

Non-linear associations of plasma 25-hydroxyvitamin D with serum homocysteine and hyperhomocysteinemia in Chinese adults: a cross-sectional study

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Article

Keywords: 25-hydroxyvitamin D, Homocysteine, Hyperhomocysteinemia, Cardiovascular Disease, Non-linear Association

Posted Date: May 7th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9353084/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on August 29th, 2026. See the published version at <https://doi.org/10.1038/s41598-026-67936-6>.

Abstract

Background

Plasma 25-hydroxyvitamin D [25(OH)D] deficiency and elevated homocysteine (Hcy) levels are both well-established risk factors for cardiovascular disease (CVD). However, the relationship between 25(OH)D and Hcy remains unclear. To explore the association between plasma 25(OH)D and serum Hcy, along with the risk of hyperhomocysteinemia (HHcy).

Methods

Based on baseline data from the Precision Nutrition and Health KAP Real-World Study (China), The associations of 25(OH)D with Hcy and HHcy were analyzed using multivariable linear regression and logistic regression models, respectively. Restricted cubic splines (RCS) served to investigate nonlinear patterns and threshold phenomena. Additionally, subgroup and sensitivity analyses were carried out to assess potential influencing factors and confirm the robustness of the findings.

Results

In the unadjusted analysis, 25(OH)D were positively associated with both Hcy and HHcy. After adjusting for age and sex, a non-linear U-shaped relationship emerged between 25(OH)D and both Hcy and HHcy, which remained significant after further multivariable adjustment. When plasma 25(OH)D levels were categorized into quintiles, individuals in quintiles Q1–Q3 (25(OH)D < 24.3 ng/mL) and Q5 (25(OH)D ≥ 28.2 ng/mL) had significantly elevated Hcy concentrations (by 0.16 μmol/L) and increased risks of HHcy (by 11% and 10%, respectively) compared with those in Q4 (24.3–28.2 ng/mL). In the overall population, the inflection point for 25(OH)D in relation to Hcy was 27.2 ng/mL. For HHcy, the inflection point was 26.1 ng/mL.

Conclusions

This study revealed a non-linear U-shaped association between plasma 25(OH)D and both Hcy and HHcy risk in Chinese adults, providing epidemiological evidence for understanding the relationship between 25(OH)D and homocysteine, with potential implications for cardiovascular risk assessment.

Introduction

Homocysteine(Hcy) serves as a metabolic junction linking the methionine cycle to cysteine synthesis (as well as glutathione synthesis). Hcy is primarily catabolized via the remethylation and transsulfuration pathways. An abnormally elevated serum Hcy concentration resulting from disruptions in these metabolic pathways is called hyperhomocysteinemia (HHcy) ¹. HHcy is involved in facilitating the development and progression of various diseases, neurodegenerative disorders, osteoporosis, and malignancy ². Additionally, increasing evidence identifies HHcy as a novel contributor to cardiovascular disease (CVD), with the harm including damage to the endothelium, stimulation of the proliferation of vascular smooth muscle cells (VSMCs), enhancement of oxidative stress, disruption of lipid metabolism, and abnormalities in coagulation and platelet function ^{3–5}. Due to its widespread impact, Hcy has been termed the "cholesterol of the 21st century".

Vitamin D (VD), measured as circulating 25-hydroxyvitamin D [25(OH)D], is a steroid hormone primarily synthesized in the skin via UVB-induced photoconversion of 7-dehydrocholesterol, with dietary intake playing a secondary role. 25(OH)D mainly regulate calcium and phosphate homeostasis and support skeletal health. However, since the VD receptor (VDR) is widely present in numerous organs and tissues, its impact on health is extensive. It signals through the VDR to exert its biological actions⁶. 25(OH)D deficiency is implicated in various diseases such as rickets, osteomalacia, osteoporosis, type 2 diabetes, CVD, autoimmune diseases, and cancer ^{7,8}. Notably, given the expression of VDR in cardiac muscle and VSMCs ^{6,9}, 25(OH)D deficiency has been identified as an independent predictor for CVD in multiple studies ¹⁰. Proposed protective mechanisms of 25(OH)D in cardiovascular health include modulating glucose and lipid metabolism, inhibiting renin-angiotensin-aldosterone system, improving endothelial function, attenuating platelet activation and aggregation, suppressing VSMC proliferation, regulating immune responses, and reducing oxidative and inflammatory stress ^{6,11}.

Therefore, the relationship between 25(OH)D and Hcy has attracted increasing attention from researchers worldwide. For instance, a study involving 14,630 asymptomatic adults showed that when the serum 25(OH)D level was below 21 ng/mL, it was negatively correlated with Hcy; however, this relationship was unclear when 25(OH)D levels exceeded 21 ng/mL ¹². Another study involving 1,375 asymptomatic Korean adults reported 25(OH)D levels are inversely linked to Hcy concentrations after adjusting for covariates ¹³. Additionally, data from a Canadian preventive health program comprising 4,475 participants demonstrated that plasma 25(OH)D levels were inversely correlated with the prevalence of hyperhomocysteinemia ⁸.

Recently, the burden of CVD in China has risen substantially, with an estimated current prevalence of 330 million cases. Among these, approximately 245 million individuals have hypertension, and 13 million have experienced a stroke ¹⁴. The prevalence of HHcy is about 75% among hypertensive patients, and more importantly, hypertension and HHcy raise the risk of CVD and stroke, underscoring the importance of assessing and managing HHcy ¹⁵. Therefore, this study focuses on the relationship between 25(OH)D and serum Hcy and HHcy, aiming to inform new strategies for CVD and stroke prevention and management.

Methods

Study Overview and Ethical Statement

This was a cross-sectional analysis based on baseline data from the "China Precision Nutrition and Health - KAP Field Study" ¹⁶ cohort, which later renamed as CPNAS ¹⁷. Precision nutrition, as a multi-dimensional and multi-stage comprehensive framework, integrates individual characteristics and starts from eight stages and five dimensions to promote personalized health management, disease prevention and treatment, and achieve an improvement in overall health levels ^{18,19}. Ethical approval for this study was granted by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University. All participants gave written informed consent prior to participation. All methods were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies. This study has been registered on the International Clinical Trial Registry Platform (<https://www.chictr.org.cn>), with the registration number being ChiCTR2100051983. Additionally, the collection of biological samples has received formal approval from the China Human Genetic Resources Administration Office (Approval Number: [2021]CJ2958).

