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Review

Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis

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ABSTRACT

Cardiometabolic disorders and vitamin D deficiency are becoming increasingly more prevalent across multiple populations. Different studies have suggested a potential association between abnormal vitamin D levels and multiple pathological conditions including cardiovascular diseases and diabetes.

We aimed to evaluate the association between vitamin D levels, using 25-hydroxy vitamin D (25OHD) as an indicator of vitamin D status, and the presence of cardiometabolic disorders including cardiovascular disease, diabetes and metabolic syndrome.

We performed a systematic review of the current literature on vitamin D and cardiometabolic disorders using the PubMed and Web of Knowledge databases in September 2009. Studies in adults looking at the effect of vitamin D levels on outcomes relating to cardiometabolic disorders were selected. We performed a meta-analysis to assess the risk of developing cardiometabolic disorders comparing the highest and lowest groups of serum 25OHD.

From 6130 references we identified 28 studies that met our inclusion criteria, including 99,745 participants. There was moderate variation between the studies in their grouping of 25OHD levels, design and analytical approach. We found that the highest levels of serum 25OHD were associated with a 43% reduction in cardiometabolic disorders [OR 0.57, 95% (CI 0.48–0.68)]. Similar levels were observed, irrespective of the individual cardiometabolic outcome evaluated or study design. High levels of vitamin D among middle-age and elderly populations are associated with a substantial decrease in cardiovascular disease, type 2 diabetes and metabolic syndrome. If the relationship proves to be causal, interventions targeting vitamin D deficiency in adult populations could potentially slow the current epidemics of cardiometabolic disorders.

Contents

Abbreviations: CI, 95% confidence interval; CVD, Cardiovascular disease; DM, Type 2 diabetes mellitus; MetS, Metabolic syndrome; MI, Myocardial infarction; OR, Odds ratio; RCT, Randomised control trial; 25OHD, 25-Hydroxy vitamin D.

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[1] Oscar H. Franco as guarantor of this paper accepts full responsibility for the integrity of the data and the accuracy of the data analysis, had full access to all the data in the study, and controlled the decision to publish.

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1. Introduction

Cardiometabolic disorders including cardiovascular disease (CVD), type 2 diabetes mellitus (DM) and metabolic syndrome (MetS) are major causes of morbidity and mortality worldwide [1,2]. Hypertension, dyslipidema, central obesity and glycaemic dysregulations are known risk factors for CVD [2]. Metabolic syndrome represents the clustering of these risk factors that together lead to increased risk of developing CVD and DM [3].

Vitamin D deficiency is also highly prevalent in different populations across the world. Studies suggest that approximately 30–50% of the adult population are at risk of vitamin D deficiency [4,5]. The older adult population is especially vulnerable to vitamin D deficiency, due to a decreased capacity to synthesise vitamin D from sunlight [6]. Additionally, aging is associated with lower 7-dehydrocholesterol levels [7], which is a precursor required for synthesis of vitamin D in the skin.

Vitamin D is known to play an important role in bone and mineral homeostasis and has also been linked with multiple other pathophysiological mechanisms. The vitamin D binding receptor is not only expressed in tissues involved in calcium homeostasis but also found in more than 36 other tissue types [8] and vitamin D has more recently been implicated in a number of additional pathological processes. These processes include cancer, multiple sclerosis, psoriasis and the inflammatory response [9–11], supporting a role for vitamin D in delineating healthy trajectories of aging.

There is also growing evidence to support the link between abnormal levels of vitamin D and CVD and DM [4,12–14]. However, the published literature differs substantially in terms of methodology, populations and results presented. Therefore the evidence remains inconclusive or incongruent.

We aimed, by critically appraising the current evidence, to evaluate the overall effects of vitamin D levels on potential risk of developing cardiometabolic disorders (CVD, DM and MetS). We also aimed to evaluate whether the association between vitamin D and cardiovascular disease, diabetes and metabolic syndrome would differ by type of cardiometabolic disorder, study design, gender, age and ethnicity.

2. Methods

We performed a systematic review and meta-analysis of studies that evaluate the relationship between vitamin D levels and cardiometabolic disorders in adults. We used the measurement of serum 25-hydroxy vitamin D (25OHD) as a proxy for vitamin D status [15].

2.1. Search strategy

We searched the PubMed and Web Of Knowledge databases, which include Web of Science with conference proceedings 1970 to present, BIOSIS 1969 to present, MEDLINE 1950 to present and journal citation reports 1997–2008. The searches were run between September 29th and October 2nd 2009. Cross-sectional, case–control and cohort studies analysing the effects of vitamin D levels on outcomes relating to cardiometabolic disease were included.

Search terms included vitamin D, cholecalcif*, vit D, metabolic syndrome metabolic syndrome*, metabolic syndrome X [MESH], diabetes, diabetes type 2, diabeti*, diabete*, diabetes mellitus [MESH], diabetes mellitus type 2 [MESH], cardiovascular disease, cardiovascualar disease*, coronary heart disease, coronary heart disease*, cardiovascular, coronary, myocardial, myocardial*, ischaemic heart disease, ischaemic heart disease*, ischemic heart disease, ischemic heart disease*, cardiovascular diseases [MESH], coronary disease [MESH], myocardial ischemia [MESH], stroke, cerebral vascular, cerebrovascular, CVA, cerebrovascular accident, cerebral vascular accident, stroke [MESH]. Relevant studies were obtained without language restriction.

2.2. Selection

2.2.1. Inclusion criteria

Studies were included if they fulfilled the following criteria: (1) cross-sectional studies, case–control, cohort or randomised controlled trials (RCTs), (2) measure of vitamin D status using serum 25OHD concentration, (3) studies looking at the effects 25OHD levels on outcomes relating to cardiometabolic disorder [Cardiovascular disease (myocardial infarction, stroke, ischaemic heart disease and peripheral vascular disease), diabetes and metabolic syndrome)] and (4) any language.

2.2.2. Exclusion criteria

Studies were excluded if they included: (1) participants younger than 18 years of age, (2) pregnant women, (3) participants with type 1 diabetes, (4) patients with hyperparathyroid disease or any other disease or conditions that might interfere with calcium or vitamin D homeostasis including participants on dialysis, or (5) research conducted on animals. We also excluded studies evaluating the effects of vitamin D supplementation and calcium, as well as letters, abstracts, and conference papers.

Working in pairs, two authors (JP, OH, DD, AM, SS, AC, OhF) independently reviewed each reference title and abstract to determine whether the studies satisfied the inclusion criteria. Any disagreements with article selection were resolved through discussion and a

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third author was available to resolve disagreement. Full text articles were retrieved for the selected titles. Reference lists of the retrieved articles were searched for additional publications. We also contacted the authors directly for any additional and unpublished studies. When a non-English paper was identified, services were available for translation. Studies retrieved were assessed again by two independent authors to ensure that they satisfied the inclusion criteria. Any disagreements were resolved through discussion.

2.3. Data extraction

Two independent reviewers extracted the data using a data collection form, designed prior to the database searches. The study and participant characteristics, comparison groups, outcomes, analysis and conclusions were recorded. Study characteristics recorded included date of publication, geographic origin and setting of the study, design and funding source. We extracted data about the study participants including the total number included in the analysis, recruitment procedures, residential region, health care setting, age, gender and ethnicity. Outcome measures including the outcomes evaluated, numbers of withdrawals, exclusions and loss to follow up were collected. The results, types of statistical analysis and the conclusions were also extracted. Where the same data set had been published in more than one paper, only the result from the study with the most complete data set was included in the analysis.

