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Vitamin D status, vitamin D receptor polymorphisms, and risk of cardiometabolic multimorbidity

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Abstract

Background The prevalence of cardiometabolic multimorbidity (CMM) has increased substantially in recent years. Previous studies have established the associations between vitamin D, vitamin D receptor (VDR) polymorphisms, and the risk of individual cardiometabolic disease (CMD). However, the role of these factors in the progression of CMD to CMM or mortality remains unclear. This study aimed to investigate the associations between vitamin D, VDR polymorphisms, and the dynamic progression of CMM, as well as to explore the potential modification effect of VDR polymorphisms.

Methods Data for this cohort study were extracted from the UK Biobank. CMM was defined as the coexistence of at least two CMDs, including type 2 diabetes (T2D), coronary heart disease (CHD), and stroke. A multi-state model was used to analyze associations between serum 25(OH)D, VDR polymorphisms and the dynamic progression of CMM.

Results The sample included 396,192 participants. Over a median follow-up of 13.8 years, 55,772 individuals experienced at least one CMD and 28,624 died. Compared to participants with 25(OH)D < 25 nmol/L, those with 25(OH)D ≥ 75 nmol/L had HRs of 0.70 (95% CI, 0.67, 0.72) for baseline to first CMD (FCMD), 0.74 (95% CI, 0.67, 0.82) for FCMD to CMM, 0.66 (95% CI, 0.62, 0.70) for baseline to death, 0.84 (95% CI, 0.77, 0.92) for FCMD to death, and 0.85 (95% CI, 0.70, 1.03) for CMM to death. L-shaped relationships of these associations were noted, with a threshold around 45 nmol/L. The rs1544410 (BsmI) T alleles may have a detrimental effect, while the rs11568820 (Cdx2) T alleles may exert a protective effect in the early stages of CMM progression. Additionally, VDR polymorphisms significantly modified the association between serum 25(OH)D and certain stages of CMM progression.

Conclusions Maintaining adequate vitamin D levels, as a readily implementable intervention strategy, not only reduces the risk of initial CMD but also delays the progression to CMM or death. Risk stratification based on VDR polymorphisms provides further insights for developing personalized prevention strategies.

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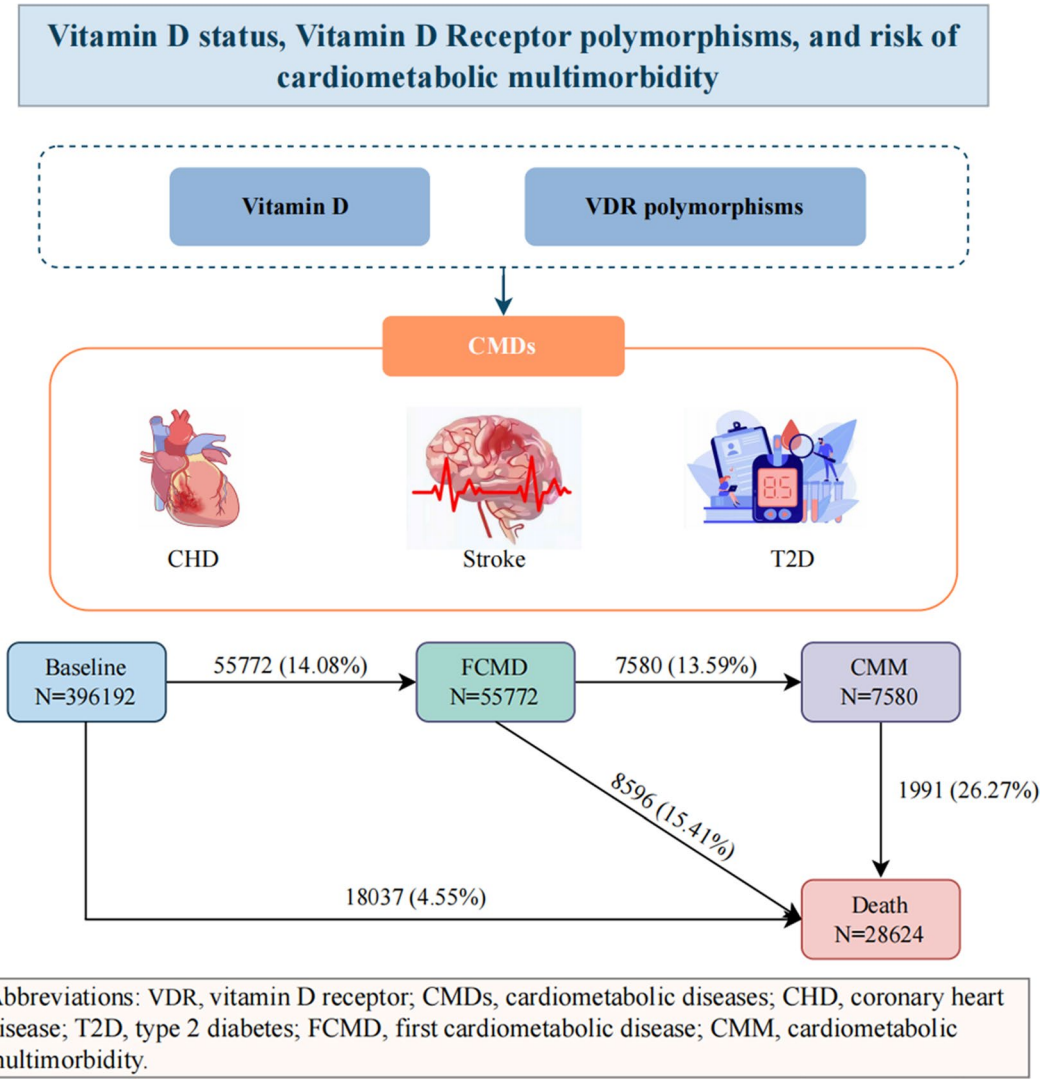
Graphical Abstract



