed using a random-effects meta-analysis model with R and Stata Version 17.0 software.**

Results: **In this study, 22 papers were included. This meta-analysis of 12 cohort studies (n = 39,396) found that lower serum vitamin D levels were significantly associated with increased risk of cardiovascular disease (HR = 1.38, 95 % CI: 1.24−1.53) and all-cause mortality (HR = 1.64, 95 % CI: 1.33−2.03). Dose-response analysis showed that each 10 nmol/L increase in vitamin D reduced CVD risk by 8.2 % (HR = 0.992, 95 % CI: 0.990−0.993). A non-linear inverse association was observed for all-cause mortality, with stronger protective effects at lower vitamin D levels. These results, in addition to most of the studies included in the systematic review, support a potential protective role of higher vitamin D concentrations.**

Conclusion: **The results of this study showed a relationship between serum 25(OH)Vit D levels and cardiovascular outcomes; the lower the serum 25(OH)Vit D level, the higher the risk of cardiovascular disease.**

Keywords: Vitamin D, Cardiovascular, Meta-analysis, CHD, MI

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death in most countries of the world and is the most crucial factor in becoming disabled [1]. According to the World Health Organization (WHO), it is anticipated that in 2020, 76 % of the 25 million deaths from cardiovascular diseases will occur in developing countries [2]. It has been reported that CVDs are responsible for more than half of the mortality in different countries. However, these CVDs have various causes and differ in patients due to their different characteristics and conditions [3].

Received 30 October 2024; revised 11 April 2025; accepted 14 April 2025.
Available online June 1 2025

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https://doi.org/10.37616/2212-5043.1432

There is a consensus that smoking, increased LDL cholesterol, low HDL cholesterol, high blood pressure, and high blood sugar are the most critical risk factors for cardiovascular diseases [4]. The lifestyle of individuals has an important effect on the emergence of cardiovascular disease, which is associated with a variety of factors, including race, nutrition, culture, and the economy of societies [5]. Some researchers believe that physical inactivity, inappropriate diet, and low socioeconomic status are risk factors that have a significant role in the development of cardiovascular diseases by affecting other variables [6,7].

However, it seems that there are other risk factors involved in the development of cardiovascular disease, but they are currently unknown. There is increasing evidence indicating that 25-hydroxyvitamin D [25(OH)Vit D] levels may be a major contributor to cardiovascular diseases [8]. Also, in recent years, gender differences have been mentioned in this field [9,10].

25(OH)Vit D in the form of 1, 25 (OH) $_{2D}$ is a steroid hormone that, in addition to its classical application, includes the regulation of genes effective in bone mineralization and the transfer of calcium in the intestine [11], Unknown or new effects have been described, especially after the concept that vitamin D receptor (VRD) is present in most tissues [11,12]. However, because many extra-renal tissues, such as endothelial and vascular smooth muscle cells, immune cells, the brain, prostate, breast, and gastrointestinal tract could convert 25 (OH) D to 1.25)OH) 2D due to the alpha-hydroxylase enzyme, a new insight raised about the broad spectrum role of vitamin D in various tissue functions [12,13].

Several studies have shown the role of vitamin D in the regulation of the renin-angiotensin system and blood pressure [14], coronary artery calcification [15], pancreatic beta-cell function and insulin resistance [16], proliferation of vascular smooth muscle cells [17], myocardial cell hypertrophy [18], vascular dilatation [19], production of inflammatory and cytokine parameters [20].

Various studies have evaluated the association between vitamin D deficiency and cardiovascular risk factors such as high cholesterol [21], insulin resistance [22], hypertension [14], and diabetes [22]. On the other hand, the association between serum 25(OH)Vit D level and cardiovascular events, including acute myocardial infarction (MI), cerebral stroke, cardiovascular heart diseases (CHD), a cardiovascular disease caused by diabetes, peripheral arterial diseases, and heart failure, have been investigated in several cases [23–26].

Abbreviations

BMI	Body mass index
CHD	coronary artery heart disease
CVD	cardiovascular disease
MI	myocardial infarction
NIST	National Institute of Standards and Technology
PTH	Parathyroid hormone
VRD	determined that vitamin D receptor
WHO	World Health Organization

However, due to the lack of coordination between the findings from these studies, the lack of relevant information about the effect of serum 25(OH)Vit D levels on the dose and the effect of serum 25(OH)Vit D levels in terms of gender on the cardiovascular outcome, it seems that a meta-analysis study is necessary to evaluate the relationship between serum 25(OH)Vit D levels and cardiovascular outcomes. Therefore, we aimed to conduct a systematic review and meta-analysis to investigate the relationship between serum 25(OH)Vit D levels and the risk of cardiovascular diseases, including stroke, coronary heart disease, peripheral arterial disease, and aortic disease in the population.

2. Methods

2.1. Data sources and search strategies

The present study is a meta-analysis of the relationship between serum 25(OH)Vit D levels and cardiovascular outcomes, written according to the PRISMA checklist, which was carried out by reviewing the documentation and meta-analysis of existing electronic sources between January 2003 and January 2021. To find reviews, domestic and foreign scientific journals, and articles presented at seminars and congresses in databases: Magiran, PubMed, Iranmedx, SID, Medlib, Science Direct, Scopus, and Web of Science have been used. The search for articles was mainly done using a systematic search and valid keywords such as vitamin D, cardiovascular diseases, cardiovascular risk factors, and possible combinations in both Persian and English. In addition, the list of selected sources of articles was screened to find relevant studies.

2.2. Selection of study

First, a list of titles and abstracts of all articles in the databases was prepared by two independent researchers and examined in order to determine and select the related topics. The main criterion for the introduction of various articles into this study was

observational studies, including cohort, cross-sectional, and case−control studies that referred to a serum 25(OH)Vit D level in relation to cardiovascular outcomes or cardiovascular risk factors in healthy people, diabetic patients, or patients with cardiovascular diseases. Exclusion criteria included: studies on patients with a history of acute or chronic liver or kidney disease, hypercortisolism, malabsorption, breastfeeding, pregnancy, smoking and alcohol, and drugs that affect vitamin D levels, studies that have not investigated the level of incidence of cardiovascular events in different concentrations of vitamin D, and studies without measuring serum levels of 25(OH)Vit D as well as qualitative studies.

In the following, the related articles were independently entered into the research process. If the two researchers did not agree on the selection of specific articles, the judgment would be left to the third-person opinion holder.

2.3. Assessment of methodological quality of included studies

Two authors used the Newcastle−Ottawa Quality Assessment checklist, adapted for Cohort, Case-control, and cross-sectional studies, to assess the quality of included studies. If there were any discrepancies, a third author assessed the study. A study with a total score of 6 or above is considered to have a low risk of bias. Studies with a high risk of bias (overall score below 6) were excluded.

2.4. Data extraction

In the next step, after determining the relevant studies from the point of view of the titles, the abstract of the various selected articles was evaluated by the researcher using the STROBE checklist. In the first stage, 2195 articles were found. According to the inclusion and exclusion criteria mentioned, 22 papers were finally selected to be included in our study (Fig. 1). The selected articles were fully examined, and all of their information was entered into the form designed and prepared in order to extract the data, and then the data was entered into Excel software. In the next step, data was transferred from Excel software to R and Stata Version 17.0. In this study, the risk of CVD in healthy people was evaluated in people with low vitamin D levels. The reference group is people with normal vitamin D. Low vitamin D was defined as the concentration of vitamin D below 75 nmol/L. Also, studies that considered 50−75 nmol/L as the vitamin D threshold for the low vitamin D group were included in our meta-analysis. Moreover, studies that reported the risk of CVD but were not included in the meta-analysis, and the studies that reported other outcomes related to the cardiovascular system, were included in our systematic review.

