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Serum 25(OH)D concentration and risk of all-cause and cause-specific mortality in patients with chronic kidney disease: systematic review and dose-response meta-analysis of observational cohort studies

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Short title: Vitamin D and mortality in CKD patients

ABSTRACT

Background

To summarize the evidence on the associations between 25-hydroxyvitamin D (25(OH)D) and risk of mortality in patients with chronic kidney disease (CKD).

Methods

A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar for relevant papers published up to November 2025 that assessed the association between serum vitamin D levels and the risk of all-cause, cardiovascular disease (CVD), non-CVD, and cancer mortality was conducted. The lowest-versus-highest analysis and the linear and non-linear dose-response analyses were performed using a random-effects model.

Results

Overall, 36 publications (35 studies) with a total sample size of 129,135 participants, aged between 18 to 90 years, were included in the current meta-analysis. During the follow-up periods ranging between 3 months and 18 years, 117,403 cases of all-cause mortality, 2,568 cases of CVD mortality, 886 cases of non-CVD mortality, and 289 cases of cancer mortality were identified. The summary relative risk (RR) and 95% confidence intervals (CIs) comparing lowest versus highest levels of 25(OH)D was 1.61 (95% CI: 1.41-1.84, I^2 = 89%, n=28 studies, very low certainty) for all-cause mortality, 1.68 (95% CI: 1.41-2.00, I^2 = 20%, n=9, very low certainty) for CVD mortality, 1.33 (95% CI: 0.94-1.89, I^2 = 26%, n=3, very low certainty) for non-CVD mortality,

and 1.51 (95% CI: 1.09-2.09, I^2 = 26%, n=1, very low certainty) for cancer mortality. There was evidence of non-linearity in the analysis of all-cause and CVD mortality, with a greater reduction in risk from serum levels of 12.5 nmol/L up to 60 nmol/L compared to higher levels, but with slight further reductions in risk with serum levels up to 110 nmol/L.

Conclusions

This meta-analysis provides further evidence that lower levels of 25(OH)D are associated with a higher risk of all-cause, CVD, and cancer mortality in CKD patients. However, all outcomes were graded as very low certainty, and the observed associations may be influenced by confounding, small-study effects, and wide prediction intervals that include the null. Observed low-risk range around ~60 nmol/L in the non-linear dose-response analyses, should be interpreted cautiously and requires validation in randomized controlled trials.

Keywords: cohort studies, mortality, vitamin D, serum 25(OH)D, chronic kidney disease, meta-analysis

INTRODUCTION

The body of evidence from experimental and epidemiological studies indicates that vitamin D is essential not only for its impacts on the skeletal system, but also for its benefits on muscle, immune function, and cardiovascular health [1, 2]. The relationship between vitamin D and mortality has emerged as a prominent area of growing research interest, demonstrated by the substantial body of scientific literature currently available on this issue [3]. The growing interest toward this issue could be attributed to the high prevalence of vitamin D deficiency [4]. Despite the fact that vitamin D supplements are widely used, vitamin D deficiency still remains prevalent, ranging from 6%–13% in Western nations [5]. Moreover, the prevalence of vitamin D insufficiency is reported to be four times greater [5]. The prevalence of vitamin D deficiency in patients with life-threatening conditions like chronic kidney disease (CKD) increases with disease severity, ranging from 40.7% in stage 3 to 85.7% in stage 5 [5, 6]. This high prevalence may significantly impact mortality rates. CKD has become as one of the most important causes of suffering and death in the 21st century affecting nearly 843.6 million people globally in 2017 [7]. While mortality rates among patients with end-stage renal disease (ESRD) have decreased, the Global Burden of Disease (GBD) studies indicate that CKD has emerged as a leading cause of death worldwide [8]. Research has demonstrated that, among many other factors, urinary vitamin D binding protein (VDBP) loss due to increased proteinuria, decreased sunlight exposure, dietary restrictions, and reduced

