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The associations of lifestyle factors and behaviors with multimorbidity

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The associations of lifestyle factors and behaviors with multimorbidity

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Editorial: The associations of lifestyle factors and behaviors with multimorbidity

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Editorial on the Research Topic
The associations of lifestyle factors and behaviors with multimorbidity

The global trend of increasing life expectancy and the growing prevalence of multimorbidity, characterized by the coexistence of two or more chronic conditions, present significant challenges for healthcare systems due to their negative impact on health outcomes (1–3). Lifestyle factors, such as nutrition, physical activity, and smoking, have been found to be associated with the development of multiple chronic conditions, indicating their potential role in preventing individual diseases as well as multimorbidity (4, 5). However, the understanding of multimorbidity epidemiology remains limited, primarily due to previous studies focusing on single-disease outcomes and excluding comorbid patients. Therefore, it is crucial to gain a comprehensive understanding of the relationship between various health-related lifestyle factors, behaviors, and multimorbidity within specific populations, to develop effective prevention, diagnosis, and treatment strategies. This Research Topic aims to provide a dedicated platform for researchers to share advancements in investigating the association between health-related lifestyle factors, behaviors, and the development or progression of multimorbidity. The collection includes nine articles that explore different aspects of multimorbidity, such as prevalence, impact on mortality, associated risk factors, and disease combinations across diverse geographical areas and populations.

The study by Arshadipour et al. aimed to determine the prevalence of multimorbidity and common chronic disease combinations, as well as their impact on mortality in men and women aged $\geq$ 65 years. The authors demonstrated a positive association between multimorbidity and all-cause mortality, and they observed a higher mortality risk in men compared to women. The authors identified hypertension as the most prevalent chronic condition, both in isolation and in combination with other diseases. Notably, the combination of heart disease and diabetes was found to be the most hazardous in both males and females, with a higher risk observed in women compared to men, even when combined with other diseases (Arshadipour et al.).

de Sousa et al. utilized data from the 2019 National Health Survey, a household survey in Brazil, to examine health patterns and their association with chronic kidney disease (CKD) in the Brazilian general population. A total of 90,846 individuals were assessed, and the authors identified using factor analysis three patterns related to health: metabolic factors, behavioral risk factors, and behavioral protective factors. The presence of arterial hypertension, diabetes mellitus, hyperlipidemia, and cardiovascular diseases, collectively referred to as metabolic factors, was found to be associated with the likelihood of presenting CKD. These noteworthy findings underscore the importance of evaluating these metabolic factors together, as individuals often exhibit interconnected factors, highlighting the role of multimorbidity in the development of CKD (de Sousa et al.).

In the longitudinal study conducted by Chen C. et al., the association between multimorbidity and fertility history among middle-aged and older adult women in China was investigated. Data from 10,182 female participants in the China Health and Retirement Longitudinal Study (CHARLS) were utilized. The findings demonstrated that high parity and early childbearing were significantly associated with an increased risk of multimorbidity and a higher number of chronic conditions. Conversely, late childbearing was identified as a significant protective factor against multimorbidity. Moreover, the relationship between fertility history and multimorbidity was influenced by age and the urban-rural dual structure. This study provided valuable data supporting the exploration of sex-specific risk factors for multimorbidity (Chen C. et al.).

Gaskell et al. conducted an online pilot study comparing the lifestyle and health-related characteristics of residents in Qatar and the United Kingdom (UK). The study revealed the co-morbidity of psychiatric disorders in individuals with a BMI $>$ 25 in both Qatar and the UK. Interestingly, the study results indicated no statistically significant associations between comorbidity and several predictors, such as drinking habits, smoking status, physical activity, vegetable consumption etc. Nevertheless, a significant association between sleep perception and comorbidity was found within the UK population (Gaskell et al.).

Hu et al. conducted a study using data from the Diverse Life-Course Cohort study. The goal was to examine the prevalence of common chronic diseases, identify multimorbidity patterns, and explore their diversity across different age groups and cultural backgrounds among adults in the Guangdong province in China. The findings revealed a prevalence of multimorbidity of almost 40%, with the frequency increasing as age advanced. Dyslipidemia was the most common disease, with a prevalence as high as 45%. The study also identified the top three binary multimorbidity combinations being dyslipidemia and hyperuricemia, dyslipidemia and hypertension, and hyperuricemia and hypertension. This exploration of multimorbidity patterns across different cultural backgrounds provides insights into the diversity of health profiles (Hu et al.).

The cross-sectional study conducted by Zheng et al. aimed to investigate the association between multiple lifestyle factors and cardiometabolic multimorbidity. The authors found that participants who engaged in two or more high-risk dietary behaviors, such as overeating and drinking water during meals, had a higher risk of developing cardiometabolic multimorbidity. The authors concluded that identifying individuals with specific high-risk lifestyle behaviors and managing their lifestyle may contribute to improved health outcomes for patients with cardiometabolic multimorbidity (Zheng et al.).

Wang et al. conducted a study using the UK Biobank dataset, to investigate the potential influencing factors associated with the Charlson Comorbidity Index (CCI), a widely used measure of multimorbidity. The study suggested that high waist-to-hip ratio (WHR) and high body mass index were statistically significant predictors of elevated CCI, with WHR having a greater impact. Socioeconomic factors, such as income and the Townsend deprivation index, were also found to be associated with CCI. The authors point out that these factors may interact with each other, emphasizing the need for comprehensive, rational, and robust interventions to promote health (Wang et al.).

The study conducted by Chen M. et al. aimed to investigate the cross-sectional and longitudinal associations between multimorbidity and memory-related diseases (MDs) among middle-aged and older adults in China. The authors utilized data from CHARLS, an ongoing nationally representative study conducted every 2 years, focusing on community-dwelling adults aged 45 years and above. The findings identified significant associations between multimorbidity and MDs, with the strength of the association being more pronounced in middle-aged adults. Specifically, stroke, cancer, heart problems, dyslipidemia, and kidney diseases exhibited stronger cross-sectional relationships with MDs (Chen M. et al.).

Shen et al. utilized data from the Chinese Urban Adults Diet and Health Study to investigate the interaction between overweight/obesity and high glycated hemoglobin (HbA1c) status in relation to elevated high-sensitivity C-reactive protein (hs-CRP) levels among adults in the Chinese population. The study revealed that higher HbA1c levels and overweight/obesity, both independently and in combination, were associated with an increased risk of elevated hs-CRP, particularly among females and younger individuals. The authors concluded that implementing intervention strategies aimed at preventing high blood glucose levels and concurrently managing body weight could play a crucial role in reducing the occurrence of hs-CRP-related diseases (Shen et al.).

Overall, the results of the studies in this Research Topic shed light on the prevalence and impact of multimorbidity in diverse populations. They revealed associations between multimorbidity and increased mortality, identified specific risk factors and disease combinations, and underscored the importance of lifestyle management and early intervention in reducing multimorbidity risk and related diseases. The findings enhance our understanding of multimorbidity and provide valuable insights for the development of targeted interventions and healthcare strategies. We anticipate that this Research Topic will serve as a guide for future researchers to delve further into the intricate nature of multimorbidity, explore novel risk factors, comprehend disease interactions, consider sex-specific and age-specific factors, account for cultural diversity, and conduct more longitudinal and intervention studies. These advancements can contribute to the formulation of effective strategies for preventing,

managing, and improving outcomes for individuals affected by multimorbidity.

Author contributions

KG drafted and wrote the first draft of the manuscript. All authors reviewed, revised, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A study of factors impacting disease based on the Charlson Comorbidity Index in UK Biobank

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Objective: With advances in medical diagnosis, more people are diagnosed with more than one disease. The damage caused by different diseases varies, so relying solely on the number of diseases to represent multimorbidity is limited. The Charlson comorbidity index (CCI) is widely used to measure multimorbidity and has been validated in various studies. However, CCI's demographic and behavioral risk factors still need more exploration.

Methods: We conduct multivariate logistic regression analysis and restricted cubic splines to examine the influence factors of CCI and the relationship between covariates and risk of CCI, respectively. Our research employs the Multivariate Imputation by Chained Equations method to interpolate missing values. In addition, the CCI score for each participant is calculated based on the inpatient's condition using the International Classification of Diseases, edition 10 (ICD10). Considering the differences in the disease burden between males and females, the research was finally subgroup analyzed by sex.

Results: This study includes 5,02,411 participants (2,29,086 female) with CCI scores ranging from 0 to 98. All covariates differed between CCI groups. High waist-hip ratio (WHR) increases the risk of CCI in both males [OR = 19.439, 95% CI = (16.261, 23.241)] and females [OR = 12.575, 95% CI = (11.005, 14.370)], and the effect of WHR on CCI is more significant in males. Associations between age, Body Mass Index (BMI) and WHR, and CCI risk are J-shaped for all participants, males, and females. Concerning the association between Townsend deprivation index (TDI) and CCI risk, the U-shape was found in all participants and males and varied to a greater extent in males, but it is a J-shape in females.

Conclusions: Increased WHR, BMI, and TDI are significant predictors of poor health, and WHR showed a greater role. The impact of deprivation indices on health showed differences by sex. Socio-economic factors, such as income and TDI, are associated with CCI. The association of social status differences caused by these socioeconomic factors with health conditions

should be considered. Factors might interact with each other; therefore, a comprehensive, rational, and robust intervention will be necessary for health.

KEYWORDS

multimorbidity, Charlson Comorbidity Index (CCI), deprivation indices, impact factors, Restricted Cubic Spline (RCS)

1. Introduction

Communicable and non-communicable diseases have always been significant problems affecting human health and quality of life, especially for middle-aged and elderly people. In 2019, ischaemic heart disease and stroke were already significant causes of disability-adjusted life years (DALYs) for people aged above 25 years. They ranked as the top two DALYs for people aged above 50 years (1). The Global Burden of Disease Study 2016 reported that cardiovascular disease was the non-communicable disease responsible for the highest number of secondary deaths, followed by neoplasms and chronic respiratory diseases (2). With advances in medical diagnosis, more people have been found to suffer from two or more major diseases, known as comorbidity or multimorbidity. Although "comorbidity" and "multimorbidity" (3) were defined as different Medical Subject Headings (MeSH) terms in 2018, both focus on the occurrence of multiple chronic conditions in the same person. In contrast, "multimorbidity" preferred that no one disease had priority in the case of coexisting diseases (3). Whether it was "comorbidity" or "multimorbidity," the co-existence of multiple conditions was already a complex issue because multiple co-existing diseases might interact with each other, and there could be complex interactions and potential associations (4).

A Scotland study identified that the number of diseases and the proportion of people with multimorbidity increased with age, and almost all people over 65 had at least one disease (5). Not only was the healthy lifespan of older people negatively affected by multimorbidity (6), but the Australian cohort study also found that the coexistence of multiple conditions was becoming increasingly common at younger ages (7). In Europe, multimorbidity lowered the quality of life and raised the costs of medication, health care, etc., i.e., the cost of health (8, 9). There are limitations in relying solely on the number of diseases to represent multimorbidity; for example, the degree of damage caused by different diseases varies. Weighted measures focusing on co-morbidities have provided better predictions than assessing individual diseases alone (10). We, therefore, use the Charlson Comorbidity Index (CCI) to represent individual multimorbidity (11).

The CCI is a widely used measure of multimorbidity and has been validated in various studies (11, 12). Several studies have demonstrated that CCI accurately predicted many types of patients, including cancer patients and those in intensive care (13–15). The efficient and effective management of multimorbidity has become a new task and challenge for patients and professionals in the field of public health. Risk factors for many diseases, including obesity (16) and smoking (17) have been identified. However, CCI's demographic and behavioral risk factors were not explored much. Therefore, this study aimed to explore the possible influencing factors associated with CCI using the United Kingdom (UK) biobank dataset.

2. Materials and methods

2.1. Population and study design

Our study is a cross-sectional analysis based on the UK Biobank (Application Title: Integration of clinical data and genomic data to construct diagnosis and prognosis system for digestive diseases and related complications, Application ID: 84347). The UK Biobank is the world's most detailed, long-term prospective health study. Recruitment occurred in 22 centers in Scotland, England and Wales between 2006 and 2010. People aged 40–69 living in the UK were invited by mail inquiry and telephone to their nearest assessment center, where trained professionals collected baseline information, physical measures and biological samples. Of the 9.23 million people invited to join the UK Biobank, 5,03,317 (5.45%) agreed and were recruited (18). The UK Biobank assessment process had five components which include: written consent, touch screen questionnaires, face-to-face interviews, measurements and blood, urine and saliva sample collection. All participants approved this UK Biobank study and provided written informed consent to participate in the UK Biobank study. Further details of these measurements, study design, and data collection are available in the UK Biobank online protocol and study protocol (http://www.ukbiobank.ac.uk). We obtained data on 5,02,411 participants from UK Biobank when our application was approved. For this study, we included all participants and conducted both the primary and sensitivity analyzes.

