

Habitual vitamin D supplementation and mortality across diabetes and chronic kidney disease status: A prospective UK Biobank study

Konsumsi suplemen vitamin D secara teratur dan angka kematian berdasarkan status diabetes dan penyakit ginjal kronis: Studi prospektif dari UK Biobank

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Abstract

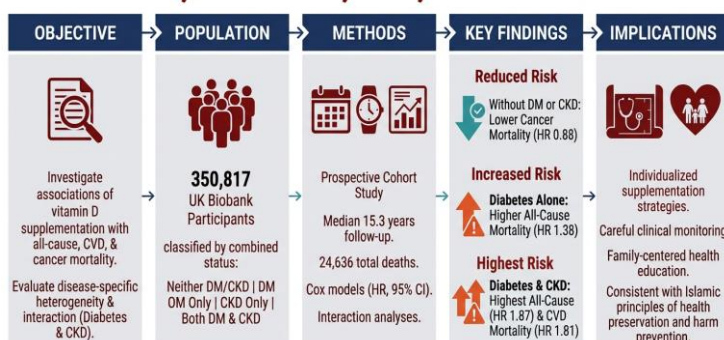
Habitual vitamin D supplementation is increasingly common for chronic disease prevention, yet evidence regarding its long-term mortality effects across combined diabetes and chronic kidney disease (CKD) status remains limited, making this study novel in evaluating disease-specific heterogeneity and interaction. This prospective cohort study investigated associations between habitual vitamin D supplementation and all-cause, cardiovascular disease (CVD), and cancer mortality among 350,817 UK Biobank participants classified as having neither diabetes nor CKD, diabetes only, CKD only, or both conditions. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), while additive and multiplicative interactions were assessed using relative excess risk due to interaction, attributable proportion, Cox models, and Aalen additive hazard models. During a median 15.3-year follow-up, 24,636 deaths occurred, including 7,748 CVD and 12,214 cancer deaths. Vitamin D supplementation was associated with lower cancer mortality among participants without diabetes or CKD (HR 0.88, 95% CI 0.80–0.98), but higher all-cause mortality in diabetes alone (HR 1.38, 95% CI 1.09–1.75), with the greatest risks observed among participants with both diabetes and CKD for all-cause mortality (HR 1.87, 95% CI 1.27–2.76) and CVD mortality (HR 1.81, 95% CI 1.11–2.95). These findings support individualized supplementation strategies, careful clinical monitoring, and family-centered health education, consistent with Islamic principles of preserving health, preventing harm, and promoting responsible use of health interventions.

Abstrak

Habitual vitamin D supplementation is increasingly common for chronic disease prevention, yet evidence regarding its long-term mortality effects across combined diabetes and chronic kidney disease (CKD) status remains limited, making this study novel in evaluating disease-specific heterogeneity and interaction. This prospective cohort study investigated associations between habitual vitamin D supplementation and all-cause, cardiovascular disease (CVD), and cancer mortality among 350,817 UK Biobank participants classified as having neither diabetes nor CKD, diabetes only, CKD only, or both conditions. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs), while additive and multiplicative interactions were assessed using relative excess risk due to interaction, attributable proportion, Cox models, and Aalen additive hazard models. During a median 15.3-year follow-up, 24,636 deaths occurred, including 7,748 CVD and 12,214 cancer deaths. Vitamin D supplementation was associated with lower cancer mortality among participants without diabetes or CKD (HR 0.88, 95% CI 0.80–0.98), but higher all-cause mortality in diabetes alone (HR 1.38, 95% CI 1.09–1.75), with the greatest risks observed among participants with both diabetes and CKD for all-cause mortality (HR 1.87, 95% CI 1.27–2.76) and CVD mortality (HR 1.81, 95% CI 1.11–2.95). These findings support individualized supplementation strategies, careful clinical monitoring, and family-centered health education, consistent with Islamic principles of preserving health, preventing harm, and promoting responsible use of health interventions.

Graphical Abstract

VITAMIN D, DIABETES, CKD, & MORTALITY RISK



Keyword

cardiovascular diseases; chronic disease; diabetes mellitus; dietary supplements; vitamin d

Artikel History

Submitted : 21 July 2026
In Reviewed : 02 August 2026
Accepted : 28 August 2026
Published : 30 August 2026

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INTRODUCTION

Diabetes and chronic kidney disease (CKD) constitute major and rapidly expanding global public health challenges. Approximately 589 million adults worldwide are living with diabetes, while an estimated 788 million are affected by CKD; in the United Kingdom alone, approximately 5.8 million people live with diabetes and 7.2 million with CKD (Amy, 2023; Genitsaridi et al., 2026; Ortiz et al., 2026; Valabhji & Kar, 2023). Both conditions contribute substantially to premature mortality, cardiovascular complications, functional decline, and increasing demands on health systems and families. Their growing burden is particularly relevant to Sustainable Development Goal (SDG) 3, especially Target 3.4, which aims to reduce premature mortality from noncommunicable diseases through prevention and treatment, and Target 3.8, which emphasizes access to effective and appropriate health interventions. Identifying safe and effective strategies to reduce mortality among individuals with diabetes, CKD, or both conditions is therefore an important public health priority.

