

Vitamin D and Multiple Health Outcomes: An Umbrella Review of Observational Studies, Randomized Controlled Trials, and Mendelian Randomization Studies

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ABSTRACT

Observational studies, randomized controlled trials (RCTs), and Mendelian randomization (MR) studies have yielded inconsistent results on the associations of vitamin D concentrations with multiple health outcomes. In the present umbrella review we aimed to evaluate the effects of low vitamin D concentrations and vitamin D supplementation on multiple health outcomes. We summarized current evidence obtained from meta-analyses of observational studies that examined associations between vitamin D concentrations and multiple health outcomes, meta-analyses of RCTs that investigated the effect of vitamin D supplementation on multiple health outcomes, and MR studies that explored the causal associations of vitamin D concentrations with various diseases (international prospective register of systematic reviews PROSPERO registration number CRD42018091434). A total of 296 meta-analyses of observational studies comprising 111 unique outcomes, 139 meta-analyses of RCTs comprising 46 unique outcomes, and 73 MR studies comprising 43 unique outcomes were included in the present umbrella review. Twenty-eight disease outcomes were identified by both meta-analyses of observational studies and MR studies. Seventeen of these reported disease outcomes had consistent results, demonstrating that lower concentrations of vitamin D were associated with a higher risk for all-cause mortality, Alzheimer's disease, hypertension, schizophrenia, and type 2 diabetes. The combinations of consistent evidence obtained by meta-analyses of observational studies and MR studies together with meta-analyses of RCTs showed that vitamin D supplementation was associated with a decreased risk for all-cause mortality but not associated with the risk for Alzheimer's disease, hypertension, schizophrenia, or type 2 diabetes. The results indicated that vitamin D supplementation is a promising strategy with long-term preventive effects on multiple chronic diseases and thus has the potential to decrease all-cause mortality. However, the current vitamin D supplementation strategy might not be an efficient intervention approach for these diseases, suggesting that new strategies are highly needed to improve the intervention outcomes. *Adv Nutr* 2022;13:1044–1062.

Statement of Significance: No previous systematic effort, to our knowledge, has been made to summarize and appraise evidence obtained in meta-analyses of observational studies, meta-analyses of RCTs, and MR studies on associations of vitamin D concentrations with a range of disease outcomes. This umbrella review takes advantage of the respective strengths of meta-analyses of observational studies, meta-analyses of RCTs, and MR studies by combining and comparing the findings to explore the potential importance of vitamin D in detail and to assess the implications for clinical practice and public health.

Keywords: umbrella review, vitamin D deficiency, vitamin D supplementation, meta-analysis, multiple health outcomes, observational studies, randomized controlled trials, Mendelian randomization studies

Introduction

Vitamin D deficiency is one of the most common health problems worldwide, resulting in poor musculoskeletal

health and a range of acute and chronic diseases, such as infectious diseases, pneumonia, cancer, metabolic disorders, cardiovascular disease (CVD), and mortality (1, 2).

Additionally, vitamin D supplementation appears to be associated with a decreased risk for several common diseases (i.e., infectious diseases, asthma, cancer, and CVD) and lower all-cause mortality in randomized controlled trials (RCTs) (3–7). Previous studies exploring the associations of vitamin D concentrations with multiple outcomes were biased by many confounding variables, and the observed associations may not be causal (8, 9). Therefore, causality and the direction of associations between vitamin D concentrations and disease outcomes to date remain uncertain.

Genetic data may partially address the limitations of confounding and reverse causality and provide more convincing evidence to explain the underlying causal effects known as Mendelian randomization (MR) (10–12). An MR study exploited natural randomization of genetic variants and prospective design involving exposed genetic variants to provide insight into disease pathogenesis based on observational data (13). Certain genetic variants, which are robustly associated with risk factors but are not associated with confounders, can be used as instrumental variables (IVs) in causal inferences. However, the accumulated results of MR studies have demonstrated that vitamin D deficiency-related genetic risk factors do not predict disease risk (14–19).

RCTs are designed to explore a causal effect of an intervention on a disease; however, the small sample size, limited external validity, short duration of an intervention, and ethical concerns limit the implementation of RCTs. Observational studies are relatively less work than MR studies or RCTs; however, the results provide weak inference of causality due to residual confounding bias, reverse causality, or undetected bias. MR studies, with evidence at the interface between observational studies and RCTs (20), are less susceptible to confounding bias and reverse causality but are restricted by potentially weak IVs and genetic pleiotropy. The 3 types of studies have specific advantages and disadvantages that can complement each other to some extent (21). The present study combined the summary estimates for identical outcomes of observational studies and MR studies. The consistency of these estimates between observational studies and MR studies was tested to provide evidence of statistically significant differences (22, 23). If the results of observational studies and MR studies are consistent, the findings can be

combined and compared with the findings of RCTs. The present study made a tradeoff between the effects of vitamin D deficiency and vitamin D supplementation on the diseases to outline the applications and clinical practices related to vitamin D as a causal factor or an intervention factor.

An umbrella review (21, 24, 25) is a popular method for the systematic assessment of evidence from multiple sources and may help in the evaluation of potential biases in associations of exposure with outcome. Therefore, our umbrella review aimed to provide a comprehensive synopsis of associations of low vitamin D concentrations and vitamin D supplementation with multiple outcomes by combining the results of meta-analyses of observational studies, meta-analyses of RCTs, and MR studies.

Methods

This umbrella review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42018091434.

The umbrella review protocol was designed on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (26). The present umbrella review included meta-analyses of observational studies on associations of vitamin D concentration with disease outcomes, meta-analyses of RCTs on associations of vitamin D supplementation with disease outcomes, and MR studies on causal associations of vitamin D concentration with disease outcomes. The results of MR studies and meta-analyses of observational studies or RCTs were combined whenever the data were available for identical disease outcomes. The study design is presented in **Figure 1**.

Search and eligibility criteria

Based on the search strategy, we identified meta-analyses of observational studies, meta-analyses of RCTs, and MR studies by searching the Cochrane, Embase, and PubMed databases from inception to May 2019. The literature search was limited to English language studies involving humans. The search strategy is presented in detail in **Supplemental Table 1**. Initially, 2 authors of the present study (QT and XM) screened the titles and abstracts of the literature and then reviewed the full text of eligible studies. The detailed process for the present umbrella review is presented in a schematic flowchart in **Figure 2**. Points of divergence were resolved by discussion among 3 authors of the present study (DL, XM, and QT).

