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Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A Cross-Sectional Study in Northwest China

Abstract

Background: Elevated homocysteine (Hcy) levels have been linked to cardiovascular disease (CVD), but their association with cardiometabolic multimorbidity (CMM) remains uncertain.

Methods: Data from the baseline survey of the China Northwest Cohort-Ningxia Project (CNC-NX) were used to recruit 22,566 participants. Demographic characteristics, lifestyle factors, and laboratory exam results were collected to evaluate the association between Hcy levels and the risk of CMM.

Results: The final analysis included 18,126 participants. Higher Hcy levels were significantly associated with an increased risk of CMM (adjusted OR=1.005, P=0.003), with a linear relationship confirmed by Restricted Cubic Spline (RCS) analysis (P for non-linearity=0.142). There was a stronger association between Hcy-CMM in high-risk people, including elderly, males, and those with high BMI (P<0.05). No significant association was observed between Hcy levels and more severe types of CMM.

Conclusions: Elevated Hcy levels are correlated with an increased risk of CMM, warranting further investigation into the underlying mechanisms and potential interventions. Given the individual differences in the Hcy-CMM relationship, targeted comprehensive interventions for high-risk groups are necessary to reduce the risk of CMM.

Keywords: Homocysteine; Cardiometabolic multimorbidity; Risk factors; Individual differences; Cross-sectional study

Background

With the acceleration of global population aging and urbanization, individuals are increasingly at risk of suffering from multiple chronic diseases, mainly cardiovascular disease (CVD) and its related complications, with morbidity and mortality rates continuously rising [1–3]. As a result, it has become a significant public health issue affecting patients, their families, and healthcare systems. The term cardiometabolic multimorbidity (CMM) describes the coexistence of two or more cardiometabolic diseases (CMDs), such as coronary heart disease (CHD), hypertension, stroke, and diabetes [4]. Research indicates that CMM incidence rises significantly with age [5]. CMM patients have a 3.7 to 6.9 times higher risk of all-cause mortality at 60 than those without CMDs, resulting in a reduced life expectancy of 12 to 15 years [6].

Numerous epidemiological studies have linked lifestyle behaviors with the development and occurrence of individual CMDs and CMMs in recent years. However, results have been inconsistent across different ethnicity, regions, and research methods [7–9]. Due to the multifactorial etiology, complex pathogenesis, and multiple biological markers of CMDs, their specific mechanisms of action have yet to be discovered [10]. To prevent and treat chronic diseases such as diabetes, strokes, hypertension and CHD, it is important to identify the common biomarker of exposure. As an intermediate in the synthesis of cysteine, homocysteine (Hcy) is a sulfur-containing amino acid derived from methionine metabolism [11]. Previous studies have shown that hyperhomocysteinemia (HHcy) is a risk factor for CHD and stroke, with potential effects on cardiovascular health through increased formation of atherosclerotic plaques and platelet aggregation [12,13]. A systematic review found a dose-response relationship between stroke and Hcy levels. For each 1μmol/L rise in Hcy concentration, the risk of stroke increased by 1.06 times. [14].

Furthermore, hypertension, diabetes, and obesity have been linked to fluctuations in Hcy levels. Hcy contributes to vascular damage caused by hypertension and can serve as a predictor of target organ damage in individuals with hypertension. This makes it a valuable indicator for guiding first-line antihypertensive therapy [15]. Plasma Hcy levels were found to be significantly elevated in diabetic patients when compared to control groups [16], and HHcy may induce thickening of small arteries, leading to interstitial cell and podocyte injury in the early kidney injury of type 2 diabetes patients [17]. Hcy concentrations in obese individuals were markedly higher than in control groups, irrespective of their nutrition, insulin resistance, dietary habits, medical history, medication use, or genetic background [18]. Insulin is a key factor linked to Hcy levels in obese children and adolescents. Hyperinsulinemia may lead to impaired Hcy metabolism in obese children [19].

Hcy is a crucial biomarker that links different metabolic diseases with damage to organs. Systematically studying the role of Hcy in the pathogenesis of CMM can help shed light on the inherent connections between diseases. As a result, an observational study was carried out to investigate the relationship between Hcy and CMM. In this study, it was hypothesized that there would a significant relationship between Hcy and CMM. Although previous research has explored the role of Hcy in cardiovascular diseases, its relationship with CMM has not yet been systematically evaluated. Through detailed analysis, this study further expands the existing body of research.

Methods

Study design and population

The study was based on the baseline survey of the China Northwest Cohort-Ningxia Project (CNC-NX) and employed a multi-stage clusters sampling approach to select participants from three different time periods. In the first stage, 15,802 individuals were recruited by randomly selecting four towns in each

of the Wu Zhong and Shi Zuishan cities and then selecting two samples from each town. The selected participants, aged between 35 and 74, were surveyed from March 2018 to May 2019. Each subject provided informed written permission, the following were excluded: (i) severe mental illness or impairment, (ii) major infectious disorders, and (iii) incapacity to converse regularly. In the second stage, 1,728 freshmen aged 18 years and above were recruited from Ningxia Medical University in September 2018. In the third stage, 5,035 elderly individuals were recruited from community households in Yinchuan City in 2020. The recruitment criteria for the second and third stages were consistent with those for the first stage of the survey.

