Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies[1–3]

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ABSTRACT

Background: During the past decade, an increasing number of prospective studies have focused on the association between vitamin D and cardiovascular disease (CVD). However, the evidence on the relation between serum 25-hydroxyvitamin D [25(OH)D] and the risk of overt CVD is inconclusive.

Objective: We performed a dose-response meta-analysis to summarize and prospectively quantify the RR of low serum 25(OH)D concentration and total CVD (events and mortality).

Design: We identified relevant studies by searching PubMed and EMBASE up to December 2015 and by hand-searching reference lists. Prospective studies based on the general population and reported RRs and 95% CIs were included. A random-effects model was used to calculate the pooled RRs. Nonlinear association was assessed by using restricted cubic spline analyses.

Results: A total of 34 publications with 180,667 participants were eligible for the meta-analysis. We included 32 publications (27 independent studies) for total CVD events and 17 publications (17 independent studies) for CVD mortality. We observed an inverse association between serum 25(OH)D and total CVD events and CVD mortality, and the pooled RRs per 10-ng/mL increment were 0.90 (95% CI: 0.86, 0.94) for total CVD events and 0.88 (95% CI: 0.80, 0.96) for CVD mortality. A nonlinear association was detected for total CVD events (P-nonlinear < 0.001) and CVD mortality (P-nonlinear = 0.022).

Conclusion: Serum 25(OH)D concentration was inversely associated with total CVD events and CVD mortality from the observed studies. *Am J Clin Nutr* 2017;105:810–9.

Keywords: 25-hydroxyvitamin D, cardiovascular disease, meta-analysis, dose-response, CVD mortality

INTRODUCTION

Historically, vitamin D is well known for its crucial role in skeletal disease, including bone metabolism (1, 2), fractures (3, 4), and falls (5). In recent decades, a large and rapidly expanding literature has focused on the associations between vitamin D and hypertension (6), diabetes (7, 8), metabolic syndrome (9), cardiovascular disease (CVD)[9] (10, 11), cancer (12, 13), and mortality (14, 15). The Institute of Medicine released advice on Recommended Dietary Allowances for achieving a 25-hydroxyvitamin D [25(OH)D] concentration ≥20 ng/mL, which was based on bone health (16). Unlike for skeletal disease, the evidence for vitamin D and the risk of extraskeletal chronic disease has been inconclusive. CVD is the leading cause of deaths and disability (17), and the prevalence of vitamin D insufficiency is high in the general population (18). If there is a cause-and-effect relation found between low vitamin D status and incident CVD, this would be of considerable benefit to public health (19). To date, there have been few clinical trials specifically designed to explore this relation. The VITAL (Vitamin D and OmegA-3 Trial), which was designed to explore this relation, has not been completed and the results have not yet been reported (20). In fact, some (21, 22) but not all (23, 24) of the reviewed studies showed inverse associations between serum 25(OH)D concentration and the risk of CVD, and recent research showed a reverse J-shaped association (25). Some studies reported that high serum 25(OH)D was linked to an elevated risk of total mortality (26), and the association shown between high concentrations of 25(OH)D and CVD events was controversial (26, 27). Conflicting outcomes may be due in part to participant characteristics. In some studies, participants were enrolled from the hospital and were usually experiencing acute illness (28, 29). A

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[3] Supplemental Methods and Supplemental Figures 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[9] Abbreviations used: CVD, cardiovascular disease; HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarction; MMP, matrix metalloproteinase; 25(OH)D, 25-hydroxyvitamin D.

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TABLE 1
Characteristics of the included studies in the current dose-response meta-analysis[1]