Keywords Vitamin D, Vitamin D receptor polymorphisms, Cardiometabolic Multimorbidity

Introduction

Cardiometabolic multimorbidity (CMM) is defined as the coexistence of at least two cardiometabolic diseases (CMDs). In this study, CMDs primarily include type 2 diabetes (T2D), coronary heart disease (CHD), and stroke [1, 2]. Research has shown that individuals with any combination of multiple CMDs have a multiplicatively higher risk of death and a substantially shorter life expectancy compared to those without CMD or those with only a single CMD [1]. Epidemiological studies revealed that nearly 25% of patients with CMDs in Canada [3] and South Asia [4] were affected by CMM. With population aging, the prevalence of CMM is rising [5], with one third of older adults affected by at least two comorbidities of CMDs [6]. CMM leads to adverse health outcomes, including reduced quality of life and an increased risk of disability, hospitalization and mortality in older individuals [7, 8]. Notably, recent evidence suggests that the prevalence of cardiometabolic diseases has increased among young adults in recent years [9, 10]. Therefore, identifying modifiable factors and implementing effective interventions to prevent CMM are vital for reducing the risk of its onset and mitigating its long-term health impacts.

Among various interventions, easy-to-implement dietary modification plays a crucial role in delaying the development of CMM [11, 12]. Vitamin D, a fat-soluble vitamin, can be synthesized in the human body through

skin exposure to sunlight and is also obtainable from dietary sources or supplements [13, 14]. The prevalence of vitamin D deficiency is generally high worldwide [15], especially in the middle-aged and elderly population [16]. A significant negative correlation was observed between higher serum vitamin D and morbidity of individual CMD [17–20]. However, the role of vitamin D levels in the onset and dynamic progression of CMM remains unclear, including from baseline to first cardiometabolic disease (FCMD), then to CMM, and finally to death.

Vitamin D binds to the vitamin D receptor (VDR) to exert its biological effects [14]. Studies have shown that VDR polymorphisms may influence the association between vitamin D and certain health outcomes, such as tuberculosis [21], hepatocellular carcinoma survival [22], and diabetic complications [23]. However, it remains unclear whether VDR polymorphisms alter the association between serum vitamin D and the progression of CMM.

In this study, we aimed to assess the associations between serum 25-hydroxyvitamin D [25(OH)D] levels, VDR polymorphisms, and the dynamic progression of CMM, from baseline to FCMD, then to CMM, and finally to death. In addition, we examined the modifying effect of VDR polymorphisms on the role of serum 25(OH)D in these processes. Our findings aimed to provide key insights for improving primary and secondary prevention strategies for CMM, reducing disease burden, and promoting healthy aging.

Methods

Study design and population

The data for this study were extracted from the UK Biobank, a large population-based cohort study. The study recruited over 500,000 middle-aged and older adults, aged 37 to 74, from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010. The UK Biobank has received approval from the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent at baseline. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [24].