We included meta-analyses of observational studies exploring the associations of vitamin D concentration with diseases, meta-analyses of RCTs investigating the effects of vitamin D supplementation on diseases (≥ 1 intervention of vitamin D compared with either placebo or no vitamin D supplementation), and MR studies investigating causal associations of vitamin D concentration with diseases using vitamin D-related genetic instruments. Only formal quantitative meta-analyses or MR studies were considered. Studies exploring the associations between multiple micronutrient supplements (including vitamin D) and various disease

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Supplemental Figures 1–2 and Supplemental Tables 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Abbreviations used: 25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CVD, cardiovascular disease; IVs, instrumental variables; MR, Mendelian randomization; PI, prediction interval; PRISMA, Preferred Reporting Items of Systematic Reviews and Meta-analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized controlled trial; ROBIS, Risk of Bias in Systematic Reviews.

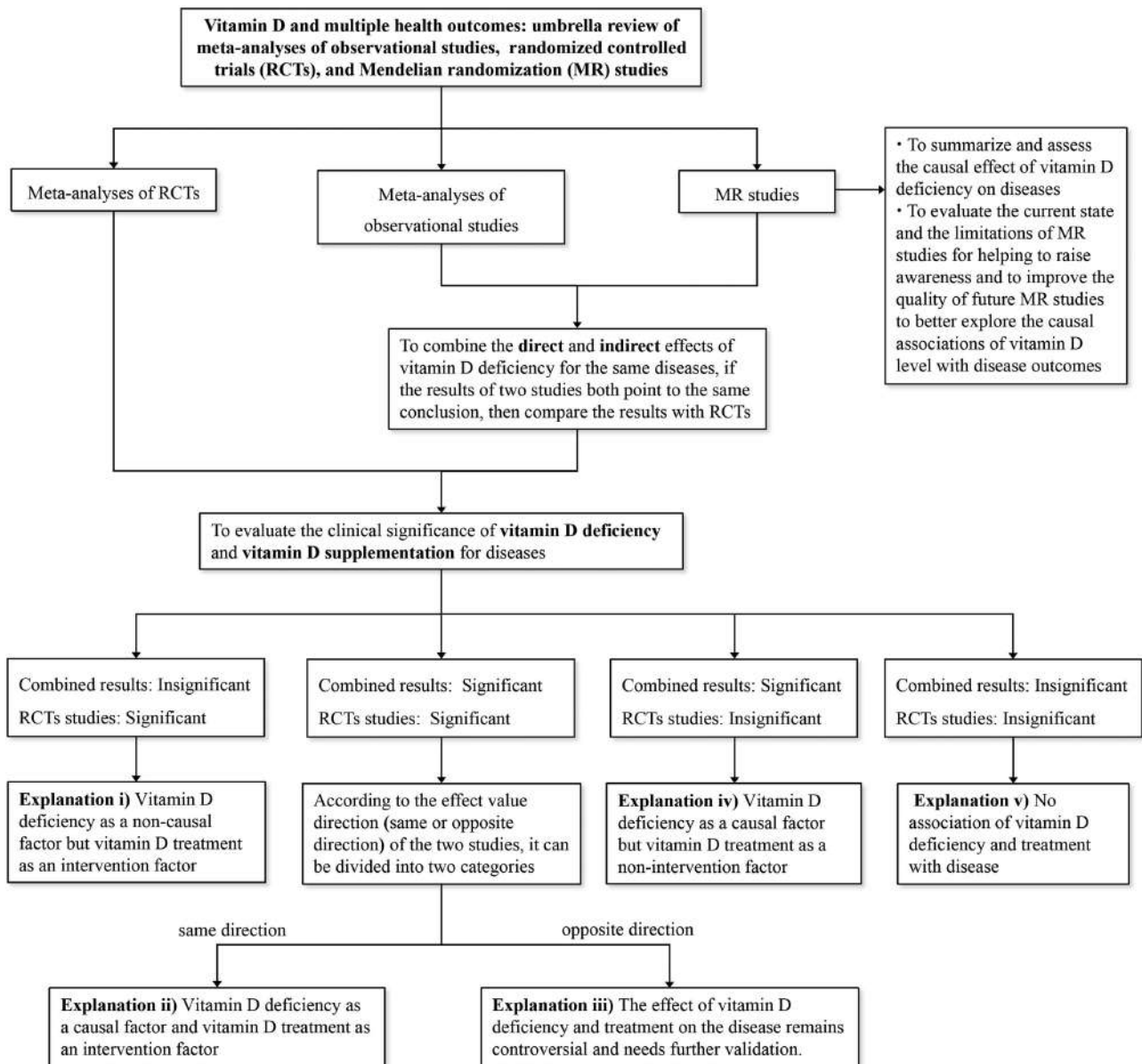


FIGURE 1 Flow diagram of the selection process. MR, Mendelian randomization; RCT, randomized controlled trial.

outcomes, systematic reviews or meta-analyses of genetic factors related to vitamin D, studies published in languages other than English, systematic reviews without quantitative assessments, reports containing only an abstract or meeting reports without original data, meta-analyses of observational studies, and RCTs that mainly involved investigations of the effects of a reduction in vitamin D concentration rather than focusing on the effects of vitamin D concentration or vitamin D supplementation on various diseases were further excluded.

Data extraction

Two researchers (QT and XM) were responsible for the extraction of the data, and the third author (DL) verified the data. Included studies were subsequently assessed by 2

authors of the present study (YW and MS) for accuracy and completeness of available information.