2.4. Statistical analyses

Results were pooled using a random effects model and tests for heterogeneity and publication bias were undertaken. Sensitivity analysis and meta-regression were performed on the different study methods, outcomes and participant subgroups to assess the validity of our findings. Results were expressed as pooled odds ratios (OR [95% confidence intervals, CIs]).

We compared the highest group of serum 25OHD with the lowest group using the lower group as the reference value. Where the data was presented inversely, with the highest serum 25OHD level as the reference value, we extracted the relevant data from the paper and calculated odds ratios and 95% confidence intervals. We performed a cumulative meta-analysis by chronological order of publication in which the pooled estimate of the treatment effect is updated each time the results of a new study are published. This makes it possible to track the accumulation of evidence over time. We examined possible sources of heterogeneity between the studies using a meta-regression technique. We performed the Breslow–Day test for homogeneity of ORs, Cochran–Mantel–Haenszel's test for the null hypothesis of no effect (OR = 1), and the Mantel–Haenszel common OR estimate [16]. We also report the 'I square statistic', which is the percentage of variation attributable to heterogeneity [17]. We assessed publication bias by using a funnel plot and Begg's test to find out whether there was a bias towards publication of studies with positive results among studies with a smaller sample size [18].

We also examined the influence of individual studies, from which the meta-analysis estimates are derived, omitting one study at a time to examine the extent to which inferences depend on a particular study or group of studies.

2.5. Subgroup analysis

To test the robustness of our findings we repeated the meta-analysis by different outcomes (CVD, DM, MetS) and different study design. We also replicated the analysis after excluding any studies where ORs had been manually calculated, to take into account any potential errors introduced during conversion of the original data into the OR estimate.

3. Results

3.1. Study selection

We retrieved 3952 references from the PubMed database and 4088 from Web of Knowledge databases. 1910 duplications were identified and removed, leaving a total of 6130 references (Fig. 1). Initial screening of the title and abstract resulted in the exclusion of 6049 references leaving 81 articles to source in full text. No additional references were identified from searching reference lists of the 81 full text papers. We received eight articles from authors directly, three of which were already included in our own reference list, and four of which did not meet our inclusion criteria. One paper was sent from the author after a request due to difficulty in retrieving the article in full text. After further inspection we excluded 46 papers from the 81 full text articles. Five studies did not meet the inclusion criteria as they were not cross-sectional, case–control, randomised controlled trials or cohort studies [19–23]. Two of these references were the same paper; one version in German [22] and the second translated into English [23]. Three studies were excluded as they did not record a measurement of serum 25OHD [24–26]. A further 16 papers were excluded as they did not report cardiometabolic disease outcomes [27–42], two were excluded as they included supplementation of vitamin D [43,44], one study was conducted on rats [45]. The remaining papers were excluded because they were letters, abstracts or conference proceedings [46–66].

A further five papers were not included in the pooled analysis because their results were not presented in a format that allowed us to combine the results with the other studies [67–70]. One final study was excluded because one data set had been used to look at two different CVD outcomes, and these fell into the same outcome criteria in our analysis. We chose the study which presented the results in the most similar way to the other studies included in the pooled analysis [71] and removed the other study from the analysis [72]. 33 ORs from 28 independent studies were included in the final pooled result.

3.2. Study characteristics

Characteristics of the 28 independent studies included in the final analysis [71,73–99] are presented in Table 1.

Overall the studies included 99,745 participants. All studies were published between 1990 and 2009 with the majority (89%) published between 2004 and 2009. Nineteen of the 28 were cross-sectional, 3 were case–control and 6 were cohort studies, no randomised control trials were selected. Half of the studies were conducted in the United States, eight were European (29%) two studies were from Iran, three from Australasia and one from India. The participants were from both rural and urban regionsin over half of the studies (15 out of 28). Most were conducted in the community (17 out of 28), 9 were conducted in outpatient departments and 2 studies were performed at hospitals on inpatients. The mean age of the participants ranged between 40.5 and 74.5 years and the majority of the studies, 25 out of 28 (89%) included both male and female patients. Two studies reported separate ORs for men and women. Ten papers (36%) included only Caucasian participants, two studies (7%) included only Hispanic, nearly half (46%) included a mix ethnicity group and 11% of studies did not specify the ethnicity of their study population. Over half the studies (57%) reported cardiovascular disease as their outcome including myocardial infarction (MI), stroke and peripheral artery disease. Metabolic syndrome was reported in seven studies (25%) and DM was the outcome in five studies (18%). In two studies more than one outcome was measured, and for these studies the OR for each outcome was included in the analysis.

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Table 1
Characteristics of studies included by principal outcome evaluated (cardiovascular disease, or type 2 diabetes or metabolic syndrome).

Author	Date of publication	Study name	Study design	Geographic setting	No in analysis	Gender	Ethnicity	Comorbidities
CVD								
Pilz et al. [73]	2009	Vitamin D and mortality in older men and women	Cohort	Europe	614	Both	Caucasian	T2DM, mixed CVD
Wang et al. [75]	2008	Vitamin D deficiency and risk of cardiovascular disease	Cohort	USA	1739	Both	Caucasian	
Ginde et al. [77]	2009	Prospective study of serum 25-hydroxy vitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults	Cohort	Iran	3408	Women	Mixed	T2DM, MI, stroke, hypertension, cancers, COPD, asthma
Kilkkinen et al. [78]	2009	Vitamin D status and the risk of cardiovascular disease death	Cohort	USA	6219	Both	Caucasian	T2DM, hypertension
Melamed et al. [80]	2008	Serum 25-hydroxy vitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001–2004	Cross-sectional	USA	4839	Both	Mixed	T2DM, MI, CKD
Pilz et al. [71]	2008	Low vitamin D levels predict stroke in patients referred to coronary angiography	Cohort	Europe	3299	Both	Caucasian	T2DM, CAD, HF
Melamed et al. [79]	2008	25-Hydroxy vitamin D levels and the risk of mortality in the general population	Cross-sectional	USA	13,331	Both	Mixed	
Reis et al. [81]	2008	Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease	Cross-sectional	USA	2897	Both	Mixed	
Chonchol et al. [83]	2008	Association between 25-hydroxy vitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction	Cross-sectional	Europe	462	Both	Caucasian	T2DM, mild renal impairment
Giovanucci et al. [84]	2008	25-Hydroxy vitamin D and risk of myocardial infarction in men: a prospective study	Case–control	USA	1354	Men	Mixed	T2DM, hypertension
Kendrick et al. [85]	2009	25-Hydroxy vitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey	Cross-sectional	USA	16,603	Both	Mixed	
Kim et al. [86]	2008	Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001–2004).	Cross-sectional	USA	8351	Both	Caucasian	T2DM, hypertension, CKD
Marniemi et al. [93]	2005	Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects	Cross-sectional	Europe	755	Both		
Cigolini et al. [95]	2005	Serum 25-hydroxy vitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients	Cross-sectional	Europe	459	Both	Hispanic	T2DM
Rajasree et al. [97]	2001	Serum 25-hydroxy vitamin D3 levels are elevated in South Indian patients with ischemic heart disease	Case–control	India	213	Men	Sub-Continent Asia	T2DM, hypertension
Scragg et al. [99]	1990	Myocardial infarction is inversely associated with plasma 25-hydroxy vitamin D3 levels: a community-based study	Cross-sectional	Australasia	179	Both		CKD
DM								
Ginde et al. [77]	2009	Prospective study of serum 25-hydroxy vitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults	Cohort	Iran	3408	Women	Mixed	T2DM, MI, stroke, hypertension, cancers, COPD, asthma
Knekt et al. [87]	2008	Serum vitamin D and subsequent occurrence of type 2 diabetes	Case–control	USA	1364	Mixed	Caucasian	
Mattila et al. [88]	2007	Serum 25-hydroxy vitamin D concentration and subsequent risk of type 2 diabetes	Control	Europe	4097	Mixed		
Martins et al. [89]	2007	Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxy vitamin D in the United States: data from the Third National Health and Nutrition Examination Survey	Cross-sectional	USA	15,088	Mixed	Mixed	