We excluded the following participants who did not meet the criteria: (1) lost to follow-up or withdrew ($n = 1130$), (2) missing information on serum 25(OH)D concentration ($n = 54{,}430$), (3) had at least one cardiometabolic disease ($n = 50{,}601$), (4) unreliable information on outcomes ($n = 16$), 396,192 participants were included in the final phenotypic data analysis. For the genetic analysis, we also excluded 6167 participants without available data on genetic polymorphisms (Fig. 1).

Assessment of serum 25(OH)D

Measurement of serum 25(OH)D has been detailed previously (https://www.ukbiobank.ac.uk). In summary, serum 25(OH)D concentrations were measured at the baseline visit using chemiluminescent immunoassay method on the DiaSorin Liaison XL Analyze. Serum 25(OH)D was measured in nmol/L.

Assessment of VDR polymorphisms

In this study, we selected two well-studied VDR single nucleotide polymorphisms (SNPs), including rs1544410 (BsmI) and rs11568820 (Cdx2), which may influence VDR activity. Previous studies have suggested that the minor allele of Cdx2 may be associated with increased VDR expression or activity [25, 26], whereas the minor allele of BsmI may be linked to reduced VDR activity [27]. Furthermore, the degree of linkage disequilibrium between BsmI and Cdx2 is low, with an R^2 value of 0.003 and a D' value of 0.089, indicating that these two loci are genetically independent.

Assessment of outcomes

In this study, CMM is defined as the presence of two or more concurrent CMDs (e.g., T2D, CHD, and stroke), consistent with previous studies [28]. The incidence of these events was derived from hospital inpatient visits and all-cause mortality events were identified through

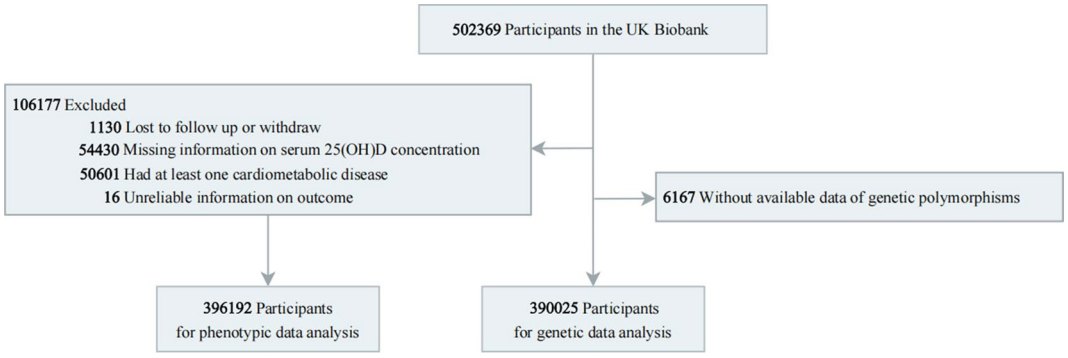


Fig. 1 Flowchart of participant selection in the UK Biobank

a link to the national death registries. According to the International Classification of Diseases, 10th Revision (ICD10th), outcome events were coded as T2D (E11), CHD (I20-I25), and stroke (I60-I69, H34).

Assessment of covariates

Covariates included age, sex, ethnicity, season of blood collection, Townsend Deprivation Index (TDI), education, smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer. Based on the months that participants visited the assessment center, blood draw seasons were divided into four seasons: spring (March–May), summer (June–August), autumn (September–November), and winter (December–February) [29]. The Townsend Deprivation Index (TDI) combined four Census variables: unemployment, lack of car ownership, lack of home ownership, and household overcrowding, with lower TDI values indicating higher socioeconomic status. A healthy diet met at least two of the following criteria: total fruit and vegetable intake > 4.5 pieces or servings/week [One piece of fruit (e.g., one apple, one banana, 10 grapes) or 3 tablespoons of vegetables was considered one serving], total fish intake > 2 times/week, processed m eat intake ≤ 2 times per week, and red meat intake ≤ 5 times per week [30]. BMI was calculated as weight in kilograms divided by the square of height in meters. Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short form and categorized into low, moderate, and high groups [28].