Study population and design (parent design, CPNAS)

As a large-scale, prospective cohort study initiated in 2023, CPNAS aims to recruit one million individuals aged 18 and above from various regions across China and to conduct long-term follow-up. The wide variation in dietary habits, lifestyle behaviors, and health-related knowledge, attitudes, and practices across China's diverse geographic and cultural landscapes provides a valuable framework for exploring how these factors interact with the development of chronic conditions. Serving as a complementary resource to other prominent international cohorts, such as the All of Us program in the United States and the UK Biobank, CPNAS offers a distinctive perspective by emphasizing rural and previously underrepresented populations. This positions the study to make significant contributions to the advancement of precision nutrition and the formulation of effective strategies for health education, prevention, and chronic disease management ^{16–18}.

Nutrition Biomarker Sub Study

This analysis utilized data from the CPNAS, including 53,695 participants with available physical examination records, questionnaire data, biochemical indices, nutritional profiles, and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism information. The following exclusion criteria were applied to minimize potential confounding effects on circulating vitamin D levels: 9,031 individuals taking enalapril-folic acid tablets, 2,539 individuals using VD or multivitamin supplements, and 1,219 individuals with missing or aberrant VD or Hcy levels data. After exclusions, 40,906 individuals were finally included (Figure S1).

Physical examination and questionnaire

At baseline, study physicians conducted physical examinations, administered baseline questionnaires, and collected biological samples from participants. Trained research staff measured each individual's weight, height, hip circumference, and waist circumference. The baseline questionnaire gathered information on demographics, lifestyle factors, use of nutritional supplements, dietary intake (including a food frequency questionnaire), medical history, medication use, and quality of life. Sex (male or female) was recorded based on the information provided on the participant's national identification card ¹⁷.

Laboratory Measurements

Biochemical Parameters

Fasting venous blood samples were collected from participants during routine physical examinations. Biochemical assays were performed using an automated chemistry analyzer (Beckman Coulter Inc., U.S.A.) to measure baseline levels of serum Hcy, uric acid (UA), creatinine (CREA), glucose (GLU), total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C).

VD and Related Micronutrients

Plasma 25-hydroxyvitamin D [25(OH)D] levels were measured using LC-MS/MS ²⁰. Serum vitamin B12 (VB₁₂) and folate levels were determined using a fully automated chemiluminescence immunoassay system (Shenzhen TAILOR Medical Co., Ltd., China).

Genotyping

Genomic DNA was extracted from fasting venous blood samples. Genotyping of the MTHFR C677T polymorphism was conducted using MALDI-TOF MS (Agena Bioscience, Shanghai, China) with reagents from the Agena Bioscience complete genotyping assay kit.

Variables

The primary exposure was plasma 25(OH)D. The primary outcomes were serum Hcy levels and HHcy, defined as Hcy ≥ 10 $\mu\text{mol/L}$. Covariates were selected based on prior literature and biological plausibility and included demographic characteristics (age, sex), lifestyle factors (smoking status, alcohol consumption, physical activity, and sleep quality), metabolic indicators (BMI, waist-to-hip ratio, blood lipids, uric acid, glucose, and eGFR), and nutritional biomarkers (serum folate, vitamin B12, and MTHFR C677T polymorphism).

Bias

Potential sources of bias, including confounding and selection bias, were addressed through predefined inclusion and exclusion criteria and multivariable adjustment. To minimize confounding, relevant demographic, lifestyle, metabolic, and nutritional factors were included in the regression models. Sensitivity analyses were performed to assess the robustness of the findings.

Statistical Analysis

Based on data characteristics, continuous variables are presented as mean (standard deviation) or median (interquartile range, IQR), with group comparisons performed using the t-test or Wilcoxon rank-sum test, as appropriate. Categorical variables are expressed as frequencies (percentages) and compared using the chi-square test. Multivariable linear regression was employed to assess the association between 25(OH)D and serum Hcy, while logistic regression was used to evaluate the relationship between 25(OH)D and the risk of HHcy. To control for confounding, three sequentially adjusted models were constructed: Model 1 adjusted for age and sex; Model 2 further adjusted for demographic characteristics, lifestyle factors, and metabolic indicators; and Model 3 additionally adjusted for serum folate, VB₁₂, and MTHFR C677T genotype. RCS were fitted to explore potential non-linear relationships and identify thresholds. Stratified analyses were conducted according to demographic characteristics, lifestyle factors, genetic variants, and nutritional indicators, with interaction tests performed. Sensitivity analyses were carried out to verify the robustness of the findings. All statistical analyses were performed using R software, with a two-sided p-value < 0.05 considered statistically significant. Participants with missing or implausible key variables were excluded from the analysis. No imputation was performed for missing data.

Results

Baseline Characteristics

Baseline characteristics stratified by sex are presented in Table 1, and the screening process is illustrated in **Figure S1**. The final analysis comprised 40,906 participants, with a median age of 65.4 years (IQR: 58.1–71.4 years). Among them, 25,860 (63.2%) were women, with a median age of 64.0 years (IQR: 57.3–70.3 years), and 15,046 were men, with a median age of 67.2 years (IQR: 59.8–73.1 years). On average, women exhibited higher levels of BMI, TC, LDL-c, TG, folate, and VB₁₂ than men. In contrast, men had higher mean concentrations of UA, Hcy, and 25(OH)D. Males reported more favorable exercise levels and sleep quality while also showing higher rates of smoking and alcohol consumption compared to females. A greater proportion of males had plasma 25(OH)D ≥ 30 ng/mL (25.3% vs. 6.7%) and Hcy concentrations ≥ 10 μmol/L (83.6% vs. 61.2%) than females (Figure S2).