First author, year (ref)	Country	Endpoint	Age, y	Cases, *n*	Participants at risk, *n*	Follow-up, y	Design (study name)	Quality score
Giovannucci, 2008 (40)	USA	MI	63.8 (mean)	454	900	10	Nested case-control study (HPFS)	6
Wang, 2008 (10)	USA	CVD	59 (mean)	120	1739	5.4 (mean)	Cohort study (Framingham Offspring Study)	7
Kilkkinen, 2009 (41)	Finland	CVD mortality	49.4 (mean)	933	6219	27.1 (median)	Cohort study (Mini-Finland Health Survey)	7
		Cerebrovascular deaths		293	6219			
		Cardiovascular deaths		640	6219			
Cawthon, 2010 (42)	USA	CVD mortality	≥65	110	1490	7.3 (mean)	Cohort study (MrOS)	6
Hutchinson, 2010 (43)	Norway	CVD mortality (nonsmokers)	58.9 (mean)	325	4751	11.7 (mean)	Cohort study (Tromsø study)	6
		CVD mortality (smokers)		188	2410			
Michaëlsson, 2010 (26)	Sweden	CVD mortality	71 (mean)	196	1312	12.7 (median)	Cohort study (ULSAM)	6
Semba, 2010 (44)	Italy	CVD mortality	≥65	107	1006	6.5	Cohort study (InCHIANTI)	7
Eaton, 2011 (45)	USA	CVD mortality	20–79	79	2429	>10.5	Nested case-control (WHI)	6
Kestenbaum, 2011 (46)	USA	CVD mortality	≥65	389	2312	14 (median)	Cohort study (CHS)	8
Brøndum-Jacobsen, 2012 (21)	Denmark	Nonfatal IHD	57 (mean)	1578	10,170	21	Cohort study (Copenhagen City Heart Study)	8
		Nonfatal MI		802	10,170			
		Fatal IHD/MI		1522	10,170			
Kritchevsky, 2012 (47)	USA	CVD mortality	74.7 (mean)	228	2638	>8.5	Cohort study (Health ABC Study)	8
Lin, 2012 (48)	China	Cerebrovascular deaths	56.5 (mean)	279	1101	>24	Cohort study (None)	6
		Cardiovascular deaths		200	1101			
Messenger, 2012 (49)	USA	CVD diseases	76.4 (mean)	140	813	4.4 (median)	Cohort study (MrOS)	6
Sun, 2012 (22)	USA	Stroke	60.8 (mean)	464	928	16	Nested case-control study (NHS)	7
Brøndum-Jacobsen, 2013 (50)	Denmark	Ischemic stroke	56 (mean)	1256	10,170	21 (median)	Cohort study (Copenhagen City Heart Study)	7
Deng, 2013 (51)	USA	CVD mortality	47 (mean)	1615	12,157	5	Cohort study (NHANES III cohort)	6
Kühn, 2013 (23)	Germany	MI	50.6 (mean)	559	2132	7.7 (mean)	Case-cohort study (EPIC-Germany)	7
		Stroke		471	2132			
		Composite endpoint		1030	2132			
Perna, 2013 (24)	Germany	Total CVD	50–74	1101	6709	6.5 (mean)	Cohort study (ESTHER study)	9
		Total IHD		536	6709			
		Total stroke		353	6709			
Robinson-Cohen, 2013 (52)	USA	IHD	62 (mean)	361	6436	8.5 (median)	Cohort study (MESA)	7
Rohrmann, 2013 (53)	Switzerland	CVD mortality	47.1 (mean)	122	3404	18 (mean)	Cohort study (Swiss National Cohort)	5
Schöttker, 2013 (54)	Germany	CVD mortality	62 (mean)	350	9254	9.5 (median)	Cohort study (ESTHER study)	8
Skaaby, 2013 (55)	Denmark	IHD	49.8 (mean)	478	9146	10 (mean)	Cohort study (Monica10 and Inter99)	6
		Stroke		316	9146			
Bansal, 2014 (56)	USA	HF	62 (mean)	180	6459	8.46 (median)	Cohort study (MESA)	8
Formiga, 2014 (57)	Spain	CVD mortality	85 (mean)	25	312	2.8 (median)	Cohort study (Octabaix study)	4
di Giuseppe, 2014 (58)	Europe	HF	51 (mean)	221	1349	8.2 (mean)	Case-cohort study (EPIC-Potsdam)	8
Khaw, 2014 (27)	United Kingdom	CVD mortality	62 (mean)	854	14,641	13 (mean)	Case-cohort study (EPIC-Norfolk)	6
		CVD events		4514	14,641			
Lee, 2014 (59)	United Kingdom	CVD mortality	60 (mean)	72	2452	4.3 (median)	Cohort study (EMAS)	6

(Continued)

TABLE 1 (*Continued*)

First author, year (ref)	Country	Endpoint	Age, y	Cases, *n*	Participants at risk, *n*	Follow-up, y	Design (study name)	Quality score
Wannamethee, 2014 (60)	United Kingdom	HF	60–79	287	3646	13 (mean)	Cohort study (British Regional Heart Study)	8
Chien, 2015 (61)	Taiwan	CVD events	60.2 (mean)	263	1816	9.6 (median)	Cohort study (CCCC)	6
Lutsey, 2015 (62)	USA	HF	56 (mean)	1763	12,215	14	Cohort study (ARIC)	7
Jassal, 2010 (63)	USA	CVD mortality	74 (mean)	111	1073	6.4 (mean)	Cohort study (Rancho Bernardo Study)	5
Anderson, 2010 (64)	USA	IHD/MI	55 (mean)	763	21,853	1.3 (mean)	Cohort study (None)	5
		HF		594	23,793			
		Stroke		197	26,025			
		CVD mortality		1193	27,686			
		Composite CVD		1304	20,069			
Afzal, 2014 (65)	Denmark	CVD mortality	58 (mean)	2877	9902	19.1 (median)	Cohort study (Copenhagen City Heart Study)	7
				317	25,432	5.8 (median)	Cohort study (Copenhagen General Population Study)	
Karakas, 2013 (66)	Germany	IHD (men)	35–74	225	964	11 (mean)	Case-cohort study (MONICA/KORA Augsburg)	6
		IHD (women)		73	819			

[1] ABC, Aging and Body Composition; ARIC, Atherosclerosis Risk in Communities Study; CCCC, Chin-Shan Community Cardiovascular Cohort Study; CHS, Cardiovascular Health Study; CVD, cardiovascular disease; EMAS, European Male Ageing Study; EPIC, European Prospective Investigation into Cancer and Nutrition; ESTHER, Epidemiological investigations of the chances of preventing, recognizing early and optimally treating chronic diseases in an elderly population; HF, heart failure; HPFS, Health Professionals Follow-Up Study; IHD, ischemic heart disease; InCHIANTI, Invecchiare in Chianti; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; MONICA/KORA Augsburg, Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Augsburg; MrOS, Osteoporotic Fractures in Men; NHS, Nurses' Health Study; ref, reference; ULSAM, Uppsala Longitudinal Study of Adult Men; WHI, Women's Health Initiative.

previous meta-analysis reviewed the association between vitamin D status and composite CVD but did not include heart failure (HF), and relevant studies were included without regard to the source of participants (30). Because an increasing number of prospective studies have speculated on the association between vitamin D status and the risk of CVD, we performed a comprehensive dose-response meta-analysis of prospective studies to reevaluate and update the relation between baseline serum 25(OH)D concentration and the risk of total CVD events and CVD mortality in the general population.

