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 (y)	Ex-smokers	n.68	72(9jTd[(Gio)19188)Tj/T1_1	24.1053--0-577((HPFS))]T.4cha	1.251.917888002.5651

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

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

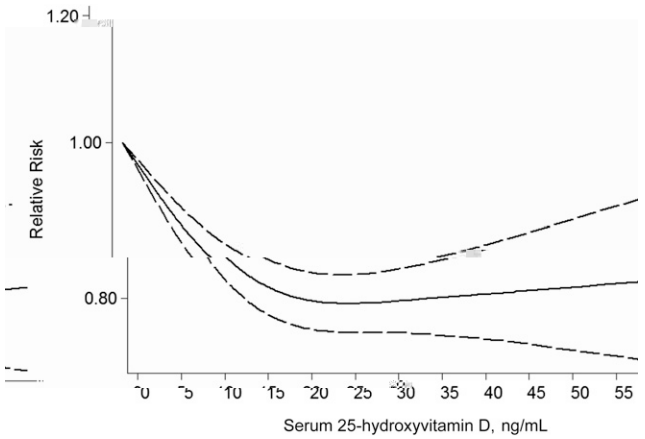

FIGURE 2 Dose-response analysis between serum 25-hydroxyvitamin D and the relative risk of total cardiovascular events. The solid line represents point estimates of the association of serum 25-hydroxyvitamin D and total cardiovascular disease risk with the use of a restricted cubic splines model, and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

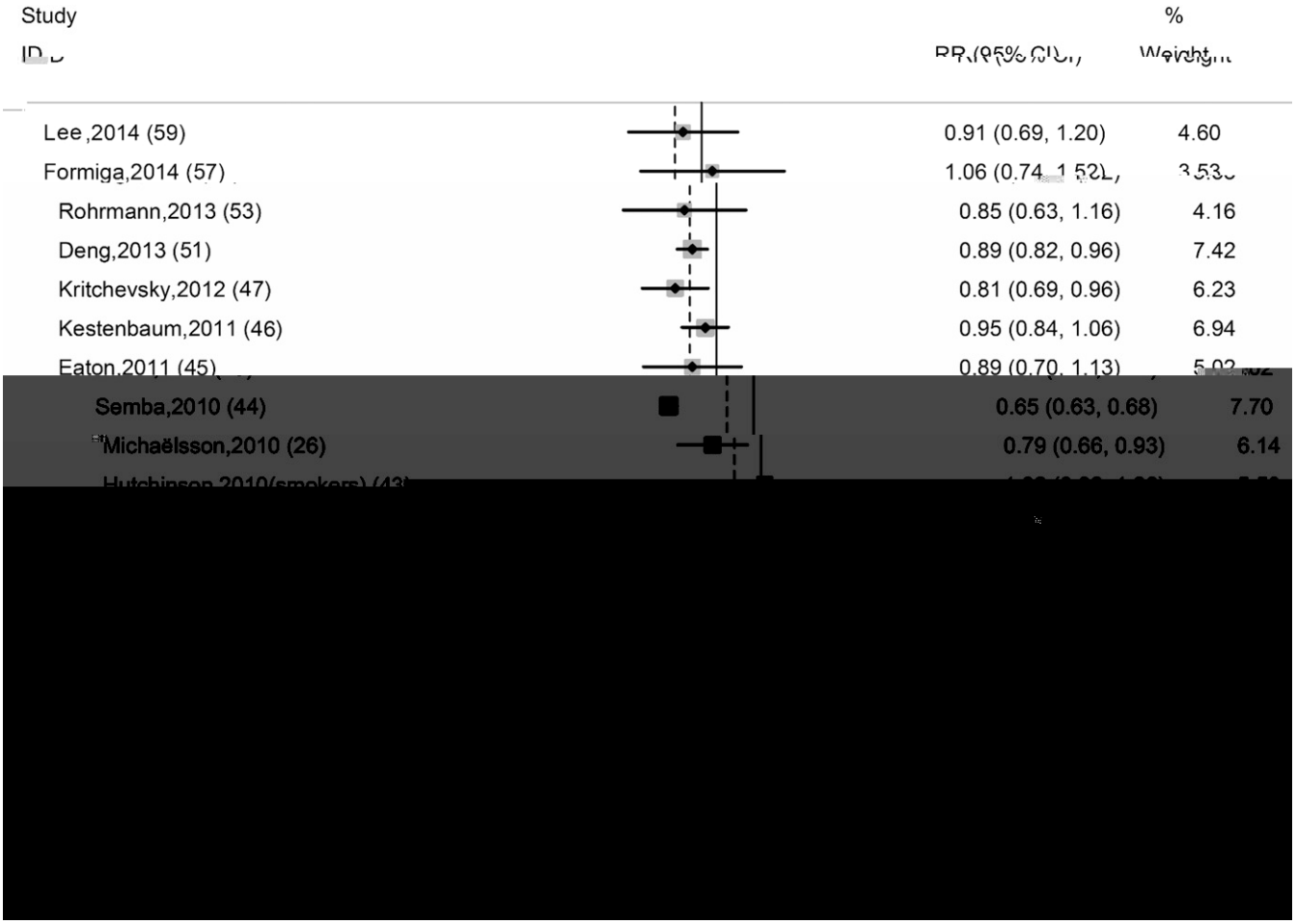

FIGURE 3 Forest plot showing the pooled effects of serum 25-hydroxyvitamin D on the risk of cardiovascular mortality with use of the random-effects model (RR: 0.87; 95% CI: 0.80, 0.95), which includes 17 studies (18 estimates). The pooled effects are shown for 10-ng/mL increments in serum 25-hydroxyvitamin 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 $0.88 \cdot 10\,ng^{21} \cdot mL^{21}$ (95% CI: 0.80, $0.96 \cdot 10\,ng^{21} \cdot mL^{21}$) 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 ($P = 0.022$).

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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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