ability to produce 25-hydroxyvitamin D (25(OH)D) in the skin put individuals with CKD at an increased risk of multifactorial vitamin D deficiency [9, 10]. According to observational studies, low 25(OH)D levels are consistently linked to unfavorable clinical outcomes in CKD patients [11]. While meta-analyses have explored the association between serum 25(OH)D levels and mortality in CKD patients [12-14], limitations remain. A meta-analysis of cohort studies reported that higher levels of serum 25(OH)D were associated with a lower risk of all-cause mortality in patients with CKD [12]. However, this review has only examined all-cause mortality and did not consider cause-specific mortality such as cardiovascular disease (CVD), non-CVD, or cancer. Another meta-analysis reported that every 10 ng/ml increase in serum 25(OH)D was associated with a reduced risk of all-cause and cardiovascular mortality [13]. Nonetheless, this meta-analysis included a small number of studies in the analysis of CVD mortality and only examined the linear relationship between serum vitamin D levels and mortality risk, and as a result, questions about the shape and strength of the non-linear relationship between serum vitamin D levels and cause-specific mortality are raised. Furthermore, previous meta-analyses have not addressed the certainty of the evidence or not reported prediction intervals for the pooled effect estimates, limiting the interpretation of existing findings in this area.

Recently, results from additional large cohort studies [15-25] have been released and included more than 90,000 participants and 10,000 mortality cases, which could increase the power to estimate dose-response

relationships. For these reasons, the present meta-analysis was designed to investigate the relationship between vitamin D serum levels and risk of all-cause and cause-specific mortality in patients with CKD.

METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26].

Search strategy: We conducted a comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar for relevant papers published up to November 2025 that assessed the association between serum vitamin D levels and the risk of all-cause, CVD, non-CVD, and cancer mortality. The details of the search strategy are presented in S**upplemental Table 1**. The literature search was not limited to publication time or the language of articles. To identify potentially missed publications, we also screened the reference lists of included articles and recent reviews. Two independent authors (SN and SK) performed literature search and screened titles and abstracts. Any disagreements were resolved through discussion and consensus; a third reviewer (HT) was consulted when consensus could not be reached.

Inclusion criteria: We included studies with cohort design including prospective cohort, case-cohort, and nested case-control studies, as well as retrospective cohort studies that were performed on adults (≥18 years) with CKD and reported risk estimates for the association of serum levels of 25(OH)D as an exposure variable and mortality from all causes, CVD, non-

CVD, and cancer as an outcome variable. To avoid duplication of data, when findings from a single dataset were presented in multiple publications, we included only the most recent publication or, in cases of equal publication dates, the publication with the greatest number of cases.

Exclusion criteria: We excluded letters, comments, reviews, ecological studies, qualitative studies, studies involving children and adolescents, and articles lacking sufficient data (i.e., studies that did not report relative risks (RRs) or 95% confidence intervals (CIs) for the association between exposure and outcome). Studies that did not report adjusted risk estimates but provided Kaplan-Meier curves were also excluded. RRs estimated from these curves can be biased due to an unbalanced distribution of confounders, and we considered such estimates to be unadjusted [27]. Moreover, we did not include those studies that assessed dietary intakes of vitamin D rather than serum levels.

Data extraction: Two investigators (SN and SK) independently extracted the required data from each paper. When studies reported both unadjusted and adjusted RRs, we recorded the adjusted RR from the most comprehensive statistical model. We also collected data on the first author's name, publication year, study characteristics (sample size, number of cases, study location, and follow-up duration), participant characteristics (age and gender), and methodological details (vitamin D measurement method and confounding variables considered in statistical analysis).

Quality assessment: Study quality was assessed using the Newcastle-Ottawa scale (NOS) which awards 0–9 stars based on the selection, comparability, and outcome assessment. We considered studies with scores of 0–3, 4–6 and 7–9 to represent low, medium, and high-quality studies, respectively.