METHODS

Literature search strategy and selection

This meta-analysis was reported in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement (31). We undertook a systematic search of PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.embase.com) through December 2015 for studies related to vitamin D and CVD. In addition, we used hand-searches of the references of all identified articles and relevant reviews to identify pertinent sources. Our search terms used for CVD included cardiovascular diseases, heart failure, myocardial infarction (MI), ischemic heart disease (IHD) and stroke. Search terms used for vitamin D included the following: vitamin D, 25-hydroxyvitamin D, 25hydroxy-vitamin D, 25(OH)D, 1,25-dihydroxyvitamin D, cholecalciferol, and ergocalciferol. CVD-related terms, vitamin D–related terms, and cohort study–related terms were combined by using the Boolean operator "AND." Finally, results were further restricted to human studies, those in English, and those in adults aged >18 y. Details on the literature search strategy are described in **Supplemental Methods**.

Study selection

The titles and abstracts of identified studies were first screened by 2 investigators (RZ and BL) for potentially relevant sources, and we retrieved the full texts of such articles to assess eligibility. Studies were included if they were of a prospective design, examined the relation between serum 25(OH)D concentration and CVD, and provided risk estimates of RRs, HRs, or ORs and CIs. The exclusion criteria were as follows: *1*) case reports, editorials, letters, meeting abstracts, or review articles; *2*) retrospective studies, cross-sectional studies, or case-control studies; *3*) studies that did not measure serum circulating 25(OH)D at baseline; *4*) studies that did not use CVD, IHD, MI, stroke, HF, or CVD mortality as an endpoint; *5*) studies that reported <3 exposure categories or did not provide RRs for per-unit changes in 25(OH)D; *6*) studies that did not publish the mean or median or range of each category; and *7*) studies that were based on a hospital inpatient population with a specific disease. In the case of multiple reported articles from the same cohort, only those with the highest number of cases or the longest follow-up times were included in the meta-analysis. If there were discrepancies between the reviewers (RZ and BL), then another author (GL), as the third investigator, was consulted to reach a consensus.

Data extraction

We collected data from each eligible study, including the name of the first author, publication year, geographical location, source

of cohort, study design, duration of follow-up, baseline year, mean age of participants, sample size, numbers of women and men, cardiovascular outcomes, number of cases, concentration of 25(OH)D in each category, effect sizes and 95% CIs in each category, and adjusted variables. When >1 RRs were reported, we extracted the risk ratio from the model containing the largest number of adjusted variables. For the studies in which results were published for separate subgroups instead of overall, data for those subgroups were extracted individually. We extracted data on all cardiovascular outcomes if several endpoints were reported. For information that was not available or clear in the publication, we directly contacted the author to obtain related data. We evaluated the quality of individual records by using Newcastle-Ottawa quality-assessment scale (32). Each study was assigned 0–9 "stars" (with more stars meaning higher quality) by 2 of the investigators (RZ and RT) to ensure the accuracy of extraction.

Data synthesis and analysis

The effect sizes between serum 25(OH)D and cardiovascular outcomes were reported in each included study. Because ORs in nested case-control studies and HRs were quite similar to RRs, we used RRs as common risk estimates for all references (22, 33). According to the