2.5. Synthesis and data analysis

Studies were combined regarding sample size, mean, and 95 % confidence interval.

A random-effects model was used to calculate the hazard ratio (HR) for CVD in patients with vitamin D deficiency versus normal vitamin D levels.

For testing heterogeneity, the Q test and I^2 index were tested at the α-error level of less than 5 % significance. In cases where the results of the studies were heterogeneous, they were analyzed using meta-analysis (random-effects model). Data analysis was done using R and Stata Version 17.0 software.

3. Results

Initially, 2195 articles were identified after an initial search using PubMed, Web of Science, Scopus, and Google Scholar. After removing repetitive studies, 1422 articles were considered for the title and abstract screening. After title and abstract screening, 137 articles were screened by their full text. Finally, 22 papers from different countries were selected for research purposes and investigated (Fig. 1). Out of 22 studies, 14 were cohort studies. Also, five of the eight remaining studies were cross-sectional, and three articles were case−control studies. The characteristics of these studies are shown in Tables 1 and 2. Also, the assessment of methodological quality of the 22 included studies is provided in Tables 3−5.

3.1. Primary outcome

3.1.1. The risk of cardiovascular events

We analyzed the existing data for the association between serum vitamin D levels and the risk of cardiovascular disease in 10 cohort studies, including 39,396 people. The results of our meta-analysis revealed that the pooled HR for CVD was 1.38 (95 % CI: 1.24−1.53), indicating a significant association between lower vitamin D levels and increased risk of cardiovascular events (Fig. 2). Individual study estimates ranged from 1.10 (95 % CI: 0.95−1.28) to 2.04 (95 % CI: 1.42−2.94). In this study, the Q-Cochran test revealed heterogeneity in the findings of the studies (I^2 = 53.1 %). Hence, the random-effect model was used.

Table 1. Characteristics of studies included in the meta-analysis.

First author (reference)	Number of patients	Year	Gender (%) M/F	Mean age ± SD	Place of research	Mean vitamin D ± SD	HR for CVD in patients with low vitamin D (95 % CI)	Frequency of vitamin D deficiency (%)	Method of measurement (Vitamin D)	Study design	Follow-Up Duration (Years)
Bolland M. [74]	1471	2010	0/100	74.5 ± 4.4	New Zealand	20.2 ± 7.1	1.5 (1, 2.2)	50	Radioimmunoassay (RIA)	Prospective cohort	5
Drechsler C. [26]	1108	2010	54/46	66 ± 8	German	15.6 ± 10.8	2.31 (1.37, 3.91)	54	Competitive binding protein recognition and chemiluminescence detection	Prospective cohort	Median 4 years
Wang T.J. [56]	1739	2007	45/55	59 ± 9	Framingham	19.7 ± 14.1	2.04 (1.42, 2.94)	28	Radioimmunoassay (RIA)	Prospective cohort	Mean 5.4 years
Dobnig H. [53]	3258	2008	67/33	62 ± 10	Graz	22.3 ± 11.3	2.28 (1.9, 2.73)	24	Radioimmunoassay (RIA)	Prospective cohort	Median 7.7 years
Kilkkinen A. [75]	6219	2009	45/55	49.4 ± 13.6	Helsinki	18.9 ± 17.3	1.32 (1.22, 1.42)	20	Radioimmunoassay (RIA)	Prospective cohort	Median 27.1 years (range: 9 days to 28.9 years)
Hutchinson M.S. [64]	7161	2010	61/39	58.9 ± 10.2	Tromso	20.8 ± 8.3	1.27 (1.02, 1.57)	58	Immunometry (ECLIA) using an automated	Prospective cohort	Median 11.7 years
Michaelsson K. [65]	1194	2010	100/0	71 ± 0.6	Uppsala		1.79 (1.16, 2.77)	80	HPLC atmospheric pressure chemical ionization (APCI) mass spectrometry (MS)	Prospective cohort	Median 12.7 years
Muhlestein J.B. [76]	234,920	2015	28/72	48 ± 20	Dallas		1.34 (1.05, 1.71)	45	Radioimmunoassay (RIA)	Retrospective cohort	Up to 5 years (3,5 years)
Anderson J.L. [77]	41,504	2010	26/74	55 ± 22	Salt Lake City		2.02 (1.73, 2.36)	47	Chemiluminescent immunoassay	Prospective cohort	Average 1.3 years (maximum 9.3 years)
Zhu K. [78]	3946	2017	43/57	45.2 ± 12.8	Nedlands	24.27 ± 7.2	1.1 (0.95, 1.28)	31.4	Liquid chromatography-tandem mass spectrometry	Prospective cohort	Median 20 years
Agelii M.L. [79]	1227	2017	0/100	46.63 ± 6.29	Sweden		1.68 (1.18, 2.4)	25.1	Electrochemiluminescence immunoassay	Prospective cohort	Up to 37 years (with intermediary analyses at 17, 22, 27, and 32 years)
Vacek J.L. [80]	10,899	2012	31/69	58 ± 15	United States	17 ± 7	1.16 (1.1, 1.33)	70.32	Chemiluminescence immunoassay	Retrospective cohort	5 years and 8 months

Table 2. Characteristics of studies included in the systematic review.

Author, Year	Study design	Population	Group	No of participants	Vitamin D concentration (nmol/L)	CVD outcomes
Giovannucci E, 2008 [27]	Case-control	The men were free of diagnosed cardiovascular disease at blood collection	Very low vitamin D Low vitamin D Low vitamin D Normal vitamin D	150 463 464 277	≤37.5 (37.5−56.25) (56.25−75) ≥75	After adjustment for matching factors, men with very low vitamin D levels had a significantly elevated risk of MI (RR, 2.42; 95 % CI, 1.53−3.84; P < 0.001 for trend). Also, Patients with low vitamin D concentrations had higher RR in comparison to patients with normal vitamin D levels.
Bonakdaran A, 2010 [28]	Cross-sectional	Type 2 Diabetic patients	Low vitamin D Normal vitamin D	31 88	<41.5 in females, <36.25 in males >41.5 in females, >36.25 in males	Patients with low Vitamin D have higher BMI, CRP, and microalbuminuria compared to patients with normal vitamin D. Patients with low Vitamin D have lower GFR than patients with normal Vitamin D. The prevalence of metabolic syndrome was higher in patients with low vitamin D in comparison to patients with normal vitamin D.
Yarjanli M, 2011 [12]	Case-control	Patients without cardiovascular diseases	Very low vitamin D Low vitamin D Normal vitamin D	133 173 196	<25 (25−50) ≥50	For very low vitamin D and low vitamin D patients, compared with normal vitamin D patients, the OR [with 95 % confidence intervals] for incident cardiovascular events was significantly higher (1.57 [1−2.46] and 2.96 [1.78−4.94], respectively).
Siadat DZ, 2012 [29]	Cross-sectional	Patients who were diagnosed with CAD	Low vitamin D Normal vitamin D	72 47	<75 ≥75	The chance of being affected by CAD in patients with vitamin D deficiency is 3.49 (1.59−7.64) times compared with those with normal vitamin D.
Kazemi Saleh D, 2013 [30]	Cross-sectional	Patients undergoing PCI	Very low vitamin D Low vitamin D Normal vitamin D	29 86 34	− − −	The number of involved vessels had a significant association with the severity of vitamin D deficiency in men (P = 0.046), not in women (P = 0.313). The length of the stent in patients with right coronary angioplasty was significantly related to vitamin D deficiency (P = 0.041).
Parham M, 2014 [31]	Case-control	Diabetic type 2 patients	−	−	−	There are no significant differences in the vitamin D concentrations between type 2 diabetic patients with and without CHD (P > 0.05).