Statistical methods: We included the RRs and 95% CIs of total and cause-specific mortality for the comparison between the lowest and highest levels of serum vitamin D in the meta-analysis. When retrospective cohort studies reported effect estimates as odds ratios, we converted these to risk ratios using the method described by Zhang et al [28]. We converted 25(OH)D levels from ng/mL to nmol/L. When the highest category was not specified as the reference in the original studies, RRs were recalculated with the highest category as the reference, following the method described by Hamling [29]. Natural logarithms of the RRs and their standard errors were calculated and combined using a random-effects meta-analysis model [30]. Statistical heterogeneity among studies was assessed using the Q-statistic and quantified with the I^2 statistics. I^2 values of <25%, 25-50%, 50-75%, and >75% were considered as low, moderate, high, and very high between-study heterogeneity, respectively [31]. When ≥5 studies were available, we explored possible sources of heterogeneity by performing priori specified subgroup and meta-regression analyses. These analyses were done based on study location (US vs. non-US), follow-up duration (≥4 vs. <4 years), and adjustment for body mass index (BMI) (yes vs. no). Because all of the studies

were done on both genders, we were unable to perform prespecified subgroup analyses based on the gender of the participants. Additional post hoc analyses were performed by type of serum 25(OH)D assay, dialysis status, and seasonal adjustment.

When ≥5 studies were available, publication bias was examined using Egger's linear regression test and by inspection of funnel plots [32]. The trim-and-fill method was implemented to evaluate the robustness of the overall RR to potential publication bias, specifically by estimating the effect of imputed missing studies [33]. To assess whether any individual study was overly influencing the overall effect estimate, we performed a sensitivity analysis, repeating the analysis and leaving out one study at a time. We also performed sensitivity analyses by excluding studies with short follow-up (e.g., <12 months) to observe changes in effect estimates. For the linear and non-linear dose-response analyses, we used the one-stage linear mixed effects meta-analysis [34]. The summary estimates were presented per 25 nmol/L increment in serum 25(OH)D in the forest plots. We first estimated study-specific slopes and then combined them using a random-effects model to calculate an overall average slope. For this analysis, we required the distribution of cases, total participants, and RRs with variance estimates for studies reporting at least two quantitative exposure categories. We assigned the median or mean serum 25(OH)D level in each category to the corresponding RR for each study. For studies reporting serum levels as ranges, we estimated the midpoint of each category by averaging the lower

and upper bounds. When the highest or lowest category was open-ended, we assumed its interval width to be equal to that of the adjacent category. We also explored potential non-linear dose-response relationships using restricted cubic splines with three knots placed at the 10th, 50th, and 90th percentiles of the distribution. STATA syntax that was used for the analyses is provided in **Supplemental Method 1**. Statistical analyses were conducted using STATA version 17.0. $P<0.05$ was considered as statistically significant for all tests.

Grading the evidence

We used the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) to assess the certainty of evidence, generating profiles graded as high, moderate, low, or very low [35, 36]. Two reviewers (SN and SK) independently performed these assessments for each outcome.

RESULTS

Our database search yielded 9518 articles. After removing 2195 duplicates, we screened the remaining articles based on their title and abstract, excluding 7264 that were irrelevant. Consequently, 59 articles underwent full-text assessment, leading to the exclusion of further articles for following specific reasons: abstract-only publication (n=1), reporting risk estimates for 1,25-dihydroxy vitamin D or vitamin D metabolic ratio (n=2), irrelevant exposure/outcome (n=8), unadjusted risk estimates (n=1), provided only Kaplan-Meier curves (n=2), use of non-original data (n=1), inclusion of kidney transplant patients (n=1), and insufficient data (n=2). In addition,

