Li *et al. Nutrition & Metabolism* (2024) 21:70
https://doi.org/10.1186/s12986-024-00845-5

Nutrition & Metabolism

RESEARCH Open Access

Impact of vitamins A, D, and homocysteine on cardiometabolic multimorbidity in Northwest China

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Abstract

Objective To investigate the impact of vitamin A (VA), vitamin D (VD), and homocysteine (Hcy) on cardiometabolic multimorbidity (CMM).

Methods This study is a cross-sectional study conducted in Ningxia Province, China. A total of 5000 participants aged 25–74 were recruited and divided into two groups based on the definition of cardiometabolic multimorbidity: the CMM group and the Non CMM group. Demographic, lifestyle, and laboratory data were collected to investigate the correlation between vitamin A, D, Hcy levels and CMM risk. The association was analyzed using multiple logistic regression and restricted cubic spline method.

Results CMM incidence increased with age, being higher in females (20.05%) compared to males, Hypertension was present in 96.20% of CMM cases. Reduced VD levels correlated with an elevated CMM risk (OR = 1.799, 95% CI: 1.466–2.238), showing an inverse dose-response relationship, even after adjusting for confounders (OR = 1.553, 95% CI: 1.233–1.956). However, VA and Hcy levels were not significantly associated with CMM risk. The inverse correlation between VD status and CMM risk was more pronounced in males, obese individuals, and those with normal blood lipid profiles ($P < 0.05$).

Conclusions The risk of CMM increases with age, especially in women. Inadequate VD status increases vulnerability to CMM, suggesting that optimising VD reduces the risk of CMM.

Keywords Vitamin A, Vitamin D, Homocysteine, Cardiometabolic multimorbidity

Introduction

It is commonly known that with the aging of the global population and advances in medical technology, more and more diseases are being controlled at a certain level meanwhile the survival time of patients with diseases is prolonged [1]. Accordingly, the increasing number of people suffering from two or more diseases poses a great challenge to the medical and health system [2]. Cardiometabolic Multimorbidity (CMM) is one of the most common and stable common disease gathering models of the metabolic comorbidity defined as the coexistence of two or three cardiometabolic diseases, including

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diabetes, hypertension, heart disease and stroke [3]. There is no denying that CMM tends to occur in older age groups, which not only increases the risk of depression and disability of the elderly [4–7], but also increases the risk of death of the elderly by 4 to 8 times [8], resulting in heavy family and social burden. Therefore, it is urgent to find the shared biomarkers of CMM.

Regarding the development of cardiovascular diseases, there have been many studies proving that dyslipidemia, obesity and hypertension have an unshirkable responsibility [9, 10], especially hypercholesterolemia triggering the inflammatory response of macrophages, which is believed to be the basis of atherosclerotic plaque formation [11].

Vitamin D (VD) is one of the main factors affecting bone and calcium metabolism. Its deficiency also increases the risk of diabetes (T2DM), metabolic syndrome (MS), and cardiovascular disease (CVD) [12, 13]. Study [14] showed that vitamin D supplementation can reduce serum total cholesterol (TC), low density lipoprotein (LDL-C) and triglyceride (TG) levels. One meta-analysis showed a 16% reduction in the risk of hypertension as vitamin D levels increased [15]. Mirhosseini [16] also emphasized that supplementing vitamin D can cause a small decrease in systolic and diastolic blood pressure. In summary, much work so far has focused on there is a relationship between vitamin D levels with the development of CMM. Vitamin A (VA) is also a lipid soluble vitamin and an essential nutrient. Its main physiological functions include maintaining vision, promoting embryonic development, influencing cell proliferation and differentiation, maintaining the integrity of epithelial cells, and regulating the immune function of the body [17]. Studies have shown that increased intake of VA can reduce the incidence of cardiovascular disease [18]. Homocysteine (Hcy) is a sulphur-containing amino acid that is an intermediate product of methionine metabolism and plays an important role in the cysteine synthesis pathway. Recent studies have shown that Hcy is associated with a variety of diseases, including diabetes mellitus, neurodegenerative diseases, osteoporosis, and cancer [19, 20]. However, the relationship between Hcy and cardiovascular disease is now considered to be much closer, with many guidelines and literature suggesting that hyperhomocysteinemia (HHcy) is an independent risk factor for cardiovascular disease, and that its mechanisms include inflammatory response and oxidative stress, damage to vascular endothelial cells, prothrombotic, pro-smooth muscle cell proliferation, methylation, and influence on lipid metabolism in vivo [21].

In previous studies, scholars have mostly focused on the risk factors of a single disease, ignoring the current development of a multimorbid disease spectrum or focusing on the impact of different lifestyles and common lipid markers on CMM, and thus comprehensive analyses of the influencing factors are still lacking. Based on the research foundation of vitamin A, D and Hcy in cardiovascular diseases, the present study aims to investigate the relationship between homocysteine and vitamin A, vitamin D and CMM by analyzing the multifaceted influencing factors of CMM, to identify the shared biomarkers of CMM, and to provide a scientific basis for the preventive and therapeutic strategies of CMM in Chinese elderly. In addition, although none of the studies on the factors affecting CMM distinguished between the number of disease types of co-morbidity, two diseases are the initial stage of co-morbidity. The influencing factors of CMM (number of disease types ≥ 2) are of great significance for targeted prevention of CMM.