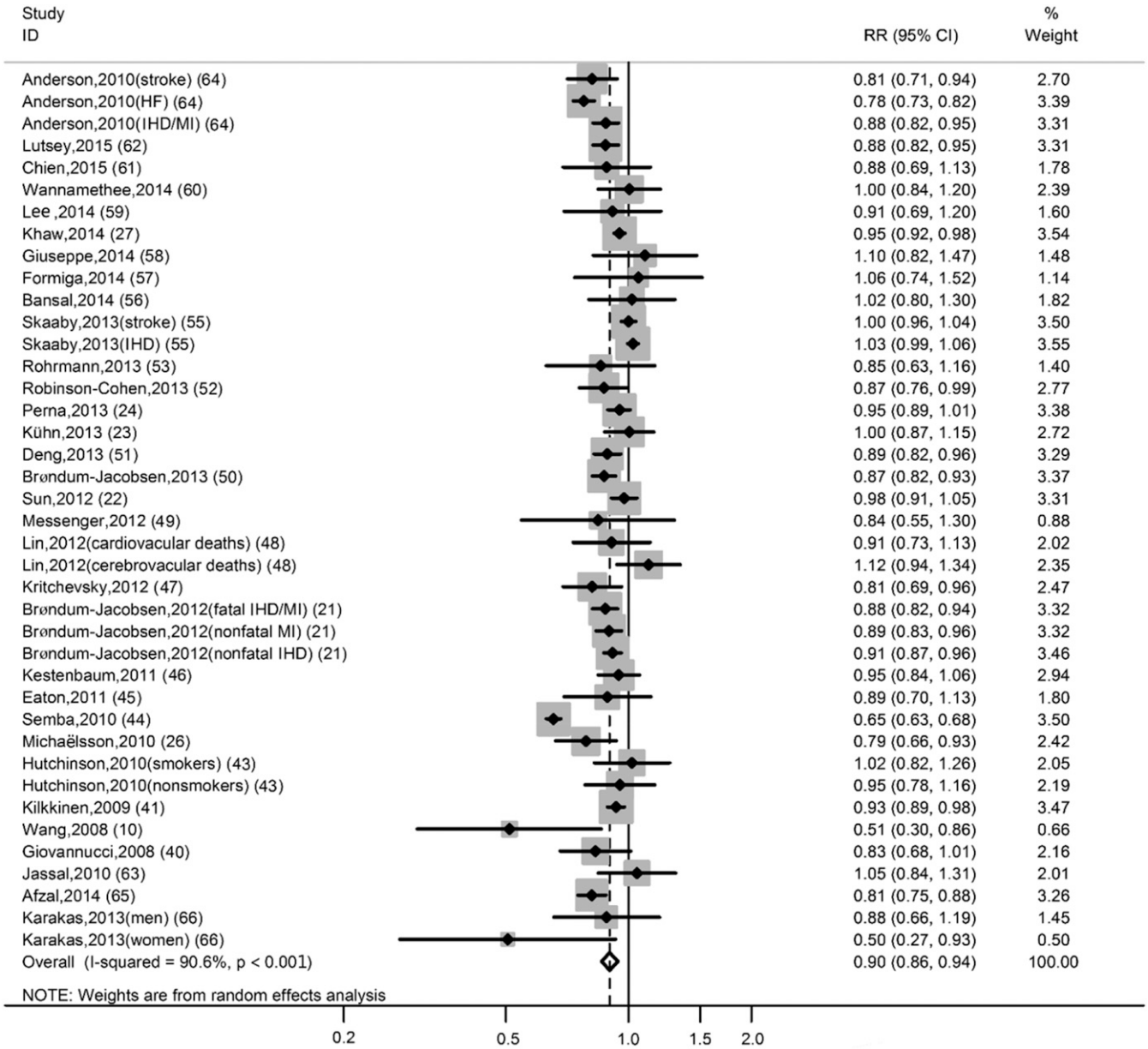

FIGURE 1 Forest plot showing the pooled effects of serum 25-hydroxyvitamin D on the risk of total cardiovascular events with the use of the random-effects model (RR: 0.90; 95% CI: 0.86, 0.94), which includes 32 studies (40 estimates). The pooled effects are shown for 10-ng/mL increments in serum 25-hydroxyvitamin D. Solid diamonds and horizontal lines represent RRs (95% CIs) for the outcome of interest. Solid circles and horizontal lines represent RRs (95% CIs); the gray boxes reflect the statistical weight of the study. The dotted vertical line denotes the point estimate for the pooled RRs and the solid vertical line indicates the line of no effect. The open diamond represents the pooled RR with its 95% CI. HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarction.

TABLE 2
Subgroup analysis of serum 25(OH)D and risk of total CVD events and CVD mortality in dose-response meta-analysis[1]

	Total CVD events					CVD mortality				
Subgroup	*n*	RR (95% CI)	I^2, %	P_h[2]	P_h[3]	*n*	RR (95% CI)	I^2, %	P_h[2]	P_h[3]
Age, y					0.542					0.534
<65	31	0.91 (0.88, 0.94)	78.2	<0.001		9	0.90 (0.86, 0.93)	22.0	0.247	
≥65	9	0.87 (0.74, 1.03)	89.8	<0.001		8	0.85 (0.72, 1.00)	88.9	<0.001	
Cases, *n*					0.201					0.063
≤200	13	0.85 (0.74, 0.98)	82.6	<0.001		9	0.87 (0.74, 1.02)	84.4	<0.001	
>200	27	0.91 (0.88, 0.94)	80.1	<0.001		8	0.89 (0.85, 0.93)	35.9	0.142	
Follow-up, *y*					0.031					0.729
≥10	23	0.92 (0.89, 0.96)	73.7	<0.001		10	0.89 (0.86, 0.93)	32.5	0.148	
5–<10	11	0.88 (0.77, 1.01)	93.6	<0.001		5	0.82 (0.67, 1.00)	86.8	<0.001	
<5	6	0.84 (0.78, 0.90)	45.8	0.101		2	0.96 (0.77, 1.20)	0.0	0.524	
Number of 8 adjusted variables[4]					0.106					0.013
<6	21	0.93 (0.89, 0.97)	80.8	<0.001		8	0.93 (0.89, 0.96)	0.0	0.451	
≥6	19	0.87 (0.80, 0.94)	92.4	<0.001		9	0.85 (0.76, 0.97)	92.4	<0.001	
Quality scores, stars					0.178					0.023
≤6	22	0.91 (0.87, 0.96)	79.5	<0.001		11	0.90 (0.86, 0.94)	0.0	0.655	
>6	18	0.89 (0.83, 0.96)	92.7	<0.001		6	0.83 (0.71, 0.98)	96.4	<0.001	

[1] *n* represents the number of estimates in the subgroup analysis. CVD, cardiovascular disease; P_h, *P*-heterogeneity; 25(OH)D, 25-hydroxyvitamin D.
[2] P_h values were for heterogeneity within a subgroup.
[3] P_h values were for heterogeneity between subgroups with the use of meta-regression.
[4] The 8 adjusted variables were sex, age, smoke, blood pressure or history of hypertension, season of blood draw, diabetes, BMI, and physical activity.

