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Review

Vitamin D and cardiovascular disease: Systematic review and meta-analysis of prospective studies

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ABSTRACT

Background. Low serum 25-hydroxyvitamin D (25-OH-D) has recently been linked to cardiovascular diseases. This review summarizes evidence from prospective studies evaluating the prognostic value of 25-OH-D for cardiovascular disease incidence and mortality.

Method. A systematic literature search in EMBASE and Pubmed-Medline databases was performed until November 2009. Prospective studies published in English were selected reporting estimates for the association of 25-OH-D with primary or secondary cardiovascular event incidence or mortality in the general population or subjects with prevalent cardiovascular disease. Pooled risk estimators were derived by meta-analysis using a random effects model approach.

Results. Four incidence and five independent mortality studies were included. Two incidence and three mortality studies reported a two- to five-fold risk increase for both outcomes in subjects with lower 25-OH-D, while the others did not detect a significant association. Meta-analysis supported the existence of an inverse association.

Conclusion. Data from prospective investigations suggest an inverse association between 25-OH-D and cardiovascular risk. However, given the heterogeneity and small number of longitudinal studies, more research is needed to corroborate a potential prognostic value of 25-OH-D for cardiovascular disease incidence and mortality.

Contents

Introduction

Vitamin D, primarily known for its essential role in bone metabolism, has recently been linked to various diseases including cancer, autoimmune or infectious diseases (Holick, 2007; Maalouf, 2008). Furthermore, cross-sectional and case–control studies have suggested a potential role of 25-hydroxyvitamin D (25-OH-D), the major circulating form of vitamin D, in risk reduction of cardiovascular diseases (CVD) (Hintzpeter et al., 2008; Kendrick et al., 2009; Scragg et al., 1990). Although the underlying biological causes are not fully understood, the association of 25-OH-D with cardiovascular pathology is speculated to be driven by various mechanisms: apart from a potential direct impact on cardiomyocytes and myocardial diseases (Pilz et al., in press), it has been suggested that 25-OH-D indirectly modifies CVD risk (Michos and Melamed, 2008) by its association with cardiovascular risk factors like

Abbreviations: 1,25-$(OH)_2$-D, calcitriol; 25-OH-D, 25-hydroxyvitamin D; CHD, coronary heart disease; CVD, cardiovascular disease(s); HR, hazard ratio; MI, myocardial infarction; RR, relative risk

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diabetes (Martins et al., 2007; Mattila et al., 2007), obesity (Aasheim et al., 2008; Martins et al., 2007), hypertension (Forman et al., 2007; Kim et al., in press), smoking (Brot et al., 1999; Hill et al., 2006), or cholesterol level (Auwerx et al., 1992; Scragg et al., 1995).

Although calcitriol (1,25-$(OH)_2$-D) is the active form of vitamin D, in the investigation of associations of vitamin D with incident cardiovascular events, serum-25-OH-D is generally used. Not only is the latter the substrate for 1-alpha-hydroxylase which produces intracellular calcitriol and is expressed in relevant tissues like cardiomyocytes (Pilz et al., in press) and the vessel wall (Somjen et al., 2005), it also is the major form circulating in serum and has been shown to be a better marker of vitamin D status (Holick, 1990; Maalouf, 2008). Longitudinal data on these relationships remain scarce.

Since cardiovascular diseases account for more deaths worldwide than any other disease (Lopez et al., 2006) while at the same time hypovitaminosis D is widespread in many populations (Ginde et al., 2009a; Prentice, 2008) and established risk factors insufficiently explain CVD occurrence (Greenland et al., 2003; Ridker, 1999; Wang et al., 2006), it would be desirable to elucidate possible associations of 25-OH-D with CVD and prognosis in order to explore further potential for CVD prevention. We therefore conducted a systematic review of prospective studies reporting on the association of serum 25-OH-D with cardiovascular disease risk.