Vitamin D has an established role in calcium and phosphate homeostasis and is essential for skeletal health, including the prevention of rickets, osteomalacia, and osteoporosis (Bouillon et al., 2023). Beyond its classical musculoskeletal functions, vitamin D has attracted considerable interest because vitamin D insufficiency has been associated with several extra-skeletal disorders, including cardiovascular disease (CVD), diabetes, and cancer (Gunta et al., 2013; Jayedi et al., 2023; Kayaniyil et al., 2010; Khaw et al., 2014; Song et al., 2013). Because suboptimal vitamin D status is common worldwide, vitamin D supplementation has been widely adopted for both clinical and preventive purposes (Amrein et al., 2020; Wang, 2016). However, whether supplementation improves major long-term health outcomes beyond its established skeletal benefits remains uncertain.

A major challenge is the discrepancy between observational evidence and randomized controlled trial findings regarding vitamin D and mortality. Earlier observational studies and meta-analyses suggested that higher vitamin D status or supplementation might be associated with reduced mortality and lower risks of cardiovascular and cancer outcomes (Chowdhury et al., 2014; Sha et al., 2025; Thompson et al., 2023). In contrast, large randomized controlled trials have generally reported little or no protective effect of vitamin D supplementation on all-cause mortality, CVD, or cancer outcomes in the general population. These inconsistencies indicate that the effects of

vitamin D supplementation may not be uniform across populations and that underlying disease status could modify its association with mortality. Accordingly, evaluating supplementation within clinically distinct risk groups may provide a more informative approach than estimating an average effect across the general population.

This issue is particularly important for people with diabetes and CKD, in whom both vitamin D deficiency and adverse clinical outcomes are highly prevalent. Coexisting diabetes and CKD impose a substantial disease burden and are associated with markedly elevated risks of fractures, cardiovascular complications, and premature death (Aleksova et al., 2025; GBD Chronic Kidney Disease Collaboration, 2020; Jepson et al., 2019; Rashid et al., 2025). Individuals with CKD may be more likely to die from cardiovascular causes than to progress to kidney failure, while diabetes further amplifies vascular and metabolic risk. Both conditions are also independently associated with a high prevalence of vitamin D deficiency, which has provided a clinical rationale for considering vitamin D supplementation in these high-risk populations (Bouillon et al., 2019; Turner et al., 2022).

Nevertheless, current scientific evidence does not establish vitamin D supplementation as an effective strategy for reducing mortality or cardiovascular risk among patients with diabetes or CKD. Recent investigations have reported no clear cardiovascular or survival benefit of supplementation among individuals with CKD or type 2 diabetes (Jayedi et al., 2023; Yeung et al., 2023). This uncertainty may partly reflect important alterations in vitamin D metabolism and cardiovascular physiology in these conditions. CKD impairs renal activation of vitamin D and disrupts calcium–phosphate balance, parathyroid hormone regulation, and fibroblast growth factor 23 homeostasis, whereas diabetes is characterized by chronic inflammation, oxidative stress, endothelial dysfunction, and vascular injury (Agoro & White, 2023; An et al., 2023; Wang et al., 2024). These abnormalities may alter the biological consequences of vitamin D supplementation and could contribute to differential associations with mortality according to disease status.

The coexistence of diabetes and CKD may be particularly important because it combines metabolic, renal, inflammatory, and vascular disturbances that could modify both the benefits and potential risks associated with habitual vitamin D supplementation. Although previous studies have evaluated vitamin D

supplementation in the general population or separately among individuals with diabetes or CKD, evidence remains limited regarding mortality outcomes among people with both conditions. Moreover, few studies have explicitly examined whether diabetes and CKD interact with vitamin D supplementation on additive and multiplicative scales. Evaluating these interactions is important because relative associations alone may not fully capture the excess mortality burden attributable to the coexistence of supplementation exposure and high-risk comorbidities.

To address these gaps, the present study used data from the large prospective UK Biobank cohort to investigate the association between habitual vitamin D supplementation and all-cause, CVD, and cancer mortality across four mutually exclusive disease categories: participants without diabetes or CKD, participants with CKD but without diabetes, participants with diabetes but without CKD, and participants with concurrent diabetes and CKD. The novelty of this study lies in evaluating whether the association of habitual vitamin D supplementation with mortality differs according to the combined status of diabetes and CKD, while simultaneously assessing additive and multiplicative interactions and estimating both relative and absolute joint effects. These analyses may clarify whether vitamin D supplementation has heterogeneous associations across clinically distinct populations and provide evidence to support more individualized approaches to supplementation and long-term risk management.

METHODS

Study population

The UK Biobank is a large population-based prospective cohort comprising over half a million adults aged 37-73. Between 2006 and 2010, participants from across England, Scotland, and Wales completed touchscreen questionnaires, underwent physical measurements, reported medical condition and provided blood samples for biomarker analysis.

Diabetes was defined based on any of these criteria: ICD-10 codes in hospitalization data, self-reported medical condition, diabetes medication, diabetes diagnosed by doctors or glycated hemoglobin A1c (HbA_{1c}) $\geq 6.5\%$ at baseline (Qiu et al., 2024). CKD was defined based on any of these criteria: ICD-10 codes in hospitalization data, estimated glomerular filtration rate (eGFR) $< 60 \text{ ml/min/1.73m}^2$ or albuminuria $> 3.4 \text{ mg/mmol}$ at baseline. In the present research analysis, we excluded participants with

physician-diagnosed cancer ($n = 41,353$) or CVD ($n = 27,241$) at baseline, those with incomplete data on vitamin D supplementation ($n = 3,231$) or covariates ($n = 69,630$), and those who were lost to follow-up ($n = 1,107$). Overall, 350,817 participants were included in the main analysis, including 323,813 participants without diabetes or CKD, 11,743 participants with diabetes alone, 13,231 participants with CKD alone, and 2,030 participants with concurrent diabetes and CKD (Supplementary Figure 1).

The UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee, Manchester, U.K. (REC reference for UK Biobank 11/NW/0382), and all participants provided written informed consent.

Assessment of Vitamin D supplements

Information about habitual use of vitamin D supplements was acquired from baseline touchscreen questionnaire. Participants were asked, "Do you regularly take any of the following?" From a list of supplements including vitamin D, participants could select multiple items. Based on their responses, individuals selecting "vitamin D" were categorized as habitual vitamin D supplement users.

Assessment of outcomes

The main outcomes of this study included all-cause mortality, CVD mortality, and cancer mortality. Death records were obtained through National Health Service Digital for individuals living in England and Wales, and via the National Health Service Central Register under the National Records of Scotland for individuals residing in Scotland. Causes of death were defined as cardiovascular disease (International Classification of Diseases, Tenth Revision [ICD-10] codes I00-I99) and cancer (codes C00-C97). Follow-up time was calculated from the date of recruitment until the date of death, loss to follow-up, or censorship.

Assessment of covariates

Population and sociodemographic characteristics (age, sex, education level, race, Townsend deprivation index and body mass index, and lifestyle) and environmental factors (drinking frequency, smoking status, physical activity, cumulative dietary risk factors, sunshine exposure time and sleep duration), and medical history (vitamin and mineral supplements, aspirin use and hypertension) were collected via questionnaires at assessment centers. Biochemical measurements including hemoglobin A_{1c}, creatine, serum calcium and serum

25[OH]D were measured at baseline. Townsend deprivation index and BMI were directly provided by UK Biobank. Physical activity was defined as inactive (moderate activity < 150 min/week and vigorous activity < 75 min/week) and active (moderate activity ≥ 150 min/week or vigorous activity ≥ 75 min/week) (Bull et al., 2020). Cumulative dietary risk factors were represented using a score ranging from 0 (healthiest) to 9 (least healthy), which was derived from 9 food items based on current UK guidelines using baseline data (Petermann-Rocha et al., 2021). EGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration formula considering creatinine, sex, age, and race. Albuminuria, represented by urinary albumin-to-creatinine ratio (ACR), was computed using paired microalbumin and creatinine measurements from the same sample (Tang et al., 2023).

Statistical analysis

Baseline characteristics were presented as mean ± standard deviation (SD) for normally distributed continuous variables, median with interquartile range for non-normally distributed variables, and percentages for categorical variables. Group comparisons were performed using Student's t-test, Wilcoxon test, or chi-square test as appropriate.

Kaplan-Meier curves were generated, and Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between vitamin D supplement use and all-cause mortality and cause-specific mortality in four groups. The proportional hazards assumption was assessed by using Schoenfeld residuals, and time interaction terms for covariates that violated assumptions were added ($p < 0.05$). Three models were fitted to adjust for potential confounding factors. Model 1 was adjusted for age (continuous), sex (male or female), education level (high [college/university degree or above], intermediate [advanced/advanced subsidiary levels, ordinary levels, general certificate of secondary education, certificate of secondary education, national vocational qualification or higher national diploma, or equivalent, and other professional qualifications] and low [none of the above]), and Townsend deprivation index (continuous). Model 2 was further adjusted for alcohol intake frequency (never, less than 3 times/week, and ≥ 3 times/week), smoking status (never, past, or current), physical activity (inactive or active), cumulative dietary risk factors (0 to 9), sleep duration (< 7 hours/day or ≥ 7 hours/day), BMI (continuous), and hypertension (yes or no). To

reduce confounding by indication, which may arise from differences in disease severity, comorbidity burden, or other unmeasured factors, we further adjusted for falls in the last year (yes or no), fractured in the last 5 years (yes or no) and insulin use (yes or no). The full model for individuals with diabetes alone was further adjusted for HbA1c (< 9 or ≥ 9%) and duration of diabetes (< 10 or ≥ 10 years), for those with CKD alone was further adjusted for eGFR (<30, or ≥ 30ml/min/1.73m²) and ACR (< 34 or ≥ 34mg/mmol), and for those with both diabetes and CKD was further adjusted for HbA1c (< 9 or ≥ 9%), duration of diabetes (<10 or ≥10 years), eGFR (<30, or ≥ 30ml/min/1.73m²) and ACR (< 34 or ≥ 34mg/mmol).

To evaluate whether coexisting diabetes and CKD could modify the association of vitamin D supplements with all-cause mortality and CVD mortality, we assessed interactions using both additive and multiplicative scales. Additive interaction was evaluated by three indexes: the relative excess risk because of the interaction (RERI), the attributable proportion because of the interaction (AP) and synergy index (SI). To investigate the absolute and relative joint effects, we further divided participants into eight groups according to habitual vitamin D supplements use (vitamin D nonusers or users) and diseases status. Using participants without diabetes, CKD, and vitamin D supplementation as the reference, we conducted dual analyses: Cox proportional hazards models to estimate HRs for all-cause and CVD mortality, and Aalen's additive hazards models to calculate hazard differences (HDs) per 100,000 person-years, modeling the hazard as a linear function of explanatory variables to quantify the absolute excess risk (Rod et al., 2020; Shin et al., 2021).