Newcastle-Ottawa scale, we considered 0–3, 4–5, and 6–9 stars to be low-, middle-, and high-quality studies, respectively.

Because most of the data we examined were published with the use of different cutoffs of 25(OH)D, we performed a dose-response meta-analysis by using the method proposed by Greenland and Longnecker (34). First, specific linear trends and 95% CIs were estimated from the natural logs of RRs across categories of serum 25(OH)D by the generalized least-square models method. Then, we conducted a random-effects model analysis to examine linear trends (35). The dose-response outcomes were presented per 10-ng/mL (25 nmol/L) increment in serum 25(OH)D in the forest plots. In addition, we assessed the potential nonlinear association between serum 25(OH)D and CVD by using restricted cubic splines with 3 knots (36). For dose-response analysis, this required ≥3 quantitative categories of use. We needed specific data for each category of serum 25(OH)D in all records, including the number of cases and total participants or person-years, RRs and CIs, and median or mean doses. For the studies that did not present the median or mean doses of serum 25(OH)D, we chose the midpoint of each category as the alternative. If the category was open-ended, the midpoint of this category was calculated by assuming the interval was the same as that of the adjacent interval. When the numbers of cases or participants in each category were not available, the number was inferred on the basis of the total number and RRs of each category (37).

I^2 statistics were used to estimate the potential heterogeneity between studies (38). If there was no evidence of between-study heterogeneity, a fixed-effects model was used to recalculate the combined RRs. In addition, we explored the source of heterogeneity by subgroup and meta-regression analyses. Studies were stratified by duration of follow-up; mean age of participants; numbers of cases; numbers of adjusted important risk factors including sex, age, smoke, blood pressure or history of hypertension, season of blood draw, diabetes, BMI, and physical activity; and study quality. We performed a sensitivity analysis by omitting 1 study at a time to assess the effectiveness of individual studies on the pooled RRs and the robustness of the pooled RRs. Heterogeneity was confirmed with a significance of $P \leq 0.10$. The possibility of publication bias in the included studies was evaluated by using visual inspection of a funnel plot, Begg's test, and Egger's test. We also used the trim-and-fill method (39) as a sensitivity analysis to explore the potential effects of unidentified studies on the results.

The primary endpoints of the analysis were total CVD events and CVD mortality. If the same cohort presented RRs of IHD/MI, stroke, HF, and composite CVD, we used the composite CVD result in the meta-analysis of total CVD events. In the case of unreported composite results, the specific outcomes of IHD/MI, stroke, and HF were combined in the meta-analysis as separate outcomes. In cases in which a study reported incident CVD and CVD mortality, we extracted the RRs of incident CVD in the analysis of total CVD events. All of the analyses were performed by using STATA software (version 12.0; StataCorp), and significance was defined as $P < 0.05$ with the use of a 2-sided test unless otherwise specified.

RESULTS

Literature research and study characteristics

By using the previously mentioned literature search strategy, a total of 1470 records were identified after duplicates had been removed. Through screening of the title and abstract, we retrieved

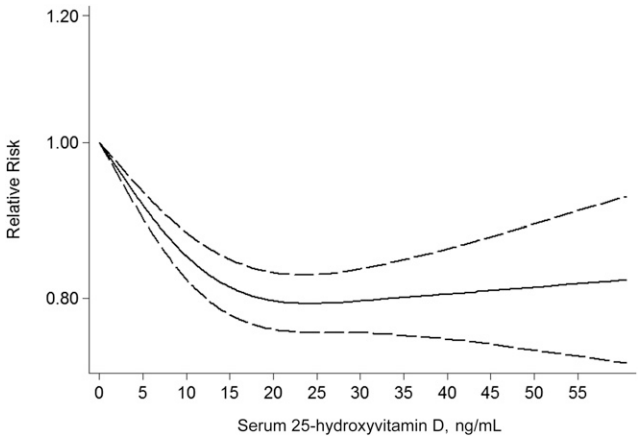

FIGURE 2 Dose-response analysis between serum 25-hydroxyvitamin D and the relative risk of total cardiovascular events. The solid line represents point estimates of the association of serum 25-hydroxyvitamin D and total cardiovascular disease risk with the use of a restricted cubic splines model, and the dashed lines indicate 95% CIs.

157 records for their full text, of which 34 were ultimately included in our meta-analysis. Details of exclusions are shown in **Supplemental Figure 1**.