Methods

Study design and population

This is a prospective study based on a natural population cohort research project conducted by the National Key Research and Development Programme in rural areas of Ningxia, Northwest China. A baseline survey of people aged 25 and above were recruited as the research participants in rural areas of Qingtongxia and Pingluo counties from March 2018 to July 2020 using randomized whole-cluster sampling. Including those who have no official household registration and have lived in the community for a long time (more than 3 years), and meet the following requirements: (1) Not pregnant; (2) Not lactating; (3) Without mental illness; (4) Without diseases that have a significant impact on the current health status such as car accidents, falls; excluding residents who live temporarily (less than 3 years) and who study or work in other places for a long time but do not live at home. A total of 15,802 individuals completed the questionnaire interview, physical examination, and biological specimen collection in the baseline cross-sectional survey, from which 30% were randomly selected to form a study population of 5,300. A total of 5000 participants were included in the final analyses after excluding 117 with missing data (smoking, alcohol consumption, body mass, blood pressure, and missing lipids) and 183 with abnormal Hcy data. A flow chart of the included studies is presented in Supplementary Figure S1.

Related data collection

Well-trained investigators conducted in-person interviews to obtain data on socioeconomic characteristics, including demographic variables (age, gender, education), lifestyle behaviors (smoking, alcohol consumption, physical activity), medical history, and medication history. Smoking was defined as consumption of at least one cigarette per day for a minimum of six months. Alcohol use status was defined as drinking alcohol at least once

daily for a minimum of six months. Physical exercise was operationalized as participation in physical exercise at minimum three times weekly, with each session lasting 30 min or longer. Anthropometric measurements included height, weight, waist circumference (WC), hip circumference (HC), body mass index (BMI) and blood pressure. Height was measured using a ruler. Weight, WC, and HC were measured using a bioelectrical impedance analyzer (Inbody-370s, Seoul, South Korea). BMI was calculated using the standard formula: BMI = Weight (kg)/Height (m)^2. Participants were instructed to remove outer garments, footwear, socks, and metal accessories. They were then instructed to stand motionless with their weight balanced evenly, keep their hands on the analyzer, and remain quiet until completion of the measurements. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed using an automated sphygmomanometer (OMRON-7124).

Biochemical measurement

In the morning, the physician collected 5 ml of peripheral venous blood from the participants who had fasted 8 h. The blood was collected into a non-anticoagulated tube and 2 ml into an EDTA-anticoagulated tube. Fasting plasma glucose (FPG), total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using automated biochemistry analyzers available at local health clinics. Plasma homocysteine was measured using an automated biochemical analyzer [22]. Vitamin A and vitamin D were determined using an Ultra High Performance Liquid Chromatograph (Agilent 1290, Agilent Technologies, USA).

Definition of diseases

Hypertension was defined as a systolic blood pressure measurement of ≥140 mmHg or a diastolic blood pressure measurement of ≥90 mmHg [23], as documented by a physician's self-diagnosis of the disease and secondary hospitalization. Diabetes mellitus was defined as a fasting blood glucose level ≥7.0 mmol/L [24], as documented by a physician's self-diagnosis of the disease and secondary hospitalization. Coronary heart disease could be defined as a self-reported disease diagnosed by a physician and secondary inpatient record. Stroke was defined as self-reported disease diagnosed by a physician and secondary hospitalization records [25]. Multimorbidity (MM) has two or more chronic diseases at the same time Cardiometabolic multimorbidity (CMM) is defined as the same individual two or more (including hypertension, diabetes, coronary heart disease and stroke) [26]. BMI: Based on the Working Group on Obesity in China's criteria, the BMI classifications are as follows: underweight, BMI < 18.5 kg/m^2; normal weight, 18.5 ≤ BMI < 24 kg/m^2; overweight, 24 ≤ BMI < 28 kg/m$^{2;}$ and obesity, BMI ≥ 28 kg/m^2 [27]. Physical exercise: Physical activity, which was rated as low, moderate, or high, was assessed using the International Physical Activity Questionnaire [28]. Education level: Based on different levels of educational attainment, education is categorized into two types: primary school or below, and middle school or above.

Statistical analysis

Statistical analyses were implemented in R software (version 4.2.3) and SPSS (version 23.0). P-values under 0.05 were regarded as statistically significant. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were shown as frequency and percentage (n (%)). Chi-square tests and one-way analysis of variance (ANOVA) were utilized for comparisons of categorical and continuous variables, respectively. Participants were categorized into two groups based on the number of CMM: ≥2 and none. Quartile classifications of VA, VD, and Hcy levels were generated, and logistic regression models were employed to evaluate the associations between VA, VD, Hcy, and CMM using odds ratios (ORs) and 95% confidence intervals (CIs). Model 1 was unadjusted; Model 2 was adjusted for gender and age based on Model 1; Model 3 was further adjusted for smoking, drinking, and BMI based on Model 2; Model 4 additionally adjusted for energy based on Model 3. Restricted cubic spline (RCS) models were utilized to examine potential non-linear relationships of VA, VD, and Hcy with CMM. To assess the robustness of the VA, VD, Hcy and CMM associations, subgroup analyses were performed.