Initially, 22,566 individuals were recruited for the study. However, after excluding 3,357 participants due to missing data on smoking, alcohol consumption, physical activity, blood pressure, and blood lipids, as well as 984 individuals with missing Hcy data and 396 individuals with abnormal Hcy and blood lipid values, the final analysis included a total of 18,126 participants. The flowchart for study inclusion is presented in Supplementary **Fig. S1**, and the detailed recruitment process for the study population is described in our previously published article [20–24].

Data collection

The survey was administered face-to-face by trained investigators using a questionnaire. This questionnaire primarily addressed demographic characteristics (such as age, gender, and education level), lifestyle behaviors (including smoking, alcohol consumption, and physical exercise), as well as medical and medication history. Smoking was defined as the use of one cigarette per day for at least six months. Alcohol consumption was defined as drinking alcohol daily for six months or more [25]. Physical exercise was defined as participating in physical activity a minimum of three times per week, with each session lasting 30 minutes or more [26].

Physical measurements collected included weight, height, and blood pressure, as well as the calculation of body mass index (BMI, kg/m²). Weight (kg) was measured using a bioelectrical impedance analyzer (Inbody-370s, Seoul, South Korea). Height was measured in centimeters using a ruler. Subjects were forced to remove their coats, shoes, socks, and metal decorations before standing barefoot on a balancing scale, gripping the handle, and remaining silent until the measurement was complete. An electronic sphygmomanometer (OMRON-7124) was used to assess both systolic (SBP, mmHg) and diastolic (DBP, mmHg) [27].

Biochemistry measurement

Venous samples of blood were obtained from subjects who had fasted for at least 8 hours. The blood was collected, centrifuged, and kept in a refrigerator at -80°C for preservation. Plasma homocysteine (Hcy, μmol/L), fasting plasma glucose (FPG, mmol/L), total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), and low-density lipoprotein cholesterol (LDL-C, mmol/L) were measured using the automated biochemical analyzer provided by the Key Laboratory of Environmental Factors and Chronic Diseases Control of Ningxia Medical University[28].

Definition of diseases

Hypertension was defined as having a SBP of ≥140 mmHg or a DBP of ≥90 mmHg [29], or by a self-reported diagnosis of hypertension from physicians and secondary hospital inpatient records. Diabetes was defined as having a FPG of ≥7.0 mmol/L [30], or by a self-reported diagnosis of diabetes from physicians and secondary hospital inpatient records. CHD and stroke were defined as having a self-reported disease diagnosed by physicians and secondary hospital inpatient records. Diagnoses were coded using the International Classification of Diseases, 10th Edition (ICD-10). According to the

comorbidity rates and patterns identified in the Chinese population from the China Kadoorie Biobank (CKB), CMM was defined as the occurrence of at least two of the following conditions: CHD (including myocardial infarction or angina), stroke (such as ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage), diabetes, and hypertension [31].

Statistical analysis

Statistical analyses were conducted using R statistical software (version 4.2.3). Statistical significance was set at a *P*-value of less than 0.05. Continuous variables were expressed as means with standard deviations, whereas categorical variables were reported as frequencies and percentages. Ccorrelation between Hcy and TC, TG, FPG, SBP, DBP, HDL-C, and LDL-C were initially analyzed. Participants were divided into two groups based on the number of CMM conditions: those with two or more conditions (≥2) and those with three or more conditions (≥3) [1]. To evaluate the relationship between plasma Hcy levels and CMM, both unadjusted and two adjusted logistic regression models were used to estimate the odds ratios (OR) and their corresponding 95% confidence intervals (CI). Model 1 was adjusted for age, sex, BMI, education level, physical activity, smoking, and alcohol consumption. Model 2 was further adjusted for TC, TG, HDL-C, and LDL-C based on Model 1.

Additionally, to investigate the association between different Hcy concentrations and CMM, plasma Hcy was divided into four groups based on quartiles (Q1, Q2, Q3, and Q4, with Q1 as reference) for logistic regression analysis. Restricted cubic spline (RCS) models, created with three knots, were used to examine the possible non-linear relationship between Hcy and CMM [32]. Furthermore, the sensitivity analysis was conducted to account for the variability of clusters. The analysis was performed using a mixed-effects logistic regression model, where the clusters was included as a random effect in the model. Finally, subgroup analyses were performed using the following variables: age (0~64

years, >64 years), sex (Male, Female), BMI (<24 kg/m^2, ≥24 kg/m^2), TC (<6.2 mmol/L, ≥6.2 mmol/L), TG (<2.3 mmol/L, ≥2.3 mmol/L), HDL-C (<1 mmol/L, ≥1 mmol/L) and LDL-C (<4.1 mmol/L, ≥4.1 mmol/L). The categorization of lipid indices followed the guidelines established by the 2016 Revised Guidelines for the Prevention and Treatment of Dyslipidemia in Chinese Adults [33].