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Marniemi et al. [93]	2005	Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects	Cross-sectional	USA	755			
Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Cross-sectional	Australasia	2766	Mixed	Caucasian	
Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Cross-sectional	Australasia	1736	Mixed	Black	
Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Cross-sectional	Australasia	1726	Mixed	Hispanic	
Scragg et al. [98]	1995	Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects	Cross-sectional	Australasia	476	Mixed	Mixed	
MetS								
Maki et al. [74]	2009	Serum 25-hydroxy vitamin D is independently associated with high-density lipoprotein cholesterol and the metabolic syndrome in men and women	Cross-sectional	USA	257	Mixed	Caucasian	
Bonakdaran et al. [76]	2009	Correlation between serum 25-hydroxy vitamin D3 and laboratory risk markers of cardiovascular diseases in type 2 diabetic patients	Cross-sectional	Iran	119	Mixed	Iranian	T2DM
Reis et al. [82]	2008	Relation of 25-hydroxy vitamin D and parathyroid hormone levels with metabolic syndrome among U.S. adults	Cross-sectional	USA	1654	Mixed	Mixed	
Reis et al. [90]	2007	Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults	Cross-sectional	USA	410	Mixed	Caucasian	
Reis et al. [90]	2007	Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults	Cross-sectional	USA	660	Mixed	Caucasian	
Botella-Carretero et al. [91]	2007	Vitamin D deficiency is associated with the metabolic syndrome in morbid obesity	Cross-sectional	Europe	73	Mixed	Hispanic	T2DM, hypertension, statin use and morbid obesity
Rueda et al. [92]	2007	Vitamin D, PTH, and the metabolic syndrome in severely obese subjects	Cross-sectional	Europe	298	Mixed	Caucasian	Morbid obesity
Ford et al. [94]	2005	Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults	Cross-sectional	USA	8421	Mixed	Mixed	

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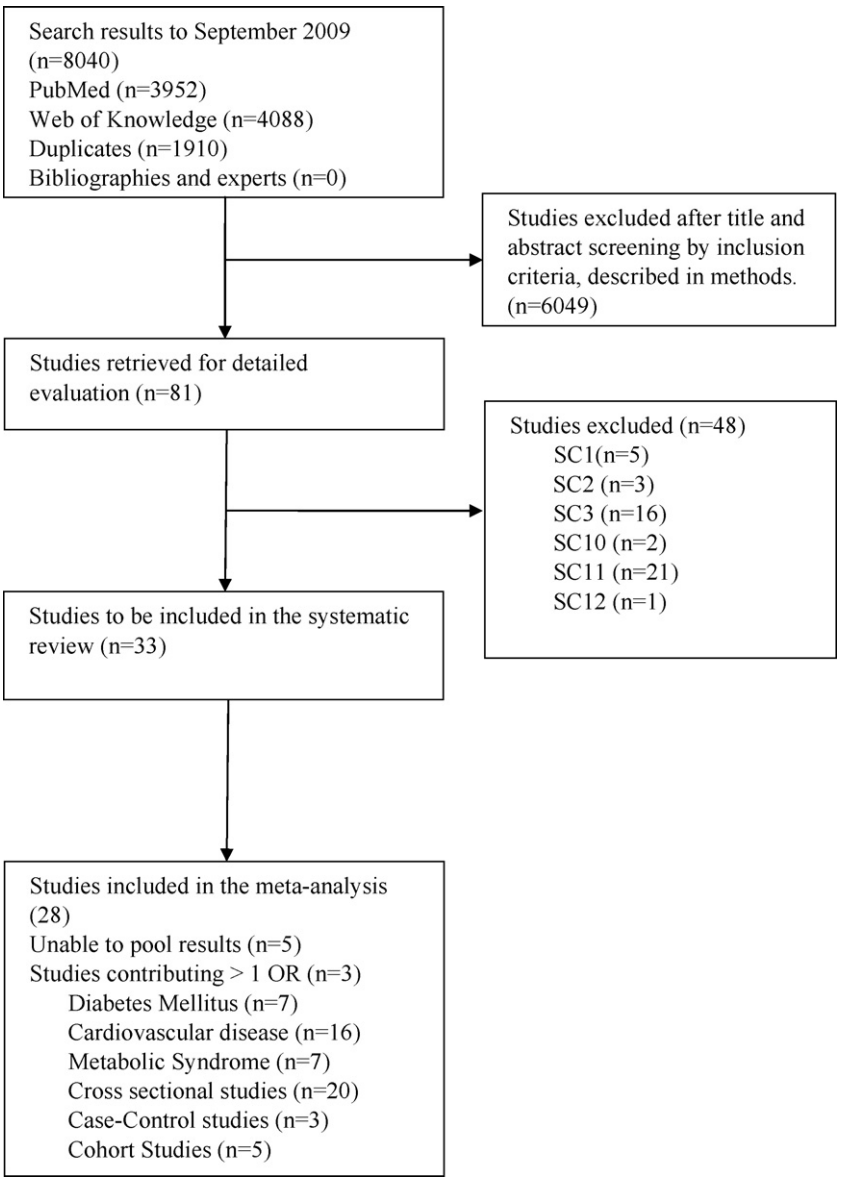

Fig. 1. Flow diagram for the selection of studies evaluating the effect of serum 25OHD on cardiometabolic disease.

3.3. Effects of 25OHD levels on the risk of cardiometabolic disorders

We pooled the estimated ORs comparing the effect of low and high levels of 25OHD on the risk of having cardiometabolic disorders. Thirty-three ORs from 28 studies were reported in the papers or manually calculated from the data, 99,745 participants were included in the pooled analysis (Fig. 2a).

Over 85% of the study results (29 of the 33 ORs) showed that high levels of vitamin D are associated with a lower prevalence of cardiometabolic disorders. Three studies showed an opposite association, and 1 study showed no effect. When the data were pooled the result was an OR of 0.57 (95% CI 0.48–0.68).

Sensitivity analysis was performed by removing each study result in turn from the pooled result, there was no substantial difference in the effect size of any of the pooled results (data not presented). When we evaluated the historical trend in results by adding the ORs in chronological order of publication we found a consistent trend in reporting a beneficial effect of high levels of vitamin D on reducing the risk of cardiometabolic disorders (Fig. 3).

3.4. The effects of 25OHD on cardiometabolic disorders by study design

100% of the cohort studies results supported the association between high levels of vitamin D and reduced cardiometabolic disease with a pooled OR of 0.42 (95% CI 0.28–0.65). Of the 23 cross-sectional study results included, 19 (83%) demonstrated a reduced level of cardiometabolic disease with high levels of vitamin D. One study result showed no effect and three studies suggested that high levels of vitamin D are associated with increased CVD, DM and MetS. Pooled results for the cross-sectional studies showed an OR of 0.59 (95% CI 0.48–0.72). Two of the three case–control studies demonstrated reduced cardiometabolic disorders in participants with high levels of vitamin D. However one study showed the opposite effect. The pooled result for the three case–control studies resulted in an OR of 0.81 (95% CI 0.33–2.01) (Fig. 2a).