Methods

A systematic literature search was performed by the first author (NCG) in the EMBASE (up to 13 November 2009) and Pubmed-Medline (up to 17 November 2009) databases, using the keywords vitamin D, cholecalciferol, calcidiol, calcitriol, 25-hydroxyvitamin D or 25-OH-D, connected by "AND" with the keywords cardiovascular diseases, cardiovascular, cardiovascular risk, cardiovascular system, coronary risk, ischemic heart disease, myocardial infarction, CHD, CAD, coronary heart disease, coronary artery disease, acute coronary syndrome or stroke. The sensitivity of this search strategy was confirmed by cross-referencing (i.e. no additional relevant references were identified in the literature lists of included articles). Unpublished material was not considered. The final cut-off date for literature inclusion was 2 December 2009 when an additional mortality study was published in electronic form ahead of print and was subsequently included.

Original cohort or nested case–control studies reporting hazard ratios, relative risks or odds ratios for the association of initial 25-OH-D levels with incident cardiovascular events or cardiovascular mortality either in a general (initially healthy) human population or in a population with preexisting coronary heart disease were eligible for inclusion. Studies investigating incident fatal or non-fatal myocardial infarction (MI), acute coronary syndrome, coronary heart disease (CHD) or combined outcomes of cardiovascular and cerebrovascular diseases (stroke) were eligible. Articles were excluded if they were not in English language or if the study population was selected according to presence of a disease other than CVD. Moreover, studies where exposure and disease status had been determined simultaneously were excluded. Studies analyzing clinical outcomes of peripheral arterial disease, congestive heart failure, atherosclerosis or stroke were only eligible if those outcomes were analyzed in combination with coronary heart disease endpoints.

The results obtained from both literature databases were combined, and, after removal of duplicates, screened by title and abstract. All articles judged potentially relevant to the topic and published in English language were then reviewed in full text. After exclusion of articles that did not provide original data (reviews, letters, editorials), the remaining original articles were checked with respect to the inclusion and exclusion criteria detailed above.

From the eligible articles, data were extracted according to a standardized protocol. Extracted information included first author, publication year, country, design, time of blood sampling, duration of follow-up, characteristics of the study population, clinical endpoints, risk estimators for the association of different exposure levels of 25-OH-D with incidence or mortality, and factors adjusted for in the main analysis. Since especially coronary heart disease events and deaths were of great interest, data as closely as possible referring to this outcome were reported. Results from models fully adjusted for confounders (i.e. factors associated with 25-OH-D and cardiovascular disease without being in the causal pathway, for example smoking (Brot et al.,