2.2. Charlson comorbidity index

The Charlson Comorbidity Index (CCI) is calculated based on the inpatient's disease obtained from the diagnosis made

during the admission (Supplementary Table 1). There are 17 categories of conditions that could contribute to the CCI score, each assigned a value ranging from 1 to 6 depending on the condition (11). We assess CCI scores using the International Classification of Diseases, edition 10 (ICD-10). Each disease category in the CCI corresponds to one or more ICD-10 codes. We assign each ICD-10 code to a corresponding disease weighting score based on Quan et al. (19). The total score for the CCI is a simple sum of the weights, and higher scores represent more severe comorbidity or multimorbidity.

2.3. Ascertainment of covariates

Townsend deprivation index (TDI) (20), which combines information on housing, employment, and car availability, was calculated based on census and postcode prior to participant recruitment. The index mainly measures socioeconomic status, with higher values meaning higher deprivation.

Body Mass Index (BMI) was calculated as weight (kg)/height $(m)^2$. Weight was measured using a Tanita BC-418 MA body composition analyzer, accurate to 0.1 kg, and height was measured using a Seca 202 height measure. Participants were required to remove their shoes and heavy clothing while the measurements were being taken. Waist-hip ratio (WHR) was calculated as waist circumference/hip circumference. Hip and waist circumference (at the level of the umbilicus) will be measured using a Wessex non-stretchable sprung tape measure and entered manually by staff. Trained staff carried out these measurements (21).

In addition, we also select age, ethnicity (22), income, International Physical Activity Questionnaire (IPAQ) (23), smoking, alcohol, maternal smoking around birth, illnesses of father, illnesses of mother and illnesses of siblings and as covariates for the study. These illnesses include mainly Prostate cancer (males only), Severe depression, Parkinson's disease, Alzheimer's disease/dementia, Diabetes, High blood pressure, Chronic bronchitis/emphysema, Breast cancer (females only), Bowel cancer, Lung cancer, Stroke, and Heart disease. Data on sociodemographics, income, IPAQ, smoking, alcohol, maternal smoking around birth and relatives' illnesses were collected from the touch screen questionnaire. Information on CCI and all covariates were obtained from baseline characteristics in 2006–2010.

2.4. Statistical analysis

In the primary analysis, all participants are included in the study. Responses that were "Preferred not to answer," "uncertain/unknown," or invalid are recoded as missing or null. Missing values are interpolated using the Multivariate Imputation by Chained Equations method with the R software "mice" package (with 5 imputed datasets, 10 iterations, and random forest method) and divide participants into two groups according to whether CCI = 0. CCI = 0, and CCI > 0 indicated good and poor health conditions, respectively. Continuous variables with normal distribution are described using mean ± standard deviation ($\bar{x} \pm$ sd) and Student's t-test for comparison between groups; continuous variables with non-normal distribution are described using median and quartiles [M (Q1, Q3)] and Mann-Whitney U-test for comparison between groups; categorical variables are described using frequencies and percentages, and χ^2 test is used for the analysis of differences in distribution.

We conduct a univariate logistic regression analysis with the CCI group as the dependent variable. Then the significant independent variables ($P < 0.05$) are included in a multivariate logistic regression analysis to explore possible impact factors. Discriminatory is assessed based on the mean of the area under the curve (AUC) for 10-fold cross-validation. We also perform Restricted Cubic Spline (RCS) curves to model the association of age, TDI, WHR, and BMI with CCI risk while adjusting for general condition variables such as ethnicity, smoking, alcohol, income, and maternal smoking at birth. Considering the differences in the burden of disease between males and females (24), the research is finally subgroup analyzed by sex.

For a sensitivity analysis of the preliminary study, we repeat the analyzes, excluding cases with missing values, to compare whether there is a significant change in the primary outcome. Using R software version 4.1.2 for all data analyzes in this research.

3. Results

UK Biobank investigators sent postal invitations to 92,38,453 people and 5,03,317 participants agreed to join the study cohort, for a participation rate of 5.45%. We ultimately obtain 5,02,411 participants from the UK Biobank application and include all of them in this study, with 2,29,086 males (aged: 37–73) and 2,73,325 females (aged: 39–71) (Table 1). CCI score equals the sum of individual scores, and the range is 0–98 points (males: 0–98; females: 0–93) (Figure 1). Following the AUROC (area under the receiver operating characteristic curve), our multivariate logistic models all possessed robust discrimination (AUROC means for all participants, males and females, were 0.707, 0.723, and 0.688, respectively, Supplementary Figure 1).

The distributions of all covariates are statistically different between the different CCI groups (Table 1). Age and TDI are probably higher in the CCI > 0 groups than in the CCI = 0 groups, and BMI and WHR are also, although only slightly higher. Whites are the most represented ethnic group (94.6%). Current smokers account for only 10.6% of the total population (9.1% and 12.9% in the CCI = 0 and CCI > 0 groups, respectively). However, current drinkers occupy over 90% of the

TABLE 1 General characteristics of the CCI group [Median (Q1, Q3)/*n* (%)].

Variables	Total ($n = 5,02,411$)	CCI = 0 ($n = 3,02,344$)	CCI > 0 ($n = 2,00,067$)	*P*-value
Sex				
Female	2,73,325 (54.4)	1,72,451 (57)	1,00,874 (50.4)	<0.001
Male	2,29,086 (45.6)	1,29,893 (43)	99,193 (49.6)	
Age (years)	58 (50, 63)	55 (48, 61)	61 (54, 65)	<0.001
Ethnic				
Asian or Asian British	11,553 (2.3)	6,642 (2.2)	4,911 (2.5)	<0.001
Black or Black British	8,131 (1.6)	4,803 (1.6)	3,328 (1.7)	
Mixed	2,969 (0.6)	1,875 (0.6)	1,094 (0.5)	
Others	4,596 (0.9)	2,817 (0.9)	1,779 (0.9)	
White	4,75,162 (94.6)	2,86,207 (94.7)	1,88,955 (94.4)	
BMI (Kg/m^2)	26.75 (24.14, 29.91)	26.22 (23.77, 29.15)	27.62 (24.82, 31.08)	<0.001
WHR	0.87 (0.8, 0.94)	0.86 (0.79, 0.92)	0.9 (0.83, 0.96)	<0.001
Income (£)[#]				
<18,000	1,18,903 (23.7)	54,889 (18.2)	64,014 (32)	<0.001
18,000–31,000	1,28,975 (25.7)	73,154 (24.2)	55,821 (27.9)	
31,000–52,000	1,29,124 (25.7)	83,964 (27.8)	45,160 (22.6)	
52,000–1,00,000	99,117 (19.7)	70,546 (23.3)	28,571 (14.3)	
>1,00,000	26,292 (5.2)	19,791 (6.5)	6,501 (3.2)	
TDI	−2.14 (−3.64, 0.55)	−2.27 (−3.71, 0.23)	−1.9 (−3.52, 1.04)	<0.001
IPAQ				
Low	95,267 (19)	52,824 (17.5)	42,443 (21.2)	<0.001
Moderate	2,05,023 (40.8)	1,24,503 (41.2)	80,520 (40.2)	
High	2,02,121 (40.2)	1,25,017 (41.3)	77,104 (38.5)	
Smoking				
Never	2,75,033 (54.7)	1,79,058 (59.2)	95,975 (48)	<0.001
Previous	1,74,038 (34.6)	95,728 (31.7)	78,310 (39.1)	
Current	53,340 (10.6)	27,558 (9.1)	25,782 (12.9)	
Alcohol				
Never	22,492 (4.5)	11,917 (3.9)	10,575 (5.3)	<0.001
Previous	18,174 (3.6)	8,273 (2.7)	9,901 (4.9)	
Current	4,61,745 (91.9)	2,82,154 (93.3)	1,79,591 (89.8)	
Maternal smoking around birth				
No	3,54,668 (70.6)	2,16,411 (71.6)	1,38,257 (69.1)	<0.001
Yes	1,47,743 (29.4)	85,933 (28.4)	61,810 (30.9)	
Illnesses of father				
No	1,16,383 (23.2)	74,046 (24.5)	42,337 (21.2)	<0.001
Yes	3,86,028 (76.8)	2,28,298 (75.5)	1,57,730 (78.8)	

(Continued)

TABLE 1 (Continued)

Variables	Total (n = 5,02,411)	CCI = 0 (n = 3,02,344)	CCI > 0 (n = 2,00,067)	P-value
Illnesses of mother				
No	1,43,464 (28.6)	91,962 (30.4)	51,502 (25.7)	<0.001
Yes	3,58,947 (71.4)	2,10,382 (69.6)	1,48,565 (74.3)	
Illnesses of siblings				
No	2,80,218 (55.8)	1,83,165 (60.6)	97,053 (48.5)	<0.001
Yes	2,22,193 (44.2)	1,19,179 (39.4)	1,03,014 (51.5)	

[#]1 pound was worth about $1.529 in December 2010.
CCI, Charlson comorbidity index; BMI, body mass index; WHR, waist-hip ratio; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire.

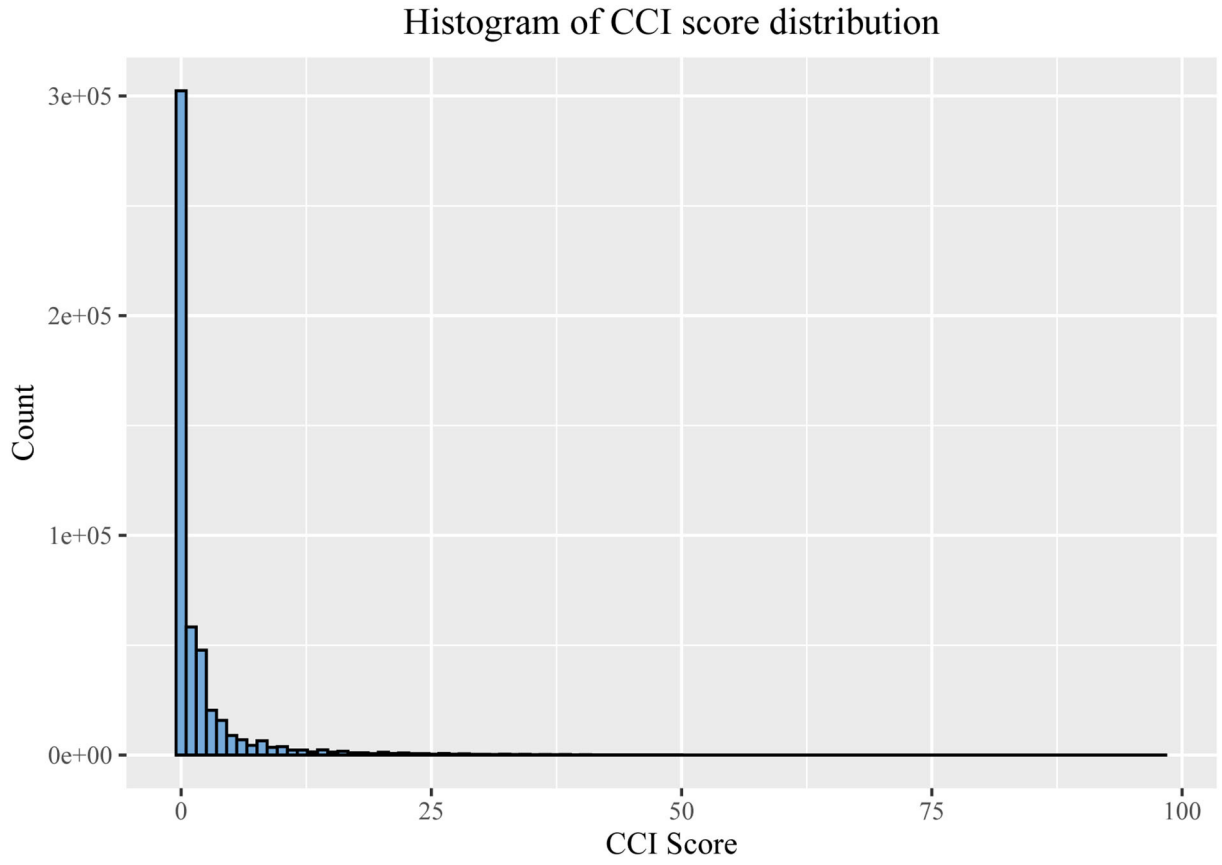

FIGURE 1
Distribution of different CCI scores.

whole population (93.3 and 89.8% in the CCI = 0 and CCI > 0 groups, respectively). Regarding relative illnesses, over 70% of fathers or mothers suffer from a significant illness, but only 44.2% of siblings have some severe illness (39.4 and 51.5% in the CCI = 0 and CCI > 0 groups, respectively).