Result

Characteristics of the subjects

A total of 5,000 participants were enrolled in this study for analysis. Among them, 2,057 (41.14%) were males and 2,943 (58.86%) were females. The mean age of the participants was 58.00 ± 10.00 years. Compared to the No-CMM group, participants in the CMM group were older (with a mean age of 62.33 ± 8.43 years), and had smoking and alcohol drinking rates of 12.80% and 19.10%, respectively. The CMM group exhibited elevated mean levels of FPG, SBP, DBP, TG, TC, LDL-C, Hcy, and vitamin A (8.60 ± 4.06, 148.48 ± 18.40, 89.60 ± 12.64, 2.19 ± 1.54, 5.04 ± 1.22, 3.00 ± 0.98, 20.28 ± 12.38, 446.23 ± 178.97, respectively) compared to the No-CMM group. With the exception of Hcy and vitamin A, these differences were statistically significant ($P < 0.05$). Furthermore, the mean levels of vitamin D and HDL-C (13.27 ± 8.62 and 1.28 ± 0.34, respectively) were lower in the CMM group compared to the No-CMM group, and these differences were also statistically significant ($P < 0.05$). Other

indicators are presented in Table 1. Table 2 presents the serum levels of Hcy, vitamin A and vitamin D across different groups. In comparison to the No-CMM group, no statistically significant differences in Hcy levels were observed between the CMM group ($P>0.05$). The vitamin A levels showed a significant difference between the hypertension and non-hypertension groups ($P<0.05$), however no overt discrepancies were evidenced among the other groups. With the exception of the stroke and coronary heart disease groups, vitamin D levels demonstrated statistically significant differences in the CMM group relative to the No-CMM group ($P<0.05$), with diminished vitamin D levels exhibited universally across the CMM group.

Multimorbidity pattern analysis

Among the 5,000 participants enrolled in this study, 973 (19.46%) met the diagnostic criteria for cardiometabolic syndrome, which includes metabolic disorders such as hypertension, diabetes mellitus, stroke and coronary artery disease. Of those with cardiometabolic syndrome, the majority ($n=642$, 65.96%) had concurrent diabetes mellitus and hypertension, followed by those ($n=130$, 13.36%) with both hypertension and coronary artery disease. Additionally, among the total study cohort, 19.46% had two or more component conditions of cardiometabolic syndrome, while 2.66% had three or more components (Fig. 1). Furthermore, the prevalence of cardiometabolic syndrome was slightly higher in females compared to males (20.05% vs. 18.62%). The prevalence also demonstrated an age-dependent increase, with the fastest growth occurring in the 45–59 years age group (Figure S2).

Associations between vitamin D, vitamin A and hcy and CMM

Table 3 illustrates the correlations between vitamin A, vitamin D, Hcy and various indicators. Vitamin D displayed weak negative correlations with the indicators ($P<0.05$) except for TG and LDL-C. Weak positive correlations of vitamin A with the indicators were observed ($P<0.05$), excluding SBP. No correlations were evident between Hcy and the indicators ($P>0.05$). Logistic regression analysis was conducted to examine the association between serum levels of vitamin D, vitamin A, and Hcy concentrations and the risk of CMM (Fig. 2). In the unadjusted models, compared with the highest quartile, the lower three quartiles of vitamin D were significantly and positively associated with increased CMM risk (third quartile: OR=1.427, 95% CI 1.151–1.768; second quartile: OR=1.781, 95% CI 1.440–2.204; first quartile: OR=1.799, 95% CI 1.446–2.238, $P<0.001$). After adjusting for confounding factors, decreased serum vitamin D levels remained negatively correlated with increased CMM risk (third quartile: OR=1.251, 95% CI 1.003–1.561; second quartile: OR=1.527, 95% CI 1.223–1.907; first quartile: OR=1.553, 95% CI 1.233–1.956, $P<0.001$), while vitamin A and Hcy were not statistically significantly associated with CMM risk ($P>0.05$). Moreover, to validate the reliability of the linear association between vitamin D and CMM, we implemented RCS analysis and observed an inverse dose-response relationship between vitamin D concentrations and CMM (Fig. 3), indicating that escalating levels of vitamin D were associated with a declining risk of developing CMM (P-overall<0.0001; P-non-linear=0.003).

Stratified analyses

To evaluate the robustness of the association between vitamin D and CMM, subsequent subgroup analyses stratified by sex, age, TC, TG, HDL-C, LDL-C, FPG, and BMI were conducted. Figure 4 presents the odds ratios for developing CMM in stratified analyses. In the stratified analyses, the first three quartile groups with lower vitamin D levels, compared to the fourth quartile group, showed positive associations with CMM to a certain extent among the subgroups of females, TG, TC<6.2 mmol/L, HDL-C≥1 mmol/L, LDL-C<4.1 mmol/L, and BMI≥24 kg/m^2. These associations attained statistical significance ($P<0.05$).

Discussion

The current study analyzed cohort data from a natural population in northwest China to examine the associations between vitamin D, vitamin A, Hcy, and CMM in the northwest Chinese population. The findings revealed that the prevalence of CMM was higher in females and increased with advancing age. Furthermore, an inverse association and dose-response relationship were observed between CMM occurrence and vitamin D levels, whereas no significant relationships were found between CMM and either vitamin A or Hcy.