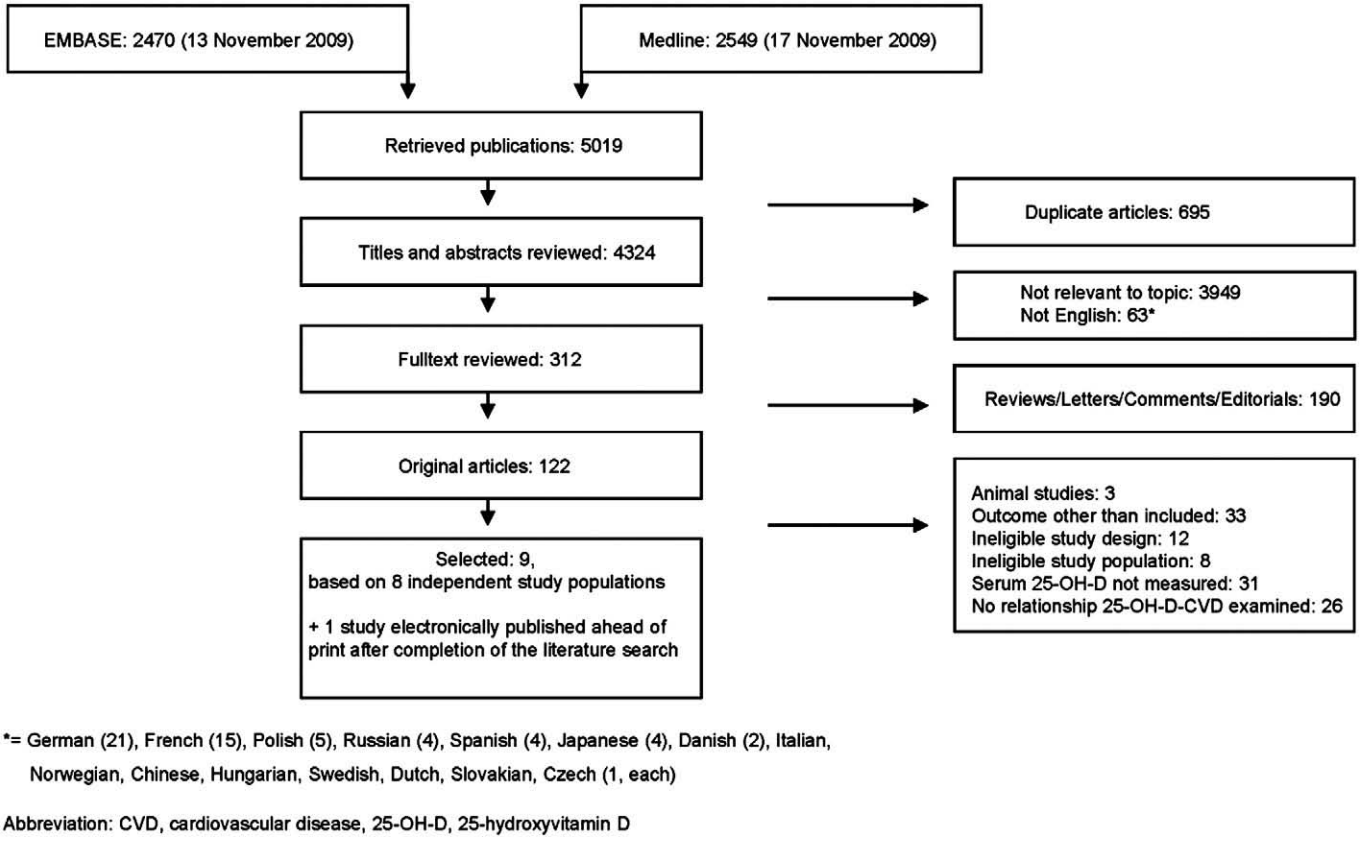

Fig. 1. Flow diagram of literature search.

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1999)) but not intermediate variables (i.e. factors that might be in the causal pathway between vitamin D and cardiovascular disease, for example diabetes (Mattila et al., 2007)) were considered. Data extraction was performed independently by two investigators (NCG, LPB), and any discrepancy was reviewed and resolved in consensus.

In addition, an overall relative risk for lowest vs. highest 25-OH-D categories was derived by meta-analysis combining estimators from fully adjusted models. Combined estimators were calculated by means of the Comprehensive Meta Analysis Software version 2.2.048 (Biostat, Englewood, NJ, USA) for the outcomes cardiovascular events (four studies), cardiovascular mortality (five studies), and for both outcomes combined using the random effects model approach. If fully adjusted models with different exposure categorizations were presented, selection for meta-analysis was based on comparability with models from other studies. Hazard ratios and confidence limits were converted if the lowest instead of the highest category was used as reference. To graphically display the meta-analysis results a forest plot was created. The Q-statistic (which reflects the observed dispersion among effects) was calculated by means of the above-mentioned software to assess heterogeneity among incidence and mortality studies, as well as Kendall-tau and Egger's t to identify a potential over-all publication bias.

Results

Literature search

The database search initially yielded 5019 results of which 695 duplicates were deleted (Fig. 1). From the remaining 4324 publications, 3949 were excluded because they were classified as not relevant to the topic after title and abstract review and another 63 because they were not published in English language. The remaining 312 references were full text reviewed, identifying 122 original articles. Of these, 3 animal studies were excluded. Other reasons for final exclusion were assessment of outcomes other than the prespecified ones ($n=33$), ineligible study design ($n=12$) and selection of study population according to prevalent non-cardiovascular diseases ($n=8$). Furthermore, studies were excluded in which 25-OH-D was not actually measured ($n=31$) as well as studies not analyzing a potential relationship between 25-OH-D and cardiovascular events or not giving risk estimates for this relationship and providing insufficient data to calculate such measures ($n=26$).