(*continued on next page*)

Table 2. (continued)

Author, Year	Study design	Population	Group	No of participants	Vitamin D concentration (nmol/L)	CVD outcomes
Pandit A, 2014 [10]	retrospective cross-sectional observational study	Patients who had an echocardiogram and a serum 25(OH)Vit D level performed	Low vitamin D Normal vitamin D	204 807	≤50 >50	None of the LV diastolic dysfunction parameters (including left atrial volume index, E/e',e' velocity, LV mass index, and deceleration time) were significantly different between low vitamin D and normal vitamin D patients.
Durup D, 2015 [32]	Prospective cohort (7 years follow-up)	A cohort of men and women	Low vitamin D Normal vitamin D	– –	≤70 >70	An inverse association between serum 25(OH)Vit D level below 28 ng/mL and mortality risk from cardiovascular disease and acute MI ($P < 0.001$). An inverse association between serum 25(OH)Vit D levels above 28 ng/mL was also found for cardiovascular disease and acute MI mortality risk ($P < 0.001$).
Wang T, 2019 [33]	Cross-sectional	Participants without recent acute illness	Low vitamin D Insufficient vitamin D Normal vitamin D	578 311 180	<50 (50–75) >75	A significant decrease of CVD prevalence was observed in the two other groups when compared to the serum 25(OH)Vit D deficient group, 48.55 % in the serum 25(OH)Vit D insufficient group, and 52.78 % in the serum 25(OH) Vit D sufficient group, respectively ($P < 0.001$). A decrease in CVD risk was observed in higher serum 25(OH)Vit D level groups, compared with the serum 25 (OH)D deficient group, the ORs (95%CI) were 0.68 (0.50, 0.91) and 0.81 (0.56, 1.16) in the insufficient and sufficient groups, respectively.
Shah SIA, 2021 [34]	Cross-sectional	Adult patients with a recent MI (<1-month history) and without any previous history of CVDs, and their healthy controls.	–	–	–	MI patients had lower Vitamin D levels than their healthy controls ($27.52 + 12.99$ ng/mL vs. $51.10 + 6.48$ ng/mL; $p = 0.001$).

Table 3. Quality assessment of included cohort studies using the Newcastle–Ottawa Quality Assessment Form for Cohort Studies.

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study		Assessment of the outcome	follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Pandit A. [10]	*	*	*	*	**	*			7
Bolland M. [74]	*		*	*	**	*	*	*	8
Drechsler C. [26]	*	*	*	*	**	*	*	*	9
Wang T.J. [56]	*	*	*	*	**	*	*	*	9
Dobnig H. [53]	*	*	*	*	**	*	*	*	9
Kilkkinen A. [75]	*	*	*	*	**	*	*	*	9
Hutchinson M.S. [64]	*	*	*		**	*	*	*	8
Michaelsson K. [65]	*	*	*	*	**	*	*	*	9
Muhlestein J.B. [76]	*	*	*	*	**	*	*		8
Durup D. [32]	*	*	*	*	**	*	*	*	9
Anderson J.L. [77]	*	*	*	*	**	*			7
Zhu K. [78]	*	*	*	*	**	*	*	*	9
Agelii M.L. [79]		*	*	*	**	*	*	*	8
Vacek J.L. [80]	*	*	*	*	**		*	*	8

Table 4. Quality assessment of included cohort studies using the Newcastle–Ottawa Quality Assessment Form for Cross-Sectional studies.

Study	Selection				Comparability		Outcome		Total
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)			Assessment of the outcome	Statistical test	
Bonakdaran A. [28]	*	*			**	*	**	*	8
Kazemi Saleh D. [30]	*	*	*		**	*	**	*	10
Dana Siadat Z. [29]	*	*			**	**	**	*	9
Ali Shah I. [34]	*	*			**	**	*	*	8
Wang T. [33]	*	*	*		**	*	**	*	9

Table 5. Quality assessment of included cohort studies using the Newcastle–Ottawa Quality Assessment Form for Case-Control studies.

Study	Selection				Comparability	Outcome			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Yarjanli M. [12]	*	*	*	*	**	*	*		8
Parham M. [31]	*	*		*	**	*	*	*	8
Giovannucci E. [27]	*	*	*	*	**	*	*	*	9

3.1.2. The risk of all-cause mortality

The data from eight studies was pooled to assess the relationship between serum vitamin D levels and all-cause mortality. The pooled HR for mortality was 1.64 (95 % CI: 1.33−2.03), indicating that lower vitamin D levels were significantly associated with increased mortality risk (Fig. 3). Individual study estimates varied from 1.00 (95 % CI: 0.59−1.68) to 2.96 (95 % CI: 1.44−6.07). Also, there was a high degree of heterogeneity among the studies ($I^2 = 87.7$ %, $p < 0.0001$). So, the meta-analysis was performed using a random-effect model.

3.1.3. Dose-response meta-analysis

A dose−response analysis was conducted to investigate the relationship between serum vitamin D levels and cardiovascular outcomes further. The vitamin D level of 75 nmol/L was considered the reference. For the risk of CVD, the one-stage fixed-effect dose−response model with a linear trend was identified as the best-fitting model based on an Akaike Information Criterion (AIC) value of 1.79 and a P-value of <0.001 (Fig. 4). The analysis demonstrated a significant inverse association between serum vitamin D levels and CVD risk, suggesting that higher vitamin D levels were associated with a lower hazard ratio for CVD, where each 10 unit increase in vitamin D concentration was associated with a 8.2 % reduction in the hazard ratio (HR = 0.992, 95 % CI: 0.990, 0.993, $p < 0.001$).

For all-cause mortality, the best-fitting model was a one-stage random-effects dose−response model using restricted cubic splines with three knots (AIC = 17.99). The results suggested a non-linear association, with a significant inverse relationship between vitamin D levels and mortality risk ($p < 0.001$ for non-linearity, Fig. 5). The coefficients for the spline terms were −0.0219 ($p < 0.001$) and 0.0111 ($p = 0.015$), indicating a stronger protective effect at lower vitamin D concentrations, which diminishes at higher levels.