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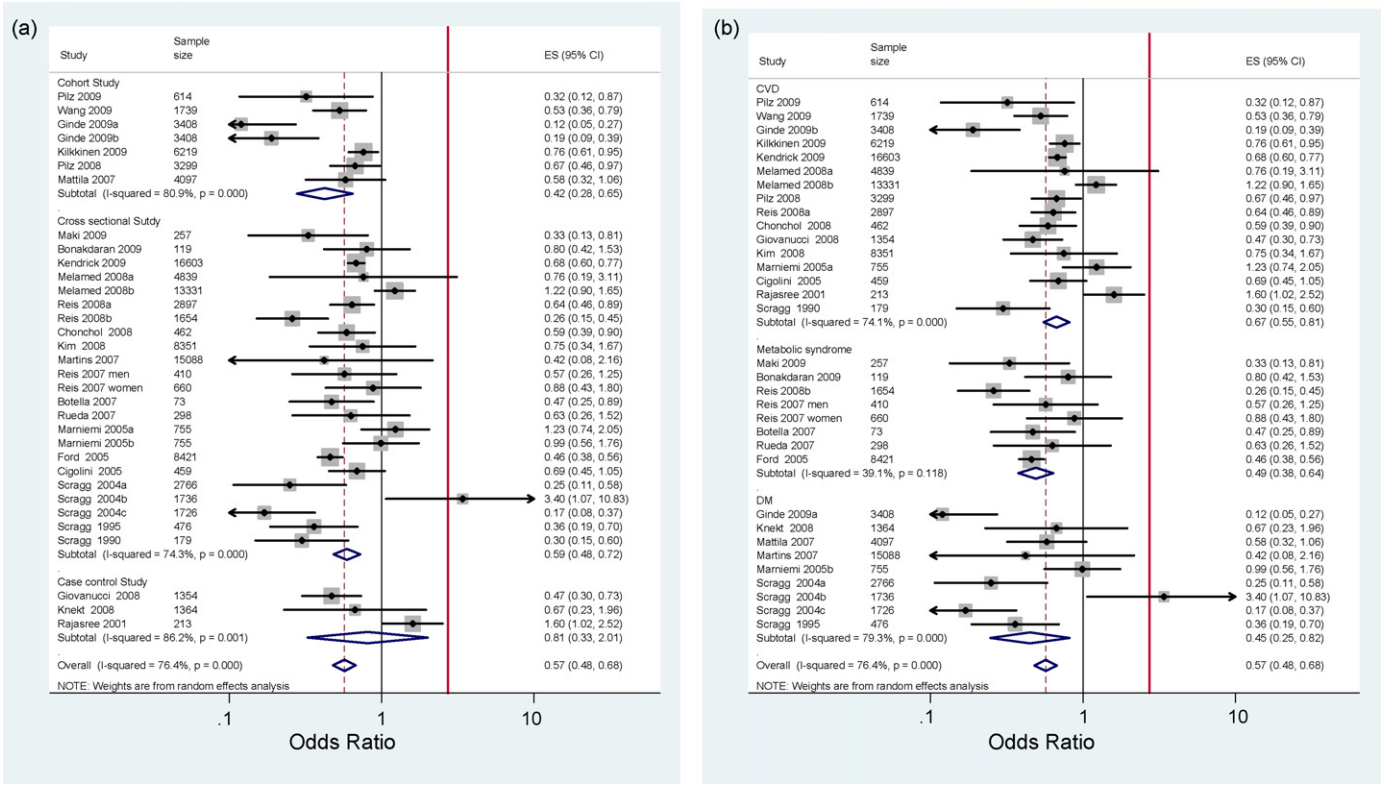

Fig. 2. Forest plot: (a) odds ratios levels for vitamin D and risk of cardiometabolic disease by study design (Cohort studies, cross-sectional and case–control studies). (b) Odds ratios levels for vitamin D and risk of cardiometabolic disease by outcome (CVD, DM and metabolic syndrome).

3.5. The effects of 25OHD levels on cardiometabolic disorders by outcome

All but three of the study results showed that high levels of vitamin D are associated with a reduced prevalence of cardiovascular disease, pooled OR 0.67 (0.55–0.81) (Table 2 and Fig. 2b).

All eight of the studies with metabolic syndrome as the outcome showed that high levels of vitamin D are associated with reduced prevalence of metabolic syndrome, pooled result OR 0.49 (95% CI 0.38–0.64) (Table 2). The results for studies looking at the effect on diabetes showed that high levels of vitamin D are associated with reduced levels of diabetes in seven of the nine results. One study showed no effect and one study suggested that high levels of vitamin D were associated with a higher level of DM. The pooled result demonstrated an overall decrease in the prevalence of diabetes associated with high levels of vitamin D, OR 0.45 (95% CI 0.25–0.82) (Fig. 2b and Table 2).

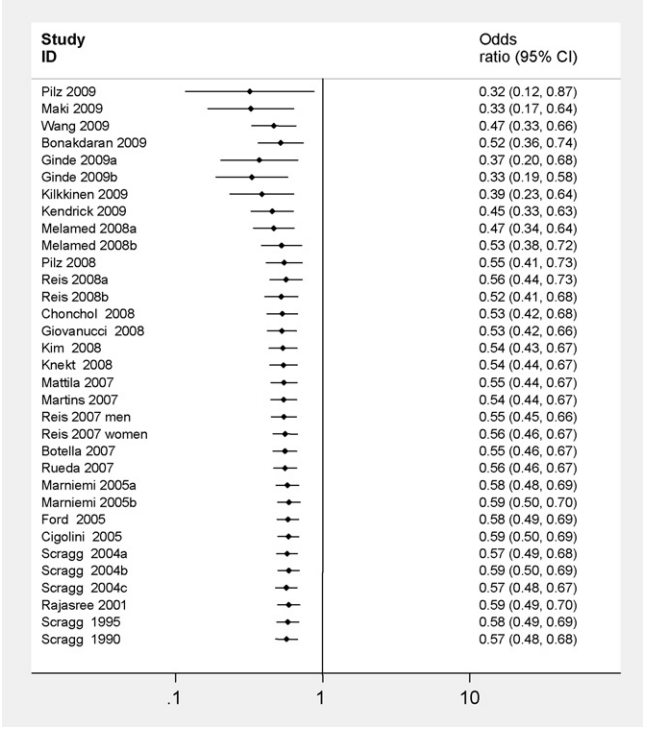

Fig. 3. Cumulative Forest plot: odds ratios levels for vitamin D and risk of cardiometabolic disorders added in chronological order of publication.

3.6. Results excluding manually converted ORs

Seventeen of the ORs were manually calculated from data presented in the papers. All of the manually converted ratios were excluded from a pooled analysis (Fig. 4). We pooled the results from the 16 studies that were presented as ORs (adjusted for covariates) in the original papers. An OR of 0.57 (95% CI 0.43–0.74) was the result, which is of the same magnitude but with a wider confidence interval when compared to the pooled result of all the studies OR 0.57 (95% CI 0.48–0.68).