Results

Characteristics of the subjects

The study included a total of 18,126 participants, of whom 7,544 (41.6%) were male and 10,582 (58.4%) were female. As Hcy levels increase from Q1 (0.1-13.0 μmol/L) to Q4 (22.8-80 μmol/L), there is a notable trend of increasing age, with the mean age rising from 58.6 years in Q1 to 61.9 years in Q4 (P<0.001). Although BMI remains relatively stable across the quartiles, higher Hcy levels are associated with increased TG (P<0.001) and lower HDL-C (P=0.007). Furthermore, the prevalence of CMM rises with Hcy levels, with 15.7% of individuals in Q4 having at least two diseases compared to 10.9% in Q1 (P<0.001). Additionally, higher Hcy levels are associated with lower educational attainment (P<0.001) and an increased frequency of high-intensity physical activity (P<0.001). See **Table 1** and **Table S2** for other indicators. The prevalence of CMM increased with age, particularly between ages 45 and 65 (**Fig. 1**).

The correlation matrix indicated a weak negative correlation between Hcy and LDL-C (r=-0.02) and TC (r=-0.01), while a weak positive correlation existed between Hcy and TG (r=0.02) (Supplementary **Fig. S2**). However, no significant correlations were found between Hcy and HDL-C, FPG, SBP, or DBP.

Association between Homocysteine and Cardiometabolic Multimorbidity

When at least two types of diseases were taken as the study endpoint, the crude model demonstrated a

statistically significant correlation between Hcy and CMM (OR=1.008, *P*<0.001). After adjusting for age, sex, BMI, education, physical activity, smoking, alcohol drinking, TC, TG, HDL-C, and LDL-C, the model still showed statistical significance (Model 1: OR=1.006, *P*=0.001; Model 2: OR=1.005, *P*=0.003). With respect to Hcy quartile grouping, CMM risk was significantly increased for the second and fourth quartiles compared to the first quartile (Model 2: Q2 vs. Q1, OR=1.161, *P*=0.026; Q4 vs. Q1, OR=1.203, *P*=0.005). Model 1 also showed a correlation for the third quartile (Q3 vs. Q1, OR=1.164, *P*=0.022). When at least three types of diseases were taken as the study endpoint, none of the three models yielded significant results. In terms of Hcy quartile grouping, only the crude model showed a correlation with CMM risk (Q2 vs. Q1, OR=1.355, *P*=0.049, Q4 vs. Q1, OR=1.492, *P*=0.008). After adjusting for confounding factors, Models 1 and 2 did not show statistical significance (**Table 2**).

The logistic regression results seemed to suggest a linear relationship between Hcy and CMM, at least when the indications for two types of diseases were changed. By plotting the dose-response relationship of Hcy and CMM, the RCS results showed no evidence of nonlinearity between Hcy and CMM (*P* for non-linearity=0.142). The risk of CMM increased linearly and then gradually flattened with increasing Hcy concentrations (*P* for Hcy=0.004), as shown in **Fig. 2A**. However, CMM with at least three indications as the outcome did not show any statistical significance, which was consistent with the logistic regression results (**Fig. 2B**). The results of the sensitivity analysis were consistent with those of the primary analysis, confirming the robustness of our findings (Supplementary **Table S3**).

Subgroup analyses

Hcy concentrations were compared among different subgroups. The concentration of Hcy in the group aged above 64 was higher than that in the group aged under 64 (*P*<0.001). Furthermore, the male participants demonstrated a higher Hcy concentration than the female participants (*P*<0.001). The Hcy

concentration was higher in the abnormal TG group than in the normal group (P=0.011), and it was higher in the abnormal HDL-C group that in the control group (P=0.011). However, no statistically significant differences were observed among the BMI, TC, and LDL-C groups (**Fig. 4**).

The subgroup analysis results showed a correlation between Hcy and CMM (having at least 2 diseases) after adjusting for the confounding factors such as age, gender, BMI, TC, TG, HDL-C, and LDL-C (**Fig. 3)**. For individuals aged≥64, the correlation between Hcy and CMM was stronger, with an OR (95%CI) of 1.006(1.002, 1.001). Males had a stronger correlation than females, 1.007(1.002, 1.012), and those with a BMI≥24 kg/m^2 had a stronger correlation, 1.995(1.000, 1.009). In addition, the individuals with a TC<6.2 mmol/L or TG≥2.3 mmol/L had a stronger correlation, with an OR of 1.005(95%CI:1.001, 1.009). and 1.010(1.003, 1.016), respectively, and those with HDL-C>1 mmol/L or LDL-C<4.1 mmol/L had a stronger correlation, 1.005(1.002, 1.009) and 1.005(1.001, 1.009), respectively (Supplementary **Table S1**). However, in more severe CMM (having at least 3 diseases), none of the variables exhibited any statistically significant correlations, which was consistent with the previous results of Model 1 and Model 2 in **Fig. 2B** and **Table S1** Model 1 and Model 2.