Stratified analyses were performed by age (<60, ≥60 years), sex (female, male), falls in the last years (yes or no) and fractured/broken bones in last 5 years (yes or no) in individuals without diabetes or CKD. In individuals with coexisting diabetes and CKD, we further stratified by diabetes duration (<10, ≥10 years), HbA1c (<9%, ≥9%), eGFR (<30, 30-59 mL/min/1.73m²), ACR (<34, ≥34 mg/mmol) and insulin use (yes or no).

We also conducted a series of sensitivity analyses. First of all, we repeated main analyses in a 1:4 propensity score-matched cohort to further reduce the risk of confounding. Propensity scores were estimated using a logistic regression model that included all covariates previously detailed in model 3. Second, we applied multiple imputations with chained equations to account for missing values of covariates.

Third, we used Fine and Gray's proportional sub-hazards model to address competing risks from other causes in the analyses of CVD and cancer mortality, respectively. Fourth, to reduce the potential impact of reverse causation, we excluded participants who died within the first 2 years of follow-up. Fifth, to address potential confounding by indication, we used an active comparator design with glucosamine or fish oil users as the comparator group for vitamin D. Lastly, to assess whether commonly prescribed medications in patients with coexisting diabetes and CKD might interact with vitamin D supplements, we performed stratified analyses according to the use of metformin, ACE inhibitors, angiotensin-receptor blockers, beta-blockers, aspirin, and statins. P-values were adjusted for multiple comparisons using the false discovery rate (FDR) method. All statistical analyses were performed with R (version 4.5.0; R Core Team, 2025). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the participants with coexisting diabetes and CKD and those without either condition are shown in [Table 1](#); Compared to vitamin D non-users, individuals who took vitamin D supplements (including those with both diabetes and CKD, diabetes alone, CKD alone, and those without diabetes or CKD) were more likely to be female, non-white people, nondrinkers, have a lower cumulative dietary risk factor score.

Association between vitamin D supplementation and the risk of mortality

During a median [interquartile range (IQR)] follow-up of 15.3 (1.4) years, a total of 24,636 death events were recorded. Of these death events, 7,748 were caused by CVD and 12,214 were caused by cancer (see [Table 1](#)).

[Table 2](#) presents the associations of habitual vitamin D supplementation with all-cause mortality and specific mortality in participants with and without diabetes and CKD. After fully adjusting for confounders, habitual vitamin D supplementation was associated with lower risk of cancer mortality (HR 0.88 [95% CI 0.80, 0.98]) among participants without diabetes or CKD. In contrast, among participants with both diabetes and CKD, we found hazardous associations between vitamin D supplement use and all-cause mortality (HR 1.87 [95% CI 1.27, 2.76]) and CVD mortality (HR 1.81 [95% CI 1.11, 2.95]). Similar

positive association was observed between vitamin D supplement use and all-cause mortality (HR 1.38 [95% CI 1.09, 1.75]) in participants with diabetes alone, whereas no significant association was observed in participants with CKD alone (for all-cause mortality, HR 1.01 [95% CI 0.79, 1.29]; for CVD mortality, HR 0.94 [95% CI 0.64, 1.38], for cancer mortality, HR 1.01 [95% CI 0.71, 1.46]). According to the Kaplan-Meier curves, survival for all-cause and CVD mortality was significantly lower in vitamin D users than in non-users only among participants with both diabetes and CKD ([Supplementary 12](#)). No such difference was found in the other participant groups ([Supplementary 13-15](#)).

Joint association of habitual vitamin D supplementation, diabetes and CKD status with mortality risk

We observed additive and multiplicative interactions between habitual vitamin D supplementation and disease status on mortality (see [Table 3](#)). For participants with diabetes and CKD, the RERI was 1.34 (95% CI 0.34, 2.35) for all-cause mortality and 1.82 (95% CI 0.16, 3.49) for CVD mortality. The AP due to interaction was 41% (0.23, 0.59) for all-cause mortality and 43% (95% CI 0.20, 0.65) for CVD mortality, indicating that a substantial fraction of the risk in this population is attributable to the synergistic effect. The SI was 2.44 (95% CI 1.53, 3.87) for all-cause mortality and 2.26 (95% CI 1.33, 3.85) for CVD mortality. The HR for the multiplicative interaction term was 1.69 (95% CI 1.23, 2.33) for all-cause mortality and 1.71 (95% CI 1.13, 2.58) for CVD mortality, respectively ($P_{\text{interaction}} < 0.001$).