Table 1
Baseline characteristics of research participants stratified by gender

Characteristics	Total (N = 40906)	Male (N = 15046)	Female (N = 25860)	P Value
Age(years)	65.4 [58.1, 71.4]	67.2 [59.8, 73.1]	64.0 [57.3, 70.3]	< 0.001
BMI (kg/m ²)	25.6 [23.2, 28.1]	25.0 [22.6, 27.4]	25.9 [23.6, 28.5]	< 0.001
WHR	0.9 [0.9, 0.9]	0.9 [0.9, 1.0]	0.9 [0.8, 0.9]	< 0.001
Smoke (%)				
No	31342 (76.7)	5720 (38.0)	25622 (99.2)	< 0.001
Former	2902 (7.1)	2861 (19.0)	41 (0.2)	
Current	6633 (16.2)	6461 (43.0)	172 (0.7)	
Alcohol (%)				
No	30343 (74.4)	5917 (39.4)	24426 (94.7)	< 0.001
Former	1261 (3.1)	1157 (7.7)	104 (0.4)	
Current	9203 (22.6)	7946 (52.9)	1257 (4.9)	
Exercise (%)				
< 2 km/day	18632 (51.0)	5999 (44.0)	12633 (55.2)	< 0.001
2–4 km/day	12624 (34.6)	4934 (36.2)	7690 (33.6)	
4–6 km/day	3315 (9.1)	1612 (11.8)	1703 (7.4)	
≥ 6 km/day	1934 (5.3)	1083 (7.9)	851 (3.7)	
Sleep quality (%)	22621 (58.3)	9584 (67.0)	13037 (53.2)	< 0.001
Good				
Average	10878 (28.0)	3412 (23.8)	7466 (30.5)	
Poor	4713 (12.1)	1168 (8.2)	3545 (14.5)	
Extremely	600 (1.5)	144 (1.0)	456 (1.9)	
TC (mmol/L)	5.5 [4.8, 6.2]	5.2 [4.6, 5.9]	5.6 [4.9, 6.4]	< 0.001
LDL-c (mmol/L)	3.2 [2.7, 3.8]	3.0 [2.6, 3.5]	3.3 [2.8, 3.9]	< 0.001
TG (mmol/L)	1.4 [1.0, 2.1]	1.2 [0.9, 1.8]	1.6 [1.1, 2.2]	< 0.001
UA (μmol/L)	329.0 [279.0, 386.0]	364.0 [311.0, 425.0]	311.0 [266.0, 360.0]	< 0.001
Glu (mmol/L)	5.4 [5.0, 6.0]	5.4 [5.0, 6.0]	5.4 [5.0, 6.0]	0.615
eGFR (mL/min/1.73m ²)	96.9 [89.8, 102.7]	96.9 [90.5, 102.6]	96.9 [89.3, 102.9]	0.106
Hcy (μmol/L)	11.3 [9.6, 13.5]	12.5 [10.7, 14.9]	10.7 [9.1, 12.6]	< 0.001
Folate (ng/ml)	5.7 [4.4, 8.9]	5.0 [3.9, 7.1]	6.3 [4.8, 9.6]	< 0.001
VB ₁₂ (pg/mL)	417.4 [359.8, 489.4]	399.5 [343.2, 461.8]	428.2 [370.7, 506.2]	< 0.001
25(OH)D (ng/mL)	22.7 [18.4, 27.0]	26.2 [22.4, 30.1]	20.8 [16.8, 24.6]	< 0.001
MTHFR C677T (%)				
CC	9906 (24.4)	3642 (24.5)	6264 (24.4)	0.089
CT	19918 (49.1)	7395 (49.7)	12523 (48.8)	
TT	10703 (26.4)	3838 (25.8)	6865 (26.8)	
VD (%)				
< 20 ng/mL	13680 (33.4)	2090 (13.9)	11590 (44.8)	< 0.001
20–30 ng/mL	21682 (53.0)	9141 (60.8)	12541 (48.5)	
Notes: BMI, Body Mass Index; WHR, Waist-to-Hip Ratio; Smoke, Smoking status (never, former, current); Alcohol, Alcohol consumption status (never, former, current); Exercise, Daily walking distance (< 2 km, 2–4 km, 4–6 km, ≥ 6 km); Sleep quality, Self-reported sleep quality (very good, average, poor, very poor); TC, Total Cholesterol; LDL-c, Low-Density Lipoprotein Cholesterol; TG, Triglycerides; UA, Uric Acid; GLU, Glucose; eGFR, Estimated Glomerular Filtration Rate; Hcy, Homocysteine; VB ₁₂ , Vitamin B12; 25(OH)D, 25-hydroxyvitamin D; MTHFR C677T polymorphism:(MTHFR) C677T genotype (CC, CT or TT)				

Characteristics	Total (N = 40906)	Male (N = 15046)	Female (N = 25860)	P Value
≥ 30 ng/mL	5544 (13.6)	3815 (25.3)	1729 (6.7)	
Hcy (%)				
≥ 10 μmol/L	28397 (69.4)	12581 (83.6)	15816 (61.2)	< 0.001
< 10 μmol/L	12509 (30.6)	2465 (16.4)	10044 (38.8)	
Notes: BMI, Body Mass Index; WHR, Waist-to-Hip Ratio; Smoke, Smoking status (never, former, current); Alcohol, Alcohol consumption status (never, former, current); Exercise, Daily walking distance (< 2 km, 2–4 km, 4–6 km, ≥ 6 km); Sleep quality, Self-reported sleep quality (very good, average, poor, very poor); TC, Total Cholesterol; LDL-c, Low-Density Lipoprotein Cholesterol; TG, Triglycerides; UA, Uric Acid; GLU, Glucose; eGFR, Estimated Glomerular Filtration Rate; Hcy, Homocysteine; VB ₁₂ , Vitamin B12; 25(OH)D, 25-hydroxyvitamin D; MTHFR C677T polymorphism:(MTHFR) C677T genotype (CC, CT or TT)				

Multivariable Linear Regression: Plasma 25(OH)D and Serum Hcy

As indicated in Table 2, plasma 25(OH)D levels were positively associated with serum Hcy in unadjusted models. However, after adjustment for age and sex, the association followed a U-shaped pattern. This U-shaped relationship remained robust after adjustment for additional covariates. When stratifying 25(OH)D levels into quintiles, participants in quintiles Q1–Q3 [25(OH)D < 24.3 ng/mL] and Q5 [25(OH)D ≥ 28.2 ng/mL] exhibited significantly higher Hcy concentrations compared to those in Q4 [25(OH)D 24.3–28.2 ng/mL], with an average increase of 0.16 μmol/L in both comparisons.