Discussion

This cross-sectional study,, which included a sample size of 18,126 individuals, aimed to investigate the association between plasma Hcy levels and the risk of CMM. A linear dose-response relationship was observed between Hcy and CMM (at least two diseases), indicating that higher Hcy levels were correlated with a higher risk of CMM. These findings indicate a potential role for Hcy in the development of CMM and provide insights for future prevention and treatment strategies.. Using a reference value of Hcy=16.7 μmol/L, the OR for CMM increased gradually towards 1 as Hcy levels decreased below a certain point, and increased with increasing Hcy concentrations until reaching the

highest peak, yet. According to the American Heart Association [34], plasma Hcy levels are categorized as follows: ≤15 μmol/L is considered normal, 15-30 μmol/L is classified as moderately elevated, and >30 μmol/L is regarded as significantly elevated. The study also indicated that individuals with elevated Hcy concentrations have a higher risk of developing CMM. These findings are consistent with previous large-scale cohort studies and meta-analyses [35–37]. Moreover, the possible mechanisms by which Hcy affects CMM include promoting atherosclerosis, platelet aggregation, oxidative stress, and endothelial dysfunction, which indirectly influence the development of CMM [38,39]. The results were independent of demographic, lifestyle, and clinical factors, and were not driven by the incidental diagnosis of any specific disease. Instead, they reflected the overall burden of multiple comorbidities in CMM. Although the effect size was modest, the biological consistency, dose-response relationships, and statistical strength of the findings suggest that Hcy could play a potentially significant role in the detection and pathogenesis of CMM. Controlling Hcy levels may reduce CMM risk and improve quality of life.

The weak correlation between Hcy and more severe CMM (at least three diseases) was not statistically significant even after adjusting for confounding factors, which could be due to the limited effect of Hcy as a single risk factor for CMM. As the severity of CMM increases, a wider range of more complex factors are activated and interacted synergistically to change the onset, progression, and outcome of the diseases, which dilutes the effect of Hcy, making it difficult to accurately predict the impact of more severe diseases or establish a clear association with them [40]. A review study suggested that patients with HHcy had a lower risk of ischemic stroke [41], contrasting with Wang's findings of no association between total Hcy and functional outcomes in elderly stroke patients [42]. Guéant's study revealed that although lowering Hcy levels in CVD patients with Hcy toxicity offered limited benefits, adhering to

current guidelines for assessing and treating B-vitamin deficiencies and genetic disorders remains crucial [43]. The results seem to support this view, suggesting that Hcy may play a greater role in the early stages of CMM. Besides, patients with multiple comorbidities tend to receive multiple treatments, and the interactions between different medications may influence Hcy levels [44]. Finally, the sample size of individuals with at least 3 CMM might be small, resulting in insufficient statistical power, which affects the significance of the test results. Further research with bigger sample numbers is required to confirm this conclusion.

The association of Hcy and CMM is more significant in certain subgroups, such as the elderly, males, and those with a higher BMI, which may be due to the fact that these groups already have a higher risk of developing CMM and that the role of Hcy is more pronounced in these populations. Age is a risk factor for metabolic diseases such as diabetes, hypertension, and coronary heart disease, the prevalence of which increases with age. The study found that CMM occurrence begins gradually increasing from the age of 45 at a more rapid rate, which is consistent with prior study findings [4,6]. Males have a higher incidence of hypertension relative to females [45], and are more exposed to pathogenic factors [46]. The focus on obesity and overweight populations has been increasing, as obesity can lead to abnormal blood lipids, induce hypertension, affect endothelial cells, and increase cardiac load, thereby increasing the risk of CVD [47]. Therefore, these high-risk populations should be given priority in the prevention and treatment of CMM. Additionally, the subgroup analysis revealed that Hcy had a greater impact on CMM in populations with relatively normal blood lipids, but this was not the case for TG (Supplementary **Table S1**). It is hypothesized that individuals with CMM and abnormal blood lipid levels may have undergone certain physiological or pathological alterations resulting from chronic conditions or lipid abnormalities [33]. Specifically, in individuals with normal TC, HDL-C, and LDL-C,

lipid metabolism and vascular health are relatively good, making the effect of Hcy more direct. However, in individuals with abnormal lipid levels, other lipid abnormalities may complicate the effect of Hcy. High TG levels are an important marker of the metabolic syndrome and usually accompanied by inflammation, insulin resistance, and elevated Hcy levels [48]. High TG levels are associated with systemic inflammatory response and oxidative stress, which may enhance the association of Hcy with CMM [49].

Although this study showed an association between Hcy concentrations and CMM, the complexity of Hcy's mechanism of action may limit its preventive effects on CMM. Currently, intervention studies targeting Hcy have yielded inconsistent results, so more long-term and high-quality randomized controlled trials are required to prove its effects. Given the individual variability in the relationship between Hcy and CMM, in the future, specific adjunctive therapies, such as B-vitamin supplementation based on the Hcy levels, can potentially achieve better results in addition to the traditional therapies such as lipid lowering and blood pressure control. Although B-vitamins may not have achieved the expected effect on the incidence of CVD, they still play a crucial role in regulating Hcy levels [50]. Additionally, B-vitamin interventions may be more important for certain combinations of chronic diseases or specific populations.