We extracted the name of the first author, publication year, study population, study design, vitamin D measurements, number of included studies, number of included participants, number of cases, and investigated diseases from all eligible publications. Depending on 3 specific study types, we further extracted study-specific risk estimates (OR, RR, HR, or regression coefficient β together with their 95% CI) and evaluated the heterogeneity of the studies using the I^2 metric. If a meta-analysis presented both overall results and subgroup results, only the overall results were extracted because of the larger sample size. If a publication reported separate meta-analyses for >1 disease, all diseases were assessed separately. If more than a single meta-analysis

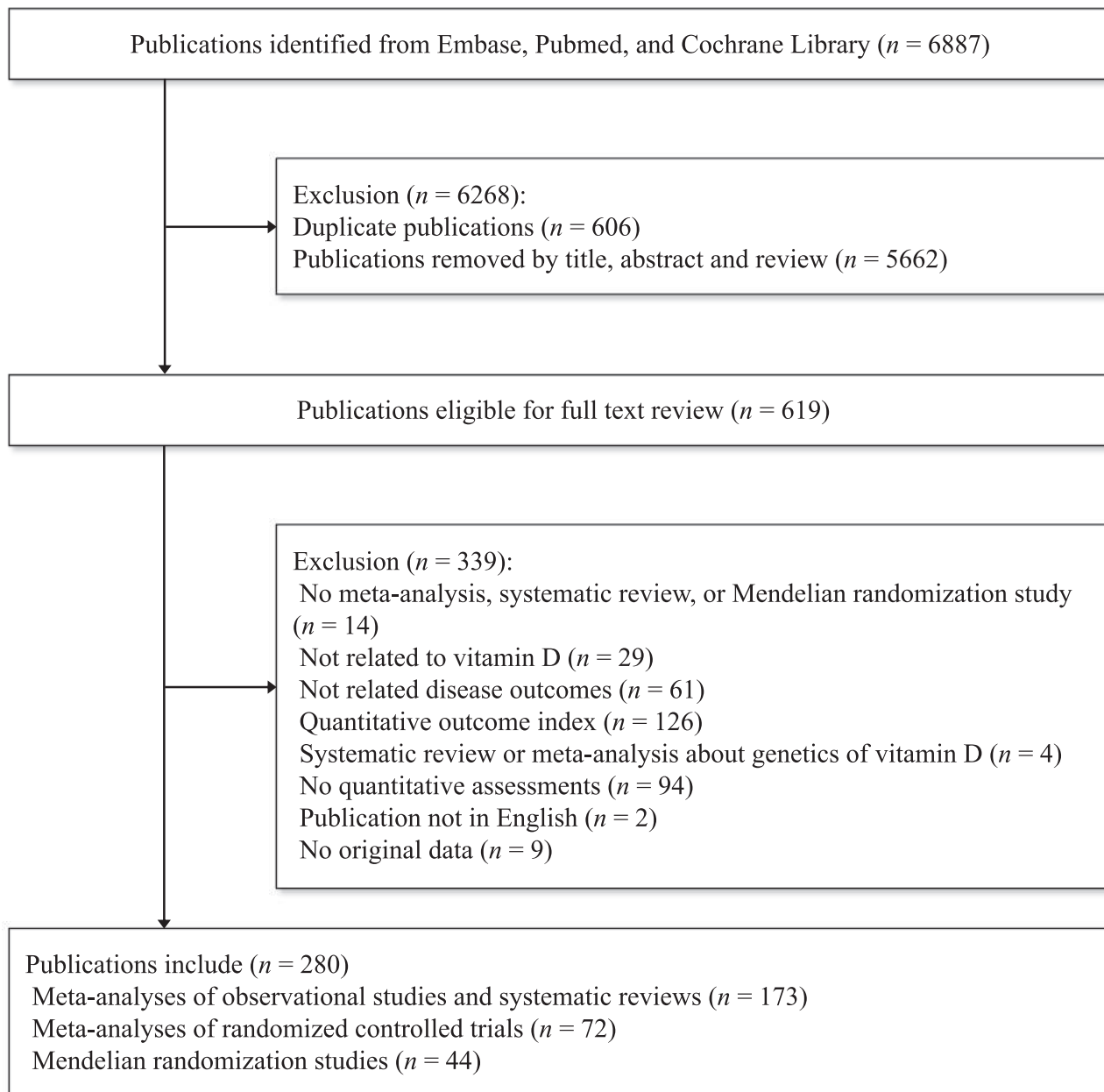


FIGURE 2 Flow chart of the study design.

reported an identical disease in the same population, the results of the largest and most recent study were extracted. In the case of MR studies of identical diseases and populations, we extracted the data corresponding to the largest number of cases and participants. Finally, we assessed the consistency of the findings based on the effects and levels of statistical significance/direction of the reported association for each disease. For MR studies, the data on genetic instruments and the proportion of the variance of a risk factor explained by genetic instruments (percentage explained, R^2) were extracted.

Statistical analysis

The 95% prediction interval (PI) was calculated to assess the effect and uncertainty for an expected effect in a new original study (27, 28), which was estimated based on a parametric bootstrap for confidence distribution (R version 4.0.1, R packages: “pimeta”) (29). The I^2 metric was used to evaluate the heterogeneity; $I^2 > 50\%$ was assumed to correspond to high heterogeneity with potential bias. Two measures of publication bias, small study effect and excess significance bias, were calculated (R packages: “meta,” “powerAnalysis” and “pwr”), with $P < 0.10$ considered to be the result

of publication bias (30–32). The small study effect was estimated using Egger's test. The chi-squared test was applied to estimate the excess statistical significance bias of nominally significant results [if observed (O) number > expected (E) number]. For MR studies, the noncentrality parameter-based approach was used to estimate the power of MR studies (33). Statistical power calculations were based on the sample size, a type I error rate (α) of 0.05, proportion of cases in a study, risk estimates (e.g., OR), and R^2 and were performed using the online tool mRnd (<https://shiny.cnsgenomics.com/mRnd/>).

Furthermore, if the data were available for the same disease the findings of meta-analyses of observational studies and MR studies were combined by using tests for the differences and tests for consistency of the estimates (22, 23). The present study used random-effects models based on a normal distribution. Many parameters were not normally distributed; therefore, we transformed these parameters into log-scales that resulted in an approximately normal distribution, and these transformed values were used in subsequent analyses. Rejection of the null hypothesis (at a significance level of 0.05) indicated that risk estimates in meta-analyses of observational studies and MR studies were inconsistent. If obvious inconsistencies were not detected, the findings of meta-analyses of observational studies and MR studies were combined, and random-effects models were used to account for heterogeneity. We then combined and compared prior results of meta-analyses of observational studies and MR studies to assess the level of consistency with the data of meta-analyses of RCTs. If the statistical significance levels of the estimates provided by meta-analyses of observational studies and MR studies were inconsistent, we reported the results of the MR studies, which limited the bias due to confounding and reverse causality. Overall, the results of observational studies, MR studies, and RCTs exploring associations of low vitamin D concentrations and vitamin D supplementation with the same disease were divided into 5 categories based on the effects and level of statistical significance/direction, as shown in detail in Figure 1.