Table 2
Multiple linear regression analysis of plasma 25(OH)D and serum Hcy

25(OH)D	Adjusted model									
	N	Hcy	Crude model		Model 1		Model 2		Model 3	
(ng/ml)		Median (IQR)	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
Continuous	40906	11.3(9.6–13.5)	0.07(0.06,0.07)	< 0.001	-0.00(-0.01,0.00)	0.055	-0.01(-0.01,-0.00)	< 0.001	-0.01(-0.01,-0.00)	0.030
Quintiles										
Q1 (< 17.3)	8180	10.7 (9.1–12.8)	-0.80 (-0.91, -0.70)	< 0.001	0.24 (0.14, 0.34)	< 0.001	0.24 (0.14, 0.34)	< 0.001	0.21 (0.11, 0.30)	< 0.001
Q2 (17.3 ~ 21.1)	8182	11 (9.4–13.1)	-0.55 (-0.66, -0.45)	< 0.001	0.17 (0.07, 0.27)	< 0.001	0.18 (0.08, 0.28)	< 0.001	0.18 (0.08, 0.27)	< 0.001
Q3 (21.1 ~ 24.3)	8181	11.2 (9.6–13.3)	-0.31 (-0.41, -0.21)	< 0.001	0.09 (-0.00, 0.19)	0.061	0.10 (0.00, 0.19)	0.050	0.11 (0.02, 0.20)	0.022
Q4 (24.3 ~ 28.2)	8181	11.5 (9.8–13.7)	Ref		Ref		Ref		Ref	
Q5 (≥ 28.2)	8182	12.1 (10.2–14.4)	0.59 (0.49, 0.70)	< 0.001	0.19 (0.09, 0.28)	< 0.001	0.11 (0.01, 0.21)	0.026	0.15 (0.06, 0.25)	0.001
P for trend				< 0.001		0.023		0.326		0.032
Categories										
Q1-Q3 (< 24.3)	24543	11 (9.3–13.1)	-0.56 (-0.64, -0.47)	< 0.001	0.16 (0.08, 0.24)	< 0.001	0.17 (0.09, 0.25)	< 0.001	0.16 (0.08, 0.24)	< 0.001
Q4 (24.3 ~ 28.2)	8181	11.5 (9.8–13.7)	Ref		Ref		Ref		Ref	
Q5 (≥ 28.2)	8182	12.1 (10.2–14.4)	0.59 (0.49, 0.70)	< 0.001	0.19 (0.09, 0.29)	< 0.001	0.11 (0.02, 0.21)	0.022	0.16 (0.06, 0.25)	0.001
P for trend				< 0.001		< 0.001		0.013		< 0.001
Notes: Model 1 adjusted for Age, Sex; Model 2 adjusted for Model 1 + (BMI, WHR, Smoke, Alcohol, Exercise, Sleep Quality, TC, LDL-c, TG, UA, GLU, eGFR); Model 3 adjusted for Model 2+ (Folate, Vitamin B ₁₂ , and MTHFR C677T). Abbreviation: 25(OH)D, 25-hydroxyvitamin D; Hcy, Homocysteine										

RCS curve and threshold analysis of plasma 25(OH)D and serum Hcy in the total population

The RCS analysis showed a U-shaped relationship between 25(OH)D and Hcy after multivariate adjustment. The inflection point of 25(OH)D in the total population was 27.2 ng/mL. When 25(OH)D was less than 27.2 ng/mL, it was negatively correlated with Hcy levels ($\beta = -0.02$, 95% CI: -0.03, -0.01). Conversely, when 25(OH)D exceeded 27.2 ng/mL, the relationship between 25(OH)D and Hcy was positive ($\beta = 0.02$, 95% CI: 0.01, 0.03) (Fig. 1).

Logistic Regression Analysis of Plasma 25(OH)D and HHcy

Plasma 25(OH)D was positively associated with the risk of HHcy in unadjusted models. In model 2, the association followed a U-shaped pattern, which remained significant after further adjustment for additional covariates (Table 3). When stratified into quintiles, the results showed individuals in Q1-Q3 [25(OH)D < 24.3 ng/mL] and Q5 [25(OH)D $\geq$ 28.2 ng/mL] had higher risks of HHcy (by 11% and 10%, respectively) compared with those in Q4 [25(OH)D 24.3–28.2 ng/mL].

Table 3
Logistic regression analysis of plasma 25(OH)D and serum HHcy

25(OH)D	Adjusted model									
	N	HHcy	Crude model		Model 1		Model 2		Model 3	
(ng/ml)		Event (%)	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Continuous		40906	28397(69.4)	1.04(1.04,1.04)	< 0.001	1.00(0.99,1.00)	0.165	0.99(0.99,1.00)	0.017	1.00(0.99,1.00)
Quintiles										
Q1 (< 17.3)	8180	5073 (62.0)	0.63 (0.59, 0.67)	< 0.001	1.11 (1.03, 1.19)	0.004	1.13 (1.04, 1.23)	0.003	1.12 (1.03, 1.22)	0.008
Q2 (17.3 ~ 21.1)	8182	5385 (65.8)	0.74 (0.69, 0.79)	< 0.001	1.10 (1.03, 1.19)	0.008	1.12 (1.03, 1.21)	0.008	1.12 (1.03, 1.21)	0.009
Q3 (21.1 ~ 24.3)	8181	5649 (69.1)	0.86 (0.80, 0.92)	< 0.001	1.07 (1.00, 1.15)	0.062	1.08 (1.00, 1.17)	0.064	1.09 (1.00, 1.18)	0.043
Q4 (24.3 ~ 28.2)	8181	5913 (72.3)	Ref		Ref		Ref		Ref	
Q5 ($\geq$ 28.2)	8182	6377 (77.9)	1.36 (1.26, 1.46)	< 0.001	1.09 (1.01, 1.17)	0.030	1.06 (0.97, 1.16)	0.187	1.10 (1.00, 1.20)	0.041
P for trend				< 0.001		0.111		0.397		0.095
Categories										
Q1-Q3 (< 24.3)	24543	16107 (65.6)	0.73 (0.69, 0.77)	< 0.001	1.09 (1.03, 1.16)	0.003	1.11 (1.04, 1.19)	0.003	1.11 (1.03, 1.19)	0.004
Q4 (24.3 ~ 28.2)	8181	5913 (72.3)	Ref		Ref		Ref		Ref	
Q5 ($\geq$ 28.2)	8182	6377 (77.9)	1.36 (1.26, 1.46)	< 0.001	1.09 (1.01, 1.18)	0.029	1.06 (0.97, 1.16)	0.181	1.10 (1.00, 1.20)	0.040
P for trend1				< 0.001		0.018		0.110		0.024
Notes: Model 1 adjusted for Age, Sex; Model 2 adjusted for Model 1 + (BMI, WHR, Smoke, Alcohol, Exercise, Sleep Quality, TC, LDL-c, TG, UA, GLu, eGFR); Mo adjusted for Model 2 + (Folate, Vitamin B ₁₂ , and MTHFR C677T). Abbreviation: 25(OH)D, 25-hydroxyvitamin D; HHcy, Hyperhomocysteinemia										

RCS curve and threshold analysis of plasma 25(OH)D and HHcy in the overall population

RCS curves identified a nonlinear U-shaped association between 25(OH)D and HHcy. When 25(OH)D was below 26.1 ng/mL, 25(OH)D exerted a protective effect against HHcy (OR = 0.99, 95% CI: 0.99, 1.00) (Fig. 2). In contrast, when 25(OH)D exceeded 26.1 ng/mL, the risk of HHcy increased with rising 25(OH)D levels (OR = 1.01, 95% CI: 0.99, 1.02).