Strengths and limitations

A large sample size was used in the current study, which allowed for a higher statistical power to detect the association between Hcy and CMM. The study subjects ranged from young to elderly individuals, making the results representative. The study provided detailed available clinical and potential confounding factors, making the results more reliable. However, several limitations should be taken into consideration. A cross-sectional design was used in this investigation, which did not allow for the

establishment of a causal relationship between Hcy and CMM. Potential reverse causality should also be considered when interpreting the relationship between the two. For instance, the progression and complications of chronic diseases could lead to metabolic changes, thereby influencing Hcy concentrations. The identification of CMM was accomplished through clinical data and self-reports by integrating different data sources, which may lead to mis-classification of results and detection limitations. Thus, future studies should take these limitations into account for improvement and expansion.

Conclusions

In summary, this study has demonstrated a significant linear association between Hcy and the CMM, particularly in individuals with mild illness. Increased Hcy levels are linked to a higher risk of developing CMM., highlighting the potential value of monitoring Hcy levels in clinical settings. These findings suggest that targeted interventions aimed at reducing Hcy levels may be beneficial for high-risk groups, including the elderly, males, and obese individuals. Future research should focus on elucidating the underlying biological mechanisms of the Hcy-CMM correlation and exploring how individual variations may influence this association. By understanding these mechanisms, more effective prevention and treatment strategies can be developed, ultimately improving patient outcomes in these vulnerable populations.

Abbreviations

BMI: Body mass index

CHD: Coronary heart disease

CI: Confidence interval

CMDs: Cardiometabolic diseases (CMDs)

CMM: Cardiometabolic multimorbidity

CNC-NX: China Northwest 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: Odds ratio

RCS: Restricted cubic spline

TC: Total cholesterol

TG: Triglyceride

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Author contributions

XL, JL, JZ, JQ and QW participated in field investigations; SM, XL, WL, KC, KW, XL and JL participated in Hcy experiment; JQ and JZ performed data cleaning and management; QW performed statistical analysis and visualization; JQ and QW wrote the paper; HZ, YJ, YZ and YZ designed the research; the final content was primarily the responsibility of YZ and YZ. The manuscript was reviewed and approved by all authors.

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Data Availability

The datasets used and/or analyzed in this work are accessible from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Approval for this study was granted by the Institutional Ethics Committee (IEC) at Ningxia Medical University (Ethics ID: 2018-012, 2020-689). All participants provided written informed consent, and the research procedures adhered to the guidelines set forth in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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457 **Table 1** Characteristics of subjects by quartiles of plasma Homocysteine levels (Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A
458 Cross-Sectional Study in Northwest China, 2018-2020).

Characteristic	Q1: 0.1-13.0 μmol/L	Q2: 13.1-16.6 μmol/L	Q3: 16.7-22.7 μmol/L	Q4: 22.8-80 μmol/L	*P* value*
Mean (SD)					
Age (years)	58.6 (10.4)	60.3 (10.7)	61.1 (10.8)	61.9 (11.1)	**<0.001**
BMI (kg/m^2)	25.0 (3.9)	24.9 (3.4)	25.1 (5.0)	25.0 (3.4)	0.132
TC (mmol/L)	4.84 (0.99)	4.87 (1.04)	4.85 (1.04)	4.80 (1.01)	**0.017**
TG (mmol/L)	1.66 (0.96)	1.72 (0.99)	1.76 (1.05)	1.77 (1.09)	**<0.001**
HDL-C (mmol/L)	1.33 (0.31)	1.34 (0.31)	1.33 (0.31)	1.32 (0.31)	**0.004**
LDL-C (mmol/L)	2.84 (0.78)	2.87 (0.83)	2.86 (0.86)	2.79 (0.86)	**<0.001**
Number (%)					
Smoking					
Never/seldom	3807 (85.7)	3965 (87.1)	3987 (87.2)	3900 (85.5)	**0.032**
Often	633 (14.3)	587 (12.9)	587 (12.8)	660 (14.5)	
Alcohol drinking					
Never/seldom	4215 (94.9)	4334 (95.2)	4388 (95.9)	4353 (95.5)	0.135
Often	225 (5.1)	218 (4.8)	186 (4.1)	207 (4.5)	
Physical activity					
Low	1327 (29.9)	1234 (27.1)	1189 (25.9)	1191 (26.1)	**<0.001**
Medium	2054 (46.3)	1923 (42.2)	1795 (39.3)	1775 (38.9)	
High	1059 (23.8)	1395 (30.7)	1590 (34.8)	1594 (35.0)	
Education level					
Primary school or below	3076 (69.3)	3335 (73.3)	3424 (74.9)	3503 (76.8)	**<0.001**
Middle school or above	1364 (30.7)	1217 (26.7)	1150 (25.1)	1057 (23.2)	
CMM					

having at least 2 diseases	485 (10.9)	621 (13.6)	674 (14.7)	716 (15.7)	**<0.001**
having at least 3 diseases	73 (1.6)	102 (2.2)	100 (2.2)	111 (2.4)	0.060

*: *P* value represents the probability of the null hypothesis obtained using Kruskal-Wallis test or chi-square test. Hcy, homocysteine; BMI, Body mass index; TC, Total cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; CMM, cardiometabolic multimorbidity.