We perform univariate logistic regression analyzes on all covariates, and the results indicate that they are all possible factors influencing CCI. After fitting these data into a multivariate logistic regression model, the age, BMI, WHR, TDI, smoking (both previous and current smoking), previous alcohol, maternal smoking around birth, and illnesses of kinship (illnesses of father, mother, or sibling) might be risk factors for CCI. WHR [Odds Ratios (OR) = 11.45, 95%CI = (10.605, 12.363)], previous smoking [OR = 1.226, 95%CI = (1.210, 1.243)], current smoking [OR = 1.662, 95%CI = (1.629, 1.697)], previous alcohol consumption [OR = 1.208, 95%CI = (1.158,

TABLE 2 Univariate and multivariate logistic regression analyzes of factors influencing CCI in all participants [Median (Q1, Q3)/*n* (%)].

Variables	Univariate logistic regression		Multivariate logistic regression	
	P-value	OR (95%CI)	*P*-value	OR (95%CI)
Age (years)	<0.001	1.073 (1.072, 1.074)	<0.001	1.062 (1.061, 1.063)
Ethnic (Reference: Asian or Asian British)				
Black or Black British	0.027	0.937 (0.885, 0.993)	<0.001	0.900 (0.846, 0.958)
Mixed	<0.001	0.789 (0.726, 0.857)	0.012	0.891 (0.814, 0.975)
Others	<0.001	0.854 (0.796, 0.916)	<0.001	0.834 (0.774, 0.899)
White	<0.001	0.893 (0.860, 0.927)	<0.001	0.818 (0.785, 0.853)
BMI (Kg/m^2)	<0.001	1.071 (1.070, 1.073)	<0.001	1.042 (1.040, 1.043)
WHR	<0.001	82.419 (77.176, 88.024)	<0.001	11.45 (10.605, 12.363)
Income (Reference: <18,000 £)[#]				
18,000–31,000	<0.001	0.654 (0.644, 0.665)	<0.001	0.791 (0.778, 0.805)
31,000–52,000	<0.001	0.461 (0.454, 0.469)	<0.001	0.698 (0.686, 0.711)
52,000–1,00,000	<0.001	0.347 (0.341, 0.354)	<0.001	0.621 (0.609, 0.634)
>1,00,000	<0.001	0.282 (0.273, 0.290)	<0.001	0.534 (0.517, 0.551)
TDI	<0.001	1.047 (1.046, 1.049)	<0.001	1.026 (1.024, 1.028)
IPAQ (Reference: Low)				
Moderate	<0.001	0.805 (0.792, 0.818)	<0.001	0.852 (0.838, 0.866)
High	<0.001	0.768 (0.756, 0.780)	<0.001	0.830 (0.816, 0.844)
Smoking (Reference: No)				
Previous	<0.001	1.526 (1.508, 1.545)	<0.001	1.226 (1.210, 1.243)
Current	<0.001	1.745 (1.713, 1.778)	<0.001	1.662 (1.629, 1.697)
Alcohol (Reference: No)				
Previous	<0.001	1.349 (1.297, 1.403)	<0.001	1.208 (1.158, 1.261)
Current	<0.001	0.717 (0.698, 0.737)	<0.001	0.798 (0.774, 0.822)
Maternal smoking around birth (Reference: No)	<0.001	1.126 (1.112, 1.140)	<0.001	1.103 (1.088, 1.118)
Illnesses of father (Reference: No)	<0.001	1.208 (1.192, 1.225)	<0.001	1.070 (1.055, 1.086)
Illnesses of mother (Reference: No)	<0.001	1.261 (1.245, 1.277)	<0.001	1.089 (1.074, 1.104)
Illnesses of siblings (Reference: No)	<0.001	1.631 (1.613, 1.650)	<0.001	1.195 (1.180, 1.210)

[#]1 pound was worth about $1.529 in December 2010.
OR, odds ratios; CI, confidence interval; BMI, body mass index; WHR, waist-hip ratio; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire.

1.261)] and illnesses of sibling [OR = 1.195, 95%CI = (1.180, 1.210)] showed higher values for OR (Table 2). The study also found that non-Asian or Asian British, higher income, moderate or high physical activity, and current alcohol may be protective factors for CCI, and that high income, white [OR = 0.818, 95% CI = (0.785, 0.853)] and current alcohol [OR = 0.798, 95% CI = (0.774, 0.822)] exhibited lower OR (Table 2). We report the AUC and ROC plots for the 10-fold cross-validation of the multivariate logistic regression model in Supplementary Figure 1.

The rate of CCI > 0 is higher among males (43.3%) than females (36.9%), and the proportion of males with high income, smoking and drinking, and high physical activity is also higher than that of females. Compared to the males, the females have a higher proportion of illnesses of kinship and lower BMI, WHR, and TDI (Table 3).

Multivariate logistic regression analyzes (univariate logistic regressions were shown in Supplementary Table 2) for females and males separately reveal that mixed-race in female [OR = 0.924, 95% CI = (0.823, 1.038)] and black or black British in male [OR = 0.943, 95% CI = (0.859, 1.035)] are not statistically significant predictors compared with Asian or Asian British (Table 4). High WHR increases the risk of CCI in both males [OR = 19.439, 95% CI = (16.261, 23.241)] and females [OR

TABLE 3 Differences in characteristics between males and females [Median (Q1, Q3)/*n* (%)].

Variables	Total ($n = 5,02,411$)	Female ($n = 2,73,325$)	Male ($n = 2,29,086$)	*P*-value
Age (years)	58 (50, 63)	57 (50, 63)	58 (50, 64)	<0.001
Ethnic				
Asian or Asian British	11,553 (2.3)	5,615 (2.1)	5,938 (2.6)	<0.001
Black or Black British	8,131 (1.6)	4,688 (1.7)	3,443 (1.5)	
Mixed	2,969 (0.6)	1,858 (0.7)	1,111 (0.5)	
Others	4,596 (0.9)	2,611 (1)	1,985 (0.9)	
White	4,75,162 (94.6)	2,58,553 (94.6)	2,16,609 (94.6)	
BMI (Kg/m^2)	26.75 (24.14, 29.91)	26.13 (23.46, 29.74)	27.31 (24.99, 30.07)	<0.001
WHR, median (Q1, Q3)	0.87 (0.8, 0.94)	0.81 (0.77, 0.86)	0.93 (0.89, 0.98)	<0.001
Income (£) [#]				
<18,000	1,18,903 (23.7)	69,990 (25.6)	48,913 (21.4)	<0.001
18,000–31,000	1,28,975 (25.7)	72,615 (26.6)	56,360 (24.6)	
31,000–52,000	1,29,124 (25.7)	68,365 (25)	60,759 (26.5)	
52,000–1,00,000	99,117 (19.7)	49,597 (18.1)	49,520 (21.6)	
>1,00,000	26,292 (5.2)	12,758 (4.7)	13,534 (5.9)	
TDI	−2.14 (−3.64, 0.55)	−2.14 (−3.63, 0.49)	−2.12 (−3.65, 0.63)	<0.001
IPAQ				
Low	95,267 (19)	51,123 (18.7)	44,144 (19.3)	<0.001
Moderate	2,05,023 (40.8)	1,17,051 (42.8)	87,972 (38.4)	
High	2,02,121 (40.2)	1,05,151 (38.5)	96,970 (42.3)	
Smoking				
Never	2,75,033 (54.7)	1,62,915 (59.6)	1,12,118 (48.9)	<0.001
Previous	1,74,038 (34.6)	85,897 (31.4)	88,141 (38.5)	
Current	53,340 (10.6)	24,513 (9)	28,827 (12.6)	
Alcohol				
Never	22,492 (4.5)	16,038 (5.9)	6,454 (2.8)	<0.001
Previous	18,174 (3.6)	10,018 (3.7)	8,156 (3.6)	
Current	4,61,745 (91.9)	2,47,269 (90.5)	2,14,476 (93.6)	
Maternal smoking around birth				
No	3,54,668 (70.6)	1,95,176 (71.4)	1,59,492 (69.6)	<0.001
Yes	1,47,743 (29.4)	78,149 (28.6)	69,594 (30.4)	
Illnesses of father				
No	1,16,383 (23.2)	61,134 (22.4)	55,249 (24.1)	<0.001
Yes	3,86,028 (76.8)	2,12,191 (77.6)	1,73,837 (75.9)	
Illnesses of mother				
No	1,43,464 (28.6)	71,362 (26.1)	72,102 (31.5)	<0.001
Yes	3,58,947 (71.4)	2,01,963 (73.9)	1,56,984 (68.5)	
Illnesses of siblings				
No	2,80,218 (55.8)	1,47,538 (54)	1,32,680 (57.9)	<0.001
Yes	2,22,193 (44.2)	1,25,787 (46)	96,406 (42.1)	

[#]1 pound was worth about $1.529 in December 2010.

CCI, Charlson comorbidity index; BMI, body mass index; WHR, waist-hip ratio; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire.

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TABLE 4 Multivariate logistic regression analyzes of factors influencing CCI in females and males [Median (Q1, Q3)/*n* (%)].

Variables	Females		Males	
	P-value	OR (95%CI)	*P*-value	OR (95%CI)
Age (years)	<0.001	1.051 (1.050, 1.052)	<0.001	1.075 (1.074, 1.076)
Ethnic (Reference: Asian or Asian British)				
Black or Black British	0.003	0.880 (0.809, 0.958)	0.216	0.943 (0.859, 1.035)
Mixed	0.184	0.924 (0.823, 1.038)	0.017	0.839 (0.726, 0.969)
Others	0.004	0.863 (0.780, 0.955)	<0.001	0.809 (0.723, 0.904)
White	<0.001	0.842 (0.793, 0.894)	<0.001	0.806 (0.760, 0.855)
BMI (Kg/m^2)	<0.001	1.043 (1.041, 1.044)	<0.001	1.037 (1.034, 1.039)
WHR	<0.001	12.575 (11.005, 14.370)	<0.001	19.439 (16.261, 23.241)
Income (Reference: <18,000 £) [#]				
18,000–31,000	<0.001	0.812 (0.794, 0.830)	<0.001	0.754 (0.734, 0.774)
31,000–52,000	<0.001	0.718 (0.701, 0.735)	<0.001	0.666 (0.648, 0.684)
52,000–1,00,000	<0.001	0.654 (0.636, 0.672)	<0.001	0.586 (0.569, 0.604)
>1,00,000	<0.001	0.541 (0.516, 0.567)	<0.001	0.525 (0.502, 0.549)
TDI	<0.001	1.023 (1.020, 1.026)	<0.001	1.029 (1.026, 1.032)
IPAQ (Reference: Low)				
Moderate	<0.001	0.839 (0.820, 0.858)	<0.001	0.871 (0.849, 0.893)
High	<0.001	0.838 (0.818, 0.857)	<0.001	0.836 (0.816, 0.857)
Smoking (Reference: No)				
Previous	<0.001	1.186 (1.164, 1.208)	<0.001	1.248 (1.224, 1.273)
Current	<0.001	1.658 (1.610, 1.708)	<0.001	1.668 (1.621, 1.717)
Alcohol (Reference: No)				
Previous	<0.001	1.223 (1.158, 1.291)	<0.001	1.185 (1.102, 1.275)
Current	<0.001	0.793 (0.765, 0.822)	<0.001	0.798 (0.754, 0.844)
Maternal smoking around birth (Reference: No)	<0.001	1.098 (1.079, 1.119)	<0.001	1.108 (1.086, 1.130)
Illnesses of father (Reference: No)	<0.001	1.054 (1.033, 1.075)	<0.001	1.086 (1.063, 1.109)
Illnesses of mother (Reference: No)	<0.001	1.076 (1.055, 1.097)	<0.001	1.097 (1.075, 1.119)
Illnesses of siblings (Reference: No)	<0.001	1.169 (1.149, 1.189)	<0.001	1.224 (1.202, 1.247)

[#]1 pound was worth about $1.529 in December 2010.