3.1.4. Meta-regression analysis

Meta-regression analyses were conducted to investigate whether follow-up duration contributed to the heterogeneity observed in the association between serum vitamin D levels and HRs for CVD and all-cause mortality. The analysis for CVD included 10 studies and showed that follow-up time was not a significant moderator (coefficient = −0.0064, 95 % CI: −0.0211 to 0.0083, $p = 0.346$), suggesting that differences in follow-up duration across studies did not significantly impact the observed effect estimates (Fig. 6). Similarly, the meta-regression for all-cause mortality included 8 studies, showed no significant

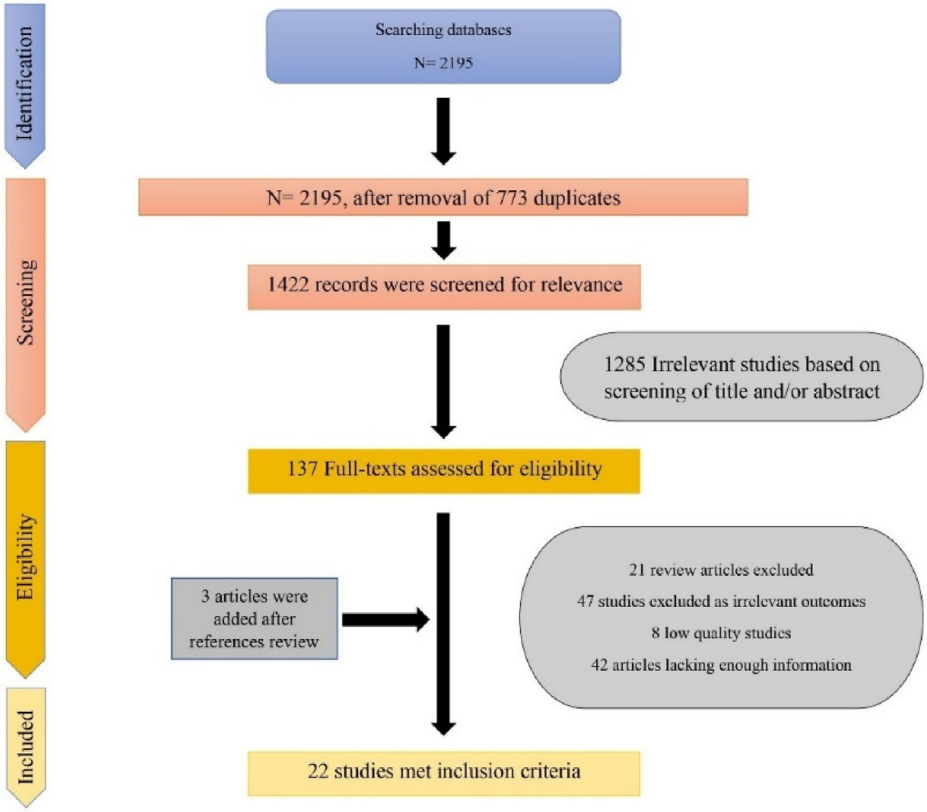

Fig. 1. Flowcharts for the process of entering studies into a systematic review and meta-analysis.

association between follow-up time and HR (coefficient = 0.00017, 95 % CI: −0.0479 to 0.0483, p = 0.993), which is shown in Fig. 7.

3.2. Descriptive results

We also conducted a systematic review of 10 studies [10,12,27−34] comparing the risk of CVD or CVD predictors between patients with different levels of serum 25(OH)Vit D. Five studies [12,27,32−34] reported the difference in CVD risk between patients with low and normal serum levels of 25(OH)Vit D. Three articles [29−31] reported data about coronary involvement in both the low vitamin D and normal vitamin D groups. Moreover, two studies [10,28] stated the differences in some cardiac-related markers, parameters, and diseases among patients with low and normal serum 25(OH)Vit D.

3.3. CVD risk

Five articles [12,27,32−34], including 86,905 men and 159,307 women, reported data about CVD risk. Giovannucci et al. [27], in their case−control study, stated that healthy males with very low (≤37.5 nmol/L) and low (37.5−75 nmol/L) serum 25(OH)Vit D had a higher risk of MI. Also, a cross-sectional study done by Shah et al. [34] reported that MI patients have lower vitamin levels than healthy controls. One case−control study conducted by Yarjanli et al. [12] and one cross-sectional study done by Wang et al. [33] showed that the risk of cardiovascular events is higher in healthy people with low serum 25(OH)Vit D in comparison to healthy people with normal serum 25(OH)Vit D. Durup et al. [32] revealed in a prospective cohort that the lower levels of serum 25(OH)Vit D are associated with higher cardiovascular and MI mortality risk.

3.4. Coronary vessels

Three studies [29−31], including 219 men and 173 women, reported data about coronary vessels. A cross-sectional study by Siadat et al. [29] elucidated that patients with vitamin D deficiency are more likely to be affected by CAD compared to those with normal vitamin D. Also, in a cross-sectional study, Kazemi Saleh et al. [30] revealed that patients undergoing Percutaneous coronary intervention (PCI), the number of involved vessels was significantly related to the serum concentration of 25(OH)Vit D

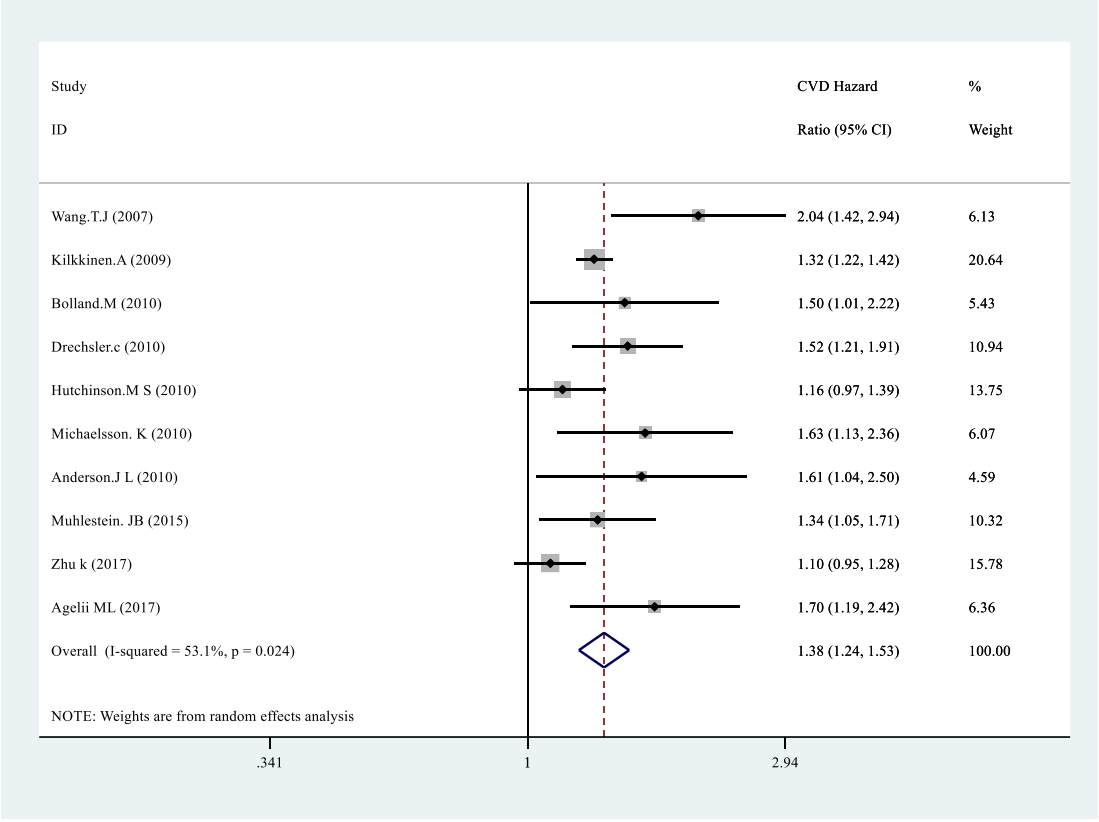

Fig. 2. The hazard ratio of cardiovascular disease (CVD) events in patients with low serum vitamin levels. Square represents effect estimate of individual studies with their 95 % confidence intervals with size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author's names, based on a random effects model.

in men, despite in women. Moreover, this study reported that the length of the stent in patients with right coronary angioplasty was significantly associated with vitamin D deficiency. However, Parham et al. [31] stated that there are no remarkable differences in the serum levels of 25(OH)Vit D between type 2 diabetic patients with and without CHD.