Statistical analysis

Serum 25(OH)D concentration was natural log-transformed for analysis as a continuous variable. As a categorical variable, it was classified into four groups based on Endocrine Society guidelines: <25.0, 25.0-49.9, 50.0-74.9, and ≥ 75.0 nmol/L [31]. Person-time was calculated from the assessment center visit date to the earliest of outcome diagnosis, death, or the end of follow-up: 31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales. Student's t-test and chi-square test were employed to evaluate baseline characteristics by incident disease status during follow-up.

Traditional Cox proportional risk models were used to estimate associations of serum 25(OH)D and VDR polymorphisms with FCMD, CMM and all-cause mortality as a preliminary analysis. To test the proportionality assumption, we used Kaplan-Meier curves and Schoenfeld residuals. In cases of assumption violation, we interpreted the hazard ratios (HRs) as weighted averages of time-varying HRs throughout the follow-up period [32, 33]. Three models were fitted: model 1 was adjusted for age, sex, ethnicity, season of blood collection; model 2 was additionally adjusted for Townsend Deprivation Index (TDI), education; model 3 was additionally adjusted for smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer. Subsequently, we further analyzed these associations between serum 25(OH)D, VDR polymorphisms and the dynamic progression of CMM using a multi-state model. Multi-state model was extensions of traditional Cox proportional and competing risk models and were widely used to explore the impact of risk factors of interest on multiple transition outcomes [34, 35]. The five stages of transformation were defined for this study: (1) baseline to FCMD, (2) FCMD to CMM, (3) baseline to death, (4) FCMD to death, and (5) CMM to death. The diagnosis date of the CMM was the date of the second diagnosis of CMD. For participants who entered different stages on the same date, we calculated the theoretical entry date of the previous state as the date of the latter state minus 0.5 days, based on the previous study [36]. For example, for patients first diagnosed with CMM, the date of entering FCMD corresponded to the date of CMM minus 0.5 day. Multi-state model was adjusted for age, sex, ethnicity, season of blood collection, Townsend Deprivation Index (TDI), education, smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer. Restricted cubic spline (RCS) model with four knots (5th, 35th, 65th and 95th percentiles) was used to explore the dose-response relationship between serum 25(OH)D and different stages of CMM progression. Besides, the multiplicative interaction was examined between serum 25(OH)D concentrations and VDR polymorphisms. Multiple imputation ($n = 5$) was used to fill missing values in the covariates for statistical analyses.

Subgroup analyses were conducted based on age, sex, ethnicity, BMI, smoking status, drinking status, and physical activity. Several sensitivity analyses were performed to assess the robustness of our results. First, we excluded subjects with outcomes occurring within 2 years of follow-up to minimize potential reverse causality and induction of time bias. Second, we conducted mutual adjustment for the two polymorphisms (BsmI and Cdx2) to account for their potential confounding effects.

All analyses were performed using R software (version 4.3.3), and a two-tailed P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

The study included 396,192 middle-aged and older adults, the mean age was 56.0 years, of whom approximately 55.7% were female (Table S1). The median serum 25(OH)D concentration was 47.20 nmol/L (interquartile

range 32.80, 62.70). Over a median follow-up period of 13.8 years, 55,772 participants (14.08%) developed at least one CMD. A total of 28,624 deaths were recorded, with 8596 (30.0%) attributed to CMD and 1991 (7.0%) to CMM (Figure S1). Compared to survivors without CMD during follow-up, those with one or more CMDs were more likely to be older, male, non-white, smokers, have a lower level of education, lower socio-economic status, lower frequency of physical activity, unhealthy diet, no use of multivitamin/mineral supplements and a higher BMI (Table S1). Table S2 showed the baseline characteristics of the data after multiple interpolation.

Association between serum 25(OH)D concentrations and different stages of CMM progression