OR, odds ratios; CI, confidence interval; CCI, Charlson comorbidity index; BMI, body mass index; WHR, waist-hip ratio; TDI, Townsend deprivation index; IPAQ, International Physical Activity Questionnaire.

= 12.575, 95% CI = (11.005, 14.370)], and the effect of WHR on CCI is greater in males (Table 4). The AUC and ROC plots for the 10-fold cross-validation of the multivariate logistic regression model are also presented in Supplementary Figure 1.

We fit restricted cubic splines with four sections in a logistic regression model to investigate the potential non-linear association of age, TDI, WHR, and BMI with the risk of CCI. Associations between age, BMI, WHR, and CCI risk are J-shaped for all participants, males, and females. The elevated risk is minimal for low age, BMI, and WHR (Figure 2) but increased markedly above a certain value. We found a U-shaped association between TDI and CCI risk for all participants. The risk is flat or decreased slightly at lower TDIs and begins to increase at a faster rate at TDI above 0. Similar trends are found in males, but with more magnitude. It fell rapidly at TDI = −3 and rose at around TDI = 0.5 (Figure 2). The lowest point of CCI risk is estimated at a TDI of −0.5 and 0.5 for the whole population and men, respectively (Figure 2).

In the sensitivity analysis, 88,928 males and 1,55,902 females, excluding individuals with missing values from the analysis does not change our main results. CCI risks show the same relationship except for ethnicity in females and mixed ethnicities in males. We plotted forest plots to visualize the comparison

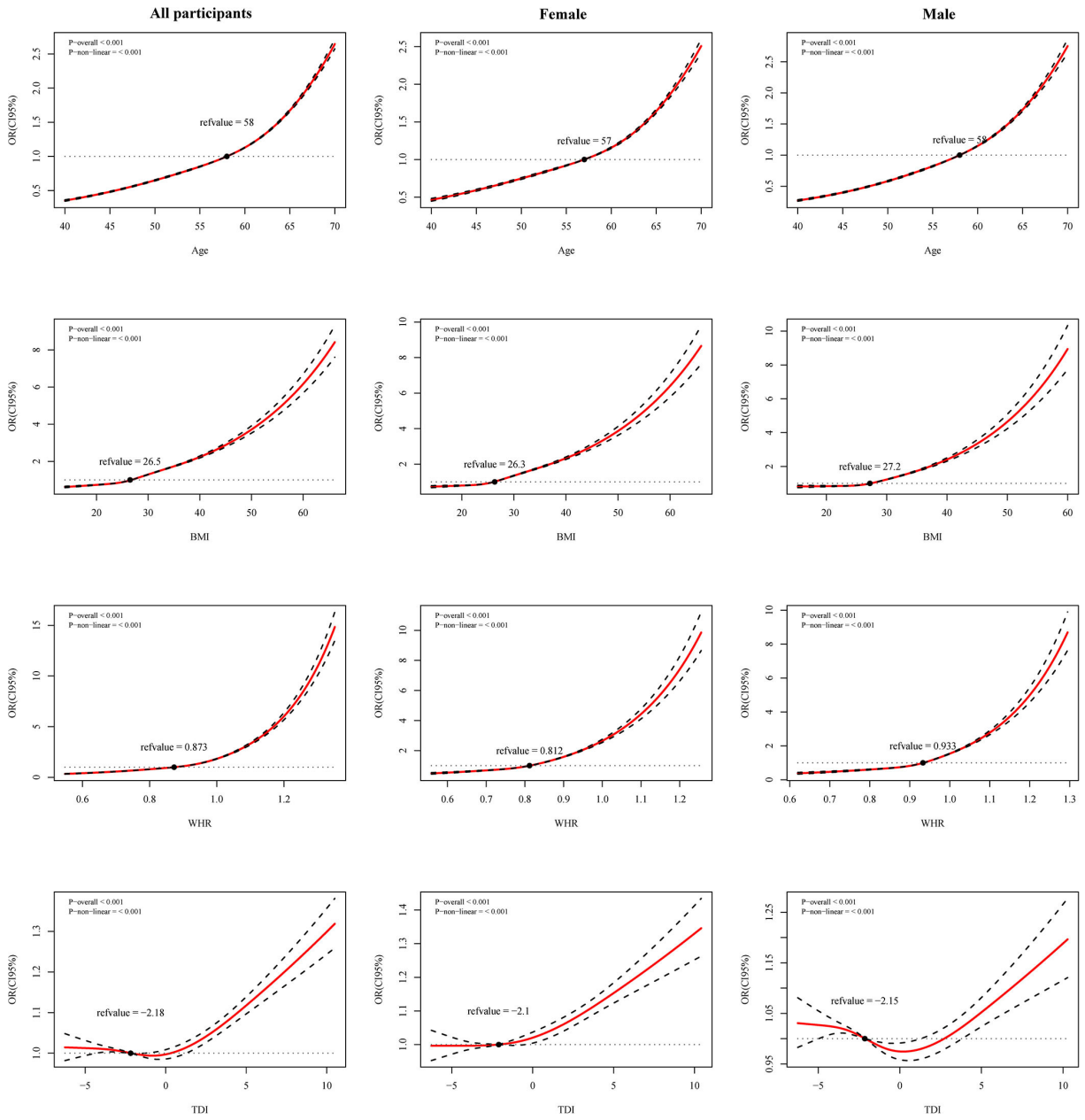

FIGURE 2
Restricted cubic spline (RCS) curves for age, Townsend deprivation index (TDI), waist-hip ratio (WHR) and body mass index (BMI) with Charlson comorbidity index (CCI) risk in all participants, female and male. Adjusted for ethnicity, smoking, alcohol, income, and maternal smoking at birth.

between the primary outcome and the sensitivity analysis (Supplementary Figures 2–4).

4. Discussion

In this large study of cross-sectional data, we investigate the factors influencing CCI in a UK biobank of over 5,00,000 participants. We represent different levels of disease by varying CCI scores and report the results of factors that might influence the risk of CCI in all participants, males, and females. Our study differed from others in that we further analyze the possible non-linear relationships between age, BMI, WHR, TDI, and CCI risk. There are several critical points that we could take away from this research:

1) Increasing age and smoking (both previous and current) seem to be risk factors for reduced health, and moderate

and vigorous physical activity seem to be beneficial to health.

2) Different drinking statuses may have opposite effects on CCI risk. Current alcohol consumption could be a protective factor for CCI risk. It may take years to see the negative impacts of current alcohol consumption.
3) High WHR and high BMI are significant predictors of CCI risk, with WHR having a greater effect.
4) TDI and CCI risk is U-shaped and sex-specific, implying that the impact of socioeconomic factors on CCI is more complex.

4.1. Age, ethnicity and illness of relatives

In this analysis, we do not use age to calculate the CCI score (25) but rather as an independent variable in the regression model to explore its non-linear relationship with CCI risk. It found that the curve inflected at around age 60 and that the OR increased rapidly. Such a feature was in line with the current principles of CCI assignment (25). Some multimorbidities, such as cardiovascular disease, hypertension, and diabetes had previously been higher in South Asians (26). Our results also demonstrate that the ethnic category "Asian or Asian British" might have a negative effect on CCI risk. This might be attributed to the fact that race could influence individual health through cultural habits, behavioral patterns, etc. Besides, genetics and susceptibility to infections might also be important in accounting for health differences across races (27); after all, some infections causing respiratory diseases were also an essential component of CCI. The presence of relatives with more severe diseases could also be a risk factor for CCI, especially in those whose siblings suffered from the illness. After identifying non-modifiable predisposing risk factors, the focus should be modifiable behavioral patterns.

4.2. Smoking, alcohol, and physical activity

Smoking and poor physical activity were considered harmful to health (28–30), and our results provide further evidence. Previous alcohol is a risk factor for health, whereas current alcohol is the opposite. Previous drinkers often abstained from alcohol because of poor health (31, 32) and showed that previous drinkers were associated with an increased risk of CCI. Some researchers have found that the association between alcohol intake and cardiovascular disease incidence was often reported as a j-shaped curve (33). Moderate alcohol consumption was not only linked to a reduced relative risk of cardiovascular disease but was also beneficial for type 2 diabetes (34). Apart from the amount of alcohol, genetic factors and frequency of drinking contributed significantly to differences in alcohol metabolism. Therefore, current drinking should be cautiously treated due to CCI protective factors.

4.3. WHR and BMI

In contrast to BMI, WHR, an important indicator for measuring obesity, has rarely been employed to investigate its impact on human health. An NHANES (National Health and Nutrition Examination Survey) study first demonstrated that obesity, determined by WHR, was associated with an increased risk of cardiovascular mortality (35). A meta-analysis showed that WHR was a valid predictor of heart attack risk with strong predictive power (36), consistent with our findings. High WHR and high BMI increased the risk of CCI in both sex but shows substantial differences in the magnitude of the effect. These differences may be because two different obesity characteristics affect two different diseases (37) (WHR was highly correlated with visceral fat, whereas BMI was highly correlated with subcutaneous fat). Previous studies have also found inconsistencies between WHR and BMI in predicting some outcome events (38). In addition, guideline developers did not consider individuals with high WHR as a priority population for prevention programs (39). This suggests that we must focus our lifestyle changes and other prevention strategies on people with central obesity characterized by high WHR.

4.4. TDI

The TDI was calculated by combining various factors, including employment and housing, and to some extent, indicates people's behavioral patterns (40). Using the TDI to represent socioeconomic status allowed the underestimation caused by a single indicator to be avoided. Our findings suggest that high deprivation indices increase the risk of CCI, which is consistent with the results of previous studies. Higher deprivation levels were associated with an increased risk of multiple morbidities (5, 41, 42) and poor health status (43). A survival analysis of cardiovascular disease showed that individuals in geographic areas with higher socioeconomic disadvantage have higher mortality rates over a follow-up period of more than 10 years, after controlling for multiple variables (44). A study by Riley et al. (45) also concluded that the risk of diabetes-related foot disease increased with increasing indices of deprivation. Cardiovascular disease and diabetes and its complications were both important components of CCI. The association between high levels of deprivation and poor health outcomes might be related to poorer collective resources in deprived areas (46). In addition, poor self-management and unhealthy lifestyle factors (e.g.,

long screen use time, irregular diet) due to poverty had a higher impact on health and mortality (47, 48). These might explain our study's association between deprivation levels and CCI risk.

In the present study, we found a U-shaped association between TDI and CCI risk among all participants. Foster's study revealed a lower risk of all-cause mortality, cardiovascular mortality, and cardiovascular morbidity in the moderately healthy lifestyle population compared to the least deprived and most deprived populations (47). Which was similar to our findings. However, this U-shaped association differed in the subsequent sex analysis. For the TDI-CCI risk association, we only observe a U-shape in the males, while a J-shape in the females. Interestingly, males with a low social deprivation index alone are associated with a high risk of CCI. This may reflect that the effect of socioeconomic status on CCI risk is more complex in males, indicating sex differences in the effect of economic status on health. This situation could be related to the differences in employment status and income between males and females. A Spanish study reported that women were more likely to experience poor health, employment conditions, and lower earnings when employed compared to men (49). White et al. (50) conducted a study exploring health factors from a male perspective, which showed significant sex differences in several social factors that harm health.

It could be noticed that although absolute inequality was declining in some countries (51), the impact of socioeconomic factors on health remained severe. Deprivation may be an essential modifiable factor in health costs, placing greater demands on public health strategies and the rational allocation of resources.

4.5. Limitations

There were some limitations to our study.

1) The cross-sectional study was unable to determine causality, i.e., it was not clear whether health led to behavior change or whether behavior led to different health outcomes;
2) Sampling and questionnaire data were inevitably subject to sampling error, recall bias, reporting bias, and non-response bias;
3) Due to the large sample size, even minimal differences could be statistically significant. Significant associations for some variables might be based on minor absolute differences, such as WHR in the two groups;
4) The sample was mainly from the UK and may lack generalizability to the world population;
5) The independent variables included in the study were limited to general conditions and did not include information such as dietary information and blood tests, which will probably be explored in a future study.