Evaluation of the quality of evidence

We next assessed the epidemiologic credibility of the 3 types of studies. Meta-analyses of observational studies were divided into 4 classes based on the level of evidence: convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) (21). The level of evidence was rated as convincing for studies that were characterized by the following features: a statistical significance level of $P < 10^{-6}$, > 1000 cases, a significant result at $P < 0.05$ reported for the study with the largest sample size in the meta-analysis, a 95% PI that excluded the null, a low heterogeneity ($I^2 < 50\%$), no evidence of small-study effects ($P > 0.10$), and no evidence of excess significance bias ($P > 0.10$). Highly suggestive evidence for studies was characterized by the following features: a statistical significance level of $P < 10^{-6}$, > 1000 cases, and a significant result at $P < 0.05$ reported for the study with the largest sample size in the meta-analysis.

Suggestive evidence for studies was characterized by the following features: a statistical significance level of $P < 10^{-3}$ and > 1000 cases. The level of evidence was rated as weak for studies that were characterized by the following feature: a statistical significance level of $P < 0.05$. The level of evidence for meta-analyses of RCTs was evaluated according to the level of statistical significance, 95% PI, I^2 , small-study effect bias, and excess significance bias. Additionally, the level of evidence of MR studies was evaluated based on statistical significance and statistical power (34).

Risk of bias assessment

We further assessed the methodological quality of the each included meta-analysis using the Risk of Bias in Systematic Reviews (ROBIS) tool (35). In brief, 4 domains of ROBIS were evaluated separately: 1) study eligibility criteria, 2) identification and selection of studies, 3) data collection and study appraisal, and 4) synthesis and findings, and then concerns about risk of bias of the domains were judged (35). Finally, an overall judgment of risk of bias was made for each meta-analysis, rated as low, high, or unclear risk of bias. Three authors (DL, XM, and QT) assessed the risk of bias of each meta-analysis independently. Any discrepancies were identified and resolved by discussion.

Results

Literature review

A total of 6887 publications were identified across the 3 databases (Embase, PubMed, and Cochrane Database). After removing 606 duplicate publications and 5662 publications based on the title and abstract, we investigated the full text of 619 publications for eligibility. Finally, 339 publications were excluded according to the exclusion criteria, leaving 280 unique publications that met the eligibility criteria (236 publications were meta-analyses, and the remaining 44 publications were MR studies). Overall, 296 meta-analyses of observational studies including 111 unique outcomes were reported in 173 articles (36–208); 139 meta-analyses of RCTs including 46 unique outcomes were reported in 72 articles (3–7, 50, 65, 81, 120, 130, 160, 165, 167, 190, 209–266), and 73 MR studies including 43 unique outcomes were reported in 44 articles (15, 17, 18, 267–307) (Supplemental Tables 2–5). As shown in Figure 3, 13 outcomes overlapped in all 3 study types. Moreover, 28 unique outcomes overlapped in the MR studies and meta-analyses of observational studies, and 24 unique outcomes overlapped in the meta-analyses of RCTs and meta-analyses of observational studies.

Risk of bias assessments for the included meta-analyses

Risk of bias assessment of the included meta-analyses is presented in Supplemental Table 4. Most meta-analyses of observational studies and meta-analyses of RCTs ($n = 235$) were evaluated as high risk of bias, except for 1 study at low risk of bias. After removal of overlapping meta-analyses, all the included meta-analyses of observational studies ($n = 104$) were at high risk of bias, with 28 (26.9%), 75 (72.1%), 73 (70.2%), and 103 (99.0%) meta-analyses at

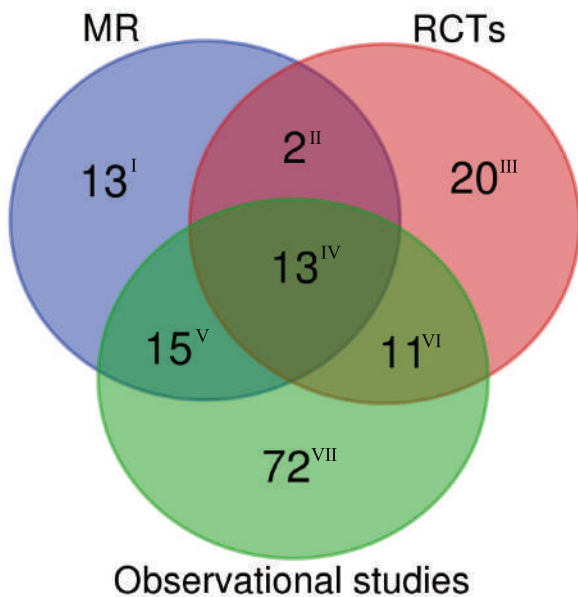


FIGURE 3 Venn diagram of meta-analyses of observational studies, meta-analyses of RCTs, and MR studies. The plot was performed by R package “VennDiagram.” The number of disease outcomes for overlapping and distinct study types is shown. I, only reported in MR studies; II, reported in MR studies and meta-analyses of RCTs; III, only reported in meta-analyses of RCTs; IV, reported in all 3 study types; V, reported in MR studies and meta-analyses of observational studies; VI, reported in meta-analyses of RCTs and meta-analyses of observational studies; VII, only reported in meta-analyses of observational studies. MR, Mendelian randomization; RCT, randomized controlled trial.

high risk in the first, second, third, and fourth domain of ROBIS, respectively (**Supplemental Figure 1, Supplemental Table 6**). Similarly, all of the included meta-analyses of RCTs ($n = 50$) were rated high risk of bias, with 11 (22.0%), 33 (66.0%), 36 (72.0%), and 47 (94.0%) of studies at high risk in the first, second, third, and fourth domain of ROBIS, respectively (**Supplemental Figure 2, Supplemental Table 7**).