three different publications were found for the National Health and Nutrition Examination Survey (NHANES) [18, 37, 38], three for TriNetX Global Health Research Network database [25, 39, 40], and two for South-Eastern European Dialysis Cohort [41, 42]. As these articles assessed the association of 25(OH)D with similar outcome variables, only those of higher quality or with the greatest number of cases for each dataset were included [18, 25, 41] and duplicate papers were excluded [37-40, 42]. Moreover, two studies were conducted using data from the Third National Health and Nutrition Examination Survey (NHANES III) [43, 44]. Because Kramer et al. [44] provided information on all-cause mortality and Mehrotra et al. [43] provided information on CVD mortality, both were included. List of excluded studies is provided in **Supplemental Table 2**. Finally, 35 cohort studies (36 publications) were included in the current systematic review and meta-analysis [15-25, 41, 43, 45-67]. A flow diagram of the study selection is shown in **Figure 1**.

Characteristics of the included studies

Supplemental Table 3 shows a summary of the study characteristics of the included studies and **Supplemental Tables 4-6** show the data extracted for the dose-response analysis. The studies were published between 2007 and 2025 and had a cohort design. The number of participants in these studies ranged from 81 to 59,308, comprising 129,135 CKD patients. During follow-up periods from 3 months to 18 years, the total number of deaths from all causes, CVD, non-CVD, and cancer was 18,952, 2,568, 886, and 289,

respectively. All studies included both men and women. In total, ten studies (eleven publications) described studies that were performed in the US [18, 42-44, 47, 50, 51, 53, 58, 61, 64], and remaining described studies that were conducted in Europe [21, 23, 24, 41, 45, 48, 49, 52, 54, 55, 59, 64, 66, 67], Asia [16, 17, 19, 20, 60, 62, 63], Brazil [15, 65], and Uruguay [22]. One study [25] used a large-scale health research database that contains electronic medical records information from 140 healthcare organizations globally. Of the studies, seventeen enrolled hemodialysis/dialysis patients [15, 41, 47-49, 56-67], seventeen enrolled non-dialysis patients [16-24, 43, 44, 50-55], and two enrolled a mix of both [25, 45]. The assay method for 25(OH)D varied across studies. Eight used radioimmunoassay [43, 44, 52, 54, 55, 57, 62, 65], sixteen used chemiluminescence [15, 16, 19, 21, 24, 41, 45, 48-51, 53, 59, 60, 63, 67], three used an unspecified immunoassay [56, 58, 61], and two used liquid chromatography–tandem mass spectrometry (LC-MS/MS) [23, 47], the gold standard for 25(OH)D measurement. Li et al. [18] (using LC-MS/MS and radioimmunoassay) and Krause et al. [66] (using competitive protein-binding assay and chemiluminescence) used mixed methods. Five studies did not specify their assay method [17, 20, 22, 25, 64]. The NOS scores of the included studies are provided in **Supplemental Table 7**.

Findings from meta-analysis

All-cause mortality

Thirty-two cohort studies [15-18, 20, 22-25, 42, 44, 45, 47-49, 51-67] provided data for the association between serum 25(OH)D and risk of all-cause

mortality, of which twenty-eight were included in the lowest versus highest analysis [15, 16, 18, 22-25, 42, 44, 47-49, 51-62, 64-67]. These studies included a total of 117,403 participants and 18,952 mortality cases. Combining data from these studies showed a significant association (Pooled RR: 1.61, 95% CI: 1.41-1.84, I^2 = 89.1%, $P_{heterogeneity}$<0.001) (**Supplemental Figure 1 and Table 1**). In the dose-response analysis, we found a linear dose-response association, such that an increment of 25 nmol/L in serum 25(OH)D levels was associated with a 20% lower risk of all-cause mortality (RR: 0.80, 95% CI: 0.75-0.85; I^2=79.1%, $P_{heterogeneity}$<0.001) (**Supplemental Figure 2**). There was evidence of non-linear association (P non-linearity<0.001), with a stronger reduction in risk from serum levels of 12.5 nmol/L up to 60 nmol/L than with higher levels, but with slight further reductions in risk with serum levels up to 110 nmol/L (**Figure 2 and Supplemental Table 8**).