The total number of participants in the included studies was 180,667, which included 9170 CVD deaths, 7074 MI or IHD cases, 3127 stroke cases, and 3037 HF cases. The results of the 34 eligible articles were derived from 27 cohorts; 8 of these articles reported >1 CVD outcomes. Among the included studies, 3 used a nested case-control design, 4 studies used a case-cohort design, and the remaining studies were all prospective cohort studies. Apart from 2 studies conducted in Asia, most were conducted in Europe and United States, with 18 and 14 studies, respectively. The participants in 2 studies were white, and 2 studies were conducted in multiethnic populations. In most of the studies, the mean age of participants was >50 y. The proportion of males was 49.5%. The number of participants in the identified studies ranged from 312 to 27,686, and cases of CVD outcomes ranged from 25 to 4514. The maximal duration of follow-up was >32 y, with the minimum follow-up being 1.3 y. Eighty-five percent of the included studies were of high quality. The extracted information is summarized in **Table 1**.

Serum 25(OH)D and the risk of total CVD events

Among the included studies, 32 were publications (27 independent studies) designed to evaluate the linear dose-response

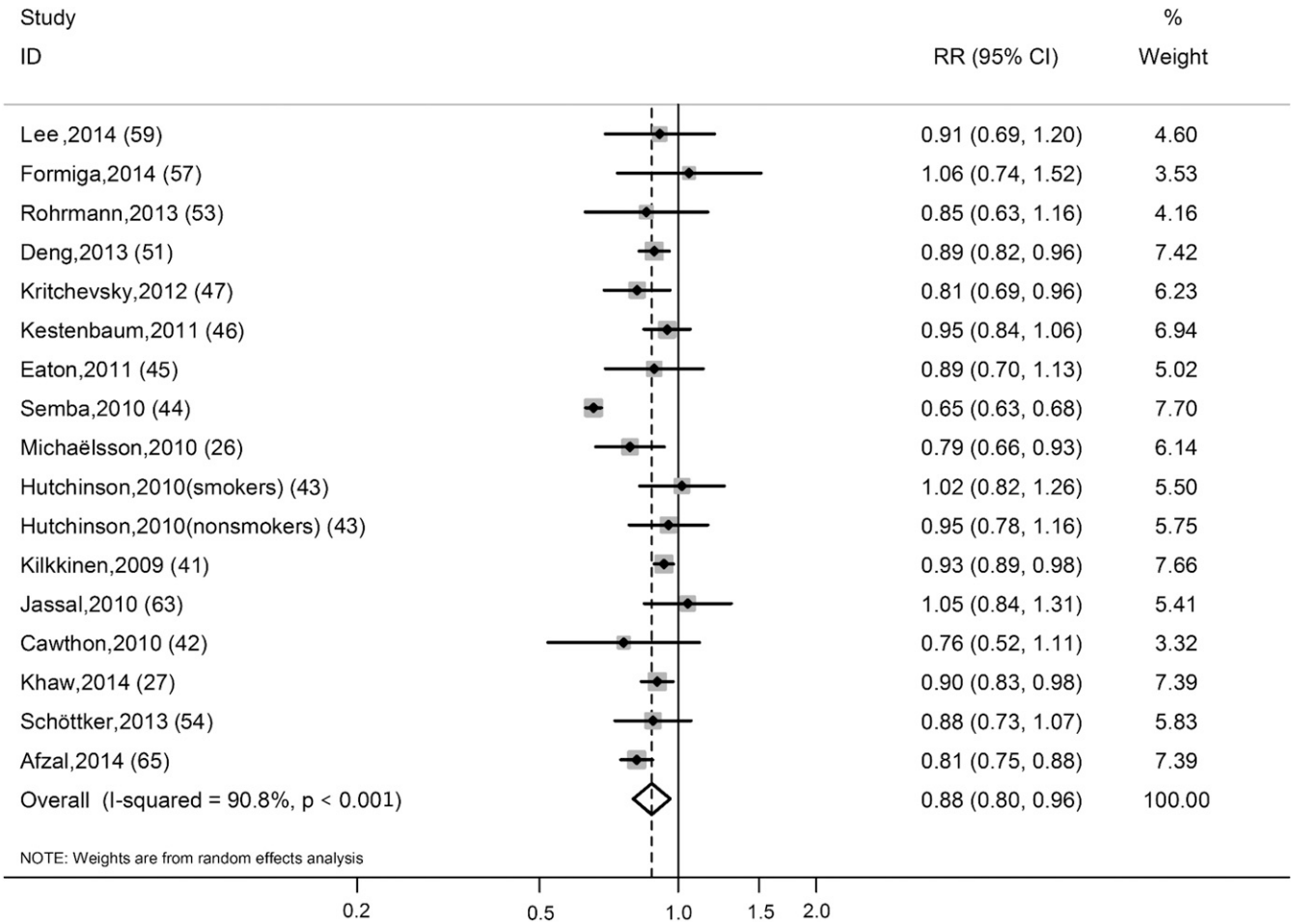

FIGURE 3 Forest plot showing the pooled effects of serum 25-hydroxyvitamin D on the risk of cardiovascular mortality with use of the random-effects model (RR: 0.87; 95% CI: 0.80, 0.95), which includes 17 studies (18 estimates). The pooled effects are shown for 10-ng/mL increments in serum 25-hydroxyvitamin D. Solid diamonds and horizontal lines represent RRs (95% CIs) for the outcome of interest. Solid circles and horizontal lines represent RRs (95% CIs); the gray boxes reflect the statistical weight of the study. The dotted vertical line denotes the point estimate for the pooled RRs and the solid vertical line indicates the line of no effect. The open diamond represents the pooled RR with its 95% CI.