Subgroup Analyses: Plasma 25(OH)D and Serum Hcy

No significant interactions were observed between plasma 25(OH)D and serum Hcy across age, BMI, alcohol consumption, sleep quality, or VB₁₂ levels ($P > 0.05$) (Fig. 3). However, Fig. 3 shows significant interactions with gender, smoking status, exercise, MTHFR C677T polymorphism, and folate levels ($P < 0.05$). Among these, the interaction with gender was particularly pronounced ($P < 0.001$).

RCS curve and threshold analyses of plasma 25(OH)D and serum Hcy in males and females

RCS curves demonstrated that the inflection points for 25(OH)D were 27.0 ng/mL in males and 22.9 ng/mL in females (Figure S3). Before the inflection points [25(OH)D < 27.0 ng/mL in males; 25(OH)D < 22.9 ng/mL in females], 25(OH)D showed a negative correlation with Hcy (males: $\beta = -0.04$, 95% CI: -0.06, -0.02; females: $\beta = -0.02$, 95% CI: -0.03, -0.01). Conversely, beyond the inflection points [25(OH)D > 27.0 ng/mL in males; 25(OH)D > 22.9 ng/mL in females], there was a positive association between 25(OH)D and Hcy (males: $\beta = 0.02$, 95% CI: 0, 0.04; females: $\beta = 0.02$, 95% CI: 0.01, 0.03).

Subgroup Analyses: Plasma 25(OH)D and HHcy

Subgroup analysis of the association between 25(OH)D and HHcy (defined as Hcy $\geq 10 \mu\text{mol/L}$) showed no significant interactions with age, BMI, exercise, sleep quality, MTHFR C677T polymorphism, or folate (FA) levels (all $P > 0.05$) (Fig. 4). However, significant interactions were observed with gender, smoking status, alcohol consumption, and VB₁₂ levels (all $P < 0.05$). Among these, the interaction with gender was the most pronounced ($P < 0.001$).

RCS curve and threshold analyses of plasma 25(OH)D and HHcy in males and females

The RCS curves indicated that the inflection points of 25(OH)D in relation to HHcy were 26.1 ng/mL for males and 24.0 ng/mL for females (Figure S4). Prior to the inflection point [25(OH)D: <26.1 ng/mL in males; <24.0 ng/mL in females], 25(OH)D exerted a protective effect against HHcy (males: OR = 0.99, 95% CI: 0.97, 1.00; females: OR = 0.99, 95% CI: 0.99, 1.00). Beyond the inflection point [25(OH)D: >26.1 ng/mL in males; >24.0 ng/mL in females], the risk of HHcy increased with rising 25(OH)D levels (males: OR = 1.00, 95% CI: 0.99, 1.02; females: OR = 1.01, 95% CI: 0.99, 1.02).

Sensitivity analysis of the correlation between plasma 25(OH)D and serum Hcy and HHcy

Additionally, we carried out sensitivity analyses to explore the associations between 25(OH)D and both Hcy and HHcy. Individuals who had taken additional 25(OH)D supplements were included ($n = 43,324$) to evaluate the independent correlation between 25(OH)D and Hcy as well as HHcy (Table S1, S2). The findings remained consistent with the main results, confirming a stable non-linear U-shaped association between 25(OH)D and both Hcy and HHcy.

Discussion

Both 25(OH)D deficiency and elevated Hcy levels are independently correlated with the higher risk of CVD^{6,21}. 25(OH)D insufficiency/deficiency-related complications are highly prevalent within a large rural population in China²². This study finds the non-linear U-shaped relationship between 25(OH)D and Hcy level and HHcy. When stratifying 25(OH)D levels into quintiles, participants in quintiles Q1–Q3 [25(OH)D < 24.3 ng/mL] and Q5 [25(OH)D ≥ 28.2 ng/mL] exhibited significantly higher Hcy concentrations compared to those in Q4 [25(OH)D 24.3–28.2 ng/mL], with an average increase of 0.16 $\mu\text{mol/L}$ in both comparisons. In the overall population, the inflection point for 25(OH)D in relation to Hcy was 27.2 ng/mL. When stratified into quintiles, the results showed individuals in Q1–Q3 [25(OH)D < 24.3 ng/mL] and Q5 [25(OH)D ≥ 28.2 ng/mL] had higher risks of HHcy (by 11% and 10%, respectively) compared with those in Q4 [25(OH)D 24.3–28.2 ng/mL]. For HHcy, the inflection point was 26.1 ng/mL. According to the 2018 Chinese consensus on the clinical application of 25(OH)D and its analogs, plasma 25(OH)D levels > 30 ng/mL (> 75 nmol/L) indicate 25(OH)D sufficiency, with levels 20–30 ng/mL (50–75 nmol/L), < 20 ng/mL (50 nmol/L), and < 10 ng/mL (< 25 nmol/L) be considered insufficiency, deficiency, severely deficiency, respectively⁷. With shifts in lifestyle and reduced sun exposure due to urbanization and extended working hours indoors, 25(OH)D deficiency has emerged a global public health hazard, affecting an estimated 1 billion people^{6,23}. In the present study, 86.4% of participants exhibited 25(OH)D insufficiency or deficiency, with a higher prevalence in female than in male (93.3% vs. 74.7%). Men also had significantly higher mean plasma 25(OH)D concentrations than women (26.2 ng/mL vs. 20.8 ng/mL; $P < 0.001$). Given that 25(OH)D is primarily synthesized through UVB-induced skin production, this disparity may reflect higher outdoor activity levels among men. The definition of HHcy remains debated, with two common thresholds: 10 $\mu\text{mol/L}$ and 15 $\mu\text{mol/L}$ ⁵. However, accumulating evidence suggests that serum Hcy concentrations $\geq 10 \mu\text{mol/L}$ are related to increased risks of CVD and neurologic disorders, and recent studies recommend using 10 $\mu\text{mol/L}$ as a diagnostic threshold^{2,5,21,24}. Therefore, this study adopted a threshold of Hcy $\geq 10 \mu\text{mol/L}$ to define HHcy. Among the study population, 69.4% had serum Hcy levels $\geq 10 \mu\text{mol/L}$. A higher prevalence was observed in men than in women (83.6% vs. 61.2%), and mean Hcy concentrations were also greater among men (12.5 $\mu\text{mol/L}$ vs. 10.7 $\mu\text{mol/L}$), which consistent with previous research^{5,25}.