Total CVD mortality

Eleven studies [18, 19, 21, 23, 24, 43, 49, 50, 54, 57, 63] containing 43,440 participants and 2,568 CVD mortality cases were included in the analysis of serum 25(OH)D levels and CVD mortality risk. Of these studies, nine were included in the lowest versus highest analysis. The summary RR was 1.68 (95% CI: 1.41-2.00, I^2 =20%, $P_{heterogeneity}$=0.27) (**Supplemental Figure 3 and Table 1**). In the dose-response analysis, we found a significant linear association (Pooled RR: 0.80, 95% CI: 0.74-0.86, I^2 = 43.4%, $P_{heterogeneity}$=0.06) (**Supplemental Figure 4**). In addition, the test for non-

linearity was significant (P non-linearity=0.01), with a stronger reduction in risk from serum levels of 12.5 nmol/L up to 60 nmol/L than with higher levels, but with slight further reductions in risk with serum levels up to 110 nmol/L (**Figure 2 and Supplemental Table 8**).

Non-CVD mortality

Three studies [21, 43, 49] investigated the association between serum 25(OH)D and risk of non-CVD mortality and included a total of 886 cases and 8019 participants. Pooling data from these studies, comparing the lowest versus highest concentration of serum 25(OH)D showed no significant association (Pooled RR: 1.33, 95% CI: 0.94-1.89, I^2 = 26%, $P_{heterogeneity}$=0.26) (**Supplemental Figure 5 and Table 1**). Such a non-significant association was also reached in the linear dose-response analysis based on 25 nmol/L increase in serum 25(OH)D levels (Pooled RR: 0.93, 95% CI: 0.84-1.03, I^2 = 16%, $P_{heterogeneity}$=0.30) (**Supplemental Figure 6).** There was no evidence of non-linearity (P non-linearity=0.07) (**Figure 2 and Supplemental Table 8**).

Cancer mortality

One study with 289 cancer mortality cases and 6518 participants was included in the analysis of serum 25(OH)D levels and cancer mortality risk. Performing meta-analysis, comparing the lowest and highest levels of 25(OH)D, revealed a significant association (RR: 1.51, 95% CI: 1.09-2.09) (**Supplemental Figure 7 and Table 1**). In the linear dose-response analysis, we found a significant association based on a 25 nmol/L increase in serum

25(OH)D levels (RR: 0.86, 95% CI: 0.76-0.96). Non-linear dose-response analysis was not possible owing to limited data.

Subgroup analyses, sensitivity analyses, and publication bias: Findings from the subgroup analyses are shown in **Supplemental Table 9**. The observed associations between serum 25(OH)D and all-cause and CVD mortality were generally consistent across most subgroups; although the magnitude varied modestly, the direction of effect was the same. For all-cause mortality, study location, dialysis status, type of serum 25(OH)D assay, and adjustment for BMI and season appeared to be factors explaining the observed between-study heterogeneity. For non-CVD mortality, the initial non-significant association with serum 25(OH)D became significant in sensitivity analyses after excluding the study by Drechsler et al. [49]. In sensitivity analyses in which we excluded studies with short follow-up (e.g., <12 months), the results remained unchanged (data not shown). Evidence of publication bias was observed for both all-cause and CVD mortality with the funnel plot and Egger's test. For all-cause mortality, trim-and-fill identified eight potentially missing studies and the pooled estimate was attenuated from 1.61 (95% CI: 1.41-1.84) to 1.46 (95% CI: 1.29–1.66) after imputation, indicating that small-study effects may have inflated the magnitude of the association. For CVD mortality, the trim-and-fill analysis identified five potentially missing studies, and imputation attenuated the pooled estimate to 1.46 (95% CI: 1.21-1.77), although the overall direction of association

remained unchanged. These attenuations highlight that the pooled magnitudes should be interpreted with caution.

Grading the evidence

Supplemental Table 10 presents the GRADE assessments of the overall certainty of the evidence for the association of serum 25(OH)D and mortality risk. The evidence was graded as very low for all-cause, CVD, non-CVD, and cancer mortality.