Of the remaining nine studies, four investigated non-fatal cardiovascular events or combined outcomes of fatal- and non-fatal cardiovascular events ("incidence studies") and five focused on CVD death ("mortality studies"). During the finalization of this review, one additional mortality study was published in electronic form ahead of print, and was included in the review. Two mortality studies were based on the same cohort, and only the more comprehensive one was included in meta-analysis and reported in detail. All studies were published rather recently (publication years 2005–2010), and with the exception of one nested case–control study they all employed a full cohort design. One study examined the prognostic value of 25-OH-D for secondary cardiovascular events in a population with cardiovascular symptoms, whereas all others concentrated mainly on primary events in the general population or subjects initially free of CVD. Tables 1 and 2 present the main characteristics and principal results of the included studies on incidence and mortality, respectively. More detailed descriptions of the studies are provided in supplemental Tables 1 and 2.

Studies on 25-OH-D and incident CVD

The incidence studies comprising three cohort studies and one nested case–control study varied as to mean age (59–79 years), follow-up length (5–10 years), exposure definition (tertiles and different predefined categories), adjustment set or study population (Table 1). While participants of all studies were initially healthy, two studies were based on the general population (Marniemi et al., 2005; Wang et al., 2008b), one on male health care professionals (Giovannucci et al., 2008) and another on female participants of a randomized clinical trial comparing the treatment effect of calcium supplementation with placebo (Bolland et al., 2010).

Two of four incidence studies reported a significantly increased CVD risk in subjects with low 25-OH-D (Giovannucci et al., 2008; Wang et al., 2008b). In contrast, the analyses by Bolland et al. (2010) and Marniemi et al. (2005) failed to detect a significant association, although the estimated risk ratio regarding MI was nevertheless consistent with a protective effect of 25-OH-D in both studies.

Meta-analysis supported an overall association of 25-OH-D baseline levels in the lowest compared to the highest categories with cardiovascular events (pooled HR = 1.54 [1.22–1.95]) (Fig. 2). This association did not differ significantly across studies ($Q=2.55$; $p=0.47$).

Studies on 25-OH-D and CVD mortality

Similar to the incidence studies, the five included cohort studies with CVD mortality outcome varied as to mean age (45–74 years), follow-up

Table 1
Studies assessing the association of serum-25-OH-D concentration with incidence of cardiovascular events.

Author, year	Study design	Follow-up length, years	Country	Study population[a]				Clinical endpoints	Relative risk (95% CI) according to 25-OH-D levels (range or median, ng/ml)[b] in fully adjusted model	
				Mean age, years	Total number (cases)	% Male	Setting			
Marniemi et al. (2005)	CS	10y (max)	Finland	78.6	689 (130)	46%	Population-based, initially healthy	Fatal and non-fatal coronary events	T1: (N/A) T2: (N/A) T3: (N/A)	1.00 0.99 (0.64–1.53) 0.77 (0.47–1.27)
Giovannucci et al. (2008)	NCCS	10y	USA	63.8	1354 (454)	100%	Health care professionals, initially healthy	Fatal coronary heart disease events and non-fatal MI	≥30.0 22.6–29.9 15.1–22.5 ≤15.0	1.00 1.60 (1.10–2.32) 1.43 (0.96–2.13) 2.09 (1.24–3.54)
Wang et al. (2008b)	CS	7.6y (max)	USA	59	1739 (120)	46%	Population-based, initially healthy	First fatal/non-fatal cardiovascular events	≥15 <15	1.00 1.62 (1.11–2.36)
Bolland et al. (2010)	CS	5y	New Zealand	74	1471 (52)	0%	Healthy postmenopausal women participating in an RCT for calcium supplementation	MI	≥20 <20[c]	1.00 1.2 (0.7–2.2)

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; CS, cohort study; y, year; max, maximum; T, Tertile; N/A, not available; NCCS, nested case–control-study; MI, myocardial infarction; RCT, randomized controlled trial.

[a] Numbers correspond as closely as possible to the analysis cohorts; age- and sex-distributions calculated from subgroup data if necessary.

[b] Concentrations given in nmol/l were converted to ng/ml dividing the value by 2.496.

[c] Seventy one subjects initially excluded because of low 25-OH-D levels were included after having started taking cholecalciferol but were analytically treated according to their initial measurement.

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Table 2
Studies assessing the association of serum-25-OH-D concentration with cardiovascular mortality.