3.5. Cardiovascular and health markers

A cross-sectional done by Bonakdaran et al. [28] showed that type 2 diabetic patients with low 25(OH)Vit D serum concentrations have higher BMI, CRP, and microalbuminuria and lower GFR than type 2 diabetic patients with normal vitamin D. Besides, the metabolic syndrome was more prevalent in type 2 diabetic patients with vitamin D deficiency compared with patients with normal vitamin D. Another study by Pandit [10] reported that None of LV diastolic dysfunction parameters (including left atrial volume index, E/e',e' velocity, LV mass index and deceleration time) were significantly different between low vitamin D and normal vitamin D patients.

4. Discussion

Since the association between serum 25(OH)Vit D levels and cardiovascular events has received much rational attention in recent decades, several meta-analyses have been conducted in recent years. A study in 2012 showed an inverse relationship between serum 25(OH)Vit D levels and CVD [35]. Another meta-analysis in 2017 to examine the relationship between serum 25(OH)Vit D levels and heart attack showed that serum 25(OH)Vit D levels in patients with myocardial infarction, especially in the United States and Asia, are significantly lower. Meanwhile, adequate 25(OH)Vit D serum levels may have a protective role against myocardial infarction [36]. Also, the results of Jacobsen (2012) and Gholami (2019) showed that the decrease in serum 25(OH)Vit D levels is related directly to the increased risk of CVD and its mortality [37,38]. Their results are consistent with this study, even though none of them examined the correlation between gender effect and serum 25(OH)Vit D levels on cardiovascular outcomes.

The results of this meta-analysis indicated that there is a correlation between serum 25(OH)Vit D levels and cardiovascular effects, including

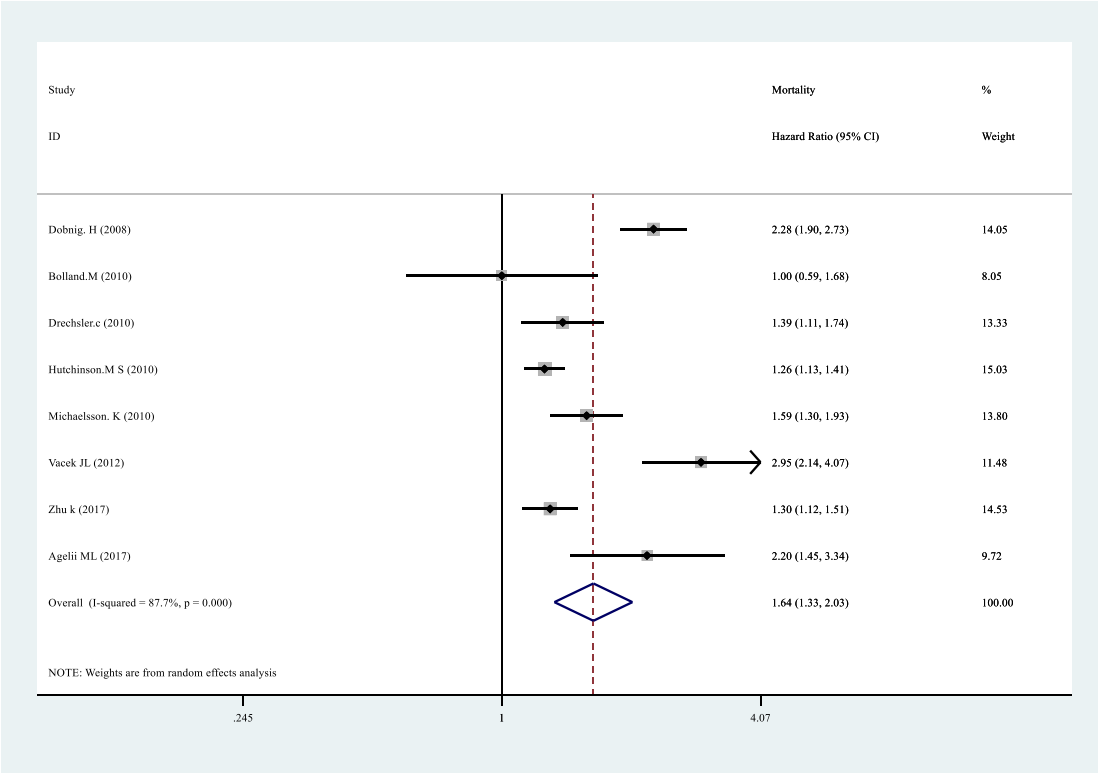

Fig. 3. The hazard ratio of all-cause mortality in patients with low serum vitamin levels. Square represents effect estimate of individual studies with their 95 % confidence intervals with size of squares proportional to the weight assigned to the study in the meta-analysis. In this chart, studies are stored in order of the year of publication and author's names, based on a random effects model.

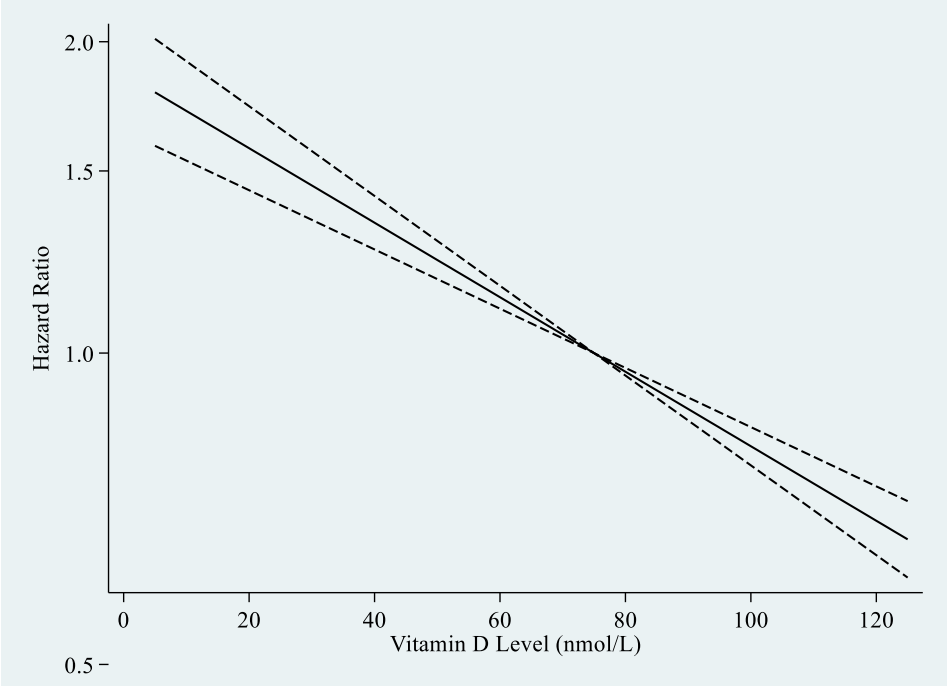

Fig. 4. Dose-response relationship between serum vitamin D levels and cardiovascular disease (CVD) risk. The solid line represents the estimated hazard ratio (HR), and the dashed lines indicate the 95 % confidence interval. The reference vitamin D level is set at 75 nmol/L. The analysis demonstrates an inverse linear association, where higher vitamin D levels are associated with a lower risk of CVD.