3.7. Heterogeneity

After performing the test for heterogeneity, we found that the heterogeneity between the studies was significant: $p < 0.01$ $I^2 = 76\%$ and therefore in the pooled analysis presented above, we used a random effects model instead of a fixed effects model. Consequently, we also performed a meta-regression analysis, which indicated no connection between mean age of study participants, gender, number in the analysis, geographical setting or ethnicity

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Table 2
Measures of disease association and variables adjusted for as reported by each study and by principal outcome evaluated (cardiovascular disease, or type 2 diabetes or metabolic syndrome).

Author	Date of publication	Study name	Adjustments	Relative risk ratio
CVD				
Pilz et al. [73]	2009	Vitamin D and mortality in older men and women		0.32 (0.11–0.82)
Wang et al. [75]	2008	Vitamin D deficiency and risk of cardiovascular disease		0.53 (0.36–0.8)
Ginde et al. [77]	2009	Prospective study of serum 25-hydroxy vitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults		0.19 (0.09–0.37)
Kilkkinen et al. [78]	2009	Vitamin D status and the risk of cardiovascular disease death	Age, sex, marital status, educational level, body mass index, alcohol consumption, smoking, leisure-time physical activity, and season HDL, LDL, BP, DM	0.76 (0.61–0.95)
Melamed et al. [80]	2008	Serum 25-hydroxy vitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001–2004		0.76 (0.17–2.85)
Pilz et al. [71]	2008	Low vitamin d levels predict stroke in patients referred to coronary angiography	Age, sex, LDL, HDL, active smoker, BMI, CRP, GFR, arterial hypertension, DM, NT pro-B type natriuretic peptide, physical activity, calcium and PTH	0.67 (0.46–0.97)
Melamed et al. [79]	2008	25-Hydroxy vitamin D levels and the risk of mortality in the general population		1.22 (0.9–1.65)
Reis et al. [81]	2008	Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease		0.67+*****
Chonchol et al. [83]	2008	Association between 25-hydroxy vitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction		0.59 (0.38–0.89)
Giovanucci et al. [84]	2008	25-Hydroxy vitamin D and risk of myocardial infarction in men: a prospective study		0.47 (0.3–0.73)
Kendrick et al. [85]	2009	25-Hydroxy vitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey		0.68 (0.6–0.77)
Kim et al. [86]	2008	Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001–2004)		0.75 (0.34–1.68)
Marniemi et al. [93]	2005	Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects		1.23 (0.74–2.06)
Cigolini et al. [95]	2005	Serum 25-hydroxy vitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients		0.69 (0.45–1.05)
Rajasree et al. [97]	2001	Serum 25-hydroxy vitamin D3 levels are elevated in South Indian patients with ischemic heart disease		1.6 (1.02–2.53)
Scragg et al. [99]	1990	Myocardial infarction is inversely associated with plasma 25-hydroxy vitamin D3 levels: a community-based study		0.3 (0.15–0.61)
DM				
Ginde et al. [77]	2009	Prospective study of serum 25-hydroxy vitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults		0.12 (0.05–0.26)
Knekt et al. [87]	2008	Serum vitamin D and subsequent occurrence of type 2 diabetes	Age, BMI, physical activity, smoking, education, blood pressure and cholesterol	0.67 (0.23–1.96)
Mattila et al. [88]	2007	Serum 25-hydroxy vitamin D concentration and subsequent risk of type 2 diabetes	Age, sex, and month of collecting blood samples, T2DM, BMI, leisure-time exercise, smoking, education and first 5 year follow up excluded	0.58 (0.32–1.06)
Martins et al. [89]	2007	Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxy vitamin D in the United States: data from the Third National Health and Nutrition Examination Survey		0.42 (0.07–1.85)
Marniemi et al. [93]	2005	Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects		0.99 (0.56–1.76)

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Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Age, sex, BMI, leisure-time physical activity, and season	0.25 (0.11–0.6)
Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Age, sex, BMI, leisure-time physical activity, and season	3.40 (1.07–10.86)
Scragg et al. [96]	2004	Serum 25-hydroxy vitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey	Age, sex, BMI, leisure-time physical activity, and season	0.17 (0.08–0.37)
Scragg et al. [98]	1995	Serum 25-hydroxy vitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus	Age, sex, ethnicity and time of year	0.36 (0.19–0.71)
MetS				
Maki et al. [74]	2009	Serum 25-hydroxy vitamin D is independently associated with high-density lipoprotein cholesterol and the metabolic syndrome in men and women		0.33 (0.13–0.79)
Bonakdaran et al. [76]	2009	Correlation between serum 25-hydroxy vitamin D3 and laboratory risk markers of cardiovascular diseases in type 2 diabetic patients		0.8 (0.42–1.53)
Reis et al. [82]	2008	Relation of 25-hydroxy vitamin D and parathyroid hormone levels with metabolic syndrome among U.S. adults	Age, sex, ethnicity, household income, smoking status, alcohol use, physical activity, total calcium intake and total energy intake	0.26 (0.15–0.44)
Reis et al. [90]	2007	Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults	Age adjusted metabolic syndrome components, health-related behaviors, 25(OH)D, and PTH levels	0.57 (0.26–1.25)
Reis et al. [90]	2007	Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults	Age adjusted metabolic syndrome components, health-related behaviors, 25(OH)D, and PTH levels	0.88 (0.43–1.8)
Botella-Carretero et al. [91]	2007	Vitamin D deficiency is associated with the metabolic syndrome in morbid obesity	Age, gender, vitamin D deficiency and calcium intake	0.47 (0.25–0.89)
Rueda et al. [92]	2007	Vitamin D, PTH, and the metabolic syndrome in severely obese subjects	Age, sex, percentage fat mass and season	0.63 (0.26–1.52)
Ford et al. [94]	2005	Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults	Age, sex, race or ethnicity, education, smoking status, cotinine concentration	0.46 (0.46–0.67)

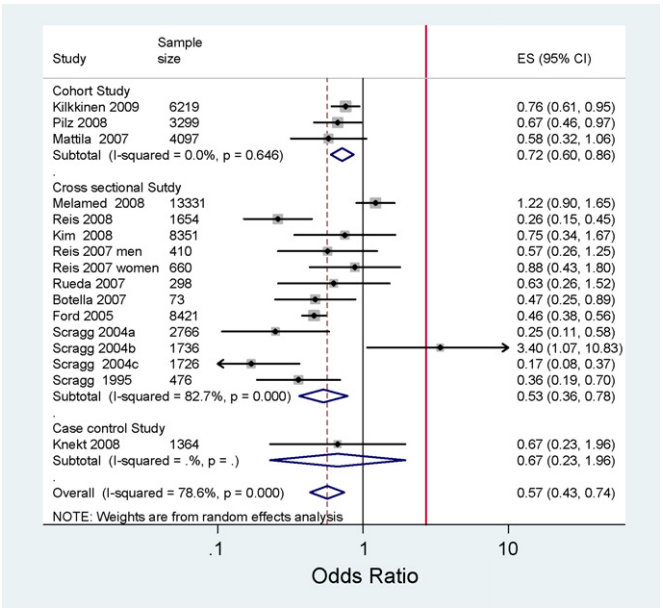

Fig. 4. Forest plot: odds ratios levels for vitamin D and risk of cardiometabolic disorders including only odds ratios that did not require additional conversion (due to alternative reference value selected).