DISCUSSION

In this meta-analysis, we found that lower levels of serum 25(OH)D were associated with 61%, 68%, and 51% higher risk of all-cause, CVD, and cancer mortality, respectively. In the linear dose-response analyses, each 25nmol/L increment in serum 25(OH)D was associated with 20%, 20%, and 14% lower risk of all-cause, CVD, and cancer mortality, respectively. There was evidence of non-linearity in the analyses of all-cause and CVD mortality, with a greater reduction in risk from serum levels of 12.5 nmol/L up to 60 nmol/L compared to higher levels, but with slight further reductions in risk with serum levels up to 110 nmol/L.

Vitamin D deficiency and insufficiency have high prevalence rates among the general and diseased adult population [5]. Observational studies mainly investigated the associations of serum 25(OH)D levels with risks of total and cause-specific mortality in the general population and reported an inverse association [68]. However, there is limited evidence on the association between vitamin D status and mortality in diseased populations, especially

CKD patients. The current study provides a comprehensive evaluation of the association of serum 25(OH)D levels and risk of all-cause and cause-specific mortality.

Several biological pathways may explain the observed associations between lower 25(OH)D levels and higher mortality risk in CKD. Lower levels of vitamin D are linked to several vascular risk factors, including hypertension [69, 70] and diabetes mellitus [71], both of which are associated with death. Available evidence suggests that vitamin D regulates cardiac hypertrophy, endothelial dysfunction, renin-angiotensin-aldosterone system, and vascular calcification [72-74]. In addition, vitamin D supports antioxidant defenses by reducing the production of reactive oxygen species and enhancing the activity of antioxidative enzymes [75]. It also modulates inflammatory processes by inhibiting the production and release of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α [74, 76]. Furthermore, vitamin D may contribute to overall health by lowering the risk of dyslipidemia [77] and secondary hyperparathyroidism [78].

A dose-response meta-analysis in 2017 found that higher levels of serum 25(OH)D were associated with a lower risk of all-cause mortality in CKD patients in the analyses of 17 cohort studies with a total of 17,053 patients and 7,517 mortality cases [12]. Another meta-analysis by Zhang et al. [13] which included 18 cohort studies with a total of 14,154 participants also suggested that each 10 ng/mL increase in serum 25(OH)D levels was associated with a lower risk of all-cause and CVD mortality. Our meta-analysis

builds upon and surpasses previous reviews in several main aspects. First, the larger sample size, with four times the participants and twice the mortality events, provides greater statistical power for a detailed examination of the associations. Furthermore, we incorporated eleven additional cohort studies [15-25] published since prior meta-analyses. Second, we investigated specific causes of mortality and conducted both linear and non-linear dose-response meta-analyses, allowing for a more comprehensive evaluation of the relationship between serum 25(OH)D and mortality. Third, the calculation of 95% prediction intervals for the summary random-effects estimates helps account for heterogeneity and allows for a better understanding of the likely range of effects in future studies. Finally, we rigorously assessed the overall quality of evidence for each outcome investigated.

In the dose-response meta-analysis, greater reduction in risk of mortality occurred from serum levels of 12.5 nmol/L up to 60 nmol/L compared to higher levels, with progressively smaller reductions observed at higher levels, up to 110 nmol/L. A recent dose-response meta-analysis in patients with type 2 diabetes and prediabetes reported the lowest risk of all-cause and CVD mortality at serum 25(OH)D levels of around 60 nmol/L [79]. Similar findings were also reported in the general population such that the lowest risk of stroke [80] and hypertension [69] was observed at serum levels of around 60 nmol/L. Taken together, our findings suggest that a minimum

serum concentration of ~60 nmol/L of serum 25(OH)D might be a potential intervention target to decrease the risk of mortality for patients with CKD.