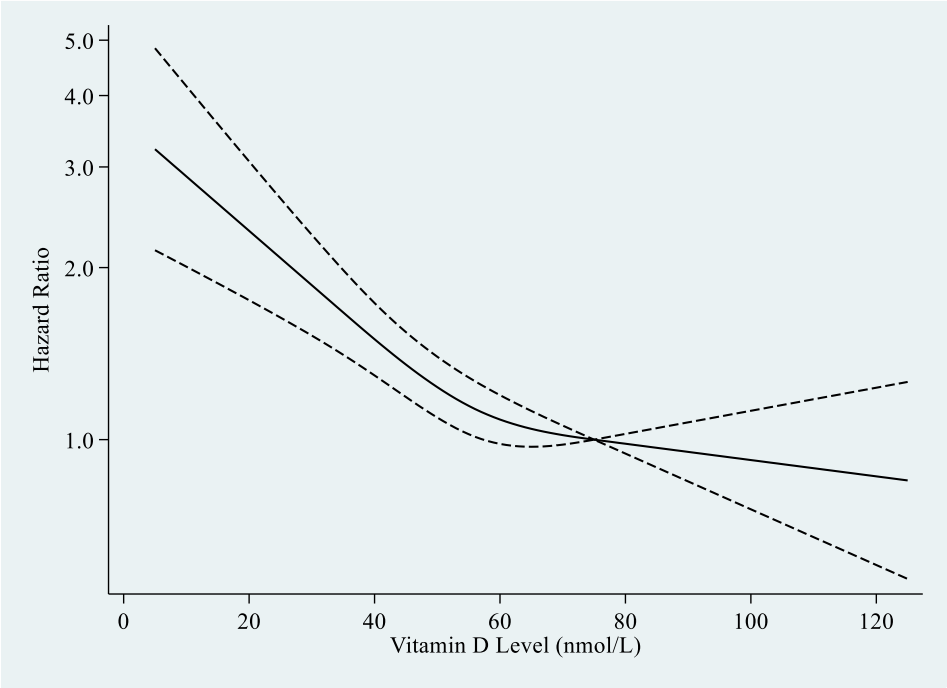

Fig. 5. Dose-response relationship between serum vitamin D levels and all-cause mortality. The solid line represents the estimated hazard ratio (HR), and the dashed lines indicate the 95 % confidence interval. A restricted cubic spline model with three knots was used, with 75 nmol/L as the reference. The analysis reveals a significant non-linear inverse association, with higher mortality risk at lower vitamin D levels that plateaus and slightly reverses at higher concentrations.

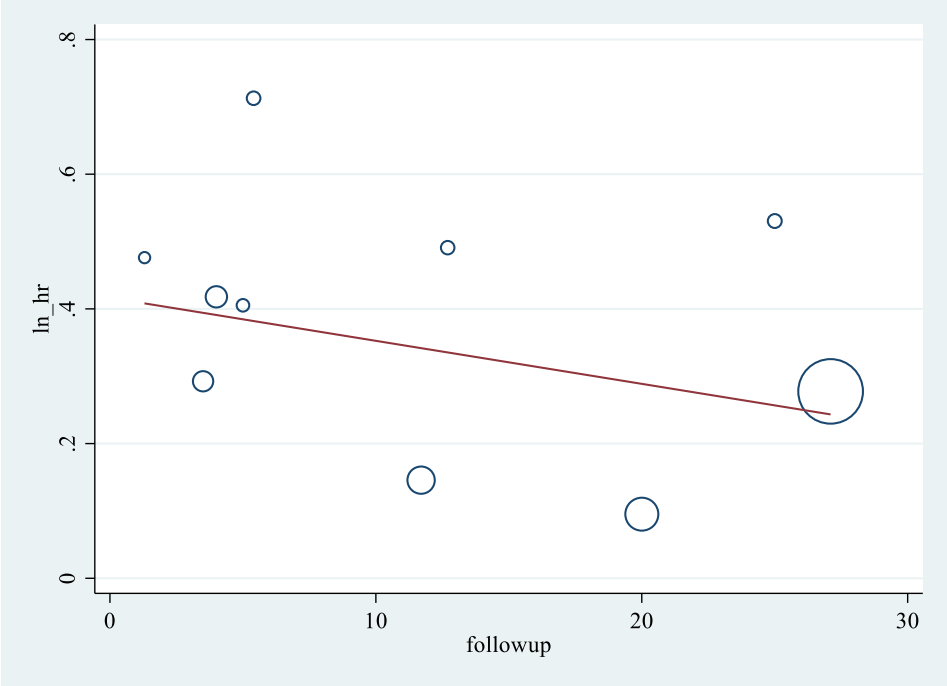

Fig. 6. Meta-regression plot assessing the effect of follow-up duration on the hazard ratio (log-transformed) for cardiovascular disease (CVD). Each circle represents an individual study, weighted by its precision. The regression line shows no significant relationship between follow-up time and CVD risk ($p = 0.346$).

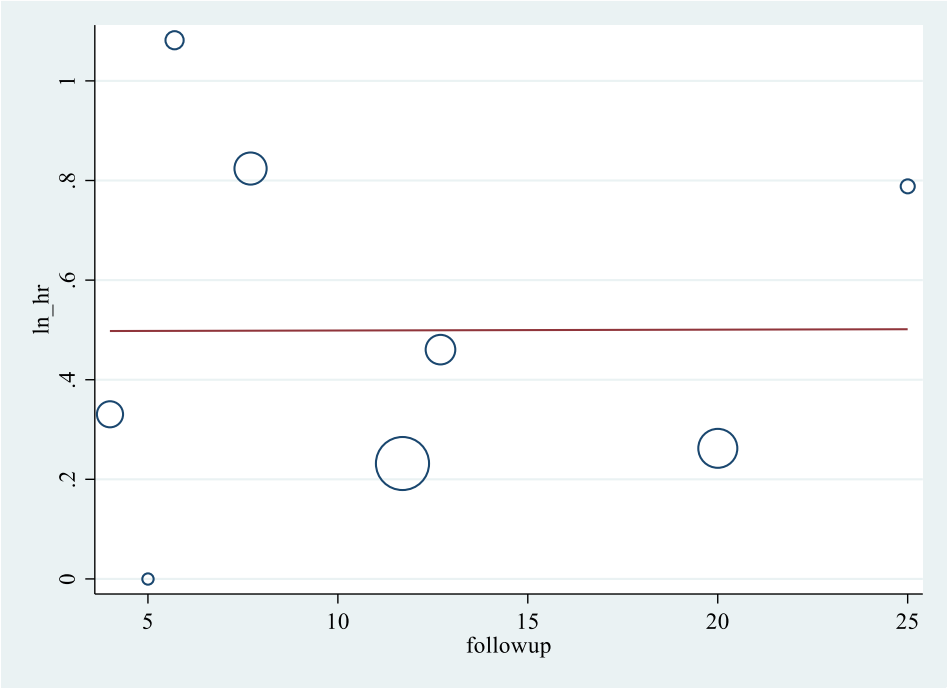

Fig. 7. Meta-regression plot assessing the effect of follow-up duration on the hazard ratio (log-transformed) for all-cause mortality. Each circle represents an individual study, with the size proportional to its weight in the analysis. The regression line indicates no significant association between follow-up time and mortality risk ($p = 0.993$).

myocardial infarction, coronary artery disease, and cardiovascular disease. The incidence of cardiovascular events in people with serum levels below normal levels of 25(OH)Vit D is higher than in those with normal serum levels of 25(OH)Vit D.