Author, year	Study design	Follow-up length, years	Country	Study population[a]				Clinical endpoints	Relative risk (95% CI) according to 25-OH-D levels (range or median, ng/ml) [b]	
				Mean age, years	Total number (cases)	% Male	Setting		in fully adjusted model	
Dobnig et al., 2008	CS	7.7y (median)	Germany	62	3217 (463)	70%	Symptomatic patients scheduled for angiography in a single tertiary center	Cardiovascular deaths	Q4:[c] 28.4 Q3: 18.9 Q2: 13.3 Q1: 7.6	1.00 approx. 1.4[d] 1.82 (1.29–2.58) 2.22 (1.57–3.13)
Melamed et al., 2008	CS	8.7y (median)	USA	44.8	13331 (777)	45%	Population-based	Cardiovascular deaths	Q4: >32.1 Q3: 24.4–32.1 Q2: 17.8–24.3 Q1: <17.8	1.00 0.85 (0.66–1.09) 0.89 (0.69–1.15) 1.22 (0.90–1.65)
Pilz et al., 2009	CS	6.2y (mean)	Netherlands	69.8	614 (20)	49%	Population-based study, enriched for diabetics	Cardiovascular deaths	Q2–Q4:[c] 24.4 (mean)[e] Q1: 12.3 (mean)	1.00 .5.38 (2.02–14.3)
Kilkkinen et al., 2009	CS	27.1y (median)	Finland	49.4	6219 (640)	45.3%	Population-based, initially healthy	Coronary heart disease deaths	Q1:[c] m:9.2, f:8.4 Q2: m:13.2, f:12.0 Q3: m:16.8, f:15.2 Q4: m:21.6, f:19.6 Q5: m:28.8, f:26.8	1.00 1.17 (0.93–1.48) 0.73 (0.56–0.95) .0.95 (0.74–1.22) 0.91 (0.70–1.18)
Semba et al., 2010	CS	6.5y	Italy	74.0 (median)	1006 (107)	75.0%	Population-based	Cardiovascular deaths	Q4: >25.6 Q3: 16.1–25.6 Q2: 10.5–16.0 Q1: <10.5	1.00 2.19 (1.05–4.60) 1.68 (0.76–3.72) 2.64 (1.14–4.79)[f]

Abbreviations: 25-OH-D, 25-hydroxyvitamin D; CI, confidence interval; CS, cohort study; y, years; Q, Quartile or Quintile; approx., approximately; m, male, f, female.
[a] Numbers correspond as closely as possible to the analysis cohorts; age- and sex-distributions calculated from subgroup data if necessary.
[b] Concentrations given in nmol/l were converted to ng/ml dividing the value by 2.496.
[c] Monthly quartiles (Dobnig et al.); season- and sex-specific quartiles (Pilz et al.); sex-specific quintiles (Kilkkinen et al.).
[d] Graphically determined.
[e] Calculated as weighted mean by the authors according to mean values for Q2, Q3 and Q4 given in the text.
[f] Confidence interval was derived from the abstract as it was most probably misreported in the original table (1.68–2.19).

length (6.2–27.1 years), exposure definition (quartiles, quintiles), adjustment set or study population (Table 2). Patients with cardiovascular symptoms (Dobnig et al., 2008) as well as the general population (Kilkkinen et al., 2009; Melamed et al., 2008; Semba et al., 2010) or a sample enriched for diabetic patients were studied (Pilz et al., 2009).

For the subgroup analysis of participants aged 65 years or older which was performed within the same study population analyzed by Melamed et al. (2008) and therefore excluded as a duplicate study, the reader is referred to Ginde et al. (2009b).

Three of the five included studies found a significant association (Dobnig et al., 2008; Pilz et al., 2009; Semba et al., 2010). One of these reported a very strong (five-fold) risk increase in the lowest quartile of 25-OH-D (Pilz et al., 2009). The remaining studies (Kilkkinen et al., 2009; Melamed et al., 2008) on primary fatal CVD did not support these findings, although the lowest quartile in one of them featured a non-significantly increased risk of CVD mortality (Melamed et al., 2008) whereas the other one provided evidence for an association of 25-OH-D with cerebrovascular mortality (Kilkkinen et al., 2009).