Table 2 Association between homocysteine and cardiometabolic multimorbidity in different models (Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A Cross-Sectional Study in Northwest China, 2018-2020).

Presence of CMM	Events (%)	Crude Model		Model 1		Model 2	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
having at least 2 diseases							
Hcy		**1.008 (1.005, 1.011)**	**<0.001**	**1.006 (1.002, 1.009)**	**0.001**	**1.005 (1.002, 1.009)**	**0.003**
Quartiles							
Q1	494 (10.9)	Reference		Reference		Reference	
Q2	625 (13.8)	**1.308 (1.153, 1.483)**	**<0.001**	**1.178 (1.034, 1.342)**	**0.014**	**1.161 (1.018, 1.323)**	**0.026**
Q3	665 (14.7)	**1.406 (1.241, 1.592)**	**<0.001**	**1.164 (1.022, 1.325)**	**0.022**	1.132 (0.994, 1.290)	0.062
Q4	712 (15.7)	**1.524 (1.348, 1.723)**	**<0.001**	**1.236 (1.087, 1.406)**	**0.001**	**1.203 (1.056, 1.370)**	**0.005**
having at least 3 diseases							
Hcy		1.007 (0.999, 1.014)	0.067	1.003 (0.995, 1.012)	0.407	1.002 (0.994, 1.011)	0.582
Quartiles							
Q1	75 (1.7)	Reference		Reference		Reference	
Q2	101 (2.2)	**1.355 (1.002, 1.831)**	**0.049**	1.125 (0.829, 1.528)	0.449	1.101 (0.810, 1.495)	0.540
Q3	99 (2.2)	1.327 (0.981, 1.797)	0.067	0.979 (0.719, 1.334)	0.894	0.921 (0.674, 1.258)	0.605
Q4	111 (2.4)	**1.492 (1.110, 2.006)**	**0.008**	1.081 (0.797, 1.465)	0.618	1.020 (0.750, 1.387)	0.899

Bold *P* value represent <0.05. Crude Model was not adjusted for any variables; Model 1 was adjusted for age, sex, BMI, education, physical activity, smoking and alcohol drinking; Model 2 was adjusted for TC, TG, HDL-C and LDL-C based on Model 1. Hcy, homocysteine (μmol/L); OR, Odds ratio; CI Confidence interval; CMM, cardiometabolic multimorbidity.

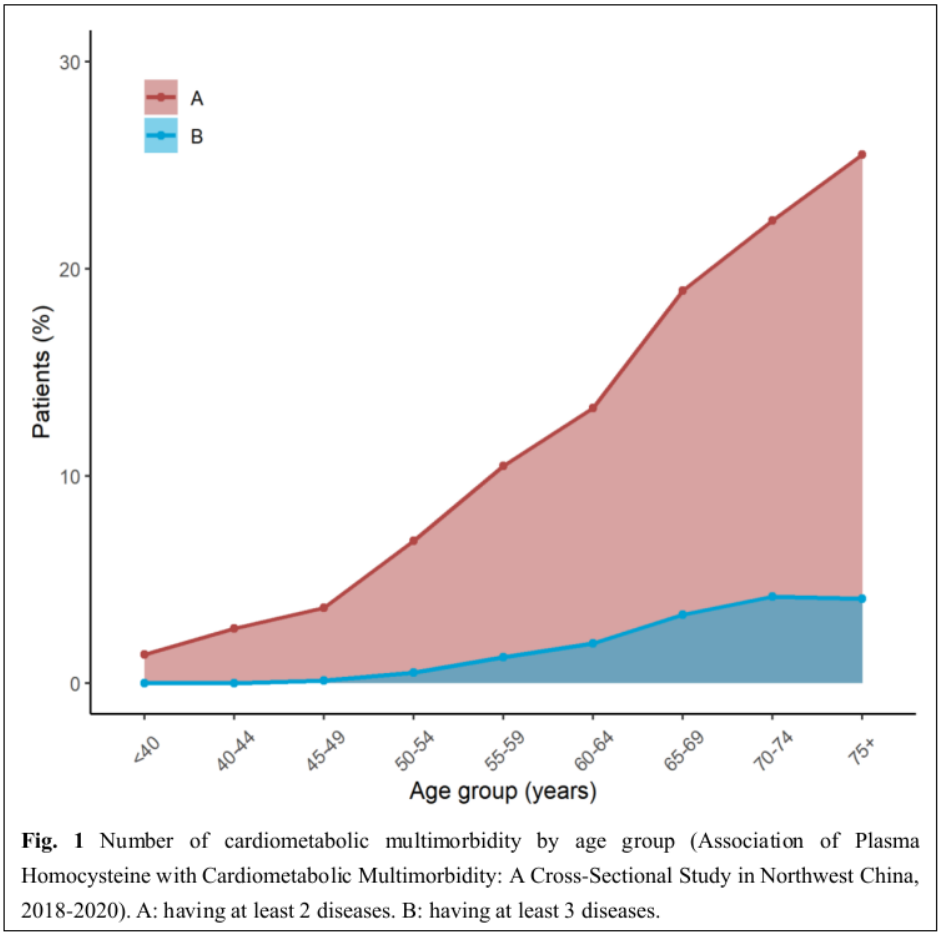

Fig. 1 Number of cardiometabolic multimorbidity by age group (Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A Cross-Sectional Study in Northwest China, 2018-2020). A: having at least 2 diseases. B: having at least 3 diseases.