Characteristics of meta-analyses of observational studies

A total of 136 unique meta-analyses remained after the removal of overlapping meta-analyses (conducted in the same population and evaluating the same outcome), and these studies reported a series of outcomes (**Supplemental Table 6**). Among these meta-analyses, 97 (71.32%) unique meta-analyses presented statistically significant summary results ($P < 0.05$). These studies included 3 (37.5%) meta-analyses for skeletal outcomes, 4 (50%) analyses for respiratory illness, 13 (43.33%) analyses for cancer diseases, 13 (100%) analyses for CVD, 5 (83.33%) analyses for diabetes-related diseases, 24 (92.31%) analyses for all-cause or cause-specific mortality, 4 (100%) analyses for neurocognitive disorders, 2 (100%) analyses for skin diseases, 3 (50%) analyses for neonatal, infant, child, or pregnancy-related

diseases, 4 (100%) analyses for mental diseases, 3 (75%) analyses for infectious diseases, and 19 (76%) analyses for other outcomes with summary estimates with $P < 0.05$, which indicated that low concentrations of vitamin D are associated with an increased risk of a disease. Additionally, 2 cancer outcomes (i.e., basal cell cancer and nonmelanoma skin cancer) had summary estimates with $P < 0.05$ and were associated with high vitamin D concentrations.

Then, we applied the evidence classification criteria described above (**Supplemental Table 6**). Eighteen (13.14%) meta-analyses had $P < 10^{-6}$, 130 (94.89%) analyses had a 95% PI that excluded the null, 72 (52.55%) analyses had >1000 cases, 64 (46.72%) analyses did not have high heterogeneity ($I^2 < 50\%$), and 34 (24.82%) analyses lacked small-study effects or excess significance bias. Based on these metrics, 3 (2.19%) outcomes presented convincing evidence (class I: hip fracture, sepsis, and sepsis in critically ill patients), 12 (8.76%) outcomes presented highly suggestive evidence, and 18 (13.14%) outcomes presented suggestive evidence. The remaining 66 (48.18%) statistically significant outcomes were assessed as weak evidence (class IV).

Characteristics of meta-analyses of RCTs

Eighty-two nonoverlapping meta-analyses (**Supplemental Table 7**) were identified for the outcomes related to all-cause or cause-specific mortality ($n = 16$); cancer diseases ($n = 7$); skeletal diseases ($n = 13$); CVD ($n = 8$); neonatal, infant, child, or pregnancy-related diseases ($n = 6$); respiratory illness ($n = 17$); and other outcomes ($n = 15$). Among 82 nonoverlapping meta-analyses, 26 meta-analyses (32.10%) reported summary results that were statistically significant at $P < 0.05$. These results included 4 (25%) meta-analyses for all-cause or cause-specific mortality; 1 (14.29%) analysis for cancer diseases; 1 (12.50%) analysis for CVD; 3 (50%) analyses for neonatal, infant, child, or pregnancy-related diseases; 12 (70.59%) analyses for respiratory illness; and 5 (33.33%) analyses for other outcomes that reported summary estimates with $P < 0.05$, suggesting that vitamin D supplementation is associated with decreased disease risk. Additionally, meta-analyses for 2 outcomes [i.e., hypercalcemia in patients with chronic kidney disease (CKD) and all-cause mortality] had summary estimates with $P < 0.05$ and suggested that vitamin D supplementation may be associated with increased disease risk.

The results of quality of evidence for meta-analyses of RCTs are showed in **Supplemental Table 7**. Overall, 28 (34.57%) meta-analyses had $P < 0.05$ (8 analyses had $P < 0.001$), 62 (76.54%) analyses had a 95% PI that excluded the null, 56 (69.14%) analyses did not have high levels of heterogeneity ($I^2 < 50\%$), and 34 (41.98%) analyses lacked small-study effects or excess significance bias. Only 4 outcomes (CVD events in predialysis CKD patients, low birth weight, pediatric asthma, and hypercalcemia in CKD patients) were characterized by $P < 0.001$, had a 95% PI excluding the null, and lacked evidence of high heterogeneity or bias.