Traditional Cox proportional hazards models showed that 25(OH)D was significantly inversely associated with FCMD, CMM, and all-cause mortality (Table S3). Using a multi-state model, we further observed that 25(OH)D reduced the risk at each stage in the development of CMM. Specifically, for participants with serum 25(OH)D ≥ 75.0 nmol/L, multivariable-adjusted HRs for the transitions from baseline to FCMD and from FCMD to CMM were 0.70 (95% CI, 0.67, 0.72) (*P* for trend < 0.001) and 0.74 (95% CI, 0.67, 0.82) (*P* for trend < 0.001), respectively, compared to those with serum 25(OH)D < 25.0 nmol/L. Serum 25(OH)D was significantly associated with both the transition from baseline to death (highest vs. lowest category: HR, 0.66, 95% CI, 0.62, 0.70) (*P* for trend < 0.001) and from FCMD to death (highest vs. lowest category: HR, 0.84, 95% CI, 0.77, 0.92) (*P* for trend < 0.001), but showed no significant association with the transition from CMM to death (highest vs. lowest category: HR, 0.85, 95% CI, 0.70, 1.03) (*P* for trend = 0.055). A one-unit increase in natural log-transformed 25(OH)D was associated with a reduced risk of transitioning by 23% from baseline to FCMD, 17% from FCMD to CMM, 27% from baseline to death, 15% from FCMD to death, and 16% from CMM to death (Table 1). It could be specifically interpreted that, for each 100 nmol/L increment in 25(OH)D levels, the risk of transitioning from baseline to FCMD decreased by approximately 28%, from FCMD to CMM by approximately 22%, from baseline to death by approximately 33%, from FCMD to death by approximately 19%, and from CMM to death by approximately 21%.

Interestingly, the RCS curve model effectively captured the nonlinear associations between serum 25(OH)D and each transition stage of the CMM progression (Fig. 2). In the multivariable-adjusted models, the associations between serum 25(OH)D and these transitions changed at these points (transition from baseline to FCMD, 46.98; transition from FCMD to CMM, 44.79; transition from baseline to death, 46.98; transition from FCMD to death 44.79; transition from CMM to death 40.54) (units: nmol/L). Each value of *P* overall and *P* nonlinear was less than 0.05.

Association between VDR polymorphisms and different stages of CMM progression

Traditional Cox regression showed that participants carrying the TT allele of rs1544410 (BsmI) had a higher risk

Table 1 Multivariable-adjusted HRs (95%CIs) of serum 25(OH)D concentrations with different stages of CMM progression

Transitions	Serum 25(OH)D concentrations (nmol/L)				*P* value for trend	Natural log-transformed 25(OH)D[b]
	< 25.0	25.0-49.9	50.0-74.9	≥ 75.0		
Baseline → FCMD						
Case/total	8715/51,318	23,954/165,381	17,668/134,519	5435/44,974		55,772/396,192
Multivariable-adjusted model[a]	1.00 [Reference]	0.83 (0.81, 0.85)	0.73 (0.71, 0.75)	0.70 (0.67, 0.72)	< 0.001	0.77 (0.75, 0.78)
FCMD → CMM						
Case/total	1372/8715	3306/23,954	2288/17,668	614/5435		7580/55,772
Multivariable-adjusted model[a]	1.00 [Reference]	0.86 (0.80, 0.92)	0.82 (0.76, 0.89)	0.74 (0.67, 0.82)	< 0.001	0.83 (0.79, 0.88)
Baseline → Death						
Case/total	2774/51,318	7457/165,381	5769/134,519	2037/44,974		18,037/396,192
Multivariable-adjusted model[a]	1.00 [Reference]	0.75 (0.71, 0.78)	0.64 (0.61, 0.67)	0.66 (0.62, 0.70)	< 0.001	0.73 (0.70, 0.75)
FCMD → Death						
Case/total	1415/8715	3618/23,954	2667/17,668	896/5435		8596/55,772
Multivariable-adjusted model[a]	1.00 [Reference]	0.86 (0.81, 0.92)	0.81 (0.75, 0.87)	0.84 (0.77, 0.92)	< 0.001	0.85 (0.81, 0.90)
CMM → Death						
Case/total	391/1372	816/3306	605/2288	179/614		1991/7580
Multivariable-adjusted model[a]	1.00 [Reference]	0.80 (0.71, 0.91)	0.80 (0.69, 0.92)	0.85 (0.70, 1.03)	0.055	0.84 (0.76, 0.93)

Abbreviations: HR, hazard ratio; CI, confidence interval; FCMD, first cardiometabolic disease; CMM, cardiometabolic multimorbidity

[a] Multivariable-adjusted models were adjusted for age, sex, ethnicity, season of blood collection, Townsend Deprivation Index (TDI), education, smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer

[b] HR indicates the risk for per unit increment of log-transformed serum 25(OH)D