The present study found hypertension to be the most prevalent disease within the CMM disease pattern, clustering more frequently with other comorbidities, aligning with findings from other studies [29]. However, some studies have also identified diabetes as the most common condition in CMM, potentially attributable to genetic predispositions in the population [30]. CMM prevalence increased with age, and was higher among females. Studies across various regions of China have also shown rising CMM prevalence over time, with increasing prevalence of cardiometabolic diseases at older ages [31]. These trends signify the emergence of cardiometabolic diseases as a novel public health concern in China. Such changes may be related to shifts in dietary patterns and lifestyle transitions [32, 33]. Furthermore, research from other countries has also documented high cardiometabolic

Table 1 Characteristics of the subjects

Variable	Total ($n=5000$)	No-CMM ($n=4027$)	CMM ($n=973$)	*P*-Value
Age n (%)				< 0.001
< 64	3444 (68.90)	2948 (73.20)	496 (51.00)	
≥ 64	1556 (31.10)	1079 (26.80)	477 (49.00)	
sex n (%)				< 0.001
Male	2057 (41.14)	1674 (41.57)	383 (39.36)	
Female	2943 (58.86)	2353 (58.43)	590 (60.34)	
Education level n (%)				< 0.001
Primary school or below	4824 (96.50)	3883 (96.40)	941 (96.70)	
Middle school or above	176 (3.50)	144 (3.60)	32 (3.30)	
Tea n %				< 0.001
No	2062 (41.20)	1583 (39.30)	479 (49.20)	
Yes	2938 (58.80)	2444 (60.70)	494 (50.80)	
Smoke n %				< 0.001
No	4266 (85.30)	3418 (84.90)	848 (87.20)	
Yes	734 (14.70)	609 (15.1)	125 (12.80)	
Drink n %				< 0.001
No	3815 (76.30)	3028 (75.20)	787 (80.90)	
Yes	1185 (23.70)	999 (24.80)	186 (19.10)	
physical activity n %				< 0.001
Low	1543 (30.90)	1252 (31.10)	291 (29.90)	
Medium	2574 (51.50)	2086 (51.80)	488 (50.20)	
High	883 (17.70)	689 (17.10)	194 (19.90)	
Diabetes n %				< 0.001
No	3827 (76.50)	3649 (90.60)	178 (18.30)	
Yes	1173 (23.50)	378 (9.40)	795 (81.70)	
Stroke n %				< 0.001
No	4901 (98.00)	4015 (99.70)	886 91.10)	
Yes	99 (2.00)	12 (0.30)	87 (8.90)	
Hypertension n %				< 0.001
No	2378 (47.60)	2341 (58.10)	37 (3.80)	
Yes	2622 (52.40)	1686 (41.90)	936 (96.20)	
Coronary heart disease n %				< 0.001
No	4644 (92.90)	3935 (97.70)	709 (72.90)	
Yes	356 (7.10)	92 (2.30)	264 (27.10)	
Height (cm)	160.00 ± 8.00	160.14 ± 7.97	159.86 ± 8.24	0.350
Weight (kg)	64.00 ± 10.80	63.62 ± 10.53	67.14 ± 11.24	< 0.001
BMI (kg/m^2)	25.00 ± 3.50	24.77 ± 3.42	26.21 ± 3.53	< 0.001
WC (cm)	87.00 ± 9.90	86.52 ± 9.67	90.81 ± 10.15	< 0.001
SBP (mmHg)	136.00 ± 19.60	132.82 ± 18.63	148.48 ± 18.40	< 0.001
DBP (mmHg)	83.00 ± 12.60	81.87 ± 12.14	89.60 ± 12.64	< 0.001
FPG (mmol/L)	6.00 ± 3.00	5.79 ± 2.36	8.60 ± 4.06	< 0.001
TG (mmol/L)	2.00 ± 1.20	1.67 ± 1.12	2.19 ± 1.54	< 0.001
TC (mmol/L)	5.00 ± 1.30	4.86 ± 1.31	5.04 ± 1.22	< 0.001
HDL-C (mmol/L)	1.00 ± 0.40	1.37 ± 0.42	1.28 ± 0.34	< 0.001
LDL-C (mmol/L)	3.00 ± 0.90	2.83 ± 0.84	3.00 ± 0.98	< 0.001
Hcy (μmol/L)	20.00 ± 12.60	20.10 ± 12.64	20.28 ± 12.38	0.688
Vitamin A (ng/ml)	441.00 ± 159.50	439.92 ± 154.47	446.23 ± 178.97	0.268
Vitamin D (ng/ml)	15.00 ± 9.90	14.89 ± 10.22	13.27 ± 8.62	< 0.001

BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Hcy, Homocysteine

Table 2 Plasma homocysteine and vitamin A, D levels in different population groups