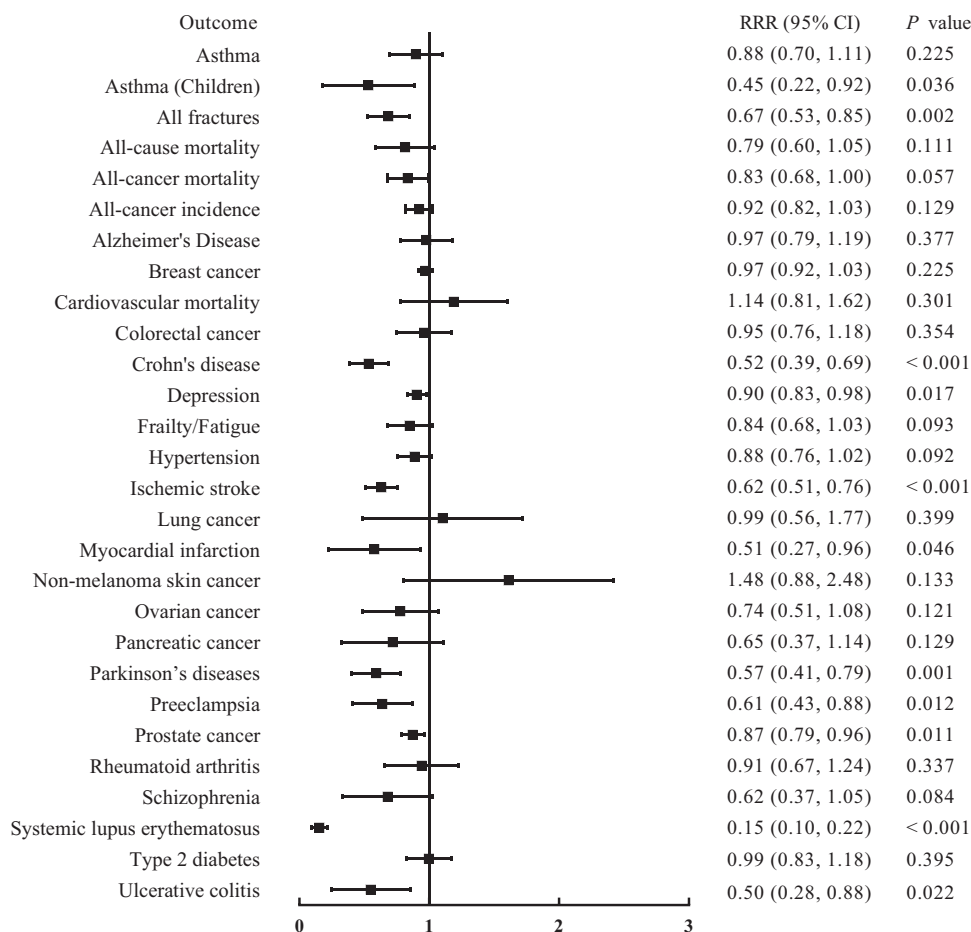


FIGURE 4 Consistency between meta-analyses of observational studies, and MR studies for the same disease outcome. *P* is the *P* value in the test for interaction. MR, Mendelian randomization; RRR, ratio of relative risks.

Characteristics of the MR studies

A total of 47 unique MR studies (**Supplemental Table 8**) were identified for the following outcomes: cardiovascular outcomes ($n = 5$), all-cause or cause-specific mortality ($n = 5$), cancer outcomes ($n = 13$), and other outcomes ($n = 24$). In total, statistically significant summary results at $P < 0.05$ were reported for 8 (17.02%) outcomes (i.e., type 2 diabetes, schizophrenia, Alzheimer's disease, multiple sclerosis, multiple sclerosis in children, hypertension, all-cause mortality, and other mortality). Notably, $P < 0.01$ was reported for 5 outcomes (hypertension, type 2 diabetes, multiple sclerosis, Alzheimer's disease, and schizophrenia), and only 4 outcomes (myocardial infarction, esophageal adenocarcinoma, fatigue/frailty, and atopic dermatitis) were characterized by power $> 80\%$.

Combination of the findings of meta-analyses of observational studies and MR studies

In contrast to the results of meta-analyses of observational studies, which demonstrated significant associations for most disease outcomes (78.57%), the results for most (82.14%) disease outcomes were not significant in the MR studies. A total of 126 outcomes were reported across these 2 study

types (i.e., meta-analyses of observational studies and MR studies); 111 outcomes were reported in meta-analyses of observational studies, 43 outcomes were reported in MR studies (some outcomes contained different subgroups, as shown in **Supplemental Table 9**), and 28 (17.72%) outcomes were assessed by both meta-analyses of observational studies and MR studies. Seventeen outcomes were not significantly different according to the results of interaction analyses testing for differences in the estimates between parallel studies ($P \geq 0.05$) (**Figure 4**). Hence, these outcomes were consistent between meta-analyses of observational studies and MR studies. The results of the present study indicated that lower concentrations of vitamin D were associated with a higher risk of all-cause mortality, Alzheimer's disease, hypertension, schizophrenia, and type 2 diabetes based on comparison of the results of meta-analyses of observational studies and MR studies, and low vitamin D concentration was not a causal risk factor for other disease outcomes (**Supplemental Table 9**).

Eleven outcomes were significantly different based on the results of the interaction analysis testing performed in the present study ($P < 0.05$), indicating that the estimates of parallel studies were different. Low vitamin D concentration

was associated with an increased risk for Crohn's disease, depression, ischemic stroke, Parkinson's disease, preeclampsia, systemic lupus erythematosus, ulcerative colitis, all fractures, and asthma (children) only according to meta-analyses of observational studies, and these results were inconsistent with the data of MR studies. Furthermore, vitamin D deficiency was not associated with the risk for lung cancer and pancreatic cancer according to meta-analyses of observational studies, and these findings were inconsistent with those in MR studies (Supplemental Table 9).

Comparison of the results for vitamin D deficiency and vitamin D supplementation

We compared the consistent results of meta-analyses of observational studies and MR studies with those of meta-analyses of RCTs; the data indicated that 7 outcomes overlapped (Table 1). Only all-cause mortality was characterized by identical conclusions (effect and level of statistical significance/direction) across the 3 study types. For the remaining outcomes, nominally significant results at $P < 0.05$ were reported for colorectal cancer, all-cancer mortality, and asthma by meta-analyses of RCTs, indicating that a low vitamin D concentration was not a causal factor for these disease outcomes; however, vitamin D supplementation was an efficient intervention factor for these disease outcomes. Additionally, only a single outcome (all-cause mortality) was reported by meta-analyses of observational studies with suggestive evidence, by meta-analyses of RCTs with a 95% PI excluding the null, and by MR studies with $P < 0.05$ (Table 1).

In addition, 14 outcomes were examined in meta-analyses of observational studies, excluding MR studies, and meta-analyses of RCTs (Table 2). According to meta-analyses of observational studies, 10 (71.43%) outcomes presented nominally significant results at $P < 0.05$. However, 3 (30%) outcomes related to all-cause mortality (prostate cancer patients, small for gestational age, and sustained virologic response to hepatitis C virus) corresponded to nominally significant results according to meta-analyses of both RCTs and observational studies. Two outcomes had consistent effects and levels of statistical significance/direction in both meta-analyses of observational studies and meta-analyses of RCTs. Only a single outcome (all-cause mortality in prostate cancer patients) was inconsistent based on the direction of the association/effect in meta-analyses of observational studies and meta-analyses of RCTs. Comparison with the most significant outcomes (71.43%) according to meta-analyses of observational studies indicated that the results for the majority (70%) of the outcomes investigated by meta-analyses of RCTs were not statistically significant.

Discussion

The present umbrella review integrated the results of MR studies and RCTs to avoid the inevitable bias or reverse causality of observational studies. The results indicated that low vitamin D concentrations were a causal risk factor for all-cause mortality, Alzheimer's disease, hypertension, schizophrenia, and type 2 diabetes. These findings were

combined with the results of meta-analyses of RCTs, and the data indicated that vitamin D supplementation decreased the risk for all-cause mortality. The present study is the first attempt to evaluate associations of low vitamin D concentration and vitamin D supplementation with health outcomes by combining the findings of meta-analyses of observational studies, meta-analyses of RCTs, and MR studies. Unlike a previous umbrella review of systematic reviews and meta-analyses of observational studies and RCTs that assessed associations of vitamin D with multiple health outcomes (25), the present study also combined and compared the findings reported by MR studies.