relation after excluding the 2 studies that reported on CVD mortality from the same cohort (42, 54). The estimated specific linear trends of identified studies between serum 25(OH)D and total CVD events are summarized in **Figure 1**. The pooled RR per 10-ng/mL increment from the random-effects dose-response model indicated an inverse association between vitamin D status and total CVD events (RR: 0.90; 95% CI: 0.86, 0.94), with high heterogeneity ($Q = 414.95$, $I^2 = 90.6\%$; P-heterogeneity < 0.001). To address the main source of heterogeneity, we implemented subgroup analyses according to prespecified characteristics, and significant evidence of heterogeneity was shown between subsets stratified by duration of follow-up and number of adjusted variables by the method of meta-regression (**Table 2**). The relation between serum 25(OH)D and total CVD events showed nonlinearity with the use of a restricted cubic model (P-nonlinear < 0.001) (**Figure 2**). The risk of total CVD events was lower when serum 25(OH)D was >25 ng/mL.

There was no evidence of publication bias on the basis of visual inspection by the funnel plot (**Supplemental Figure 2**) or Begg's or Egger's test ($P = 0.415$ and 0.590, respectively). In a sensitivity test that omitted one study each time to obtain the pooled RRs from the random-effects model, the RRs all suggested an inverse association between serum 25(OH)D and total CVD events, with little variation (data not shown). Using the trim-and-fill method, the pooled RR incorporating 2 hypothetical studies was almost unchanged (RR: 0.90; 95% CI: 0.85, 0.93).

Serum 25(OH)D and CVD mortality

A total of 17 publications (17 independent studies) were published that used RRs and 95% CIs for ≥3 categories or with the original dose-response data. By using the method proposed by Greenland and Longnecker (34), the linear trends for each specific study were calculated. The pooled RR was $0.88 \cdot 10\ ng^{-1} \cdot mL^{-1}$ (95% CI: 0.80, $0.96 \cdot 10\ ng^{-1} \cdot mL^{-1}$) increment, with substantial heterogeneity ($I^2 = 90.8\%$). The forest plot in **Figure 3** shows that 1 estimate [Semba, 2010 (44)] deviated from the other values and had the highest weight, and we inferred that it might be the source of high heterogeneity. After removing this study (44), the I^2 dramatically decreased to 17.6% and yielded a slightly different RR (RR: 0.90; 95% CI: 0.86, 0.93). In addition, subgroup analyses showed no significant associations between serum 25(OH)D and CVD mortality in participants aged >65 y and in studies with ≤200 cases and a duration of follow-up <5 y (Table 2). We noted that in other subsets inverse associations were detected. **Figure 4** shows a nonlinear relation between serum 25 (OH)D and CVD mortality ($P = 0.022$).

There was no indication of publication bias when evaluated by Begg's test ($P = 0.303$) and Egger's test ($P = 0.117$). The funnel plot is shown in **Supplemental Figure 3**. A sensitivity analysis was conducted, and the RRs did not show substantial changes when omitting one study at a time (data not shown) or when using the technique of trim-and-fill (RR: 0.85; 95% CI: 0.78, 0.93).

DISCUSSION

This dose-response meta-analysis, which was based on general populations, suggested a significant inverse relation between baseline serum 25(OH)D and total CVD events as well as CVD mortality. Because of the considerable heterogeneity, the results should be interpreted with caution. Furthermore, there was evidence of a nonlinear association between serum 25(OH)D concentration and total CVD events and CVD mortality.

The results of our meta-analysis are consistent with those of a previous meta-analysis (30), which showed an inverse association between serum 25(OH)D and total CVD events. However, Wang et al. (30), in their meta-analysis of 10 prospective studies, suggested a 7% lower risk of total CVD events per 10-ng/mL increment, whereas in the present meta-analysis there was a 10% lower risk. The small differences are probably due to 2 reasons: the previous study included patients recruited from the hospital, which may have influenced participant characteristics, and the present meta-analysis identified studies related to HF. However, HF is a disease entity with substantial heterogeneity in etiology. We included HF in our meta-analysis as one of the endpoints because it is one of the major CVDs, with a relatively high prevalence (1–2%) (67) and important clinical implications (67, 68). Furthermore, HF was defined as one of the composite CVD events in several included studies (10, 26, 27, 54). Of note, the pooled RR did not materially change after we excluded HF from the analyses (RR: 0.90; 95% CI: 0.86, 0.94). For nonlinear analysis, both studies found that at a 25(OH)D concentration of ~25 ng/mL, the RR of total CVD events was lowest. Above that concentration, the RR did not decrease significantly. Nevertheless, serum 25(OH)D may be confounded by the type of assay. For example, immune and mass spectrometric methods give different results. Still, defining a threshold of serum 25(OH)D in relation to the risk of total CVD events was an important finding.