We conducted a joint analysis of vitamin D supplement use and diseases status with risk of mortality ([Supplementary 11](#)). The association between vitamin D supplementation and the risk of all-cause mortality varied according to diseases status ($P_{\text{interaction}} = 0.001$). Compared to individuals without diabetes, CKD, and vitamin D supplementation, the risk of all-cause mortality was higher among participants with diabetes alone who did not use vitamin D (HR 1.40 [95% CI 1.33, 1.46]) and was further elevated among those who did (HR 1.80 [95% CI 1.49, 2.19]), corresponding to 954 and 1140 excess deaths per 100,000 person-years, respectively. In individuals with CKD alone, vitamin D users (HR 1.76 [95% CI 1.46, 2.12]) and nonusers (HR 1.55 [95% CI 1.49, 1.63]) had similar risks of all-cause mortality, corresponding to an excess of 877 and 961 deaths per 100,000 person-years, respectively. Among participants with both diabetes and CKD, vitamin D

Table 1

*Baseline Characteristics of study participants with and without concurrent diabetes and CKD**

Characteristic	Total	Vitamin D supplement nonusers	Vitamin D supplement users	P value
Without diabetes or CKD				
N of participants	323813	311354	12459	
Age (years)	55.52 ± 8.09	55.42 ± 8.09	57.79 ± 7.65	<0.001
Male sex	145346 (44.9)	141777 (45.5)	3569 (28.6)	<0.001
White race	287,320 (91.7)	276,791 (91.8)	10,529 (87.4)	<0.001
Education				<0.001
Low	45165 (13.9)	43566 (14.0)	1599 (12.8)	
Intermediate	164176 (50.7)	158096 (50.8)	6080 (48.8)	
High	114472 (35.4)	109692 (35.2)	4780 (38.4)	
Townsend deprivation index	-1.51 ± 2.96	-1.52 ± 2.96	-1.30 ± 3.07	<0.001
BMI (kg/m2)	26.96 ± 4.49	27.00 ± 4.49	26.08 ± 4.39	<0.001
Drinking frequency				<0.001
Never	20990 (6.5)	19785 (6.4)	1205 (9.7)	
Less than twice a week	154604 (47.7)	148683 (47.8)	5921 (47.5)	
More than three times a week	148219 (45.8)	142886 (45.9)	5333 (42.8)	
Smoking status				<0.001
Never	183908 (56.8)	176695 (56.8)	7213 (57.9)	
Previous	107322 (33.1)	103110 (33.1)	4212 (33.8)	
Current	31843 (9.8)	30834 (9.9)	1009 (8.1)	
Active physical activity	165644 (51.2)	158752 (51.0)	6892 (55.3)	<0.001
Cumulative dietary risk factors	4.97 ± 1.58	4.99 ± 1.57	4.49 ± 1.56	<0.001
Sleep duration (> 7h/d)	247050 (76.3)	237741 (76.4)	9309 (74.7)	<0.001
Falls in the last years	58421 (18.0)	55471 (17.8)	2950 (23.7)	<0.001
Fractured/broken bones in last 5 years	30014 (9.3)	28314 (9.1)	1700 (13.6)	<0.001
With both diabetes and CKD				
N of participants	2030	1962	68	
Age (years)	60.12 ± 7.04	60.12 ± 7.01	60.07 ± 7.89	0.958
Male sex	1393 (68.6)	1355 (69.1)	38 (55.9)	0.03
White race	1791 (88.2)	1736 (88.5)	55 (80.9)	0.085
Education				0.942
Low	575 (28.3)	557 (28.4)	18 (26.5)	
Intermediate	959 (47.2)	926 (47.2)	33 (48.5)	
High	496 (24.4)	479 (24.4)	17 (25.0)	
Townsend deprivation index	-0.29 ± 3.42	-0.32 ± 3.42	0.51 ± 3.36	0.05
BMI (kg/m2)	32.60 ± 6.18	32.65 ± 6.19	31.23 ± 5.81	0.064
Drinking frequency				<0.001
Never	333 (16.4)	310 (15.8)	23 (33.8)	
Less than twice a week	1104 (54.4)	1078 (54.9)	26 (38.2)	
More than three times a week	593 (29.2)	574 (29.3)	19 (27.9)	
Smoking status				0.26
Never	870 (42.9)	837 (42.7)	33 (48.5)	
Previous	916 (45.1)	884 (45.1)	32 (47.1)	
Current	236 (11.6)	233 (11.9)	3 (4.4)	
Active physical activity	780 (38.4)	751 (38.3)	29 (42.6)	0.548
Cumulative dietary risk factors	5.11 ± 1.56	5.14 ± 1.55	4.32 ± 1.60	<0.001
Sleep duration (> 7h/d)	1460 (71.9)	1411 (71.9)	49 (72.1)	0.98
Falls in the last years	495 (24.4)	477 (24.3)	18 (26.5)	0.792
Fractured/broken bones in last 5 years	187 (9.2)	179 (9.1)	8 (11.8)	0.598
HbA1c (<9%)	1765 (86.9)	1709 (87.1)	56 (82.4)	0.253
Diabetes duration (<10 years)	1245 (61.3)	1205 (61.4)	40 (58.8)	0.666
Insulin use (Yes)	530 (26.1)	514 (26.2)	16 (23.5)	0.622
eGFR				0.07
≥30 mL/min/1.73 m2	1974 (97.2)	1909 (97.3)	65 (95.6)	
15-30 mL/min/1.73 m2	46 (2.3)	45 (2.3)	1 (1.5)	
<15 mL/min/1.73 m2	10 (0.5)	8 (0.4)	2 (2.9)	
ACR (<34 mg/mmol)	1801 (88.7)	1743 (88.8)	58 (85.3)	0.364

Note: *) Continuous variables with a normal distribution were described using mean ± SD, and non-normally distributed data were described with median and interquartile range. Categorical data were presented as percentages (%). P difference in the baseline characteristic between vitamin D supplement users and nonusers in participants without diabetes or CKD and with both diabetes and CKD. HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.