In the current study, we failed to find any significant association between serum 25(OH)D levels and non-CVD mortality in CKD patients. This might be explained by the small number of studies included in the analysis and consequently the lower number of participants and non-CVD events, which could reduce the power of the study to find true significant association. In terms of cancer mortality, only one study was included and reported a higher risk in relation to serum 25(OH)D [66]. Therefore, cancer mortality findings should be interpreted with caution. Collectively, there is little evidence regarding the association between vitamin D status and cause-specific mortality, and future studies should therefore try to clarify associations between vitamin D and specific causes of mortality as well as less common causes of mortality.

The findings from our meta-analysis of observational studies contrast with the findings from randomized trials on the effect of vitamin D supplements on the incidence of mortality and CVD. For example, a meta-analysis of 13 trials reported that vitamin D supplementation did not reduce the risk of mortality or CVD risk in CKD patients [81]. However, this meta-analysis included 1469 patients and a total of 41 all-cause mortality events occurred during intervention (23 patients in the group receiving vitamin D supplements and 18 patients in the placebo group). One possible explanation is that the inadequate sample size or mortality events might have limited the

power of this study to detect the clinical effects of vitamin D in CKD patients. Therefore, in the case of trials, there is a need for well-designed studies with longer follow-up periods, larger sample sizes, and sufficient power.

The substantial heterogeneity observed in the all-cause mortality meta-analysis might be explained by following points. Vitamin D metabolism is altered differently across CKD severity and stages, potentially modifying the association with mortality. Second, the residual confounders or errors in the measurement of covariates can contribute to high heterogeneity. Third, assay variability may have contributed to between-study differences, as 25(OH)D measurements were performed using heterogeneous laboratory methods with known inter-assay variability. Fourth, regional differences and seasonal variation in sunlight exposure and background diet may also influence risk associations. These factors collectively explain the high heterogeneity despite a generally consistent direction of association.

To further account for heterogeneity between studies, 95% prediction intervals were calculated for the summary random effect estimates. We found that the null value was not excluded for all-cause and non-CVD mortality. This result suggests that in future studies, the true effect estimate could be null or small in some populations.

In the current study, there was evidence of small study effects. After applying trim-and-fill, the pooled RR for all-cause mortality attenuated, and a similar attenuation was evident for CVD mortality. These shifts suggest that smaller studies with larger effect estimates may influence the pooled estimate.

Therefore, although the direction of the association was stable, the magnitude is likely inflated.

Residual and unmeasured confounding remain a major limitation of the available evidence. Although most included studies controlled for main potential confounders such as age, sex, and BMI, far fewer accounted for CKD-specific determinants of both vitamin D status and mortality risk, such as inflammation (e.g., C-reactive protein) and parathyroid hormone (PTH) levels. The failure to control for these factors could bias the observed independent association between vitamin D status and mortality.

Strengths and limitations

Strengths of this study include the large number of studies from various geographical locations, the large number of deaths, the cohort design of included studies, and the detailed dose-response analysis. Our findings should be interpreted by considering several limitations. First, the observational nature of the included studies prevents us from establishing causality. Second, potential confounding factors related to lifestyle, diet, and socioeconomic status in CKD patients with low vitamin D levels could bias the results, and these confounders cannot be fully ruled out due to the study designs. Third, measurement errors in vitamin D levels might have led to an underestimation of the true association with mortality risk. Fourth, the analysis of all-cause mortality showed significant heterogeneity across studies. However, this heterogeneity appears to stem primarily from variations in the strength, rather than the direction, of the association

observed across studies. Fifth, we found some indication of small study effects such as publication bias in the analysis of all-cause and CVD mortality. However, application of the trim-and-fill method identified potentially missing studies, and imputation of these studies did not change the significance of the findings. Sixth, we summarized findings from studies that have used different assays for measuring serum 25(OH)D concentrations. Seventh, the certainty of evidence for all outcomes was graded as very low. Finally, our study may be subject to reverse causality.