Meta-analysis indicated a significant association of low 25-OH-D with cardiovascular mortality (HR = 1.83 [1.19–2.80]; Fig. 2). Significant heterogeneity was detected among studies ($Q = 21.01$, $p = 0.0003$).

Combining estimates from incidence and mortality studies (Fig. 2) yielded a pooled hazard ratio of 1.64 [1.27–2.11], supporting an association of low 25-OH-D with cardiovascular outcome. There was, however, some indication for a possible publication bias (Kendall's tau = 0.47, $p = 0.04$; Egger's $t = 2.35$, $p = 0.03$; one-tailed).

Discussion

Five out of nine studies prospectively assessing the association between 25-OH-D and risk of incident CVD or mortality reported a significant increase in risk in subjects with lower 25-OH-D levels. The small number of studies fulfilling the rigorous inclusion criteria of our systematic review highlights the dearth of high-level evidence for the relationship examined.

Some inconsistencies in results were observed among both incidence and mortality studies which might, at least in part, be based on variations in study size and number of events. In the case of incidence studies, considerable support for an association was provided by the two largest studies showing an approximately doubled risk in vitamin D deficient subjects (Giovannucci et al., 2008; Wang et al., 2008b). In the case of mortality studies, as indicated by meta-analysis, substantial heterogeneity of studies with respect to age structures, outcome and exposure definitions, as well as different adjustments for confounders and the seasonality of 25-OH-D might be an additional reason for inconsistent results. Different geographical latitudes of the study sites might have further complicated the issue of 25-OH-D levels and seasonality. Finally, the possibility of residual confounding always has to be kept in mind in observational studies. For instance, low 25-OH-D might be connected with a lower health status due to a variety of other comorbidities (Bischoff-Ferrari et al., 2006).

In order to facilitate the quantitative judgement of our findings, we calculated a pooled relative risk combining estimators from the studies discussed. Our meta-analysis using a random-effects model indicated a significant inverse association of 25-OH-D with cardiovascular outcomes.

Apart from the investigations summarized in the present review, the role of vitamin D in cardiovascular disease prognosis has also been analyzed in special cohort studies based on patients with renal diseases (Fahrleitner-Pammer et al., 2008; Wang et al., 2008a). In those populations low serum vitamin D levels, more pronounced vascular calcification and increased cardiovascular mortality compared to healthy subjects were observed (Zittermann and Koerfer, 2008a,b). Successful attempts already have been made in preventing adverse cardiovascular consequences by treatment with active vitamin D or vitamin D analogs in such populations (Levin and Li, 2005; Teng et al., 2005; Valdivielso and Ayus, 2008).

In a similar way, supplementation of vitamin D could potentially serve as preventive strategy in healthy subjects if its association with CVD should be causal. Yet, evidence from interventional studies