Disease	*N* (%)	Homocysteine (μmol/L)	Vitamin A (ng/ml)	Vitamin D (ng/ml)
Diabetes				
No	3827	20.15 ± 12.66	440.49 ± 156.84	14.96 ± 10.37
Yes	1173	20.10 ± 12.37	443.28 ± 168.08	13.30 ± 8.29
P		0.908	0.601	< 0.001
Stroke n %				
No	4901	20.10 ± 12.54	441.39 ± 159.39	14.57 ± 9.88
Yes	99	22.00 ± 14.87	429.01 ± 166.82	14.75 ± 12.85
P		0.138	0.445	0.859
Hypertension				
No	2378	20.04 ± 12.53	434.02 ± 152.63	15.38 ± 10.59
Yes	2622	20.22 ± 12.65	447.61 ± 165.32	13.84 ± 9.27
P		0.615	0.003	< 0.001
Coronary heart disease				
No	4644	20.16 ± 12.69	441.57 ± 156.36	14.55 ± 9.37
Yes	356	19.85 ± 11.27	435.60 ± 196.48	14.83 ± 15.69
P		0.657	0.496	0.610
CMM				
No	4027	20.10 ± 12.64	439.92 ± 154.47	14.89 ± 10.22
≥ 2 diseases	840	20.14 ± 12.05	447.33 ± 179.72	13.17 ± 8.74
P		0.622	0.468	< 0.001

CMM: Cardiometabolic multimorbidity

disease prevalence, including the U.K. (16.84%) [34], the U.S. (14.4%) [35], and South Africa (10.5%) [29]. The cross-national variation in prevalence may stem from differences in disease definitions and dietary habits across populations.

Vitamin D deficiency has been closely associated with obesity, diabetes and cardiovascular diseases [36]. Accumulating evidence demonstrates that vitamin D levels are closely related to cardiac metabolic diseases, and vitamin D deficiency may be an important etiological factor underlying the epidemic of these diseases [37]. Our study also revealed an inverse correlation between blood vitamin D concentrations and risk of CMM, with lower vitamin D levels associated with higher disease risk. The prevalence of hypertension is high among patients with cardiac metabolic diseases. Vitamin D has been implicated in maintaining blood pressure homeostasis through regulating the renin-angiotensin-aldosterone system [38]. Furthermore, vitamin D deficiency can impact carbohydrate metabolism, particularly glucose metabolism [14]. Therefore, vitamin D deficiency may be a key contributor to hypertension and diabetes development, subsequently leading to CMM. Substantial evidence indicates gut microbiota are involved in the pathogenesis of various chronic inflammatory conditions including diabetes