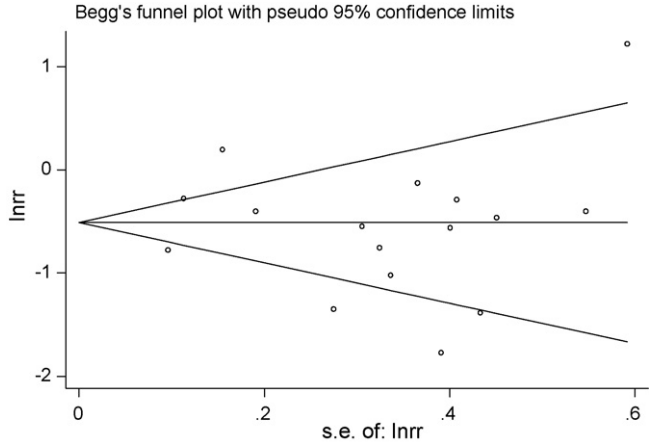

Fig. 5. Funnel plot with 95% confidence limits. The overall heterogeneity test was significant ($z = 4.09$, $p < 0.001$) and the overall percentage of variation attributable to heterogeneity between studies was 78.6% which is high. None of the study characteristics could explain the heterogeneity seen between studies using meta-regression analysis. The pooled estimate of odds ratio (OR) was 0.57 (95% CIs 0.43–0.78; $p < 0.001$). There was no evidence of publication bias using both Begg's [$p = 0.753$] and Egger's test [$p = 0.747$].

and the variability of the association of vitamin D levels and risk of cardiometabolic disorders.

3.8. Publication bias

There was no evidence of significant publication bias this was assessed using a funnel plot and the results of Begg's [$p = 0.753$] and Egger's test $p = 0.747$ (Fig. 5) [18].

4. Discussion

Overall we found that high levels of vitamin D are associated with a 43% reduction in cardiometabolic disorders, this finding applied to all outcomes reported (CVD, DM or MetS), although at different levels of magnitude, and was independent of the study design.

The majority (85%) of the studies' results were in agreement with this main finding.

When we evaluated the effects of vitamin D levels on the risk of the individual outcomes included we found a significant association between high levels of vitamin D and a reduction on the risk of having cardiovascular disease (33% reduction compared to low levels of vitamin D), type 2 diabetes (55% reduction) and metabolic syndrome (51% reduction).

An inverse association between vitamin D status and adiposity, glucose tolerance, lipid profiles and blood pressure has been supported in a number of studies [15,96,100–101]. However, the mechanism underlying these effects is not fully understood. Vitamin D may exert its effects directly through the modulation of gene expression, via activation of vitamin D receptors, or through the regulation of intracellular and extracellular calcium [15,102].

Low levels of vitamin D and the association with increased cardiovascular disease has been described by Zitterman et al. [103] who have proposed different mechanisms to explain this association [103]. The production of a matrix protein which inhibits cellular vascular calcification is up-regulated in the presence vitamin D. Therefore low levels of vitamin D may result in higher vascular calcification, which could ultimately lead to an increased risk of cardiometabolic disorders. It has also been suggested that vitamin D acts as an inhibitor of inflammatory cytokines. Furthermore the production of the anti-inflammatory cytokine interlukin-10 is increased in the presence of vitamin D, possibly linking vitamin D to inflammatory responses seen in cardiovascular insult. Low vitamin D levels have also been associated with an increased activation of the rennin–angiotensin system [104], leading to elevated blood pressure, hence insufficient vitamin D levels may contribute to cardiovascular disease through uncontrolled hypertension.

To our knowledge this is the first systematic review with meta-analysis looking at the potential association between vitamin D levels and cardiometabolic disorders (cardiovascular disease, diabetes and metabolic syndrome) as a combined outcome. The few existing meta-analysis address the association between vitamin D and either all cause mortality [105] or type 2 diabetes and metabolic syndrome separately [9]. Therefore there is no currently published comprehensive perspective of the association between vitamin D levels and the risk of developing cardiometabolic disorders.

Nevertheless our findings are similar to the reported estimates in the current published meta-analysis evaluating the effects of vitamin D on the risk of having diabetes and metabolic syndrome [9]. Our results are difficult to compare with the vitamin D and all cause mortality meta-analysis paper [105] as, although the results for cardiovascular disease mortality were reported, the study includes vitamin D supplementation and mortality as the primary outcome, which differs from our primary outcome.

Consistency of our results with the findings from the review of vitamin D and calcium in type 2 diabetes published in 2007 by Pittas et al. further supports our findings. Our OR 0.45 (95% CI 0.25–0.82) for DM outcome was similar to the OR (0.54) reported in the review and meta-analysis by Pittas et al. [9]. This OR was significant only when the data on Non-Hispanic-black populations was removed. Our findings support a statistically significant association between high vitamin D levels and lower levels of cardiometabolic disorders across all populations. However one of our study results showed a statistically significant relationship between high levels of vitamin D and an increased prevalence of DM. This was in a population of black participants. These two observations along with evidence from other studies could suggest that the effect of vitamin D on cardiometabolic disorders in black populations may not be as strong or could be reversed to that found in non-black ethnic groups, warranting further investigation in future studies that could target these specific populations.

Although we originally aimed to compare our results between gender, age, and ethnic subgroups, the data collected was not presented in enough detail to conduct further stratified pooled analyses. Further evaluation is warranted to investigate the potential differences that might exist in the association between vitamin D levels and cardiometabolic disorders among different groups of the population.

We did not include potential effects of supplementation with the aim to evaluate the natural association of vitamin D levels with the presence of cardiometabolic disorders.

Our findings may be hampered by heterogeneity, which can be explained by the multiple differences between studies regarding the study design, the way 25OHD is reported, measured and analytical procedures, including confounding and adjusting for confounders. Nevertheless it is clear that there is a majority agreement amongst the study results and an overall and historical consensus regarding the association between higher levels of vitamin D and lower prevalence of each of the three outcomes (cardiovascular disease, type 2 diabetes and metabolic syndrome) included in our analysis when evaluated as combined and as separate outcomes as well. Our results demonstrate a strong association between high levels of vitamin D and cardiometabolic disorders as a whole. This can be seen in 85% of the studies, which agree on the beneficial effects of 25OHD. However this data emanates entirely from observational studies, mostly of a cross-sectional nature, therefore further evaluations are required before a causal association can be confirmed between vitamin D levels and cardiometabolic disorders.

4.1. Conclusions

To our knowledge, this is the first meta-analysis on this topic that provides a complete picture of the potentially beneficial role that high levels of 25OHD may provide on cardiometabolic health. The association was significant across all cardiometabolic disease outcomes and study designs, in 28 studies including 99,745 participants across a variety of ethnic groups and in both men and women. Our findings suggest that high levels of vitamin D, among adult populations, are associated with a substantial decrease in cardiovascular disease, type 2 diabetes and metabolic syndrome. Interventions targeting a positive modification of vitamin D deficiency in adult and elderly populations could substantially contribute to halting the current epidemics of cardiometabolic disorders. Further controlled trials are required to evaluate the causal association between vitamin D levels and cardiometabolic disorders as well as the benefit of vitamin D supplementation in the reduction of cardiometabolic disease.

Ethical approval

Ethical approval was not required as this was a secondary data analysis.

Contributors

All authors participated actively in the preparation of the manuscript at all stages: search strategy, study selection, data analyses, and drafting of the manuscript.

Competing interest

None of the authors had any financial or personal conflict of interest to disclose.