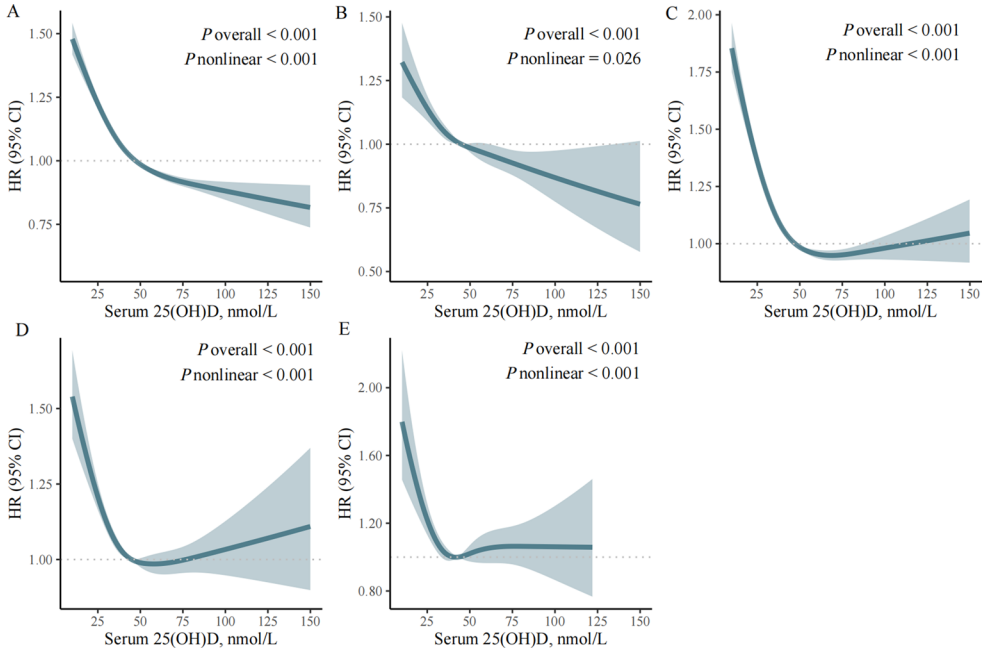


Fig. 2 Nonlinear associations between serum 25(OH)D concentration and different stages of CMM progression. The associations of serum 25(OH)D concentration with the transition from baseline to FCMD (**A**), FCMD to CMM (**B**), baseline to death (**C**), FCMD to death (**D**), CMM to death (**E**). The baseline value (HR = 1) is represented by a dashed line. All models were adjusted for age, sex, ethnicity, season of blood collection, Townsend Deprivation Index (TDI), education, smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer. Abbreviations: HR, hazard ratio; CI, confidence interval; FCMD, first cardiometabolic disease; CMM, cardiometabolic multimorbidity

of FCMD compared to the reference group (HR, 1.03, 95%CI, 1.00, 1.05). However, individuals with TT allele of rs11568820 (Cdx2) exhibited a lower risk of developing both FCMD (HR, 0.94, 95%CI, 0.91, 0.98) and CMM (HR, 0.88, 95%CI, 0.80, 0.97) (Table S4). The multi-state model further showed these associations (Table S5).

The interaction analysis indicated a significant interaction between serum 25(OH)D and VDR polymorphisms at certain transition stages of CMM. Specifically, the protective association of high serum 25(OH)D with the transition from baseline to death and from FCMD to death was weaker among individuals carrying the minor T allele of rs1544410 (BsmI). For the transition from baseline to death, the HR was 0.71 (95%CI, 0.69, 0.73) in the CC + CT group and 0.74 (95%CI, 0.69, 0.79) in the TT group (*P* for interaction = 0.040). For the transition from FCMD to death, the HR was 0.81 (95%CI, 0.77, 0.85) in the CC + CT group and 0.85 (95%CI, 0.76, 0.95) in the TT group (*P* for interaction = 0.023). In contrast, the protective association of high serum 25(OH)D with the transition from baseline to FCMD was stronger among individuals carrying the minor T allele of rs11568820 (Cdx2), with an HR of 0.77 (95%CI, 0.75, 0.79) in the CC + CT group and 0.75 (95%CI, 0.69, 0.82) in the TT group (*P* for interaction = 0.019) (Figure S3). Moreover, the association between serum 25(OH)D and other transition stages did not differ significantly across different VDR genotypes (all *P* for interaction > 0.05) (Fig. 3).