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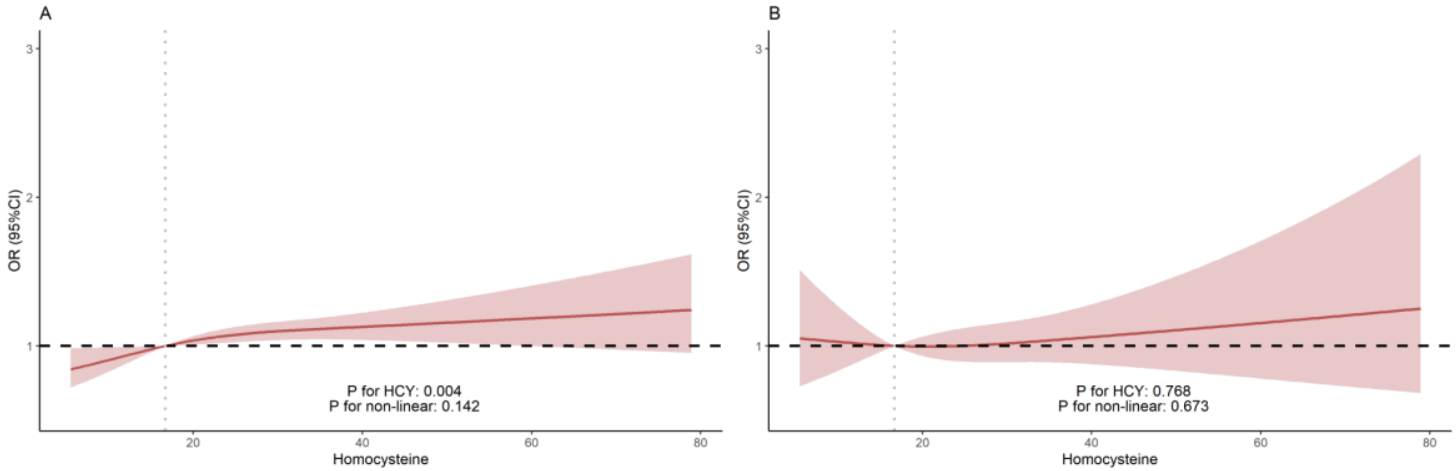

Fig. 2 The relationship between homocysteine concentration and cardiometabolic multimorbidity risk (Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A Cross-Sectional Study in Northwest China, 2018-2020). Vertical gray dotted lines represent the median value (reference value: 16.7 μmol/L) of homocysteine, horizontal black dashed lines represent the positions where OR=1. HCY, Homocysteine (μmol/L); OR, Odds ratio; CI Confidence interval. A: having at least 2 diseases. B: having at least 3 diseases.