For CVD, the leading cause of death worldwide (69), a recent large observational study found that low and high concentrations of 25(OH)D were related to CVD mortality and that the HRs were higher at low concentrations than at high concentrations, in a reverse J-shaped manner (25). In this cohort, Durup et al. (25) suggested that the concentration of 28 ng/mL was linked to the lowest risk of CVD mortality. There was some discrepancy in the results for high concentrations of 25(OH)D, primarily because there were insufficient data for high concentrations, especially for serum 25(OH)D >40 ng/mL, which might also reflect assay differences. Even in this large observational cohort, only 5% of

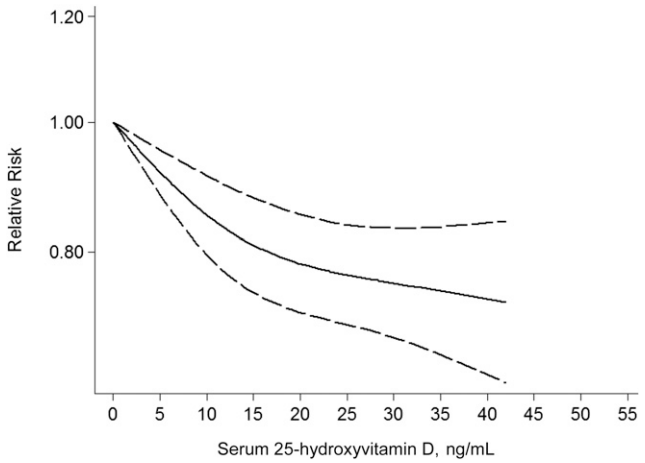

FIGURE 4 Dose-response analysis between serum 25-hydroxyvitamin D and the relative risk of cardiovascular mortality. The solid line represents point estimates of the association of serum 25-hydroxyvitamin D and cardiovascular mortality with the use of a restricted cubic splines model, and the dashed lines indicate 95% CIs.

participants had serum 25(OH)D concentrations >40 ng/mL. Contrary to the uncertainty shown for higher concentrations, the majority of related publications (15, 44, 51, 70) showed that the lower extreme concentration of serum 25(OH)D was associated with a higher risk of CVD mortality.

A protective effect of higher baseline serum 25(OH)D on total CVD events and CVD mortality was detected in our meta-analysis. Although the exact mechanism of the association between 25(OH)D and CVD is not known, experimental studies have indicated a regulatory effect of vitamin D on cardiomyocytes and vascular smooth muscle cells (71). In addition, decreased serum 25(OH)D will activate the renin angiotensin system, consequently increasing blood pressure (72). Furthermore, it was reported that vitamin D has anti-inflammatory actions, which play an important role in atherogenesis (71, 73, 74). Vitamin D also inhibits certain matrix metalloproteinases (MMPs) that are important in plaque instability and that are known to increase in MI, notably MMP-9 and MMP-2 (75). However, the majority of results from randomized vitamin D therapy trials failed to support the protective effects against CVD (76). We should note that most randomized vitamin D trials were designed to examine the effect on the skeleton and participants were mostly women and older (73). Well-designed randomized clinical trials are needed to explore the causality of the correlation between vitamin D and CVD, especially if carried out early in the natural history of CVD.

Our meta-analysis has several strengths. First, compared with previous meta-analyses, more comprehensive outcomes were evaluated in this study, including MI or IHD, stroke, HF, and CVD mortality. For total CVD events and CVD mortality, we performed separate dose-response meta-analyses. Moreover, the included studies were all population-based studies and hospital-based studies were excluded. We were therefore more confident to extend the results to the general population. In addition, serum 25(OH)D is the main biomarker for assessing vitamin D status (77). Laboratory measurements of serum 25(OH)D are more objective than measurements of dietary vitamin D intake (78). In this meta-analysis, we used serum 25(OH)D as a measure of exposure. Furthermore, to rule out recall and selection bias, case-control studies were not eligible. Finally, the sample sizes of participants and cases were large and therefore the RR data from this study were more robust.

Several potential limitations of this meta-analysis should be mentioned. First, as with any observational study, residual confounding cannot be excluded. Nevertheless, most of the results of the identified studies were adjusted for recognized risk factors of CVD (smoke, hypertension, diabetes, BMI, physical activity). In most situations, different confounders were considered in the identified studies and the results with the largest number of adjusted covariates were chosen. Second, the number of participants with high concentrations of serum 25(OH)D was small. Third, the association between 25(OH)D concentration and CVD may be confounded by assay variations across studies, especially because most of the studies did not report the use of quality assessment schemes. In consequence, the threshold of low risk should be considered with caution. Fourth, publication bias is inevitable in any meta-analysis, although it was not shown from the funnel plot. Finally, high heterogeneity was apparent in this meta-analysis, which may have been due to differences in duration of follow-up, number of adjusted risk factors, and quality of studies.

In conclusion, the present meta-analysis showed that higher serum 25(OH)D concentrations had a protective effect on total CVD events and CVD mortality. Furthermore, the dose-response analysis showed a J-shaped association between serum 25(OH)D and total CVD events. Well-designed randomized vitamin D therapy trials are needed to confirm the role of vitamin D in preventing overt CVD, as well as to define optimal vitamin D status for a reduction in overall CVD risk.

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The authors' responsibilities were as follows—RZ and GL: designed the research; BL and RT: extracted the data; RZ, XG, and YP: analyzed and interpreted the data; RZ: drafted the manuscript; XG, YP, YJ, HG, Yilong Wang, and Yongjun Wang: revised the manuscript for important intellectual content; RZ: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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