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References

[1] Despres JP, Poirier P, Bergeron J, Tremblay A, Lemieux I, Almeras N. From individual risk factors and the metabolic syndrome to global cardiometabolic risk. Eur Heart J Suppl 2008;10(B):B24–33.
[2] Grundy SM. A changing paradigm for prevention of cardiovascular disease: emergence of the metabolic syndrome as a multiplex risk factor. Eur Heart J Suppl 2008;10(B):B16–23.
[3] Fisher M. Cardiometabolic disease: the new challenge? Pract Diabetes Int 2006;23(3):95–7.
[4] Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol 2008;52(December (24)):1949–56.
[5] Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002;112(June (8)):659–62.
[6] Holick MF, Matsuoka LY, Wortsman J. Age, vitamin-D and solar ultraviolet light. Lancet 1989;2(8671):1104–5.
[7] Maclaughlin J, Holick MF. Aging decreases the capacity of human-skin to produce vitmamin-D3. J Clin Invest 1985;76(4):1536–8.
[8] McCullough ML, Bostick RM, Mayo TL. Vitamin D gene pathway polymorphisms and risk of colorectal, breast, and prostate cancer. Annu Rev Nutr 2009;29:111–32.
[9] Pittas AG, Lau J, Hu FB, Dawson-Hughes B. Review: The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92(6):2017–29.
[10] Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D-3, and the immune system. Am J Clin Nutr 2004;80(6):1717S–20S.
[11] Tangpricha V, Flanagan JN, Whitlatch LW, et al. 25-Hydroxyvitamin D-1 alpha-hydroxylase in normal and malignant colon tissue. Lancet 2001;357(9269):1673–4.
[12] Palomer X, Gonzalez-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab 2008;10(March (3)):185–97.
[13] Wallis DE, Penckofer S, Sizemore GW. The "sunshine deficit" and cardiovascular disease. Circulation 2008;118(September (14)):1476–85.
[14] Lu L, Yu Z, Pan A, et al. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. Diabetes Care 2009;32(July (7)):1278–83.
[15] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(July (3)):266–81.
[16] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22(April (4)):719–48.
[17] Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23(11):1663–82.
[18] Egger M, Smith GD, Minder C. Bias in meta-analysis detected by a simple, graphical test—reply. Br Med J 1998;316(7129):470–1.
[19] Rosenberg LE. Vitamin-responsive inherited metabolic disorders. Adv Hum Genet 1976;6:1–74.
[20] Taussig HB. Possible injury to the cardiovascular system from vitamin D. Ann Intern Med 1966;65(December (6)):1195–200.
[21] Zittermann A. Low vitamin D status and inadequate calcium intake—risk factors for the metabolic syndrome? Ernahrungs-Umschau 2003;50(3):84.
[22] Beuren AJ, Apitz J, Stoermer J, et al. Vitamin-D-hypercalcamische herz- und gefasserkrankung. Deut Med Wochenschr 1966;91(19):881.
[23] Beuren AJ, Apitz J, Stoermer J, et al. Vitamin D-hypercalcemia cardiovascular disease. Dtsch Med Wochenschr 1966;91(May (19)):881–3.
[24] Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr 2003;77(April (4)):814–8.
[25] Bid HK, Konwar R, Aggarwal CG, et al. Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: a North Indian study. Indian J Med Sci 2009;63(May (5)):187–94.
[26] Bouillon R, Verstuyf A, Mathieu C, et al. Vitamin D resistance. Best Pract Res Clin Endocrinol Metab 2006;20(December (4)):627–45.
[27] Mehrotra R, Kermah DA, Salusky IB, et al. Chronic kidney disease, hypovitaminosis D, and mortality in the United States. Kidney Int 2009;(August).
[28] Schmidt-Gayk H, Goossen J, Lendle F, Seidel D. Serum 25-hydroxycalciferol in myocardial infarction. Atherosclerosis 1977;26(January (1)):55–8.
[29] Suzuki A, Kotake M, Ono Y, et al. Hypovitaminosis D in type 2 diabetes mellitus: association with microvascular complications and type of treatment. Endocr J 2006;53(August (4)):503–10.
[30] Reis JP, von Muhlen D, Michos ED, et al. Serum vitamin D, parathyroid hormone levels, and carotid atherosclerosis. Atherosclerosis 2009;(June).
[31] Targher G, Bertolini L, Padovani R, et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin Endocrinol (Oxf) 2006;65(November (5)):593–7.
[32] Arroyo M, Laguardia SP, Bhattacharya SK, et al. Micronutrients in African-Americans with decompensated and compensated heart failure. Transl Res 2006;148(December (6)):301–8.
[33] Auwerx J, Dequeker J, Bouillon R, Geusens P, Nijs J. Mineral metabolism and bone mass at peripheral and axial skeleton in diabetes mellitus. Diabetes 1988;37(January (1)):8–12.
[34] Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly men. Diabetologia 1997;40(March (3)):344–7.
[35] Blasiak M, Kuska J, Kokot F, Woch W. Serum levels of calcitonin, parathyroid hormone and 25-hydroxycholecalciferol in patients with diabetes mellitus. Endokrynol Pol 1989;40(5):241–50.
[36] Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 2008;168(June (12)):1340–9.
[37] Fisher AA, Southcott EK, Srikusalanukul W, et al. Relationships between myocardial injury, all-cause mortality, vitamin D, PTH, and biochemical bone turnover markers in older patients with hip fractures. Ann Clin Lab Sci 2007;37(Summer (3)):222–32.
[38] Fahrleitner-Pammer A, Herberth J, Browning SR, et al. Bone markers predict cardiovascular events in chronic kidney disease. J Bone Miner Res 2008;23(November (11)):1850–8.
[39] Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia 1995;38(October (10)):1239–45.
[40] Garakyaraghi M, Kerdegari M, Siavash M. Calcium and vitamin D status in heart failure patients in Isfahan, Iran. Biol Trace Elem Res 2009;(August).
[41] Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. J Am Geriatr Soc 2008;56(March (3)):454–61.
[42] Chen JS, Sambrook PN, March L, et al. Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. Clin Endocrinol 2008;68(2):290–8.
[43] Zittermann A, Schleithoff SS, Frisch S, et al. Circulating calcitriol concentrations and total mortality. Clin Chem 2009;55(June (6)):1163–70.
[44] Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999;149(January (2)):151–61.
[45] Weishaar RE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. II. Direct and indirect effects. Am J Physiol 1987;253(December (6 Pt 1)):E675–83.
[46] Lund B, Badskjaer J, Soerensen OH. Vitamin D and ischaemic heart disease. Horm Metab Res 1978;10(November (6)):553–6.
[47] Merzon KA, Belakovskii MS. Plasma 25-hydroxyvitamin D3 level in patients with chronic cardiac insufficiency. Kardiologiia 1988;28(December (12)):108–9.
[48] Martins D, Tareen N, Pan D, Norris K. Association of low vitamin D levels with metabolic syndrome. Ethnicity Dis 2008;18(3):032.
[49] Melamed ML. Vitamin D: does it reduce risk of cardiovascular disease and all-cause mortality? Am J Epidemiol 2009;169:S87–90.
[50] Momiyama Y, Ohmori R, Taniguchi H, Nakamura H, Ohsuzu F. Ssociations of plasma vitamin D and osteopotin levels with coronary artery calcification. J Am Coll Cardiol 2002;39(5):266A–70A.
[51] Munger R, Folsom A, Kushi L, et al. Vitamin D and calcium intake and subsequent risk of stroke in a cohort of Iowa women. Circulation 1991;83(2), 724-.
[52] Pilz S, Tomaschitz A, Boehm BO, Wimkelmann BR, Marz W. Vitamin D deficiency is associated with type 2 diabetes mellitus and insulin resistance in 3290 patients referred to coronary angiography. Diabetologia 2009;52:309.
[53] Pittas AG, Li T, Willett WC, Manson JE, Dawson-Hughes B, Hu FB. A prospective study of vitamin D intake and risk of type 2 diabetes in women. Diabetes 2005;54:A426–30.
[54] Richart T, Kouznetsova T, Struijker-Boudier H, Staessen J. PTH, vitamin D and their ratio are associated with components of the metabolic syndrome in the general population. J Hypertens 2008;26:S119–20.
[55] Schneider LE, Haussler M, Schedl HP, McCain T. Diabetes and vitamin-D metabolism. Clin Res 1976;24(4):A567–70.
[56] Seelig MS. Ischaemic heart-disease, vitamin-D, vitamin-A and magnesium. Br Med J 1975;3(5984):647–8.
[57] Szep Z, Guaraldi G, Shah S, et al. Association of serum vitamin D levels and type 2 diabetes in HIV Infection in the Modena cohort. Antiviral Ther 2008;13(8):A42–50.
[58] Boucher BJ. Hypovitaminosis D and risk of Type 2 diabetes in British South Asians. Diabet Med 2006;23(March (3)):336 [author reply].
[59] Dalderup LM. Ischaemic heart-disease and vitamin D. Lancet 1973;2(July (7820)):92.
[60] Lee D, Rutter M, O'Neill T, et al. Vitamin D, parathyroid hormone and the metabolic syndrome in middle-aged and older European men. Eur J Endocrinol 2009;(September).
[61] Birkeland KI, Gulseth HL, Gjelstad IMF, et al. Relationship between vitamin D status and insulin secretion and action assessed by the frequently sampled intravenous glucose tolerance test in subjects with the metabolic syndrome. Diabetes 2009;58:A364–70.