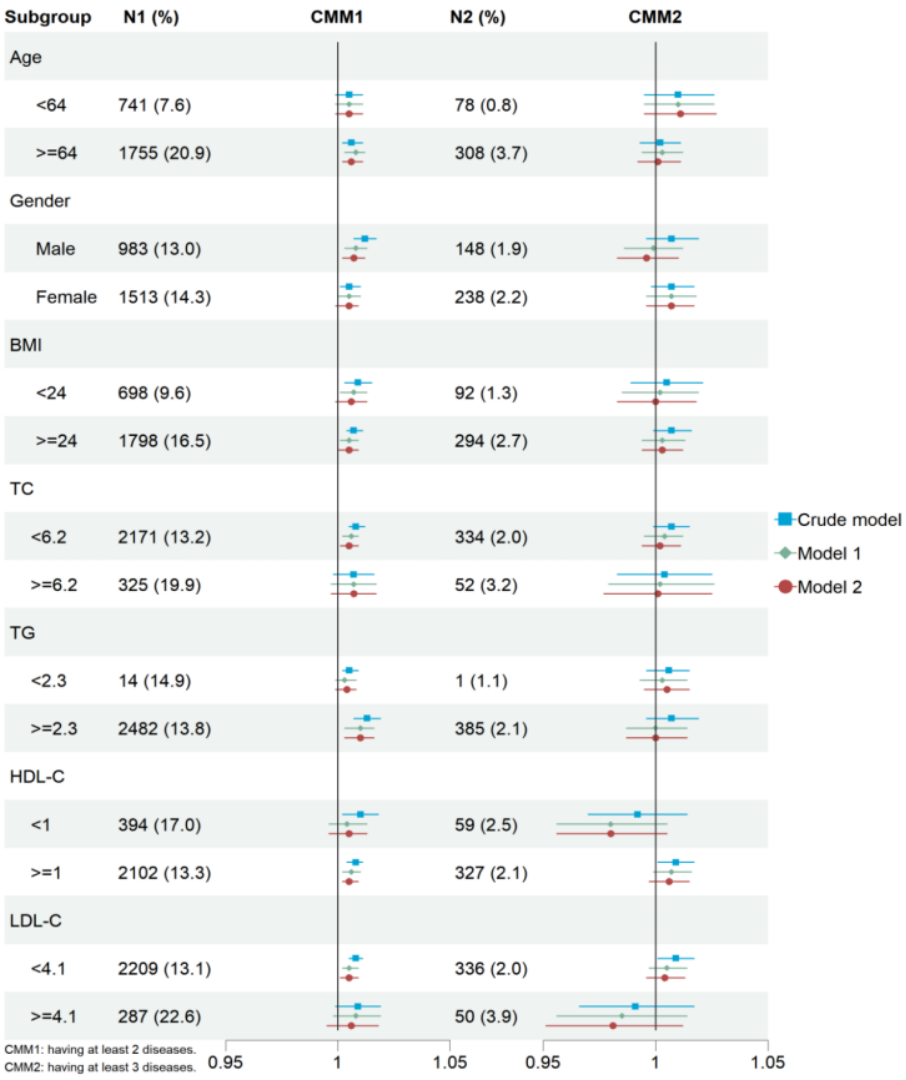

Fig. 3 Association between homocysteine and cardiometabolic multimorbidity in subset analysis with different models (Association of Plasma Homocysteine with Cardiometabolic Multimorbidity: A Cross-Sectional Study in Northwest China, 2018-2020). Crude Model was not adjusted for any variables; Model 1 was adjusted for age, sex, BMI, education, physical activity, smoking and alcohol drinking; Model 2 was adjusted for TC, TG, HDL-C and LDL-C based on Model 1. Hcy Homocysteine (μmol/L); BMI, Body mass index (kg/m^2); TC, Total cholesterol (mmol/L); TG, Triglyceride (mmol/L); HDL-C, High density lipoprotein cholesterol (mmol/L); LDL-C, Low density lipoprotein cholesterol (mmol/L).

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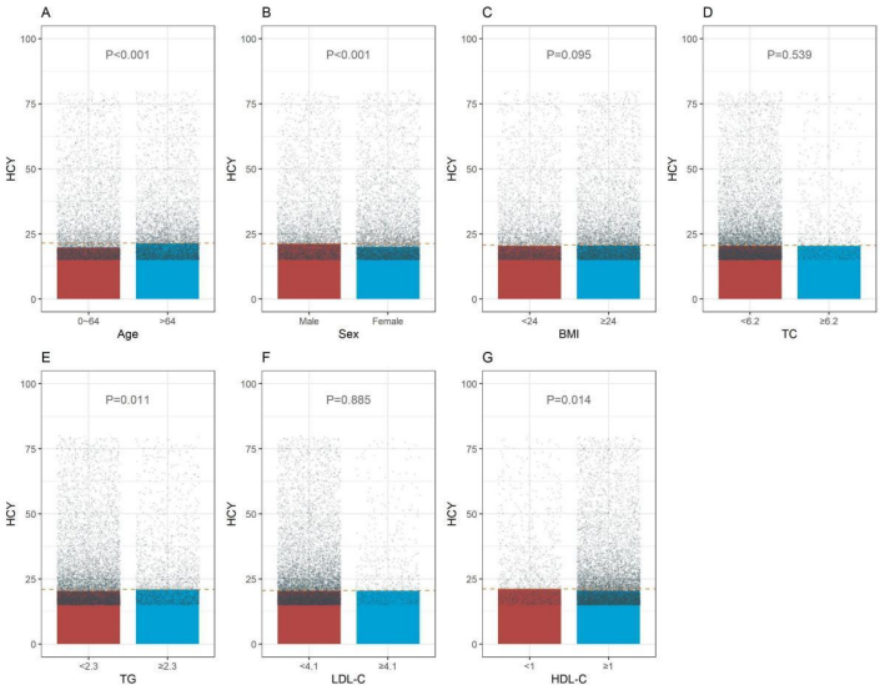

Fig. 4 Comparison of homocysteine concentrations among different subgroups (Association of Plasma homocysteine with cardiometabolic multimorbidity: A Cross-Sectional Study in Northwest China, 2018-2020). The height of the bars represents the average level of concentration. The jitter points represent the distribution of homocysteine concentrations greater than 15 μmol/L. The orange dashed lines represents the homocysteine levels of higher concentration group in the comparison. Hcy homocysteine (μmol/L); BMI, Body mass index (kg/m^2); TC, Total cholesterol (mmol/L); TG, Triglyceride (mmol/L); HDL-C, High density lipoprotein cholesterol (mmol/L); LDL-C, Low density lipoprotein cholesterol (mmol/L).

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