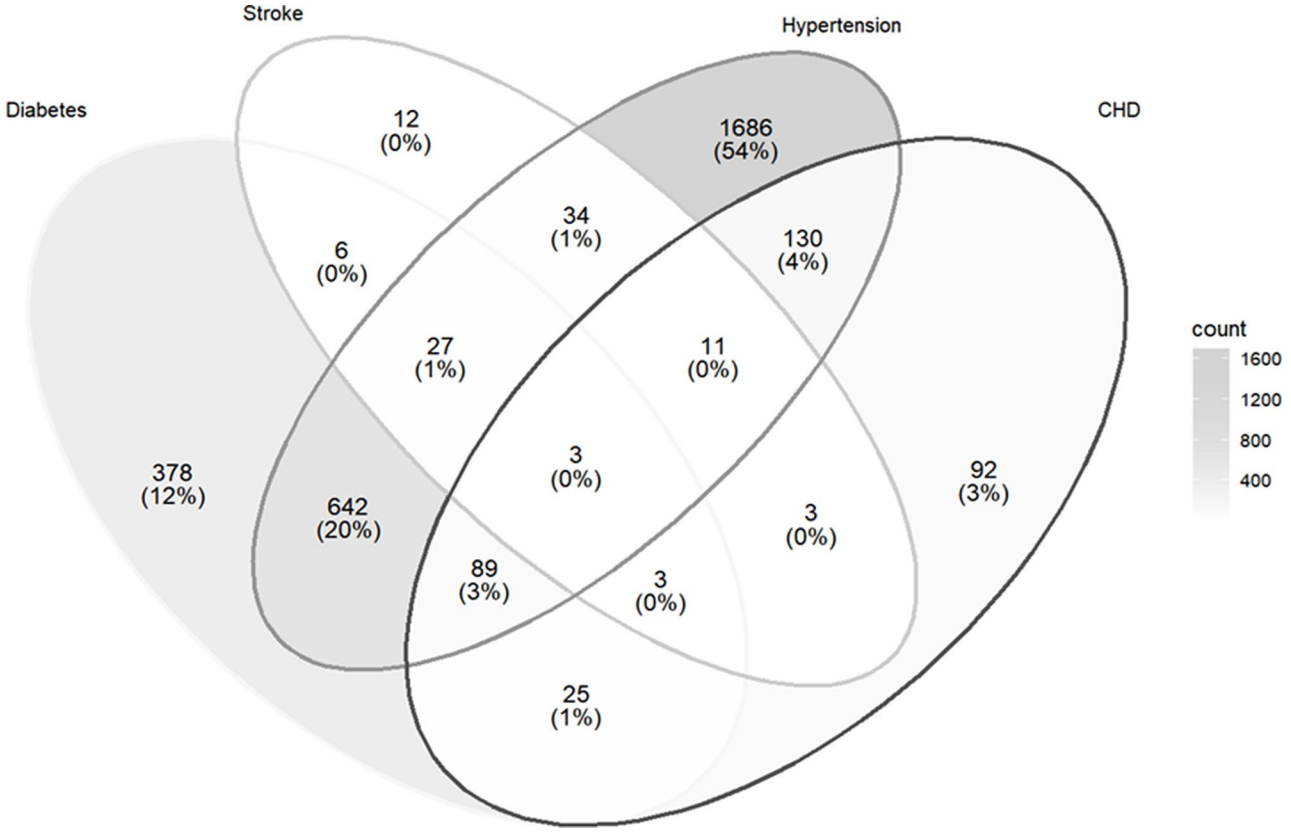

Fig. 1 Distribution patterns of CMM in the study population. CHD: coronary heart disease

Table 3 Relationship among homocysteine, vitamin A, vitamin D and different blood indexes

Variable	Vitamin D		Vitamin A		Homocysteine	
	Correlation Coefficient, r	*p*	Correlation Coefficient, r	*p*	Correlation Coefficient, r	*p*
FPG	-0.052	< 0.001	0.069	< 0.001	0.010	0.465
TC	-0.083	< 0.001	0.089	< 0.001	0.000	0.982
TG	0.024	0.084	0.185	< 0.001	-0.009	0.532
HDL-C	-0.075	< 0.001	-0.034	0.019	0.012	0.398
LDL-C	-0.007	0.630	0.081	< 0.001	-0.012	0.409
SBP	-0.122	< 0.001	0.006	0.694	0.027	0.058
DBP	-0.063	< 0.001	0.061	< 0.001	0.008	0.554

FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

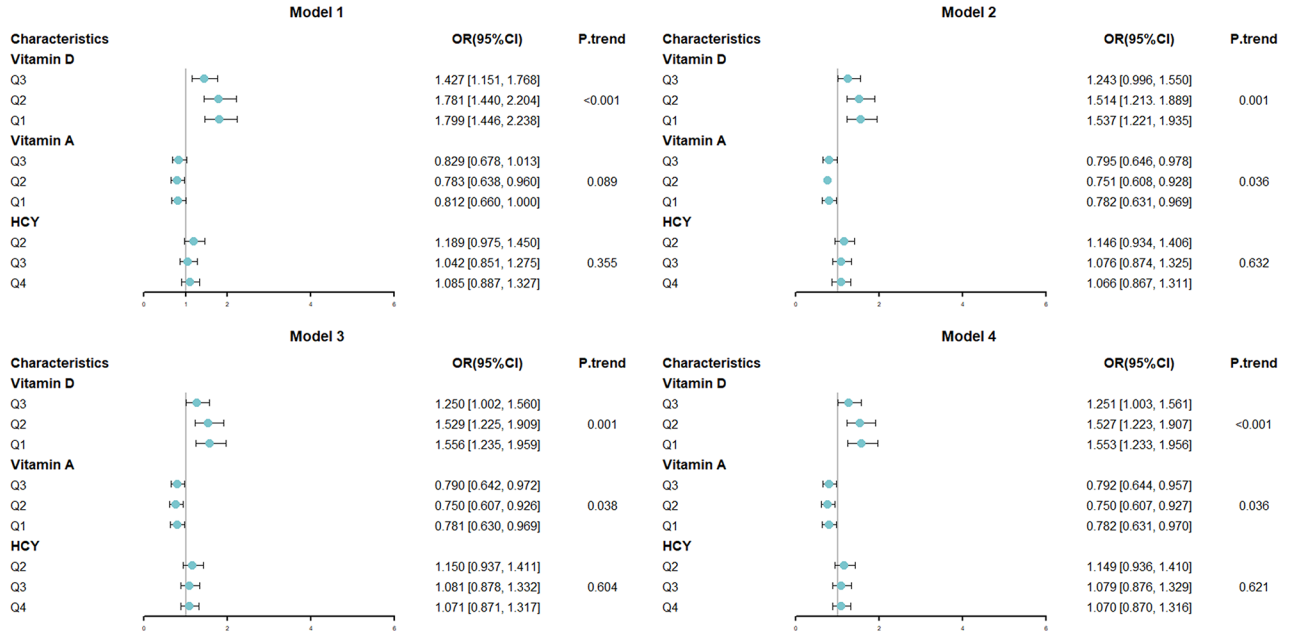

Fig. 2 Associations (ORs and 95% CIs) between tertiles of vitamin D, vitamin A and Hcy and CMM among population. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3: Model 2 + smoking, alcohol consumption, BMI; Model 4: Model 3 + Energy

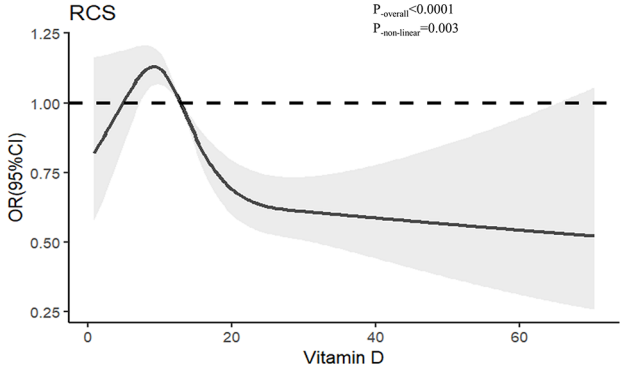

Fig. 3 The relationship between vitamin D concentration and CMM risk. Horizontal black dashed lines represent the positions where OR = 1. OR: Odds ratio; CI: Confidence interval; RCS: Restricted cubic spline

and cardiovascular diseases. Vitamin D can maintain gut barrier integrity by modulating associated proteins, thereby preventing bacterial products and metabolites from entering circulation [39]. Consequently, vitamin D deficiency may disrupt the intestinal barrier and cause dysbiosis, eventually inducing diseases such as CMM.