The dose–response meta-analysis provided deeper insight into the association between serum vitamin D levels and cardiovascular outcomes. For cardiovascular disease (CVD), a linear inverse relationship was observed, with each 10 nmol/L increase in serum 25(OH)Vit D levels associated with an 8.2 % reduction in hazard ratio. This finding underscores a consistent protective effect of higher vitamin D levels against CVD risk across the measured range. In contrast, the relationship between serum vitamin D levels and all-cause mortality followed a non-linear pattern. The analysis using restricted cubic splines revealed a stronger inverse association at lower vitamin D concentrations, which gradually attenuated at higher levels. This suggests a threshold effect, where increasing vitamin D levels may confer the most benefit in individuals with deficiency or insufficiency, but the protective effect plateaus beyond a certain point. These findings emphasize the importance of considering vitamin D as a continuous variable in cardiovascular research and support the potential clinical relevance of optimizing vitamin D status, particularly in populations with low baseline levels.

Vitamin D is a fat-soluble vitamin with hormonal activity, the role of which is well-known in calcium, phosphorus, and bone metabolism homeostasis, and is involved in regulating the immune system, proliferation, and cellular survival [39]. Lack of vitamin D is associated with a risk of diabetes, metabolic syndrome, increased blood pressure, increased blood lipids, inflammation, and cardiovascular diseases [40].

In the present study, serum 25(OH)Vit D levels below 75 nmol/L were considered vitamin D deficiencies. Vitamin D deficiency is common in Australia, the Middle East, India, Africa, and South America, with between 30 % and 50 % affected [41]. In the United States, more than 50 % of Spanish and African American teenagers in Boston and 48 % of preschool girls in Maine have been deficient in vitamin D [42]. In a multicenter study in Iran, the prevalence of deficiency was 45 % in men and 41 % in women [43]. In another study in Tehran, the overall prevalence of vitamin D deficiency was evaluated as 72.3 %. In another study, the prevalence of vitamin D deficiency among emigrants residing in Melbourne was 87.8 % [44]. Various causes can be the reason for these differences; among other things, one of the causes of this difference can be attributed to a different criterion for the diagnosis of vitamin D deficiency. Also, racial variations, exposure to sunlight, and other factors,

such as skin pigmentation and latitude in the area of life, contribute to the prevalence of vitamin D deficiency.

In preclinical studies conducted on animal specimens (Rats), it has been shown that the vitamin D endocrine system plays a regulatory role in cardiovascular function. Also, the presence of adequate vitamin D in the body can reduce and correct the symptoms of heart failure [45−48].

Studies have shown that there is a meaningful relationship between vitamin D deficiency and cardiovascular risk factors such as hypertension, increased body mass index, hyperglycemia, and insulin resistance [22,49]. For example, in this study, 41 % of people with vitamin D deficiency had hypertension. However, studies have shown a reverse relationship between serum 25(OH)Vit D concentration and hypertension [50]. In addition, low levels of vitamin D may lead to increased PTH levels, and increased PTH levels can lead to stimulation of cardiovascular disease (CVD) through increased blood pressure and stimulation of cardiometric hypertrophy and intracerebral ventricular fibrosis [51,52].

The results of the articles under study indicated that there is a relationship between vitamin D deficiency and cardiovascular events. In recent years, several studies have examined the relationship between serum 25(OH)Vit D levels and cardiovascular events [24,29,53,54]. For example, in a prospective observational study with a mean follow-up of 5.4 years, cardiovascular disease (CVD) risk has been reported in people with below 37.5 nmol/L serum 25(OH)Vit D levels. Of course, this increase in risk was more pronounced for hypertensive patients and was also associated with the severity of deficiency [55]. Also, by tracking the relationship between vitamin D intake and cardiovascular events in 91,864 American men and women over ten years and 9886 new cases of coronary artery disease or stroke, the frequency of these events was higher in people with vitamin D deficiency [52]. In another study, a one ng/ml increase in 25(OH)Vit D reduced the risk of coronary heart disease (CHD) by 2.1 % and the risk of cardiovascular disease (CVD) by 2.6 % [49,56].

There are several mechanisms for reducing vitamin D levels in cardiovascular diseases. The first mechanism is vitamin D's influence on the regulation of the renin-angiotensin system. In animal studies in rats without vitamin D receptors, renin and angiotensin production increases significantly, leading to hypertension, myocardial hypertrophy, and increased water absorption [27]. The second mechanism, the effect of vitamin D on the arteries, includes the effect on insulin secretion and regulation of blood glucose, the modulation of vascular smooth muscle cell proliferation, reduced inflammation, and the effect on the process of thrombosis in the vascular wall [41]. The third mechanism is that a decrease in the level of 25-hydroxy vitamin D leads to secondary hyperparathyroidism, in which the Parathyroid hormone itself results in hypertrophy of the smooth muscle of the arterial wall and, possibly, the release of several cytokines from these muscles, which itself has a role in the development of cardiovascular problems [57].

Regarding the vital role of vitamin D in cardiovascular regulation, quantitative randomized controlled trials have been conducted on whether prescribing vitamin D as a supplement can improve heart function [58,59]. Few studies have shown that higher levels of 1.25 (OH) 2D could benefit patients with heart failure or hypertension [60]. However, numerous studies have shown that vitamin D supplements do not help prevent cardiovascular disease [61,62]. Moreover, the question of whether vitamin D supplementation is effective in preventing or treating cardiovascular disease requires more clinical trials.

The results of the articles in this study showed that the effect pattern of vitamin D deficiency is different in women and men, so, in the case of vitamin D deficiency, the incidence of cardiovascular events in men is higher than in women. However, in normal serum concentrations, there is no significant difference in the occurrence of cardiovascular diseases between men and women, which is consistent with many other studies conducted in this area [32,54,63−65].

Although there has not been a complete biologic justification for this gender difference, the study by Mycus et al. can be helpful in this regard. The study on 1010 men showed that the effect of vitamin D deficiency was strengthened by lowering estrogen levels. However, testosterone was ineffective in this regard, so the risk for each unit of reduction in the ratio of estrogen to the sexual hormone-binding protein (in terms of nanomol/l) in men with vitamin D deficiency of developing cardiovascular diseases increases by 12 %. However, this increase in men with an adequate vitamin D level was only 1 % [66].

An important RCT of vitamin D supplementation and CVD is the ViDA trial [67], which evaluated monthly high-dose (100,000 IU) vitamin D supplementation for cardiovascular health in a general population. The ViDA trial, however, demonstrated no significant reduction in cardiovascular events (myocardial infarction, stroke, and cardiovascular death) for the intervention group compared to placebo (hazard ratio: 1.02; 95 % CI: 0.87−1.20), contradicting our systematic review and meta-analysis

findings, which indicated evidence of an association (HR = 1.55; 95 % CI: 1.33−1.81) between low serum vitamin D levels (<75 nmol/L). As found in meta-analyses, this paradox illustrates the challenges of translating observational associations into interventions - an increase in serum levels via supplementation may not provide the same benefits as higher concentrations due to non-modifiable factors. This discrepancy may be due to differences in study populations, baseline vitamin D status, and dosing regimens (monthly high-dose supplementation in ViDA vs. long-term steady serum levels in observational studies). Taken together, these differing results between our systematic review and the ViDA trial suggest that additional research could be helpful to unravel the role of vitamin D in cardiovascular health and subpopulations, most especially those with severe deficiency-who may benefit from targeted supplementation.