Stratified and sensitivity analyses

The subgroup analysis showed that among participants younger than 60 years, higher serum 25(OH)D levels were more strongly associated with a protective effect against the transition from baseline to FCMD. Sex, ethnicity, and smoking influenced the association between serum 25(OH)D levels and the transition from baseline to death, with higher serum 25(OH)D levels conferring greater protective effects in white, smokers, and males. Notably, the association between serum 25(OH)D levels and the transition from FCMD to death was particularly pronounced in males. In addition, BMI influenced the association between serum 25(OH)D levels and the risk of transitioning from baseline to FCMD, with this association being more pronounced in obese individuals (Table S6).

Sensitivity analyses excluding participants who experienced outcomes within the first two years of follow-up showed that the associations between serum 25(OH)D concentrations (Table S7), VDR polymorphisms (Table S8), and different stages of CMM progression were also largely unchanged. Furthermore, the results after mutual adjustment for the two polymorphisms (BsmI and Cdx2) also showed minimal variation (Table S9).

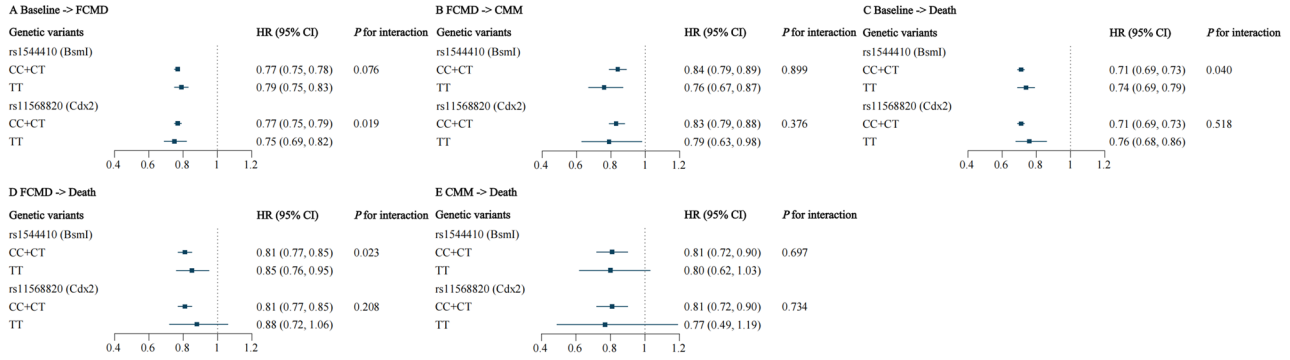


Fig. 3 The association between serum 25(OH)D VDR polymorphisms with different stages of CMM progression stratified by VDR genotypes. All models were adjusted for age, sex, ethnicity, season of blood collection, Townsend Deprivation Index (TDI), education, smoking status, drinking status, healthy diet, vitamin/mineral supplement use, body mass index (BMI), physical activity and time spent outdoors during the summer. Abbreviations: HR, hazard ratio; CI, confidence interval; FCMD, first cardiometabolic disease; CMM, cardiometabolic multimorbidity; VDR, vitamin D receptor

Discussion

In this cohort study of middle-aged and older adults from the UK Biobank, we observed an L-shaped nonlinear association between 25(OH)D and all stages of CMM progression, with a threshold around 45 mmol/L. The rs1544410 (BsmI) T alleles may have a detrimental effect, while the rs11568820 (Cdx2) T alleles may exert a protective effect in the early stages of CMM progression. Additionally, VDR polymorphisms significantly modified the association between serum 25(OH)D and certain stages of CMM progression.

Epidemiological studies have shown that the prevalence of CMM is increasing [5], particularly among middle-aged and older adults who often exhibits low levels of serum 25(OH)D [16]. Although existing studies have explored the relationship between serum 25(OH)D and a single CMD [18, 37–39], its role in the onset and dynamic progression of CMM in middle-aged and older populations remains unclear.