Clinical and public health implications

Although LC-MS/MS is widely considered as the gold standard for measuring 25(OH)D levels [82], the current body of research predominantly relies on alternative methods, such as immunoassays, which are often more cost-effective and easier to perform. However, immunoassays have limitations. Moreover, there is substantial intra- and interassay variation in 25(OH)D levels [83]. These factors can affect the accuracy of the findings and potentially lead to inconsistent associations between 25(OH)D and health outcomes. Given the limitations of the current evidence, future research efforts should prioritize the use of LC-MS/MS to assess serum vitamin D concentrations. The use of such methods will lead to a better understanding of the association of vitamin D with chronic diseases and improve the quality of evidence-based recommendations for supplements and public health interventions.

Our findings suggest that increasing vitamin D levels to approximately 60 nmol/L may reduce the risk of mortality in CKD patients. Current guidelines [84] recommend that CKD patients with vitamin D insufficiency or deficiency receive supplementation following the same strategies as the general population. While the general adult population may require at least 1500-2000 IU of vitamin D daily to consistently maintain levels above 75 nmol/L [85], achieving serum vitamin D levels above 60 nmol/L in CKD patients may require higher doses, a question that needs to be investigated in future studies. Moreover, to confirm the results of the current meta-analysis, large randomized controlled trials are needed to investigate the effect of vitamin D supplementation on mortality in CKD patients.

Conclusion

This meta-analysis provides further evidence that lower levels of 25(OH)D are associated with a higher risk of all-cause and CVD mortality in patients with CKD. Although a significant association with cancer mortality was also observed, this finding is based on limited data and requires further investigation. A serum 25(OH)D concentration of approximately 60 nmol/L is associated with the lowest mortality risk in dose-response analyses; however, this finding should be interpreted cautiously due to the very low certainty of evidence. Randomized controlled trials are needed to confirm whether achieving this range improves clinical outcomes.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.REC.1402.890). Moreover, the study was conducted in accordance with the Helsinki Declaration of 1964, and its later amendments; and all participants provided informed consent to participate in the study.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

Study data are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions:

SK and SN contributed to literature search, data analysis, data extraction, and manuscript drafting. SKH, NMA, HA, and NF contributed to the manuscript drafting, data analysis, and study conception. AB, HT, and FN contributed to study conception, manuscript drafting, and approving the final

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Legend to figure(s):

Figure 1: Flow diagram of the study selection

Figure 2: Non-linear dose-response association of serum vitamin D levels (based on nmol/L) with risk of all-cause, CVD, and non-CVD mortality in patients with chronic kidney disease. The solid lines indicate the spline model. The dashed lines present the 95% CI. CVD: cardiovascular disease, CI: confidence interval

Table 1: Association between serum 25(OH)D and risk of mortality in patients with chronic kidney disease

	Lowest v Highest meta-analysis					Dose-response meta-analysis (per 25 nmol/L increment)				GRADE certainty
Outcomes	Studies	RR (95% CI)*	I^2 (%)†	P‡	Prediction intervals	Studies	RR (95% CI)	I^2 (%)†	P‡	
All-cause mortality	28	1.61 (1.41, 1.84)	89	<0.001	(0.91, 2.87)	31	0.80 (0.75, 0.85)	79.1	<0.001	Very low
CVD mortality	9	1.68 (1.41, 2.00)	20	0.27	(1.18, 2.38)	11	0.80 (0.74, 0.86)	43.4	0.06	Very low
Non-CVD mortality	3	1.33 (0.94, 1.89)	26	0.26	(0.06, 29.0)	3	0.93 (0.84, 1.03)	16.0	0.30	Very low
Cancer mortality	1	1.51 (1.09, 2.09)	-	-	-	1	0.86 (0.76, 0.96)	-	-	Very low

RR: relative risk, CI: confidence interval, CVD: cardiovascular disease
*Obtained from the random-effects model
†Inconsistency- the percentage of variation across studies due to heterogeneity
‡Obtained from Q test.