Comparison of the findings of both MR studies and meta-analyses of observational studies with the data reported by meta-analyses of RCTs indicated significant associations of low vitamin D concentration and vitamin D supplementation with all-cause mortality (136, 214, 278). Associations of low vitamin D concentration with Alzheimer's disease, hypertension, schizophrenia, and type 2 diabetes were significant only in meta-analyses of observational studies and in MR studies, and meta-analyses of RCTs reported little or no effect of vitamin D supplementation on the prevention or treatment of these diseases. Overall, assessments of associations of vitamin D deficiency and vitamin D supplementation with the same diseases yielded conflicting results, and the effects of vitamin D deficiency and vitamin D supplementation on all-cause mortality were consistent. These findings suggested that vitamin D supplementation has a long-term effect on the prevention of overall mortality. In addition, future studies should focus on the impact of low vitamin D concentration and vitamin D supplementation on the incidence of the diseases and on healthy life expectancy. Importantly, genetic variants related to vitamin D deficiency, especially variants of the vitamin D receptor, binding protein, and metabolizing enzyme 1- α -hydroxylase, may contribute to these divergent results. Additionally, increasing evidence suggests that genetic variation may impact variable results reported in the case of vitamin D supplementation in various trials (308, 309), indicating that additional studies are required to assess the roles of genetic variations as potential determinants of beneficial and negative effects of over-the-counter supplements used for health promotion. Future studies need to focus on the combined effects of genetic variations and vitamin D supplementation on Alzheimer's disease, hypertension, schizophrenia, and type 2 diabetes. Notably, some subjects without vitamin D deficiency but with genetic variations suffered from these diseases, and in some subjects with genetic variations, vitamin D intervention had no effect. Future RCTs should consider interindividual differences and identify whether certain subgroups of individuals may benefit from vitamin D supplementation in the context of disease outcomes. The purpose of MR studies should not be limited to simple exploration of whether low vitamin D concentration is a causative factor or a biomarker of a disease and should also aim to suggest effective interventions that consider both genetic variations and low vitamin D concentration.

TABLE 1 Comparison of the evidence for disease outcomes examined by 3 types of studies¹

Outcomes	Meta-analysis of observational studies			Meta-analysis of RCTs		MR study		
	Risk estimates (95% CI)	Evidence class ²	Risk of bias level ³	Risk estimates (95% CI)	Evidence	Risk of bias level ³	Risk estimate (95% CI)	Evidence
All-cause mortality	0.61 (0.52, 0.76)	III	High	0.93 (0.88, 0.98)	P < 0.05, 95% PI excluded the null	High	0.77 (0.62, 0.95)	n = 95,766
Breast cancer	0.99 (0.98, 1.00)	NS	High	0.97 (0.95, 1.00)	P > 0.05, 95% PI excluded the null	High	1.02 (0.97, 1.08)	n = 228,95; P = 0.47; power = 0.13
CVD mortality	0.88 (0.80, 0.96)	IV	High	0.96 (0.93, 1.00)	P > 0.05, 95% PI excluded the null	High	0.77 (0.55, 1.08)	n = 95,766
Colorectal cancer	0.87 (0.77, 0.99)	IV	High	0.94 (0.91, 0.97)	NA	High	0.92 (0.76, 1.10)	n = 95,906; P = 0.36; power = 0.29
Asthma	0.92 (0.77, 1.10)	NS	High	0.73 (0.58, 0.92)	P < 0.05, 95% PI excluded the null	High	1.03 (0.90, 1.19)	n = 146,761; P = 0.63; power = 0.25
All-cancer incidence	0.89 (0.81, 0.97)	IV	High	0.98 (0.93, 1.03)	P > 0.05, 95% PI excluded the null	High	0.97 (0.91, 1.04)	n = 438,870
All-cancer mortality	0.80 (0.70, 0.91)	III	High	0.87 (0.79, 0.96)	P < 0.05, 95% PI excluded the null	High	0.97 (0.84, 1.11)	n = 438,870

¹Data are consistent results of meta-analyses of observational studies and MR studies with the results of meta-analyses of RCTs. CVD, cardiovascular disease; MR, Mendelian randomization; NA, not available; NS, not significant ($P \geq 0.05$); PI, prediction interval; RCT, randomized controlled trial; ROBIS, Risk of Bias in Systematic Reviews.

²Evidence class criteria: class I (convincing), a statistical significance level of $P < 10^{-6}$, > 1000 cases, a significant result at $P < 0.05$ reported by the study with the largest sample size in the meta-analysis, a 95% PI that excluded the null, a low heterogeneity ($I^2 < 50\%$), no evidence of small-study effects ($P > 0.10$) and of excess significance bias ($P > 0.10$); class II (highly suggestive), a statistical significance level of $P < 10^{-6}$, > 1000 cases, and a significant result at $P < 0.05$ reported by the study with the largest sample size in the meta-analysis; class III (suggestive), a statistical significance level of $P < 10^{-3}$ and > 1000 cases; class IV (weak), a statistical significance level of $P < 0.05$.