Our study extends beyond existing research by employing a multi-state model to investigate both single CMD development and CMM progression. Compared to the traditional Cox regression, the multi-state model provides a structured approach to analyzing disease progression by dividing it into distinct phases. This method better accounts for changes between disease stages and the risk of death, allowing a more accurate assessment of how serum 25(OH)D levels influence the dynamic progression of CMM [40, 41]. Our study revealed that among participants without CMD at baseline, higher serum 25(OH)D concentrations were associated with a lower risk of developing FCMD and death during follow-up, highlighting its potential role in primary prevention. Moreover, higher serum 25(OH)D concentrations were associated with a lower risk of developing CMM after FCMD and a reduced risk of death following FCMD or CMM during follow-up. This suggested that for individuals who already have FCMD, maintaining higher levels of vitamin D may help reduce the risk of later development of CMM or death, thereby mitigating long-term health impacts associated with CMM. Notably, all these associations showed L-shaped nonlinear relationships with a threshold of around 45 nmol/L, consistent with the findings of previous studies [42, 43].

Previous studies have shown that VDR polymorphisms influence the occurrence of several health outcomes [44–47]. Additionally, VDR polymorphisms and serum 25(OH)D levels have been shown to interact certain outcomes, such as susceptibility to tuberculosis and survival in hepatocellular carcinoma [21, 22]. However, the role of VDR polymorphisms in the onset and dynamic progression of CMM remains unclear.

Our study found that the rs1544410 (BsmI) T allele may have a detrimental effect, whereas the rs11568820 (Cdx2) T allele may exert a protective effect in the early stages of CMM progression. In addition, VDR polymorphisms may modify the association between serum 25(OH)D and certain stages of CMM progression. Specifically, among participants carrying the rs1544410 (BsmI) T allele, the protective association between higher serum 25(OH)D levels and both transition from baseline to death and transition from FCMD to death was weaker. In contrast, among participants carrying the rs11568820 (Cdx2) T allele, higher serum 25(OH)D levels were associated with a reduced risk of transitioning from baseline to FCMD. Previous studies suggested that the rs1544410 (BsmI) T allele might reduce VDR expression by decreasing mRNA stability, thereby attenuating the biological activity of 25(OH)D [27]. In addition, the rs11568820 (Cdx2) C allele, located in the VDR promoter region, might reduce VDR transcription by decreasing rs11568820 (Cdx2) binding [26], which supports our findings. These findings suggested that individual risk stratification through VDR polymorphism screening could have facilitated personalized prevention of CMM.

There are some limitations to this study. Firstly, as an observational study, it cannot establish causality. Secondly, despite our best efforts to adjust for potential confounders, the influence of residual or unknown confounders cannot be completely excluded. Thirdly, a single baseline measurement of serum 25(OH)D might not reflect long-term levels, though previous studies have suggested it could serve as a reliable proxy for vitamin D status [48]. Additionally, it could be influenced by seasonal variation in sampling time, despite our efforts to adjust for this in the analyses. Finally, most participants in this study were of European origin, which may limit the generalizability of our findings to other populations.

Conclusions

In this cohort study of middle-aged and older adults from the UK Biobank, our results showed an L-shaped nonlinear association between 25(OH)D and all stages of CMM progression, with a threshold around 45 nmol/L. VDR polymorphisms may modify the association between serum 25(OH)D and certain stages of CMM progression. These findings suggested that maintaining adequate vitamin D levels, as a readily implementable intervention strategy, not only reduces the risk of initial CMD but also delays the progression to CMM or death. Individual risk stratification through screening based on VDR polymorphisms may provide a novel approach for developing personalized CMM prevention strategies. However, these findings still need to be validated by rigorously designed randomized controlled trials (RCTs).

Abbreviations

CMM	Cardiometabolic multimorbidity
CMD	Cardiometabolic diseases
T2D	Type 2 diabetes
CHD	Coronary heart disease
FCMD	First cardiometabolic diseases
VDR	Vitamin D receptor
25(OH)D	25-hydroxyvitamin D
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01139-z.

Supplementary Material 1

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Author contributions

J.M: Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing–original draft, Writing–review & editing; P.L: Validation; J.W and H.Z: Data Curation; Z.L, L.T, X.Y and Y.L: Supervision; X.G: Resources, Supervision, Project Administration; B.G: Conceptualization, Validation, Writing–review & editing, Supervision. All authors approved the submitted and final versions.

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Data availability

The data that support the findings of this study are available on application to the UK Biobank.

Declarations

Ethics approval and consent to participate

UK Biobank has received ethical approvals from the North West Multi-center Research Ethics Committee (MREC), the Community Health Index Advisory Group (CHIAG), the Patient Information Advisory Group (PIAG) and National Health Service National Research Ethics Service. Permission to use the UK Biobank resource for the research was approved by UK Biobank Access subcommittee (approved research application no. 88589).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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