Table 2

Associations (HR, 95% CI) of habitual vitamin D supplementation with all-cause and specific mortality in participants with and without diabetes and CKD

Status	All-cause mortality	CVD mortality	Cancer mortality
Without diabetes or CKD			
Events/N	19222/323813	5886/323813	10552/323813
Model 1	0.94 (0.87, 1.01)	0.95 (0.83, 1.08)	0.84 (0.76, 0.93)
P	0.12	0.571	<0.001
Model 2	0.98 (0.91, 1.05)	1.00 (0.88, 1.15)	0.87 (0.79, 0.97)
P	0.551	0.902	0.009
Model 3	1.00 (0.94, 1.09)	1.04 (0.91, 1.19)	0.88 (0.80, 0.98)
P	0.792	0.542	0.023
With diabetes alone			
Events/N	1712/11743	791/11743	743/11743
Model 1	1.33 (1.05, 1.68)	1.04 (0.71, 1.54)	1.35 (0.95, 1.92)
P	0.016	0.82	0.092
Model 2	1.38 (1.09, 1.74)	1.08 (0.74, 1.59)	1.41 (0.98, 1.99)
P	0.007	0.682	0.058
Model 3	1.38 (1.09, 1.75)	1.10 (0.75, 1.62)	1.41 (0.98, 2.00)
P	0.007	0.632	0.057
With CKD alone			
Events/N	1672/13231	714/13231	764/13231
Model 1	0.98 (0.77, 1.25)	0.96 (0.65, 1.40)	0.97 (0.68, 1.39)
P	0.879	0.813	0.862
Model 2	1.06 (0.83, 1.35)	1.03 (0.71, 1.51)	1.04 (0.73, 1.49)
P	0.656	0.867	0.819
Model 3	1.01 (0.79, 1.29)	0.94 (0.64, 1.38)	1.01 (0.71, 1.46)
P	0.932	0.758	0.943
With both diabetes and CKD			
Events/N	578/2030	357/2030	155/2030
Model 1	1.66 (1.13, 2.43)	1.69 (1.05, 2.71)	0.57 (0.18, 1.79)
P	0.009	0.031	0.336
Model 2	1.78 (1.21, 2.62)	1.84 (1.13, 2.97)	0.66 (0.21, 2.08)
P	0.003	0.014	0.474
Model 3	1.87 (1.27, 2.76)	1.81 (1.11, 2.95)	0.67 (0.21, 2.13)
P	0.001	0.017	0.501

Note: Model 1, adjusted for age (continuous), sex (male or female), education level (high, intermediate and low) and Townsend deprivation index (continuous). Model 2, further adjusted for alcohol intake frequency (never, less than 3 times/week, and ≥ 3 times/week), smoking status (never, past, or current), physical activity (inactive or active), cumulative dietary risk factors (0 to 9), sleep duration (< 7 or ≥ 7 hours/day), BMI (continuous), and hypertension (yes or no). Model 3, further adjusted for falls in the last years (yes or no) and fractured/broken bones in last 5 years (yes or no). The full model for individuals with diabetes alone was adjusted for HbA_{1c} (< 9 or $\geq 9\%$) and duration of diabetes (< 10 or ≥ 10 years), for those with CKD alone was adjusted for eGFR (< 15 , 15-30, or ≥ 30 ml/min/1.73m²) and ACR (< 34 or ≥ 34 mg/mmol), and for those with both diabetes and CKD was additionally adjusted for HbA_{1c} (< 9 or $\geq 9\%$), duration of diabetes (< 10 or ≥ 10 years), eGFR (< 15 , 15-30, or ≥ 30 ml/min/1.73m²) and ACR (< 34 or ≥ 34 mg/mmol).

users (HR 3.80 [95% CI 2.81, 5.16]) had a 1.7-fold higher risk of all-cause mortality than non-users (HR 2.23 [95% CI 2.07, 2.41]), corresponding to nearly 1.5 times the number of extra deaths per 100,000 person-years (2860 versus 1930 deaths, respectively). Similar interaction patterns were observed for CVD mortality ($P_{\text{interaction}} = 0.007$).

Additional analyses

In the stratified analysis, no significant interactions were found after accounting for multiple testing (Supplementary 2).

We reran the analysis in the 1:4 propensity score-matched cohort. The standardized differences

for all covariates were < 0.1 (Supplementary 13) and highly similar matching histograms (Supplementary 16) showed good balance between vitamin D users and nonusers. The associations were not materially changed in the 1:4 propensity score-matched cohort (Supplementary 14). The results were similar in sensitivity analyses that accounted for multiple imputations with chained equations (Supplementary 15-16), competing risk of mortality for other causes, stratification according to common medications used by patients with both diabetes and CKD, and excluding deaths that occurred within first 2 years of follow-up. While results from the active comparator design remained similar, we further found that when

Table 3

Multiplicative and additive interactions between habitual vitamin D supplementation and diabetes–CKD comorbidity status on mortality risk