Previous studies have demonstrated that vitamin A and its derivatives play a crucial role in modulating cardiovascular metabolism, including energy utilization, glucose homeostasis, hepatic steatosis, and atherosclerosis. They are also implicated in the pathogenesis of various adverse cardiovascular metabolic diseases like cardiovascular disease and diabetes [40]. However, the current study did not find any definite association between vitamin A and CMM. Furthermore, several large-scale prospective studies also did not reveal any significant correlation between vitamin A and CVD as well as diabetes. Some studies even reported conclusions contradictory to other reports

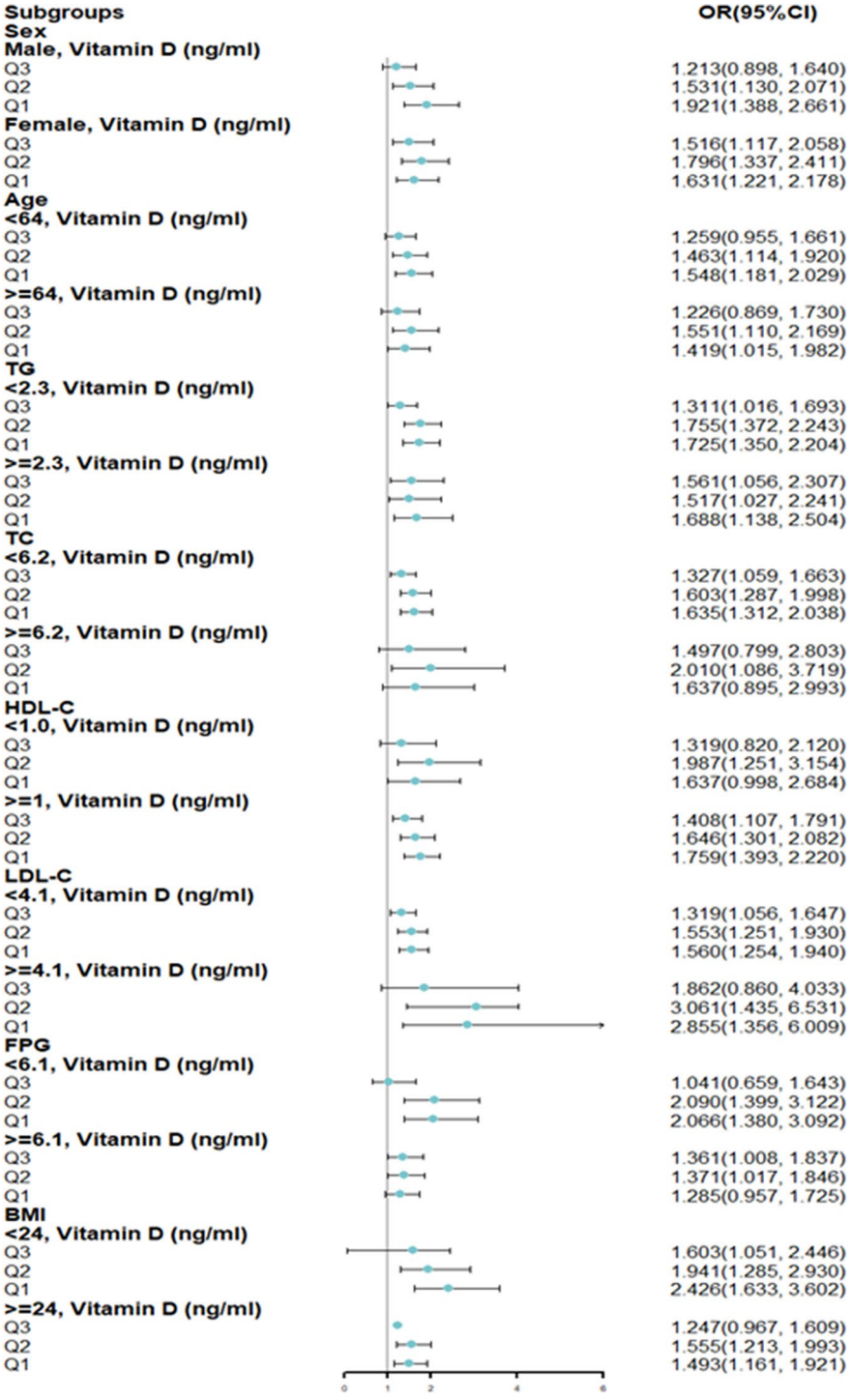

Fig. 4 Association between Vitamin D and CMM in subset analysis. Hcy: Homocysteine; BMI: Body mass index; FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol

[41]. The discrepancies among different studies could be attributed to subgroup analyses of the study population. Additionally, liver and kidney function, which play a pivotal role in vitamin A-related cardiovascular metabolism risks, may also influence the relationship between vitamin A and cardiovascular metabolic endpoints [42]. Finally, the heterogeneity between vitamin A and cardiovascular metabolism may arise from variations in outcome definitions, ethnicity, vitamin A dosage range, and study duration across different studies. Homocysteine is an important biomarker for various metabolic diseases and organ damage, but its role in cardiovascular

metabolic risk remains unclear. The present study did not find any association between homocysteine and cardiovascular metabolic abnormalities. However, some studies suggest that homocysteine may mildly influence the development of cardiovascular metabolic abnormalities through oxidative stress and endothelial dysfunction [43]. Furthermore, differences in living pressure, dietary habits, and susceptibility genes for specific diseases among various populations could also lead to discrepancies between study findings. The exact mechanisms by which homocysteine affects cardiovascular metabolic abnormalities warrant further investigation through additional studies with diverse designs.

In addition, this study found that the influence of vitamin D on CMM was more pronounced in certain subgroups. For instance, CMM occurs more frequently in males, potentially due to males engaging in more behaviors associated with CMM risk, including smoking, alcohol consumption, and physical inactivity, compared to females [33]. The association between vitamin D and CMM was stronger in populations with normal blood lipid levels than in those with dyslipidemia. This may be because dyslipidemia can affect vitamin D absorption and utilization, thus obscuring the relationship between vitamin D and CMM. Moreover, higher BMI is also closely associated with increased CMM risk. The high-paced lifestyle and lack of physical activity are key factors contributing to elevated BMI, which in turn may raise metabolic disease risk through various pathways (e.g. inflammatory response) [26].Therefore, besides examining the influence of vitamin D on CMM, consideration of other contributing factors is warranted. For CMM prevention and control, priority should be given to improving unhealthy behaviors like smoking cessation, moderating alcohol intake, increasing physical activity, and controlling life stress. Blood lipid levels need monitoring and BMI should be maintained within the normal range. Only by comprehensively mitigating the various CMM risk factors can effective prevention and control of CMM be achieved.

This study possesses both strengths and limitations. Regarding strengths, our investigation utilized large-scale, population-based survey data with a substantial sample size and broad age distribution, imparting high generalizability to the results. We verified the vitamin D-CMM relationship from multiple vantage points, bolstering the robustness of our findings. Stratification by demographic traits facilitated the identification of high-risk CMM subpopulations. However, certain limitations exist. The cross-sectional design precludes causal inferences between vitamin D and CMM. Self-reported metabolic disease data may have underestimated true morbidity. Additionally, residual confounding likely persists. In summary, our study furnished further evidence supporting the vitamin D-CMM association but was unable to establish causality. The extensive, representative sample constitutes a major strength, although self-reported data may have introduced misclassification bias. Future efforts could implement objective assessment tools to minimize potential biases.

Conclusions

In conclusion, the present study demonstrates a significant age-related increase in the incidence of CMM, especially among males who exhibit higher CMM morbidity. The data verify a linear association between vitamin D status and CMM risk, whereby lower serum vitamin D levels correlate with greater CMM risk. Our findings provide preliminary evidence that vitamin D may independently modulate CMM risk. Furthermore, cardiovascular metabolic diseases pose a pressing public health concern. Consequently, prioritizing medical resources for cardiovascular metabolic disease screening, prevention and management is warranted, alongside heightened vigilance for CMM occurrence, particularly in populations with vitamin D insufficiency.

Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CMM	Cardiometabolic Multimorbidity
CNC-NX	Northwestern Chinese Natural Population Cohort-Ningxia Project
CVD	Cardiovascular disease
FPG	Fasting blood glucose
Hcy	Homocysteine
HDL-C	High density lipoprotein cholesterol
HHcy	Hyperhomocysteinemia
LDL-C	Low density lipoprotein cholesterol
OR	Odd ratio
TC	Total cholesterol
TG	Triglyceride
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
WC	Waist circumference
RCS	Restricted cubic spline

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00845-5.

Supplementary Material 1

Acknowledgements

We are grateful to all participants in this study and the data collection staff; without them, the work of the research could never have been completed.

Author contributions

YZ and YHZ designed the study and drafted the outline. JLand XWL wrote the original draft and reviewed and edited the manuscript. XLY and YLC participated in the Hcy, vitamin A, and vitamin D experiment. JL, XWL and LL organized and analyzed the data. YHZ and YZ critically reviewed and revised the manuscript. All authors read and approved the final version to be published.

Funding
The current study was supported by the National Natural Science Foundation of China (grant number: 82060592, U22A20360), the Key Research and Development Program of Ningxia Hui Autonomous Region (grant number: 2021BEG02026). The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Committee (IEC) of Ningxia Medical University (Ethics ID 2018-012, 2020 – 689). Written informed consent was obtained from all participants. All investigations were conducted in accordance with the principles of the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 1 July 2024 / Accepted: 26 August 2024
Published online: 30 August 2024

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