5. Conclusions

In summary, increases in WHR, BMI, and TDI are significant predictors of poor health, and WHR shows a greater role. The impact of deprivation indices on health showed differences by sex. Socioeconomic factors, such as income and TDI, are associated with CCI. The association of social status differences caused by these socioeconomic factors with health conditions should be considered. Our research reveals several demographic and behavioral factors that might be associated with health conditions. This association allows individuals to estimate their health conditions based on their characteristics and to increase awareness of disease prevention and harm reduction due to disease. This could have important implications for disease prevention and health improvement. Factors might interact with each other. Therefore, a comprehensive, rational, and robust intervention will be necessary for health. Given the progressive increase in the number and prevalence of chronic diseases in individuals in recent years and our results, it remained crucial to continue investigating other factors that could be relevant to CCI.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.ukbiobank.ac.uk/.

Author contributions

DM developed the study design. CW, XZ, and BL planned the analyzes and conducted the data analysis. All authors participated in result interpretation, revised all contents of the manuscript, and critically reviewed and approved the submitted manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1050129/full#supplementary-material

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Association between composite lifestyle factors and cardiometabolic multimorbidity in Chongqing, China: A cross-sectional exploratory study in people over 45 years and older

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Introduction: Modifiable lifestyle factors are considered key to the control of cardiometabolic diseases. This study aimed to explore the association between multiple lifestyle factors and cardiometabolic multimorbidity.

Methods: A total of 14,968 participants were included in this cross-sectional exploratory study (mean age 54.33 years, range 45–91; 49.6% male). Pearson's Chi-square test, logistic regression, and latent class analysis were employed.

Results: We found that men with 4–5 high-risk lifestyle factors had a 2.54-fold higher risk (95% CI: 1.60–4.04) of developing multimorbidity compared to males with zero high-risk lifestyle factors. In an analysis of dietary behavior, we found that in women compared to men, over-eating (OR = 1.94, $P < 0.001$) and intra-meal water drinking (OR = 2.15, $P < 0.001$) were more likely to contribute to the development of cardiometabolic multimorbidity. In an analysis of taste preferences, men may be more sensitive to the effect of taste preferences and cardiometabolic multimorbidity risk, particularly for smoky (OR = 1.71, $P < 0.001$), hot (OR = 1.62, $P < 0.001$), and spicy (OR = 1.38, $P < 0.001$) tastes. Furthermore, "smoking and physical activity" and "physical activity and alcohol consumption" were men's most common high-risk lifestyle patterns. "Physical activity and dietary intake" were women's most common high-risk lifestyle patterns. A total of four common high-risk dietary behavior patterns were found in both males and females.

Conclusions: This research reveals that the likelihood of cardiometabolic multimorbidity increases as high-risk lifestyle factors accumulate. Taste preferences and unhealthy dietary behaviors were found to be associated with an increased risk of developing cardiometabolic multimorbidity and this association differed between genders. Several common lifestyle and dietary behavior patterns suggest that patients with cardiometabolic multimorbidity may achieve better health outcomes if those with certain high-risk lifestyle patterns are identified and managed.

KEYWORDS

multimorbidity, cardiometabolic diseases, lifestyle factors, dietary factors, dietary behavior, taste preference

Introduction

As life expectancy continues to increase globally (1), multimorbidity is becoming a worldwide public health problem due to its accompanying increase in disability and mortality, decrease in quality of life, and increased disease burden in the elderly (2). The global prevalence of multimorbidity is estimated to range from 12.9% in the general population to 95.1% in people aged 65 years and older (3). Cardiometabolic multimorbidity (CMM); a typical form of multimorbidity; refers to the presence of two or more cardiometabolic diseases, such as hypertension, diabetes, cardiovascular disease, heart disease, or stroke (4). Numerous studies have shown that CMM is associated with decreased cognitive function (5), a shorter life expectancy (2), a higher economic burden of the disease (6), and an uneven allocation of medical resources (7). These factors place a significant burden on individuals, families, and healthcare systems, and the burden is particularly pronounced in low- and middle-income countries.

The prevalence of chronic multimorbidity is increasing in low- and middle-income countries that are characterized by rapid urbanization, economic transition, and the spread of Western lifestyles (8). Abebe et al. showed that the prevalence of multimorbidity in low- and middle-income countries ranged from 19.4% to 80% among people aged 40 years and older (9). A cross-sectional survey showed that the prevalence of CMM in South Africa was 10.5% (10). A longitudinal cohort study including one million Chinese adults showed that the prevalence of CMM in the general population has more than doubled over 5 years (2010–2016) (11). Moreover, due to changes in nutrition and epidemiology, the burden of cardiometabolic disease is already significant in low- and middle-income countries. The fragility of social protection and health systems is not conducive to addressing these problems (12). Hence, exploring risk factors and management strategies for CMM may have significant implications for health at the individual, clinical, and public levels in these low- and middle-income countries.

China is the most populous developing country in the world and is currently experiencing a severe chronic disease epidemic (13). According to one survey, 42.4% of Chinese residents aged 50 and above suffer from multimorbidity (14). Chongqing, located in southwest China, is the most populous inland city in China and is considered an economic center. However, due to the city's rapid economic development and fast-paced way of life, most Chongqing residents live unhealthy lifestyles characterized by poor diets and physical inactivity (15). Numerous studies have revealed a connection between lifestyle factors and cardiometabolic multimorbidity (16–19). People who are obese, physically inactive, smokers, and drinkers are more likely to develop CMM. A healthy diet can help prevent or treat cardiometabolic diseases like dyslipidemia, hypertension, and diabetes (20). It is noteworthy that few studies have investigated the relationship between CMM and dietary behaviors (such as over-eating and intra-meal water drinking), despite it being a crucial lifestyle factor. Even fewer studies have explored how the combined effect of multiple dietary behaviors affects the occurrence of CMM. Chongqing's topography is primarily mountainous, and the city's climate is typically "wet" and "hot," which may be partly responsible for the locals having developed strong taste preferences for spicy foods. The number of chili peppers consumed annually per person in Chongqing is reported to be up to 96.5 kg (21). A study in the Sichuan basin of China discovered that eating spicy foods increased the risk of adult abdominal obesity (22). Few previous studies, however, have investigated the relationship between taste preferences and CMM.

It must be highlighted that an individual's lifestyle is a combination of different habits and behaviors. Unhealthy lifestyle habits tend to cluster together, thereby dramatically raising the likelihood of developing multimorbidity (23). Meanwhile, there is evidence that some lifestyle factors may interact to have a synergistic effect, causing more harm when combined (24). Exploring potential lifestyle patterns that underly CMM in affected patients may be necessary for developing intervention strategies to improve their health outcomes. It is uncertain whether dietary behaviors and taste preferences are linked to CMM, and it is also unclear how multiple high-risk lifestyle factors affect the development of CMM. Therefore, we conducted the present study to investigate the association between multiple lifestyle factors; along with their cumulative effects; and the occurrence of CMM in Chongqing residents, as well as to explore potential high-risk lifestyle patterns and dietary behavior patterns of CMM patients.

Method

Materials and participants

This cross-sectional exploratory study used data obtained from the Health Management Center of the First Affiliated Hospital of Chongqing Medical University in China. From July 2020 to January 2022, 44,516 patients underwent a health checkup at the hospital's health management center. All participants were asked to complete a self-administered questionnaire to collect information about their demographic features (age, gender), personal and family history of diseases (diagnosed by a doctor), and lifestyle factors. Participants under 45, those who had been in Chongqing for <6 months, and those whose responses contained logical errors or had more than 10% of their data missing from any questionnaire component were all excluded. Finally, 14,968 participants aged 45 and older were retained for analysis in this cross-sectional exploratory study. The study protocol was reviewed and approved by the First Affiliated Hospital of Chongqing Medical University's ethical committee (2020426). All patients/participants voluntarily signed an informed consent form to participate in this study.

Assessment of lifestyle factors and other covariates

Based on earlier studies (25–27), the questionnaire was designed to gather information on lifestyle factors, including dietary intake, dietary habits (including dietary behaviors and taste preferences), physical activity, smoking, and alcohol consumption. Dietary intake was assessed by questioning participants about their average daily water consumption and average daily intake of each food group in the last month. The food groups included fresh vegetables, fresh fruits, rice, and flour staples, eggs, soybeans and soybean-based products, milk and milk-based products, meat and meat-based products, and fish and aquatic products. Participants were questioned about their dietary habits in the last month, such as breakfast frequency per

week, night snacking per week, intra-meal water drinking, eating excessively fast, over-eating, and eating excessively late for dinner. The following dietary taste preferences were chosen from by the participants: salty, sweet, cold, hot, spicy, greasy, and smokey. Questions about physical activity included the participants' average weekly physical activity time and its degree of intensity. For smoking, participants were questioned regarding their current smoking habits, average daily cigarette consumption, and the total number of years they had smoked. Participants were questioned about their alcohol consumption, including average daily intake and type of alcohol (posed to both former and current drinkers).

The questionnaire also collected three covariates, including demographic characteristics (age and gender) and family history. Participants aged 45–59 years were included in the middle-aged group, while those aged 60 years and older were included in the older group. Participants who reported that at least one of their parents had two or more cardiometabolic diseases were considered to have a family history of cardiometabolic multimorbidity (19).

Definition of high-risk lifestyle factors

We defined high-risk lifestyle factors based on data available from the study and characteristics of the Chinese population to calculate the number of high-risk lifestyle factors per participant, ranging from 0 to 5.

Dietary intake

Dietary intake was assigned a value according to the recommended information of the Chinese Dietary Guidelines (2016 version) (28). A score of 1 was assigned if the average daily intake of each food group did not meet the standards recommended by the Chinese Dietary Guidelines. Otherwise, a score of 0 was assigned. The score range was from 0 to 9, described by median and interquartile range for the analysis. The higher the dietary intake score, the more the participants' dietary intake diverged from the guidelines. If the calculated dietary intake score was in the highest quartile, the participants were categorized as having high-risk dietary intake habits.

Dietary habits

Dietary habits in this study encompassed both dietary behaviors and taste preferences. High-risk dietary behaviors included eating breakfast <7 days per week on average, snacking at nighttime on one or more days per week on average, intra-meal water drinking, eating excessively fast, over-eating, and eating excessively late for dinner (29–32). The number of each participant's high-risk dietary behaviors was calculated as a score ranging from 0 to 6 and described by median and interquartile range analysis. If the number of calculated dietary behaviors was in the highest quartile, the participants were classified as having high-risk dietary behavior habits. In addition, due to the uniqueness of participants' taste preferences, this study did not conduct a comprehensive assessment of taste preferences.

Physical activity

The recommended duration of physical activity recommended by the physical activity guidelines for Chinese people (2021 version) is 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity aerobic activity per week or an equivalent combination of moderate-intensity and vigorous-intensity aerobic activity (33). Participants who did not meet the recommended criteria were considered physically inactive and hence were categorized as having high-risk physical activity habits.

Smoking

The smoking index is defined as the product of the number of cigarettes smoked per day and the number of years of smoking, which is used to represent the cumulative effect of cumulative smoking on the health risks of smokers and ex-smokers (34). If a participant's smoking index was more than or equal to 100, they were categorized as having high-risk smoking behavior.

Alcohol consumption

Participants' responses for average daily drinking quantity and type of wine were combined to calculate their average daily alcohol consumption according to the proportions recommended by the Chinese Dietary Guidelines (2016 version) (28). Participants were categorized as high risk if the average alcohol consumption per day exceeded the guideline's recommendation (25 g for males and 15 g for females).

Definition of cardiometabolic multimorbidity

We collected participants' disease history through the questionnaire, which included hypertension, diabetes, dyslipidemia, obesity, coronary heart disease, stroke, and osteoporosis (35). These diseases were identified from self-reported doctor diagnoses. For this study, we defined CMM as the coexistence of two or more cardiometabolic diseases (4).

Statistical analysis

In this study, age was expressed as the mean and standard deviation; the number of diseases and high-risk lifestyle factors were expressed as the median and range; the number of dietary intake scores and high-risk dietary behaviors were expressed as the median and interquartile spacing; categorical variables were expressed as the frequency and percentage. All analyses were stratified due to variations in the distribution of adherence to lifestyle variables by gender. Pearson's Chi-square test for categorical variables was used to analyze variance to determine the impact of various lifestyle factors on CMM. Binary logistic regression analysis was used to determine the association between lifestyle factors (individual and cumulative) and CMM. Tolerance and the variance inflation factor (VIF) were used to test for multicollinearity among independent variables. In

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TABLE 1 Characteristics of disease and lifestyle of the participants ($N = 14,968$).