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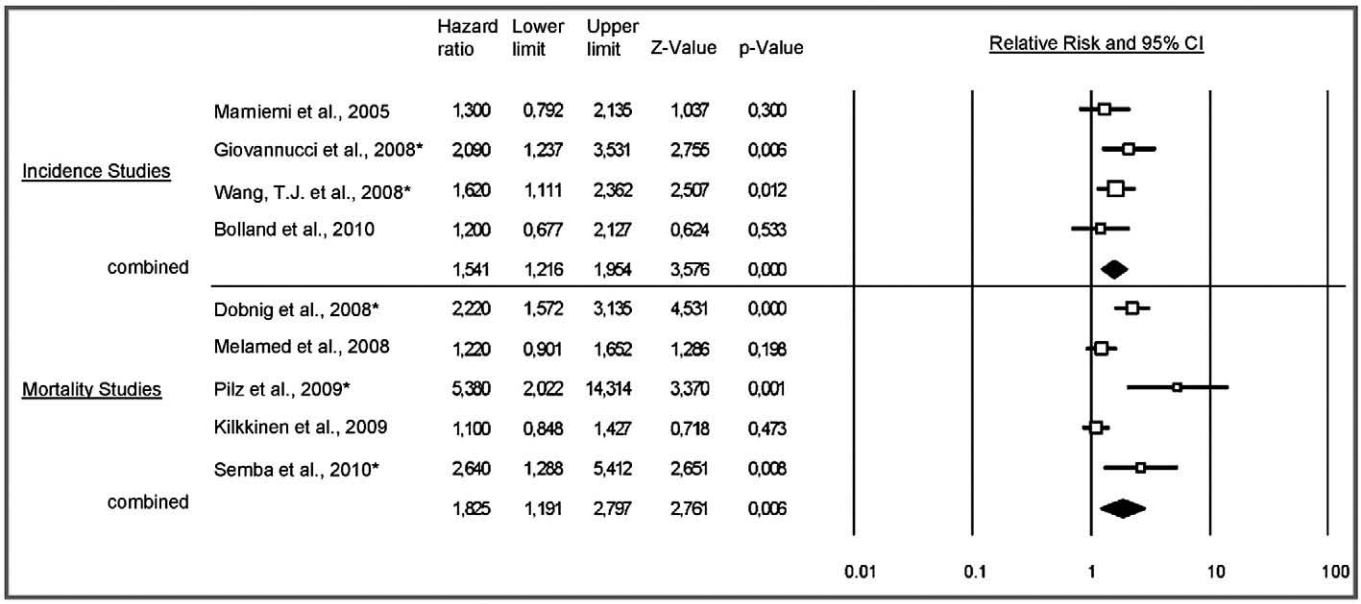

Fig. 2. Forest plot of meta-analysis of cardiovascular incidence and mortality studies.

on this issue is still scarce (Hsia et al., 2007; Lichtenstein, 2009). Risk reduction by vitamin D supplementation alone or in combination with calcium therapy has already been reported for outcomes like all-cause mortality (Autier and Gandini, 2007) and different cancer types (Lappe et al., 2007). Future interventional studies on vitamin D supplementation in CVD prevention should be conducted addressing both benefits and risks of intake because, depending on their vitamin D status, individuals might not equally profit and a possible maximum serum and/or intake level for vitamin D above which possible harms through increasing calcium levels (Hathcock et al., 2007) could occur deserves further examination.

Additional data are not only required regarding the actual association of vitamin D with CVD itself—as highlighted by the present review—but also concerning the bioavailability of vitamin D supplements (Lee et al., 2008). Regardless of causal relationships, however, risk stratification incorporating 25-OH-D levels could already serve to improve patient care by potentially highlighting individuals at particularly high risk of primary CVD or adverse prognosis. Future studies should evaluate the incremental prognostic value of vitamin D in comparison to established risk markers, and should carefully rule out that insufficient adjustment for—and residual confounding by—diet, outdoor activity, socioeconomic status, or season, has been the main reason for finding statistical associations between 25-OH-D and CVD.

In the interpretation of our review, several limitations have to be kept in mind. For practical reasons, unpublished and non-English data could not be considered. Our meta-analysis indicated the presence of some limited publication bias, and complete reporting by all research groups addressing 25-OH-D obviously must be encouraged. Regarding our meta-analysis, substantial between-study heterogeneity, especially among mortality studies, and the necessity to combine estimates based on different categorizations of 25-OH-D urge caution in the interpretation of the results.

Another limitation concerns the restriction to prospective studies of 25-OH-D with outcomes including coronary heart disease, hence neglecting studies with different study designs or other potentially relevant outcomes, in particular stroke or peripheral arterial disease. At the same time, this stringent and focused systematic approach ensured a more structured summary of published knowledge pertaining to the relationship between 25-OH-D and CVD based on the highest level of evidence currently available.

Conclusion

Prospective studies evaluating the prognostic value of 25-OH-D on cardiovascular disease outcomes in the general population or in populations with preexisting cardiovascular disease remain very rare. Overall, the published data seem to be in favor of an inverse association between 25-OH-D and cardiovascular risk. However, given the heterogeneity of eligible studies in terms of study population, outcome and exposure level definitions, there remains an urgent need for additional large-scale studies to further elucidate the role of vitamin D as a potential risk marker and maybe even a modifiable risk factor for CVD, the most important cause of morbidity and mortality world-wide.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ypmed.2010.06.013.

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