The metabolism of Hcy requires essential cofactors, including folate, VB₁₂, and vitamin B₆ (VB₆)²⁶. Hcy is primarily catabolized via the remethylation and transsulfuration pathways. The remethylation pathway depends on folate and VB₁₂, while the transsulfuration pathway is mediated by cystathionine β -synthase (CBS) and VB₆^{8,27}. 25(OH)D levels have been proved to influence Hcy metabolism²⁷. 25(OH)D may facilitate Hcy clearance through activation of specific metabolic pathways and enhancement of folate transport²⁸. CBS is essential in the transsulfuration of Hcy, has been identified as a VDR-regulated target gene^{27,29}. Folate transport is mainly mediated by folate receptor alpha (FRA/FOLR1), proton-coupled folate transporter (PCFT), and reduced folate carrier (RFC). These transport mechanisms are, in part, transcriptionally regulated by nuclear receptors, including the VDR. Eloranta and colleagues demonstrated that 25(OH)D and VDR increase the functional expression of PCFT in the intestine, thereby enhancing folate absorption³⁰. It's reported that VDR enhances RFC expression, improving cerebral folate transport³¹. Furthermore, Alam and colleagues reported that VDR could induce RFC expression in FOLR1-deficient mice³².

In our analysis of the association, a U-shaped association emerged, which remained significant after additional covariate adjustment. Consistent with our findings, Kriebitzsch et al. conducted a study using the Longitudinal Aging Study Amsterdam cohort, including 1,264 participants, and identified a significant

association between 25(OH)D₃ and Hcy levels ($P = 0.0015$), also exhibiting a U-shaped pattern²⁹. Previous large-scale cross-sectional studies from the NHANES and Korean populations focused solely on the association between 25(OH)D and Hcy in asymptomatic adults^{12,13}. In contrast, our study evaluated the relationship between 25(OH)D and Hcy and analyzed the association between 25(OH)D and HHcy. Moreover, whereas the NHANES and Korean studies examined only the overall population, we performed additional subgroup analyses. We found a robust U-shaped association between 25(OH)D, Hcy, and HHcy.

Additional evidence supports the link between 25(OH)D and Hcy metabolism. In a cohort of 3,150 individuals receiving coronary angiography, 25(OH)D levels were independently and inversely associated with Hcy concentrations³³. In a study of 40 patients with psoriasis and 25(OH)D deficiency, daily supplementation with 5,000 IU of 25(OH)D for three months led to significant increases in plasma 25(OH)D and VB₁₂ levels, accompanied by reductions in serum Hcy and folate concentrations³⁴. In a randomized controlled trial involving 100 obese women of reproductive age, two months of weekly supplementation with 50,000 IU of vitamin D₃ resulted in a significant reduction in serum homocysteine levels³⁵. A study involving 383 healthy Greek adults assessed the relationship between plasma 25(OH)D, folate, VB₁₂, Hcy, and MTHFR gene polymorphisms and found an inverse relationship between plasma 25(OH)D and Hcy levels³⁶. A separate study from Korea, which included 518 adult participants, evaluated the correlation between plasma 25(OH)D and both Hcy and apolipoprotein B (ApoB)³⁷. After adjusting for relevant covariates, the inverse correlation between 25(OH)D and Hcy was stronger than that with ApoB, and individuals in the lowest 25(OH)D category exhibited significantly elevated serum Hcy concentrations³⁷.

In middle-aged and elderly Chinese adults, a non-linear U-shaped association was observed between plasma 25(OH)D and serum Hcy and HHcy, suggesting that 25(OH)D confers a protective effect against both Hcy and HHcy when maintained within an optimal range. International guidelines continue to debate the optimal serum concentration of 25(OH)D, with growing consensus indicating that the ideal range may be varied by the specific health conditions and outcomes of interest^{6,38}. To our knowledge, this is the first large-scale, population-based study in China to investigate the relationship between 25(OH)D, Hcy, and HHcy, considering important confounding variables, including serum folate, VB₁₂, and MTHFR C677T polymorphism.

However, the study has certain limitations. First, due to the cross-sectional design, causal relationships cannot be established. Second, residual confounding cannot be fully excluded despite multivariable adjustment. Third, some variables, such as vitamin B6, were not available, which may influence homocysteine metabolism. Additionally, measurement error in laboratory parameters and self-reported data may have occurred. Finally, the study population primarily consisted of middle-aged and older Chinese adults, which may limit the generalizability of the findings to other populations.

Conclusions

In this large cohort of middle-aged and older Chinese adults, a U-shaped relationship was found between plasma 25(OH)D levels and serum Hcy/HHcy, with inflection points at 27.2 ng/mL and 26.1 ng/mL, suggesting both lower and higher 25(OH)D levels increase Hcy and HHcy risks. These findings highlight the clinical significance of tailored VD supplementation for Hcy management in precise nutrition.

Declarations

Acknowledgements

We thank all the participants in the study and members of the survey teams in all the study centers.

Authors' contributions

Study conception and design: Jinxiu Lin, Hanping Shi, Ping Li; Data collection: Jinghan Yang, Qiang Dai, Jiaxing Ke, Feng Peng; Funding acquisition: Xianhui Qin; Investigation: Jinghan Yang, Dajun Chai, Yan Zhang, Jingang Yang, Fangfang fan; Resources: Hanping Shi, Jinxiu Lin, Xinzhen Lu; Supervision: Jianping Li, Ningling Sun; Project administration: Jinxiu Lin, Hanping Shi; Formal analysis, writing: Jinghan Yang; Formal analysis and methodology: Jinghan Yang; Substantial review and editing: Jinxiu Lin and Hanping Shi. Jinxiu Lin: review and editing. All authors reviewed and approved the final version of the manuscript.

Funding

The study was supported by funding from the Development and Reform Commission of Shenzhen Municipality (Grant Number: XMHT20220104055 and XMHT20240104002).

Data availability

All relevant data for this study are available upon reasonable request from the corresponding author.

Conflict of interest

The authors declare no competing interests.

Ethical approval and consent to participate

Ethical approval for this study was granted by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University, with all participants providing written informed consent before data collection. The study is registered at ChiCTR2100051983 (<https://www.chictr.org.cn>). Additional approval for

biosample collection was obtained from the China Human Genetic Resources Management Office ([2021] CJ2958), and no animal experiments were performed.