		Total	Male ($n = 7,427$)	Female ($n = 7,541$)	*P*-value
Age[a]		54.33 ± 7.31	54.37 ± 7.37	54.29 ± 7.27	
Family history	No	11,825 (79.0%)	5,932 (79.9%)	5,893 (78.1%)	0.010
	Yes	3,143 (21.0%)	1,495 (20.1%)	1,648 (21.9%)	
Dietary intake	Good	9,919 (66.3%)	5,005 (67.4%)	4,914 (65.2%)	0.004
	Poor	5,049 (33.7%)	2,422 (32.6%)	2,627 (34.8%)	
Dietary behavior	Good	10,243 (68.4%)	4,640 (62.5%)	5,603 (74.3%)	<0.001
	Poor	4,725 (31.6%)	2,787 (37.5%)	1,938 (25.7%)	
Physical activity	Active	2,939 (19.6%)	1,577 (21.2%)	1,362 (18.1%)	<0.001
	Inactive	12,029 (80.4%)	5,850 (78.8%)	6,179 (81.9%)	
High-risk smoking	No	11,917 (79.6%)	4,484 (60.4%)	7,433 (98.6%)	<0.001
	Yes	3,051 (20.4%)	2,943 (39.6%)	108 (1.4%)	
High-risk alcohol consumption	No	10,854 (72.5%)	3,873 (52.1%)	6,981 (92.6%)	<0.001
	Yes	4,114 (27.5%)	3,554 (47.9%)	560 (7.4%)	
Hypertension	No	12,497 (83.5%)	5,853 (78.8%)	6,644 (88.1%)	<0.001
	Yes	2,471 (16.5%)	1,574 (21.2%)	897 (11.9%)	
Diabetes	No	14,007 (93.6%)	6,780 (91.3%)	7,227 (95.8%)	<0.001
	Yes	961 (6.4%)	647 (8.7%)	314 (4.2%)	
Coronary Heart Disease	No	14,623 (97.7%)	7,212 (97.1%)	7,411 (98.3%)	<0.001
	Yes	345 (2.3%)	215 (2.9%)	130 (1.7%)	
Dyslipidemia	No	12,701 (84.9%)	6,079 (81.9%)	6,622 (87.8%)	<0.001
	Yes	2,267 (15.1%)	1,348 (18.1%)	919 (12.2%)	
Obesity	No	14,560 (97.3%)	7,134 (96.1%)	7,426 (98.5%)	<0.001
	Yes	408 (2.7%)	293 (3.9%)	115 (1.5%)	
Stroke	No	14,899 (99.5%)	7,383 (99.4%)	7,516 (99.7%)	0.018
	Yes	69 (0.5%)	44 (0.6%)	25 (0.3%)	
Osteoporosis	No	14,343 (95.8%)	7,215 (97.1%)	7,128 (94.5%)	<0.001
	Yes	625 (4.2%)	212 (2.9%)	413 (5.5%)	
Number of high-risk lifestyle factors[b]	2 (0–5)	2 (0–5)	1 (0–5)		
0		1,036 (6.9%)	1,036 (6.9%)	317 (4.3%)	<0.001
1		4,743 (31.7%)	4,743 (31.7%)	1,491 (20.1%)	
2		4,932 (33.0%)	4,932 (33.0%)	2,287 (30.8%)	
3		2,910 (19.4%)	2,910 (19.4%)	2,075 (27.9%)	
4-5		1,347 (9.0%)	1,347 (9.0%)	1,257 (16.9%)	
Number of cardiometabolic diseases[b]		0 (0–7)	0 (0–7)	0 (0–7)	
0		10,180 (68.0%)	4,606 (62.0%)	5,574 (73.9%)	<0.001
1		3,114 (20.8%)	1,765 (23.8%)	1,349 (17.9%)	
2		1,165 (7.8%)	718 (9.7%)	447 (5.9%)	
3		389 (2.6%)	255 (3.4%)	134 (1.8%)	
4		89 (0.6%)	62 (0.8%)	27 (0.4%)	
5-7		31 (0.2%)	21 (0.3%)	10 (0.1%)	

(Continued)

TABLE 1 (Continued)

		Total	Male ($n = 7,427$)	Female ($n = 7,541$)	*P*-value
Dietary intake scores[c]		7 (6-8)	7 (6-8)	7 (6-8)	
Number of high-risk dietary behaviors[c]	0 (0–2)	1 (0–2)	0 (0–2)		

[a]refers to data were presented by mean and SD.
[b]refers to data were presented by median and range.
[c]refers to data were presented by Median interquartile range.

TABLE 2 Association of participant lifestyle factors with cardiometabolic multimorbidity ($N = 14,968$).

		Male ($n = 7,427$)			Female ($n = 7,541$)		
		Total	Multimorbidity/n (%)	*P*-value	Total	Multimorbidity/*n* (%)	*P*-value
Age group	45–59	6,011	725 (12.1%)	<0.001	6,124	315 (5.1%)	<0.001
	≥60	1,416	331 (23.4%)		1,417	303 (21.4%)	
Family History	No	5,932	622 (10.5%)	<0.001	5,893	340 (5.8%)	<0.001
	Yes	1,495	434 (29.0%)		1,648	278 (16.9%)	
Lifestyle factors							
Dietary intake	Good	5,005	693 (13.8%)	0.187	4,914	363 (7.4%)	<0.001
	Poor	2,422	363 (15.0%)		2,627	255 (9.7%)	
Dietary behavior	Good	4,640	624 (13.4%)	0.014	5,603	449 (8.0%)	0.328
	Poor	2,787	432 (15.5%)		1,938	169 (8.7%)	
Physical activity	Active	1,577	196 (12.4%)	0.022	1,362	88 (6.5%)	0.010
	Inactive	5,850	860 (14.7%)		6,179	530 (8.6%)	
High-risk smoking	No	4,484	630 (14.0%)	0.608	7,433	612 (8.2%)	0.314
	Yes	2,943	426 (14.5%)		108	6 (5.6%)	
High-risk alcohol consumption	No	3,873	512 (13.2%)	0.010	6,981	585 (8.4%)	0.039
	Yes	3,554	544 (15.3%)		560	33 (5.9%)	
Number of high-risk lifestyle factors							
0		317	23 (7.3%)	<0.001[a]	719	45 (6.3%)	0.004[a]
1		1,491	190 (12.7%)		3,252	243 (7.5%)	
2		2,287	330 (14.4%)		2,645	247 (9.3%)	
3		2,075	315 (15.2%)		835	76 (9.1%)	
4–5		1,257	198 (15.8%)		90	7 (7.8%)	

[a]refers to P-value for trend.

the logistic regression model, the ratio (OR) and associated 95% confidence interval (95% CI) were determined for each component. With two-sided tests and a significance threshold of 0.05, all of the aforementioned statistical analyses were carried out using SPSS version 25.0 (SPSS, Inc., Chicago, IL, USA).

Latent class analysis (LCA) was used to further explore the potential high-risk dietary behavior and lifestyle patterns in CMM patients using Mplus version 8.3 (Muthén & Muthén, Los Angeles, CA, USA). Latent class analysis, a method for person-centered classification that combines people with similar behaviors into potential classes, is crucial for determining whether subgroups of high-risk lifestyle factors exist (36). We fitted a one-class model to identify the most concise model and steadily raised the number of potential classes. The Lo-Mendell-Rubin adjusted likelihood ratio test (LMR), bootstrapped likelihood ratio test (BLRT), entropy score, and Bayesian Information Criterion (BIC) were employed to evaluate the model's fit (37).

Results

A total of 14,968 participants were included in this study, including 7,427 males and 7,541 females. The mean age of the participants was 54.33 (SD = 7.31) years, ranging from 45 to 91 years. Table 1 shows the characteristics of the participants' diseases and lifestyle factors. A total of 4,788 participants (32.0%) had at least one disease and 1,674 participants (11.2%) had CMM. The most common cardiometabolic diseases were hypertension (16.5%), followed by dyslipidemia (15.1%), and diabetes (6.4%). For lifestyle factors, patients with 4 and 5 high-risk lifestyle factors were combined

TABLE 3 Logistic regression of the number of high-risk lifestyle factors and the likelihood of cardiometabolic multimorbidity.

	Male		Female	
	OR	95% CI	OR	95% CI
Number of high-risk lifestyles (ref. 0)				
1	1.85	(1.17–2.94)*	1.12	(0.79–1.58)
2	2.21	(1.41–3.47)**	1.63	(1.15–2.30)*
3	2.48	(1.58–3.90)**	1.80	(1.20–2.69)*
4–5	2.54	(1.60–4.04)**	1.78	(0.76–4.18)

Adjustment with age group and family history of cardiometabolic multimorbidity,*$P < 0.01$, **$P < 0.001$.

into one group because few participants were characterized by five high-risk lifestyle factors. After stratification by gender, women were found to engage in significantly lower rates of high-risk smoking (3.5%) and high-risk alcohol consumption (13.6%) than men. The associations of participants' lifestyle factors with CMM are shown in Table 2. Physical inactivity and high-risk alcohol consumption were associated with CMM in both sexes ($P < 0.05$). For high-risk smoking, however, there was no discernible difference between the sexes ($P > 0.05$). High-risk dietary intake was associated with CMM in women only ($P < 0.001$) and high-risk dietary behavior in men only ($P = 0.014$).

The odds ratio (OR) of CMM associated with the number of high-risk lifestyle factors is shown in Table 3. After adjusting for age group and family history, the results varied significantly between the sexes. Men with 4 to 5 high-risk lifestyle factors had a 2.54-fold higher risk (95% CI: 1.60–4.04) of developing multimorbidity compared to males without any high-risk lifestyle factors. Two or three high-risk lifestyle factors considerably increased the probability of CMM in women. The trend test (in Table 2) for the number of high-risk lifestyle factors with CMM was significant in both men ($P < 0.001$) and women ($P = 0.004$). Accumulating the number of high-risk lifestyle factors was positively and significantly associated with an increased likelihood of CMM in both genders.

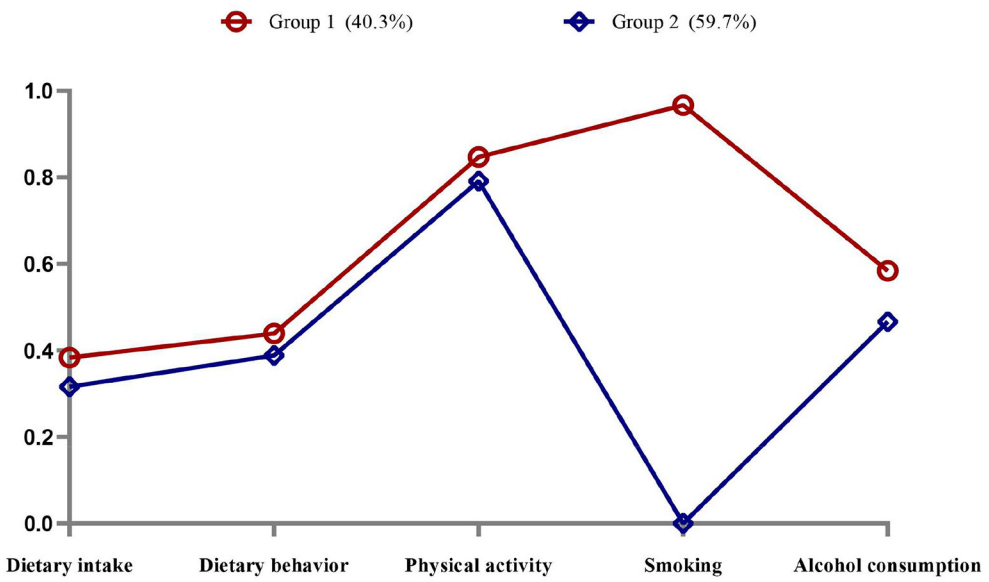
Figure 1 shows each model's conditional probabilities for each high-risk lifestyle factor among male CMM patients. Based on the results of the LCA model's relevant statistical indicators, we found that the two-class model with the lower BIC and ABIC values, significant LMR and BLRT values, and high entropy score (0.906) was the best (Supplementary Table 1). Male patients with CMM had two common high-risk lifestyle patterns. Group 1 ($N = 426$, 40.3%) consisted of individuals classified as having a "high-risk lifestyle dominated by high-risk smoking and high-risk physical activity." Similarly, group 2 ($N = 630$, 59.7%) was categorized as having "high-risk lifestyles dominated by high-risk physical activity and high-risk alcohol consumption." Figure 2 shows the model's conditional probabilities for each high-risk lifestyle factor among female CMM patients. Based on the LCA model's relevant statistical indicators, we found that the one-class model was the best (Supplementary Table 2). Female patients with CMM had one common high-risk lifestyle pattern. Group 1 ($N = 618$, 100%) consisted of individuals classified as having a "high-risk lifestyle dominated by high-risk physical activity and high-risk dietary intake." The results show that individuals in three subgroups had a high probability of having high-risk physical activity. Thus, high-risk physical activity is an important lifestyle factor that dominates the high-risk lifestyle pattern of CMM patients.