Interaction Type	All-cause mortality	CVD mortality	Cancer mortality
Multiplicative interaction			
HR (95%CI)	1.69 (1.23, 2.33)	1.71 (1.13, 2.58)	1.10 (0.54, 2.24)
Additive interaction			
RERI(95%CI)	1.34 (0.34, 2.35)	1.82 (0.16, 3.49)	0.09 (-0.73, 0.91)
AP(95%CI)	0.41 (0.23, 0.59)	0.43 (0.20, 0.65)	0.07 (-0.57, 0.73)
SI(95%CI)	2.44 (1.53, 3.87)	2.26 (1.33, 3.85)	2.28 (0.01, 573)

Note: HR represents the interaction between vitamin D supplementation and diabetes/CKD comorbidity status in the Cox regression model. Reference group: participants without diabetes or CKD and without vitamin D supplementation. Adjusted for age (continuous), sex (male or female), education level (high, intermediate and low) and Townsend deprivation index (continuous), alcohol intake frequency (never, less than 3 times/week, and ≥ 3 times/week), smoking status (never, past, or current), physical activity (inactive or active), cumulative dietary risk factors (0 to 9), sleep duration (< 7 or ≥ 7 hours/day), BMI (continuous), and hypertension (yes or no), falls in the last years (yes or no) and fractured/broken bones in last 5 years (yes or no).

glucosamine was used as the comparator, vitamin D use was associated with higher risks of both CVD mortality and cancer mortality in participants with diabetes alone.

DISCUSSION

Our analysis found a protective association with cancer mortality only in individuals without diabetes or CKD. In contrast, vitamin D supplementation was associated with a higher risk of all-cause mortality in individuals with diabetes alone. As for those with both diabetes and CKD, vitamin D use was significantly associated with higher risks of all-cause and CVD mortality. Results remained robust across a variety of sensitivity analyses. Furthermore, we quantified both additive and multiplicative interactions between habitual vitamin D supplementation and different disease conditions on mortality risks.

To our knowledge, this is the first large prospective population-based study to evaluate the association of habitual vitamin D supplementation with mortality risk in four distinct disease status. Current evidence on the association between vitamin D supplementation and mortality risk is controversial. Some studies have demonstrated that vitamin D use was inversely associated with all-cause, CVD and cancer mortality (Keum et al., 2019; Liu et al., 2022; Sha et al., 2023), while others have found no significant associations (Barbarawi et al., 2019; Manson et al., 2019). For example, a recent large RCT found no reduction in all-cause mortality with vitamin D3 supplementation (Neale et al., 2022). In observational studies, vitamin D treatment was significantly associated with reductions in both all-cause and CVD mortality in the CKD population. However, this association was not confirmed in RCTs

(Lu et al., 2017). Vitamin D supplementation did not change the risks of all-cause or CVD mortality in patients with type 2 diabetes or prediabetes (Jayedi et al., 2023). However, the effect of supplementation in individuals with concurrent diabetes and CKD has been scarcely investigated. Our study showed that the association between habitual vitamin D use and mortality may be modified by comorbid conditions.

We observed a significant reduction in cancer mortality among individuals without diabetes or CKD, aligning with prior study (Keum et al., 2019). In contrast, vitamin D use was associated with increased all-cause mortality in patients with diabetes alone, which appears to conflict with results based on low-certainty evidence (Jayedi et al., 2023). And no significant associations were observed in those with CKD alone, consistent with null findings (Lu et al., 2017; Vervloet et al., 2023). Notably, we identified a markedly elevated risk of all-cause and CVD mortality in the high-risk subgroup with coexisting diabetes and CKD. These findings offer a possible hypothesis that the divergent effects of vitamin D supplementation depend on distinct subgroups, and this may partly explain the longstanding inconsistency.

In the joint analysis, the results from the Aalen's additive hazards model were consistent with the hazardous association we observed with the all-cause mortality using the Cox model. The excess cases of all-cause mortality estimated to be due to vitamin D use provided direct estimations of the absolute public health impact of habitual vitamin D supplementation. Such association between vitamin D use and CVD mortality was also observed. Moreover, the significant measures on the additive scale (RERI, AP and SI) revealed a synergistic effect between habitual vitamin D supplementation and the presence of both diabetes and CKD on mortality risk. Both

Aalen's model and measures on the additive scale provided direct evaluation on the public health significance of the interaction. This underscores that patients suffering from both diabetes and CKD represent a vulnerable population in whom vitamin D supplementation might be associated with unexpectedly high risks. The active comparator design revealed that among individuals with diabetes alone, vitamin D supplementation was associated with a higher risk of CVD mortality (HR 1.59, 95% CI 1.03–2.45) and cancer mortality (HR 1.63, 95% CI 1.10–2.41) when compared to glucosamine users. A possible explanation for this is that glucosamine may exert a protective effect among patients with diabetes. Given that glucosamine use has been consistently linked to a lower risk of cardiovascular disease (Ma et al., n.d.), its capacity to significantly lower mortality in the diabetic subgroup would, by comparison, make vitamin D supplementation appear to carry a 'higher risk.'

Although previous studies have primarily discussed the potential benefits of vitamin D supplementation in the general population (Keum et al., 2019; Sha et al., 2023), some possible explanations may interpret the mechanisms underlying its adverse effects in patients with coexisting diabetes and CKD. A unique pathophysiological milieu in patients with coexisting diabetes and CKD underlies their vulnerability. Key features include chronic oxidative stress, persistent inflammation, and a heightened susceptibility to vascular calcification and fracture. In this context, previously reported adverse effects of vitamin D, such as the promotion of atherosclerotic calcification (Ellam et al., 2014) and an increased risk of falls (Bischoff-Ferrari et al., 2016; Km et al., 2010; Zittermann et al., 2023) may be amplified. Thus, in a population already at extreme baseline risk for cardiovascular events and fractures, vitamin D supplementation might paradoxically exacerbate the very complications it is often presumed to prevent, leading to the observed increase in mortality. Future research is needed to clarify the underlying mechanisms behind the observed relationship.