Consent for publication

Not applicable.

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Figures

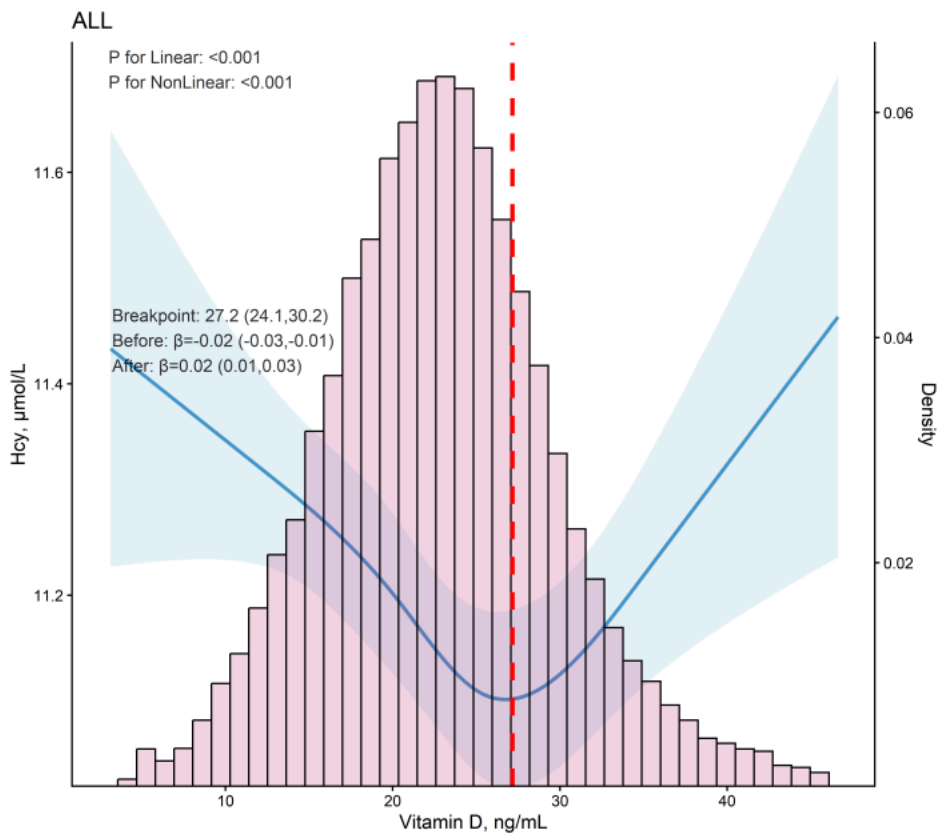


Figure 1

RCS Curve for plasma 25(OH)D and serum Hcy in the Total Population

Notes: 25(OH)D, 25-hydroxyvitamin D; Hcy, Homocysteinemia

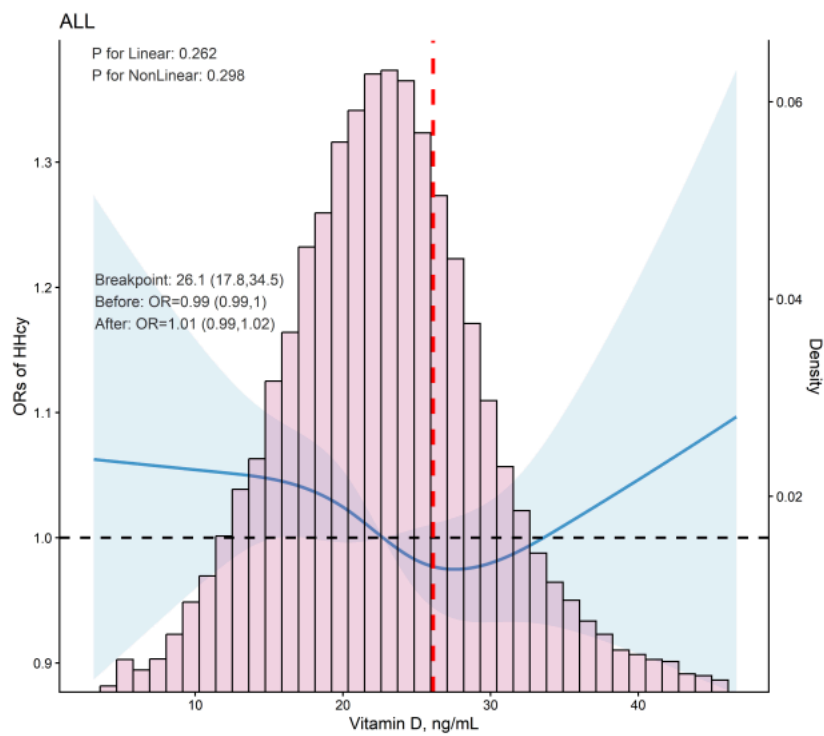


Figure 2

RCS Curve for plasma 25(OH)D and serum HHcy in the Total Population