³The risk of bias was assessed by ROBIS: low risk of bias (Low), the findings of the meta-analysis are likely to be reliable, domain 1–4 (study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings) did not raise any concerns with the review process or concerns were appropriately considered in the review conclusions, the conclusions were supported by the evidence and included consideration of the relevance of included studies; high risk of bias (High), ≥ 1 of the concerns raised during the domain 1–4 assessment was not addressed in the review conclusions, the review conclusions were not supported by the evidence, or the conclusions did not consider the relevance of the included studies to the review question; unclear risk of bias (Unclear), there is insufficient information reported to make a judgement on risk of bias

TABLE 2 Comparison of the results from the meta-analysis of observational studies and the meta-analysis of RCTs¹

Outcomes ²	Meta-analysis	
	Observational studies	RCTs
All-cause mortality		
Chronic kidney disease	0.73 (0.65, 0.82)	0.84 (0.46, 1.52)
Critically ill	0.72 (0.50, 1.04)	0.70 (0.50, 0.98)
Elderly	0.61 (0.52, 0.71)	1.04 (0.91, 1.17)
Prostate cancer	0.91 (0.84, 0.98)	1.19 (1.03, 1.38)
Bladder cancer	0.75 (0.65, 0.85)	0.92 (0.66, 1.28)
CVD	0.66 (0.56, 0.77)	0.90 (0.77, 1.05)
Hip fracture	0.68 (0.60, 0.78)	1.11 (0.97, 1.27)
Preterm birth	0.86 (0.62, 1.20)	0.57 (0.36, 0.91)
Small for gestational age	0.65 (0.48, 0.86)	0.72 (0.52, 0.99)
Stillbirth	0.98 (0.92, 1.04)	0.35 (0.06, 1.99)
Stroke	0.60 (0.48, 0.72)	1.09 (0.92, 1.30)
Sustained virological response in hepatitis C virus	0.63 (0.45, 0.89)	0.22 (0.08, 0.60)
Total CVD events	0.90 (0.86, 0.94)	1.20 (0.48, 2.99)
Tuberculosis	0.86 (0.53, 1.41)	0.61 (0.24, 1.56)

¹Values are risk estimates (95% CI). CVD, cardiovascular disease; MR, Mendelian randomization; RCT, randomized controlled trial.

²Presented disease outcomes examined with both meta-analyses of observational studies without MR studies and the meta-analyses of RCTs.

Moreover, associations of low vitamin D concentration and vitamin D supplementation with 14 overlapping health outcomes were supported by evidence that was not fully consistent. These outcomes included all-cause mortality in prostate cancer patients, small for gestational age, and sustained virologic response to hepatitis C virus, which showed a significant association in both meta-analyses of observational studies and meta-analyses of RCTs. Inconsistent evidence was presented for other outcomes. Inconsistencies between observational and randomized evidence may be due to the low frequency of these outcomes, which can limit the conclusions of randomized trials, thus necessitating additional validation by MR studies.

MR is rapidly becoming a powerful method for inferring causality based on routinely conducted observational studies. The present study aimed to investigate the current status and limitations of MR studies for exploring the causal associations of vitamin D concentrations with disease outcomes. Most of the findings of the present umbrella review indicated that genetic risk factors related to vitamin D concentration did not predict disease risk. These null findings may be explained by 4 reasons. First, the findings could have been influenced by a bias of weak IVs because variability of vitamin D concentration explained by single nucleotide polymorphisms was 1.61–2.84%. Therefore, additional genome-wide association studies are needed to systematically explore genetic variants related to vitamin D concentration. Moreover, it is important to investigate network relationships between genetic variants and other molecular intermediates (e.g., DNA methylation, gene expression, metabolites, and metagenomic information) in vitamin D deficiency to understand the molecular mechanism related to vitamin D concentration, including the application of systems biology and pharmacogenomics. Second, these null findings suggested that associations between vitamin

D concentration and diseases can be attributed to a reverse causation bias. Additional bidirectional MR studies are needed to prove this hypothesis and are expected to identify interventions aiming to reduce the prevalence of low vitamin D concentrations. Third, MR studies consider lifelong effects of genetic variations on diseases; however, the association of vitamin D concentrations with disease outcomes may vary over time and are not constant. Thus, evaluations are limited due to the cross-sectional observational nature of current MR studies. Therefore, MR studies should incorporate some follow-up data to evaluate the effects of vitamin D concentrations on various diseases and to investigate the changes in the effects of genetic variants over time on these diseases. Finally, a previous study demonstrated that vitamin D supplementation was effective only in subjects with baseline 25(OH)D concentrations of no more than 30 nmol/L, suggesting that associations between the 25(OH)D concentration and disease outcomes may be nonlinear (310–312). The MR analysis included an assumption of linearity (313), suggesting that nonlinear relationships could not be tested and could have supported the null hypothesis of the lack of an effect of 25(OH)D concentration on the diseases. Therefore, the null findings indicated a possible lack of linear causal associations of 25(OH)D concentrations with the diseases. Nonlinear MR studies are needed to prove this hypothesis and are expected to explore the real effects of the vitamin D deficiency on disease risk. Thus, we hope to contribute to more reliable evaluations of MR findings.

The present study has several limitations. First, the risk of type I errors may be increased due to testing multiple outcomes; however, this risk is generally acceptable considering the exploratory nature of umbrella reviews. Second, selected studies could have been heterogeneous due to the variable methodological quality of meta-analyses. The diagnostic criteria used for low vitamin D concentration

and outcomes could have influenced estimated effects and increased between-study heterogeneity. In addition, most included meta-analyses were at high risk of bias, which might decrease the robustness of statistical analyses. The studies did not control for confounding factors that could have mediated associations between vitamin D concentration and outcomes because this information was often unavailable in published meta-analyses. Additionally, some potential outcomes for vitamin D concentration and vitamin D supplementation have not been subjected to meta-analyses at present. Notably, comparisons of the results included evidence from MR studies that assessed the effects of vitamin D deficiency on outcomes, which was largely negative or inconclusive due to a bias of weak IVs. Comparison of the results has to account for differences in the duration and timing of exposure to vitamin D. For example, vitamin D concentrations can be influenced by various factors, such as exposure, sunlight, altitude, and race, potentially leading to unidentified biases. Considering these caveats, the main strengths of this umbrella review include a topically comprehensive literature search, inclusion of a large body of evidence, and systematic quantitative and qualitative approaches used to assess the quality of available evidence.

Conclusions

Low vitamin D concentrations are a causal factor for multiple noncommunicable chronic diseases. Accordingly, vitamin D supplementation is a promising strategy with long-term preventive effects on these diseases and thus decreases all-cause mortality. However, the current vitamin D supplementation strategy might not be an efficient intervention factor for these diseases, suggesting that new strategies are highly needed to improve the intervention outcomes. Considering the existence of high risk bias in original meta-analyses, the finding might not be robust enough, and needs confirming in future studies. Future studies should focus on personalized interventions for diseases involving considerations of genetic variations in combination with low vitamin D concentrations.

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Data Availability

The data underlying this article are available in the article and in its online supplementary material.

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