The present findings may be interpreted within the Islamic principle of preserving life (*hifz al-nafs*), one of the fundamental objectives of *Maqasid al-Shariah*. Islam encourages the maintenance of health while avoiding practices that may cause preventable harm. The Qur'an states in Surah Al-Baqarah verse 195:

"Do not let your own hands throw you into destruction."

This verse emphasizes the ethical responsibility to consider both the potential benefits and risks of health-related practices. This principle is also consistent with the Prophetic maxim narrated in Sunan Ibn Majah (Hadith No. 32:

"There should be neither harm nor reciprocating harm."

In the context of this study, the higher risks of all-cause and cardiovascular mortality associated with habitual vitamin D supplementation among individuals with coexisting diabetes and CKD should not be interpreted as evidence that vitamin D is inherently harmful. Rather, these findings reinforce the Islamic principle that health interventions should be tailored to individual needs, clinical conditions, and reliable scientific evidence. The Qur'an further instructs believers in Surah An-Nahl verse 43:

"Ask those who have knowledge if you do not know."

This guidance supports consultation with qualified healthcare professionals before initiating or continuing supplementation, particularly among individuals with complex chronic conditions.

From a family health perspective, these Islamic values emphasize shared responsibility among patients, families, and healthcare professionals in making informed decisions regarding supplement use. Families can support treatment adherence, monitor medication and supplement use, encourage appropriate clinical follow-up, and help prevent unsupervised practices that may increase health risks. Therefore, the present findings support a cautious and individualized approach to vitamin D supplementation that integrates scientific evidence with the Islamic values of preserving life, preventing harm, seeking expert knowledge, and promoting responsible health stewardship.

This study has several strengths. On the one hand, it leverages the large scale and prospective design of the UK Biobank, which allowed for comprehensive adjustment for sociodemographic, lifestyle, and confounders. On the other hand, we conducted several subgroup analyses and sensitivity analyses to examine the robustness of our findings and further examined the effects of dietary vitamin D and serum 25(OH)D. However, several limitations are worth considering. First, the assessment of vitamin D use relied on self-report at baseline, which may introduce reporting bias. Second, information on the type (e.g., vitamin D2 or D3) and dosage of vitamin D supplements was not collected. Second, changes in

vitamin D supplements use during the follow-up period may potentially influence the results. Further studies are needed to investigate the temporal relationship. Third, data on the ACR were available only for a subset of the population. This may influence its applicability as a confounding variable (Tang et al., 2023). Fourth, the exclusive inclusion of European populations may limit the generalizability of our findings to other ethnic groups or geographic regions. Finally, despite adjusting for history of falls and fractures, disease severity of diabetes and CKD in the Cox model, and using an active comparator design to reduce confounding by indication, residual confounding by indication probably remains. From a family health perspective, appropriate vitamin D use should be guided by clinical need and individual risk, while family support, responsible health behaviours, and avoidance of unnecessary supplementation are consistent with broader ethical and faith-based values that emphasise the protection of health and wellbeing.

CONCLUSIONS

In conclusion, habitual vitamin D supplementation was significantly associated with higher risks of all-cause and cardiovascular disease mortality among individuals with coexisting diabetes and chronic kidney disease, whereas these associations were not observed among participants without either condition. These findings suggest that the association between vitamin D supplementation and mortality may vary according to underlying disease status, highlighting the importance of considering clinical comorbidities when evaluating the potential benefits and risks of supplementation. The study contributes novel evidence by demonstrating heterogeneous mortality associations across combined diabetes and CKD categories and by emphasizing the potential relevance of disease-specific risk stratification. From a family health perspective, these findings support more individualized counseling, careful clinical monitoring, and informed decision-making regarding supplement use, particularly for individuals with multiple chronic conditions. Nevertheless, the observational nature of the study precludes causal inference, and the findings should not be interpreted as evidence that vitamin D supplementation directly causes harm. Future studies incorporating detailed information on supplement dosage, indication, formulation, duration, adherence, and longitudinal changes in exposure are warranted. Randomized controlled trials specifically involving

patients with concurrent diabetes and CKD are also needed to confirm these findings and to clarify the balance between the potential benefits and risks of vitamin D supplementation in this high-risk population.

ACKNOWLEDGEMENT

The authors sincerely acknowledge the UK Biobank participants and research team for providing the data and resources that made this study possible. We also express our appreciation to all colleagues and institutions that contributed scientific, technical, and academic support throughout the research process. Their valuable assistance and commitment greatly supported the completion of this study.

FUNDING

This research received no funding.

AUTHORS' CONTRIBUTIONS

Chaorui Li designed the research and conducted the statistical analysis. Qingxuan Wang prepared the tables and figures and wrote the draft of the manuscript. All authors approved the final version.

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SUPPLEMENTARY MATERIALS

Supplementary materials are available online with the published article.

COMPETING INTERESTS

The author(s) declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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