The odds ratio (OR) of the binary effect of each lifestyle factor on the presence of CMM after adjusting for age group and family history is shown in Figure 3. The effect of lifestyle factors on CMM was found to vary by gender. Men (OR: 1.20; 95% CI: 1.04–1.39) and women (OR: 1.55; 95% CI: 1.29–1.85) with high-risk dietary intake had a higher risk of CMM than participants without high-risk dietary intake. Men with high-risk dietary behavior were 1.26-fold (95% CI: 1.10–1.45) more likely to report CMM than men without high-risk dietary behavior, corresponding to 1.33-fold (95% CI: 1.09–1.63) for women. Physical inactivity was a risk factor for CMM in both men (OR: 1.26; 95% CI: 1.06–1.49) and women (OR: 1.28; 95% CI: 1.00–1.64). The association between high-risk smoking and CMM in both sexes was not statistically significant. High-risk alcohol consumption (compared to low-risk drinking) was a significant risk factor in men only (OR: 1.21; 95% CI: 1.05–1.38).

Table 4 shows the odds ratio (OR) for the binary effect of each dietary habit (including dietary behavior and taste preference) on the presence of cardiometabolic multimorbidity, adjusted for age group and family history. The association between dietary behavior and CMM varied by gender. For women, intra-meal water drinking (OR: 2.15; 95% CI: 1.60–2.89), over-eating (OR: 1.94; 95% CI: 1.49–2.53), and eating excessively late for dinner (OR: 1.53; 95% CI: 1.16–2.03) were associated with an increased likelihood of CMM. In contrast, among men, eating excessively fast (OR: 1.64; 95% CI: 1.42–1.89) and over-eating (OR: 1.54; 95% CI: 1.27–1.86) were risk factors for the development of CMM. The association of taste preferences with CMM varied by gender. In women, taste preferences for salty (OR: 1.72; 95% CI: 1.28–2.32) and greasy (OR: 1.75; 95% CI: 1.23–2.49) foods were associated with a higher likelihood of CMM, and the negative health effects were more prominent in women than in men. However, taste preferences for spicy (OR: 1.38; 95% CI: 1.18–1.61), smoky (OR: 1.71; 95% CI: 1.31–2.24), and hot (OR: 1.62; 95% CI: 1.29–2.04) foods affected the occurrence of CMM in men only.

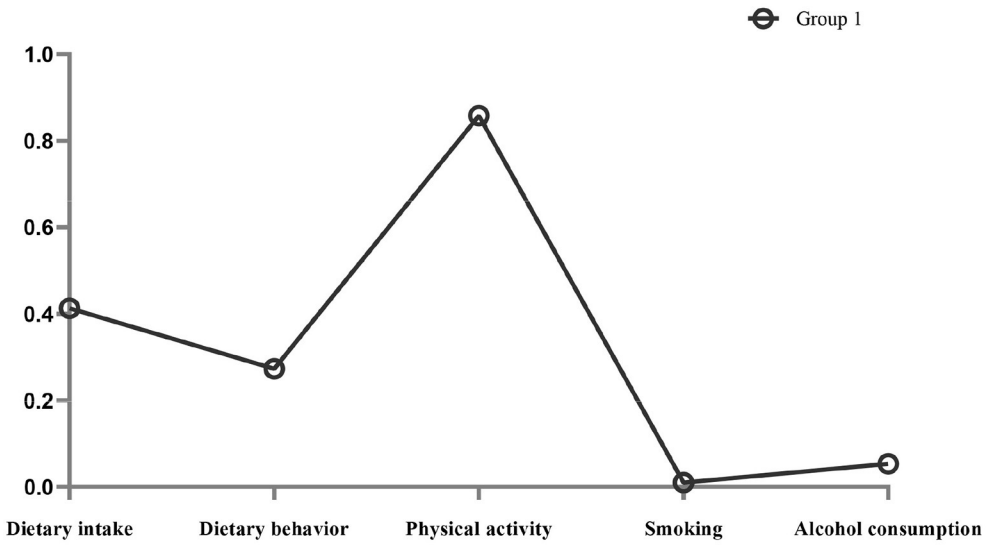
Figure 4 shows each model's conditional probabilities of high-risk dietary behavior among male CMM patients. Based on the results of the LCA model's relevant statistical indicators, the three-class model with lower BIC and ABIC values, significant LMR and BLRT values, and a high entropy score (0.767) was determined to be the best (Supplementary Table 3). Male patients with CMM were characterized by one of two common patterns of high-risk dietary behaviors. Group 1 ($N = 114$, 10.8%) and group 2 ($N = 582$, 55.1%) consisted of individuals categorized as having "high-risk dietary behavior dominated by frequent night snacking and breakfast irregularity." Similarly, group 3 ($N = 360$, 34.1%) was classified as having "high-risk dietary behaviors dominated by eating excessively fast and frequent night snacking."

Figure 5 shows each model's conditional probabilities of high-risk dietary behavior among female CMM patients. Based on the results of the LCA model's relevant statistical indicators, the two-class model with lower BIC and ABIC values, significant LMR and BLRT values, and a high entropy score (0.717) was determined to be the best (Supplementary Table 4). Female patients with CMM were characterized by one of two common patterns of high-risk dietary behaviors. Group 1 ($N = 63$, 10.2%) consisted of individuals categorized as having "high-risk dietary behavior dominated by frequent night snacking and over-eating." Similarly, group 2 ($N =$



Note: Group 1 refers to smoking and physical activity dominated high-risk lifestyle, group 2 refers to physical activity and alcohol consumption dominated high-risk lifestyle **(Male)**.

FIGURE 1
Item probabilities in the two common high-risk lifestyle patterns among male cardiometabolic multimorbidity patients.



Note: Group 1 refers to physical activity and dietary intake dominated high-risk lifestyle **(Female)**.

FIGURE 2
Item probabilities in the one common high-risk lifestyle pattern among female cardiometabolic multimorbidity patients.

555, 89.8%) was classified as having "high-risk dietary behaviors dominated by frequent night snacking and eating excessively fast."

Discussion

This study suggests that several common lifestyle factors and their combined effects are associated with the likelihood of CMM in middle-aged and older adults. Upon inspecting the lifestyle factors individually, those that may be associated with CMM include physical activity, alcohol consumption, dietary intake, and dietary behavior. The likelihood of CMM gradually increased with the accumulation of high-risk lifestyle factors when lifestyle factors were combined, starting from a threshold of one lifestyle factor in men and two in women.

Shao et al. found that participants who accumulated more unhealthy lifestyle behaviors had a higher likelihood of cardiometabolic multimorbidity, which is consistent with our

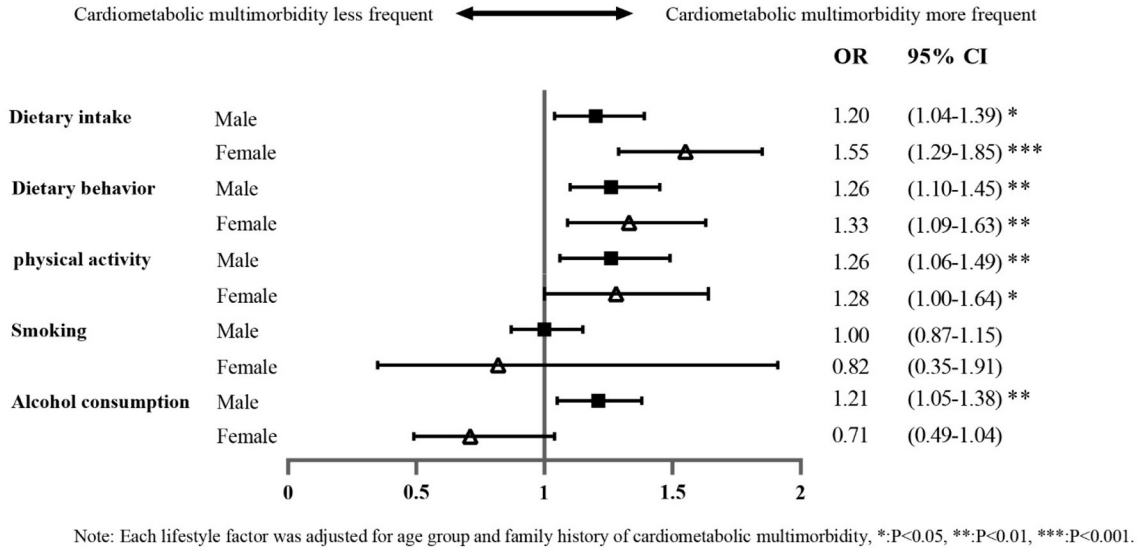


FIGURE 3
Forest plot showing the bivariate effect of each high-risk lifestyle factor on the likelihood of cardiometabolic multimorbidity.

findings in men (38). Similar to the findings of Fortin et al. (39), we found that two or three unhealthy lifestyle factors increased the likelihood of multimorbidity in women compared to those with none. Furthermore, our findings revealed that, while not significant on its own in men, high-risk smoking was most strongly related to the development of CMM when combined with other factors. Thus, we predicted that the total probability of CMM development might be influenced by the number of accumulated high-risk lifestyle factors and their specific combinations (38, 40). We discovered two common high-risk lifestyle patterns among male CMM patients: "smoking and physical activity" and "physical activity and alcohol consumption". These findings support our hypothesis that certain lifestyle factors can coexist and interact to have synergistic effects (24). Meanwhile, we discovered only one common high-risk lifestyle pattern among female CMM patients: "physical activity and dietary intake". The low rates of high-risk smoking and high-risk alcohol consumption among women may explain this result. Notably, people in three subcategories were highly likely to have engaged in high-risk physical activity, indicating that other high-risk lifestyle factors may frequently accompany these behaviors in CMM patients. This finding helps to explain why the healthcare system should shift its focus to addressing multiple behaviors for multiple diseases.

Numerous critical studies have shown that CMM is associated with inactive physical activity, smoking, and high-risk alcohol consumption in middle-aged and older adults (16–18). Our study confirmed physical inactivity to be a risk factor for CMM. However, there was a lack of association between high-risk alcohol consumption and high-risk smoking and CMM in women. We found only a low percentage of women to be characterized by high-risk alcohol consumption and high-risk smoking, regardless of cardiometabolic multimorbidity, which is consistent with other studies (41) and may explain the results. The findings could also be due to fundamental differences in the distribution of these factors between the sexes, or they could be related to historical and societal factors that impact women's smoking and alcohol-drinking habits (42). In addition, this study found the same lack of association between high-risk smoking with CMM in men, which may be related to the characteristics of the low-risk smoking population. We found a higher proportion of the remaining four high-risk lifestyle factors among men with low-risk smoking. Moreover, our data analysis showed that all four high-risk lifestyle factors, except smoking, were risk factors for CMM in men. The remaining high-risk lifestyle factors likely amplify the dangerous effect of smoking behavior in the low-risk smoking group, thereby diluting the effect of high-risk smoking on CMM.