Notes: 25(OH)D, 25-hydroxyvitamin D; HHcy, Hyperhomocysteinemia

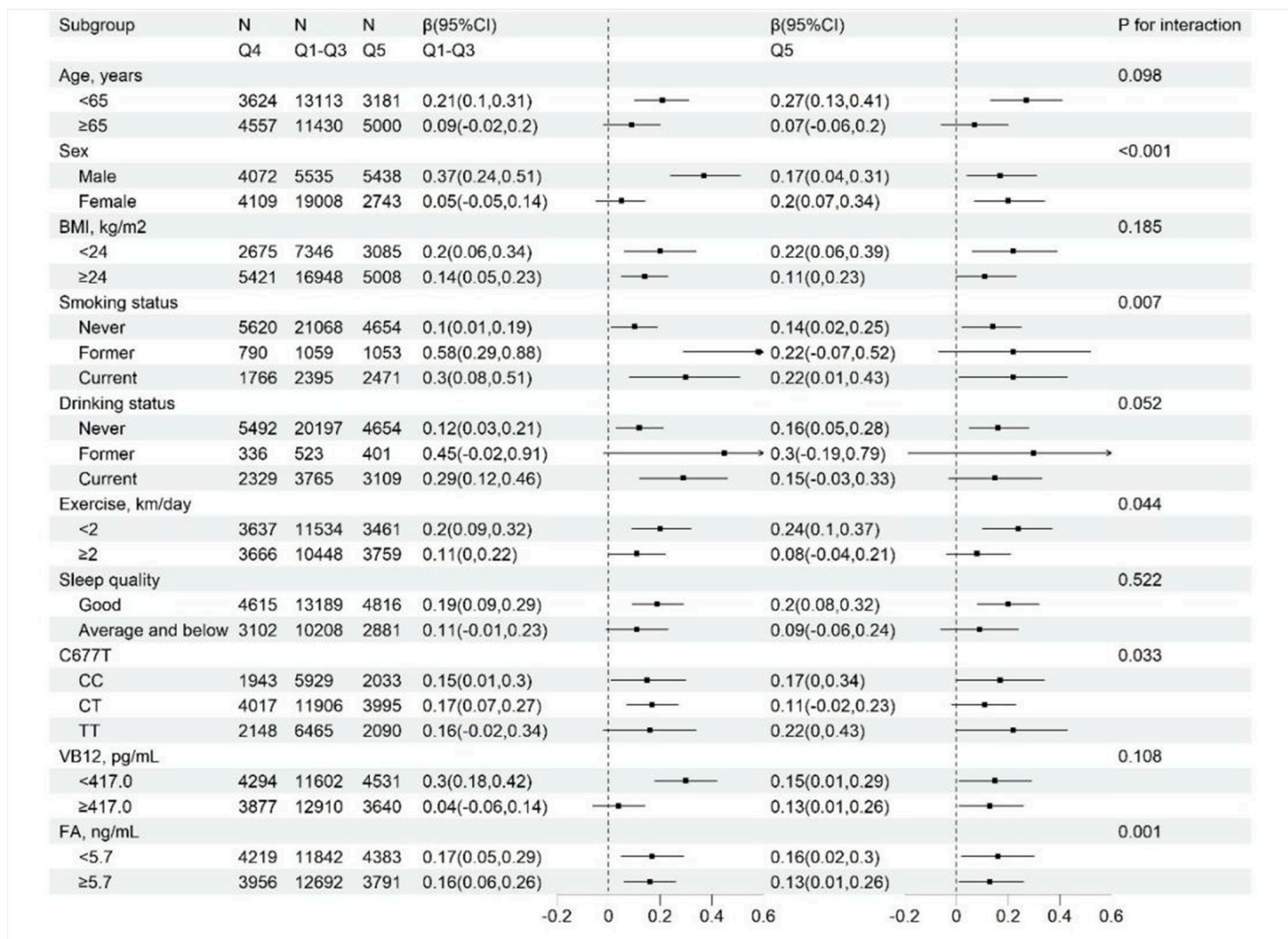


Figure 3

Forest plot of plasma 25(OH)D and serum Hcy based on subgroup analysis

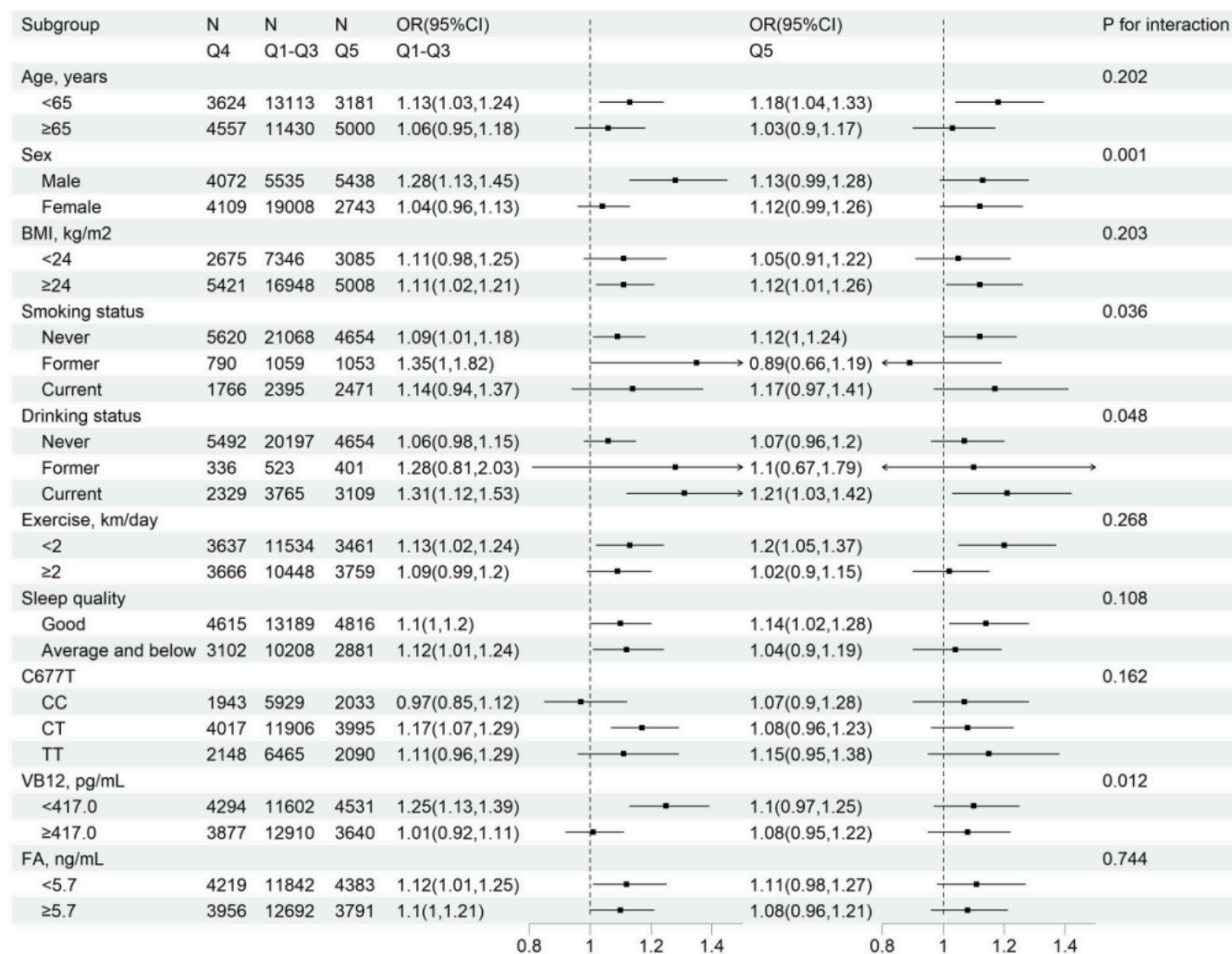


Figure 4

Forest plot of plasma 25(OH)D and serum HHcy based on subgroup analysis

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