Please cite this article in press as: Parker J, et al. Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis. Maturitas (2009), doi:10.1016/j.maturitas.2009.12.013

[62] Dobnig H, Scharnagl H, Renner W, et al. Serum concentrations of vitamin D are significant and independent predictors of mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Exp Clin Endocrinol Diabetes 2007;115:S91–100.
[63] Eskin F. Letter: Vitamin D and myocardial infarction. Br Med J 1974;4(October (5938)):232.
[64] Joergensen C, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. Diabetologia 2009;52:1361.
[65] Khalid SA, Ball LJ, Birge SJ. Vitamin D deficiency/resistance and cerebrovascular disease. J Am Geriatr Soc 2009;57:S185–6.
[66] Laaksonen M, Knekt P, Mattila C, et al. Serum vitamin D and occurrence of subsequent type 2 diabetes: a pooled analysis of two Finnish cohorts. Ann Nutr Metab 2007;51:371.
[67] Alsafwah S, Laguardia SP, Nelson MD, et al. Hypovitaminosis D in African Americans residing in Memphis, Tennessee with and without heart failure. Am J Med Sci 2008;335(April (4)):292–7.
[68] Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. Diabetes 2008;57(October (10)):2619–25.
[69] McGill AT, Stewart JM, Lithander FE, Strik CM, Poppitt SD. Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight and obesity. Nutr J 2008;7:4.
[70] Poole KES, Loveridge N, Barker PJ, et al. Reduced vitamin D in acute stroke. Stroke 2006;37(1):243–5.
[71] Pilz S, Dobnig H, Fischer JE, et al. Low vitamin d levels predict stroke in patients referred to coronary angiography. Stroke 2008;39(September (9)):2611–3.
[72] Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 2008;93(October (10)):3927–35.
[73] Pilz S, Dobnig H, Nijpels G, et al. Vitamin D and mortality in older men and women. Clin Endocrinol (Oxf) 2009;(February).
[74] Maki KC, Rubin MR, Wong LG, et al. Serum 25-hydroxyvitamin D is independently associated with high-density lipoprotein cholesterol and the metabolic syndrome in men and women. J Clin Lipidol 2009;3(4):289–96.
[75] Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117(January (4)):503–11.
[76] Bonakdaran S, Varasteh AR. Correlation between serum 25 hydroxy vitamin D3 and laboratory risk markers of cardiovascular diseases in type 2 diabetic patients. Saudi Med J 2009;30(April (4)):509–14.
[77] Ginde AA, Scragg R, Schwartz RS, Camargo Jr CA. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc 2009;(June).
[78] Kilkkinen A, Knekt P, Aro A, et al. Vitamin D status and the risk of cardiovascular disease death. Am J Epidemiol 2009;(September).
[79] Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168(August (15)):1629–37.
[80] Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arterioscler Thromb Vasc Biol 2008;28(June (6)):1179–85.
[81] Reis JP, Michos ED, von Muhlen D, Miller 3rd ER. Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease. Am J Clin Nutr 2008;88(December (6)):1469–77.
[82] Reis JP, von Muhlen D, Miller 3rd ER. Relation of 25-hydroxyvitamin D and parathyroid hormone levels with metabolic syndrome among US adults. Eur J Endocrinol 2008;159(July (1)):41–8.
[83] Chonchol M, Cigolini M, Targher G. Association between 25-hydroxyvitamin D deficiency and cardiovascular disease in type 2 diabetic patients with mild kidney dysfunction. Nephrol Dial Transplant 2008;23(January (1)):269–74.
[84] Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008;168(June (11)):1174–80.
[85] Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009;205(July (1)):255–60.
[86] Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 2008;102(December (11)):1540–4.
[87] Knekt P, Laaksonen M, Mattila C, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology 2008;19(September (5)):666–71.
[88] Mattila C, Knekt P, Mannisto S, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 2007;30(October (10)):2569–70.
[89] Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2007;167(June (11)):1159–65.
[90] Reis JP, von Muhlen D, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults. Diabetes Care 2007;30(June (6)):1549–55.
[91] Botella-Carretero JI, Alvarez-Blasco F, Villafruela JJ, Balsa JA, Vazquez C, Escobar-Morreale HF. Vitamin D deficiency is associated with the metabolic syndrome in morbid obesity. Clin Nutr 2007;26(October (5)):573–80.
[92] Rueda S, Fernandez-Fernandez C, Romero F, Martinez de Osaba J, Vidal J. Vitamin D, PTH, and the metabolic syndrome in severely obese subjects. Obes Surg 2008;18(February (2)):151–4.
[93] Marniemi J, Alanen E, Impivaara O, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. Nutr Metab Cardiovasc Dis 2005;15(June (3)):188–97.
[94] Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. Diabetes Care 2005;28(May (5)):1228–30.
[95] Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care 2006;29(March (3)):722–4.
[96] Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27(December (12)):2813–8.
[97] Rajasree S, Rajpal K, Kartha CC, et al. Serum 25-hydroxyvitamin D3 levels are elevated in South Indian patients with ischemic heart disease. Eur J Epidemiol 2001;17(6):567–71.
[98] Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract 1995;27(March (3)):181–8.
[99] Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. Int J Epidemiol 1990;19(September (3)):559–63.
[100] Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004;79(May (5)):820–5.
[101] Hypponen E, Boucher BJ, Berry DJ, Power C. 25-Hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. Diabetes 2008;57(February (2)):298–305.
[102] Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92(June (6)):2017–29.
[103] Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 2005;94(October (4)):483–92.
[104] Giovannucci E. Vitamin D and cardiovascular disease. Curr Atheroscler Rep 2009;11(November (6)):456–61 [article].
[105] Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167(September (16)):1730–7.

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