The VITAL trial [68] was the landmark, randomized controlled trial of the impact of daily supplementation of 2000 IU of vitamin D3 on major cardiovascular events in a racially and ethnically diverse cohort. The VITAL trial, in alignment with other large-scale RCTs, demonstrated no significant reduction in the risk of myocardial infarction, stroke, or cardiovascular mortality in the intervention group compared to the placebo, as indicated by HR: 0.97; 95 % CI: 0.85−1.12; p = 0.69. These findings contrast with our systematic review and meta-analysis that low serum levels of 25(OH)Vit D were associated with significantly higher cardiovascular risk: HR = 1.55, 95 % CI = 1.33−1.81. This outcome suggests that serum 25(OH)Vit D might more accurately be characterized as a biomarker indicative of poor overall health rather than as a modifiable risk factor. It thus underscores a need for exploring fundamental health determinants—including inflammation or metabolic dysfunction—through research designs combined with interventional strategies that better clarify the role of vitamin D in cardiovascular health. Jani et al. (2021) [69] conducted a comprehensive meta-analysis incorporating 79 prospective cohort studies, demonstrating significantly increased risks of cardiovascular disease (CVD) incidence (RR = 1.34) and recurrence (RR = 1.86) in individuals with low serum 25(OH)Vit D levels. While their findings align with ours (HR = 1.55; 95 % CI: 1.33−1.81), our study presents crucial enhancements, including broader population representation and stricter inclusion criteria. Three prior systematic reviews and meta-analyses by Grandi et al. (2010) [70], Zhang et al. (2017) [71], and Nudy et al. (2020) [72] provide additional context for understanding these findings. Conducted before Jani's meta-analysis, all three studies highlighted the substantial importance of vitamin D in maintaining cardiovascular health. Grandi et al. (2010) were among the first to demonstrate an inverse association between low serum 25(OH)Vit D levels and cardiovascular risk, identifying a 20 % increased risk of CVD mortality in deficient populations. However, their conclusions were constrained by limited sample sizes and significant heterogeneity. Zhang et al. (2017) expanded this field with a detailed non-linear, J-shaped analysis of serum 25(OH)Vit D levels, underscoring risks associated with both severe deficiency and excess. Nonetheless, their research was limited to prospective cohorts, which restricted its applicability to other designs and populations. Nudy et al. (2020) adopted a different approach, focusing on vitamin D supplementation, and found no substantial reductions in stroke (RR = 0.97) or coronary events (RR = 1.00), highlighting inconsistencies between observational and interventional data. By synthesizing diverse observational data and addressing heterogeneity (I^2 = 86.2 %) using updated statistical methodologies, our analysis offers nuanced insights into the role of severe 25(OH)Vit D deficiency as a modifiable cardiovascular risk factor, while addressing the challenges of translating these findings into clinical strategies.

Grübler et al. (2017) [73]investigated the epidemiological links between low serum 25(OH)Vit D levels and cardiovascular risk and mortality, underscoring the confounding effects of poor health and inflammation. While their analysis recognized an association, they raised questions about its causal validity, noting inconsistencies among interventional findings and variability across observational data. In contrast, our meta-analytic approach provided a pooled hazard ratio (HR = 1.55; 95 % CI: 1.33−1.81), offering a quantitative assessment of the cardiovascular risks linked to severe vitamin D deficiency. By incorporating a more recent and diverse dataset, including research studies from varied populations, and focusing on deficiency thresholds (<75 nmol/L), our analysis identified at-risk groups more effectively. Additionally, unlike Grübler et al., who synthesized evidence narratively, we utilized statistical techniques to address heterogeneity (I^2 = 86.2 %), providing a more robust understanding of the cardiovascular risks associated with severe vitamin D deficiency and emphasizing the need for targeted prevention strategies.

This meta-analysis has some limitations. Lack of information about important variables such as health status, family history of cardiovascular disease, education, smoking, lifestyle, and level of physical activity, as well as various methods of

measuring vitamin D, is the present study's limitation. In addition, participants were classified based on serum baseline measurements of 25(OH)Vit D, which could lead to erroneous classification because individual measurements may not reflect long-term biochemical status. Also, the optimal 25(OH)Vit D for cardiovascular health may vary by race/ethnicity. However, because almost all of the available studies were performed among predominantly white groups, we could not assess the race/ethnicity relationship between vitamin D and cardiovascular disease even after combining the data in this meta-analysis. In addition, the absence of a control group of healthy individuals does not allow us to conclude the role of vitamin D deficiency in the pathogenesis of cardiovascular disease.

In interpreting the findings of this study, it is important to consider the methodological strengths and limitations of the different study designs included in our systematic review. Cohort studies—particularly prospective cohorts—are generally considered more robust for assessing temporal relationships and minimizing recall bias. They allow for the assessment of exposure before the outcome occurs, which strengthens causal inference. However, they are not without limitations, including the potential for residual confounding, selection bias, and loss to follow-up over time. Retrospective cohort studies, while more feasible and less time-consuming, may be more prone to information bias due to reliance on pre-existing records. In contrast, case−control and cross-sectional studies, which were excluded from our meta-analysis, are more susceptible to selection and recall bias and do not allow for establishing temporality. Nevertheless, they can still provide useful insights, particularly when cohort data are limited. These methodological considerations were taken into account in our study design and interpretation of findings.

Although the possible cause-and-effect relationship between vitamin D and cardiovascular disease is biologically acceptable, further research in different populations with repeated measurements of vitamin D is needed and needs further evaluation in large-scale RCTs. In addition, further clinical and experimental studies are also needed to investigate the mechanisms underlying the increased risk of cardiovascular disease and determine whether correcting vitamin D deficiency can help prevent cardiovascular disease.

5. Conclusion

This study suggests an association between serum 25(OH)Vit D levels and cardiovascular diseases in men and women. After considering the significant outbreak of vitamin D deficiency, its effects may be remarkable on general health. Therefore, screening and treating vitamin D deficiency should be necessary in order to prevent the development of cardiovascular events. Furthermore, the benefits of treating vitamin D deficiency are likely to be reflected in reducing cardiovascular complications. However, it should be noted that research on the relationship between vitamin D and cardiovascular diseases requires conducting basic design studies with an appropriate design to make a definitive comment.

Author contribution

Conception and design of Study: RM, MZ. Literature review: RM, SB, AT, MG, RH, MZ. Acquisition of data: RM, MZ. Analysis and interpretation of data: SB, AT. Research investigation and analysis: AT, MG. Data collection: MG, RH. Drafting of manuscript: RM, SB, AT, MG, RH, MZ. Revising and editing the manuscript critically for important intellectual contents: RM, SB, AT, MG, RH, MZ. Data preparation and presentation: SB, AT. Supervision of the research: MZ. Research coordination and management: RM.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Funding

No funding was used to support this study.

Conflict of interest

No conflict of interest.

Acknowledgement

The authors would like to thank the Clinical Research Development Unit(CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study (Ethical code: IR. SBMU.RETECH.REC.1404.093).

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