A longitudinal study from Jiangsu, China, found that the high consumption of fruits and vegetables reduced the risk of CMM by analyzing the association between the average daily intake of multiple foods and multiple morbidities (26), which is consistent with findings obtained in the United States and Korea, among other countries (25, 35). However, this contrasts with our findings, which indicated that fruit and vegetable intake was not significantly associated with the risk of CMM (Supplementary Table 5). We surmise that this may be due to a significant fraction of participants (almost 80%) not achieving the recommended intake of fruits and vegetables, which could dampen the risk effect. It also implies that steps must be taken to modulate this behavior in the population, as the general residents of Chongqing may be at risk of consuming too few fruits and vegetables. In addition, we investigated the relationship between the high-risk intake of nine food groups and CMM. The results confirm the findings reported by Micha et al., namely, that nine food groups were significantly associated with CMM when evaluated collectively (25). Notably, the adverse health effects associated with high-risk dietary intake were higher in women than men. However, caution should be exercised in interpreting the results due to the inherent limitations of conducting dietary intake assessments (42), such as methodological differences in measuring different food intakes and the different risk intake thresholds identified.

Individual high-risk dietary behaviors; such as breakfast irregularity (43), frequent night snacking (29), over-eating (44),

TABLE 4 Logistic regression of the independent effects of each dietary behavior and taste preference on cardiometabolic multimorbidity.

	Male		Female	
	OR	95% CI	OR	95% CI
Dietary behavior				
Breakfast irregularity (ref. No)				
Yes	0.88	(0.72–1.04)	0.81	(0.63–1.06)
Frequent night snacking (ref. No)				
Yes	1.03	(0.90–1.18)	1.17	(0.97–1.40)
Intra-meal water drinking (ref. No)				
Yes	1.14	(0.87–1.50)	2.15	(1.60–2.89)**
Eating excessively fast (ref. No)				
Yes	1.64	(1.42–1.89)**	1.18	(0.95–1.48)
Over-eating (ref. No)				
Yes	1.54	(1.27–1.86)**	1.94	(1.49–2.53)**
Eating excessively late for dinner (ref. No)				
Yes	1.18	(0.95–1.48)	1.53	(1.16–2.03)*
Taste preference				
Salty (ref. No)				
Yes	1.57	(1.30–1.91)**	1.72	(1.28–2.32)**
Hot (ref. No)				
Yes	1.62	(1.29–2.04)**	1.19	(0.80–1.77)
Greasy (ref. No)				
Yes	1.55	(1.55–2.30)**	1.75	(1.23–2.49)*
Smoked (ref. No)				
Yes	1.71	(1.31–2.24)**	1.47	(0.97–2.23)
Spicy (ref. No)				
Yes	1.38	(1.18–1.61)**	1.13	(0.89–1.44)

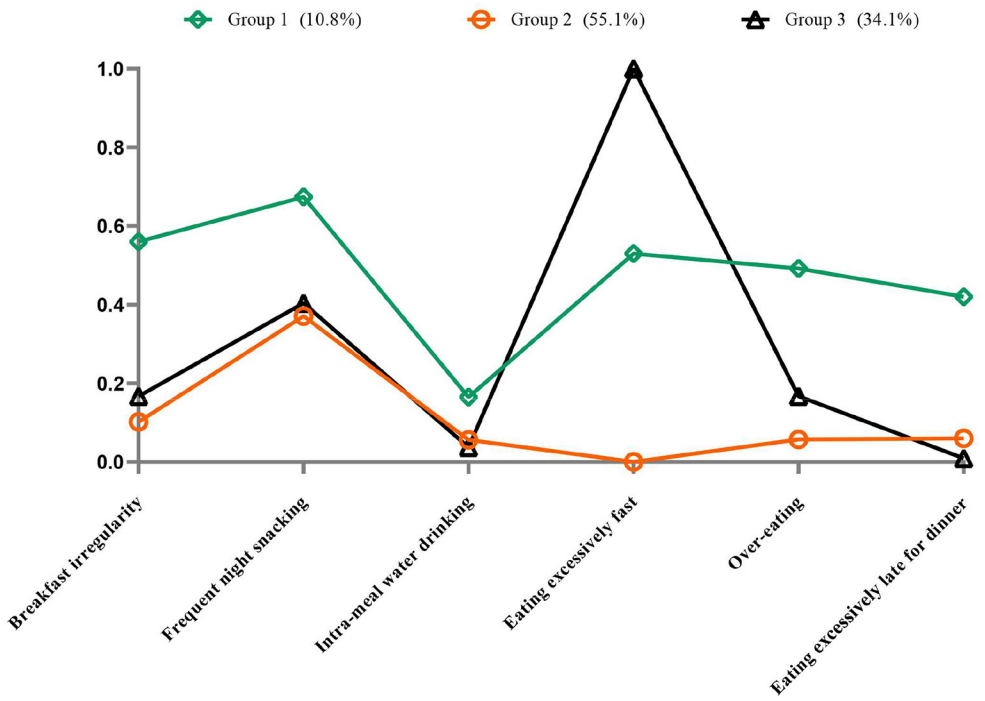
Adjustment with age group and family history of cardiometabolic multimorbidity,* $P < 0.01$,** $P < 0.001$.

and eating excessively fast (30); have a large body of evidence supporting them as risk factors for cardiometabolic disease. Our findings are generally consistent with previous studies. According to a Brazilian longitudinal study (45), over-eating was associated with a higher likelihood of developing cardiometabolic diseases. We further discovered gender-specific differences in this relationship. The adverse health effects of over-eating were more prominent in women than in men, which supports the findings of a Canadian longitudinal study (46). Additionally, present knowledge about the association between dietary behavior and CMM is limited. For example, there is no data on the relationship between intra-meal water drinking and CMM. An Iranian study found that intra-meal water drinking increased the risk of general and abdominal obesity (32). Our data reinforces this conclusion and provides the new insight that intra-meal water drinking is associated with an increased risk of CMM in women.

It is worth noting that prior research has concentrated on specific dietary behaviors, with little evidence of the combined impact of various high-risk dietary behaviors and CMM. Considering that the individual impacts of each high-risk dietary behavior may be too minor to detect, investigating the relationship between multiple dietary behaviors and CMM may reveal new insights into CMM management. Our data analysis indicates that engaging in two or more concurrent high-risk dietary behaviors is related to a greater likelihood of CMM occurrence than having either no high-risk dietary behaviors or just one, which applied to both sexes. Moreover, we predicted that specific combinations of high-risk dietary behaviors might affect the likelihood of developing CMM. We examined serval potential patterns of high-risk dietary behaviors using LCA in CMM patients stratified by gender. Our results suggest that while frequent night snacking has no effect on the risk of CMM in men and women, participants with frequent night snacking may commonly engage in other high-risk dietary behaviors. The results support that participants with two or more high-risk dietary behaviors had a higher risk of developing CMM. Identifying individuals with high-risk dietary behaviors, such as frequent night snacking, and intervening with a focus on modulating their dietary behavior patterns may thus benefit the achievement of a healthy cardiometabolic status (31). Future research should focus on the underlying connectivity of several high-risk dietary behavior clusters to help develop individualized dietary behavior management strategies for CMM patients.

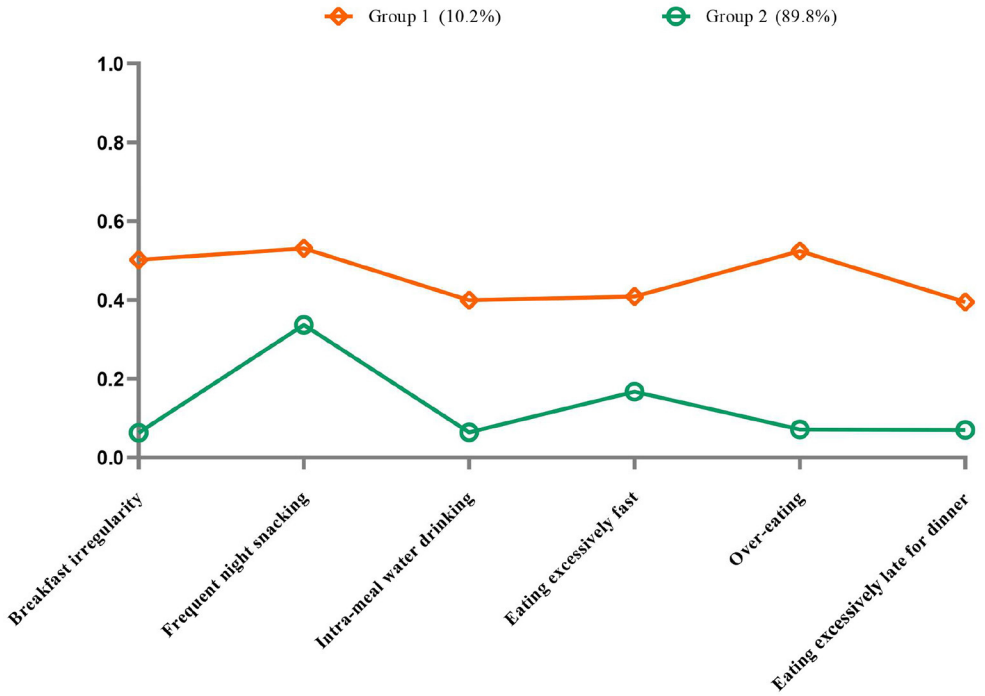
In addition, we examined the taste preferences of individuals to investigate their relationship with CMM. Chongqing locals are characterized by an overall preference for spicy food due to their region's topography and climatic factors, which is consistent with our findings. According to our data analysis, Chongqing inhabitants' top four dietary taste preferences were spicy, salty, sweet, and greasy, in that order. A higher frequency and intensity of spicy food intake (47) as well as an oil- and salt-rich diet (48) have been reported to be associated with unfavorable cardiovascular disease risk profiles in middle-aged and older adults, which is generally consistent with our findings. However, we investigated these relationships further in gender-segregated subgroups. In particular, taste preferences for smoky, hot, and spicy foods in men were more highly associated with CMM risk. This difference could be attributed to the higher proportion of men reporting taste preferences among the participants in this study. More research is needed to establish the gender variations in taste preferences associations with CMM and to elucidate the underlying mechanisms.

This study had several limitations that should be considered when interpreting the results. First, the temporal bias in cross-sectional studies prevents cause-and-effect linkages from being established, and future longitudinal research is needed to overcome this. Second, CMM was measured by self-reported chronic conditions, and hence may have been under- or over-reported in this study. Furthermore, memory bias may affect self-reported lifestyle data, and the dichotomous classification of lifestyles may lead to unintentional misclassification. For example, we did not consider the differential effects between under-intake and excessive food intake on CMM. Third, the factors in this study could not be all-inclusive because they are based on real-world data. All pertinent factors could not



Note: Group 1 refers to frequent night snacking and breakfast irregularity dominated high-risk dietary behavior, group 2 refers to frequent night snacking and breakfast irregularity dominated high-risk dietary behavior, group 3 refers to eating excessively fast and frequent night snacking dominated high-risk dietary behavior **(Male)**.

FIGURE 4
Item probabilities in the three common high-risk dietary behavior patterns among male cardiometabolic multimorbidity patients.



Note: Group 1 refers to frequent night snacking and over-eating dominated high-risk dietary behavior, group 2 refers to frequent night snacking and eating excessively fast dominated high-risk dietary behavior **(Female)**.

FIGURE 5
Item probabilities in the two common high-risk dietary behavior patterns among female cardiometabolic multimorbidity patients.

be considered, including participant sleep quality, BMI, and more specific dietary behavior data. Furthermore, due to participants' concerns about information privacy and study time constraints, socio-demographic information; such as economic income and educational attainment; were not collected in this study. Finally, we urge careful consideration of the results because the study's data were gathered from a single hospital health management center, which may not be representative of the wider population or other subpopulations. Further research is needed to confirm our findings, explicitly expanding the study coverage to include more comprehensive lifestyle factors and detailed information on dietary behavior. Our findings may help develop CMM management strategies and allocate healthcare services. The findings could be helpful for other low- and middle-income countries characterized by similar topography and climate.

Conclusion

The accumulation of poor lifestyle factors increases the risk of CMM in middle-aged and older patients in Chongqing, Southwest China. Although the associations differed by gender, unhealthy dietary behaviors (such as over-eating and intra-meal water drinking) and taste preferences (such as smoky, hot, and spicy) were linked to an increased risk of CMM. The necessity for a change in the health care system to assess and modulate multiple behaviors for multiple diseases is further explained by the several common high-risk lifestyle patterns and dietary behavior patterns. Our results show that identifying people with certain high-risk lifestyle factors, such as high-risk physical activity, and managing them with a focus on their lifestyle patterns may assist patients with CMM to achieve better health outcomes. Further research is required to elucidate potential underlying mechanisms and establish causation between these lifestyle factors and CMM, particularly prospective and interventional investigations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2020426). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ: conceptualization, methodology, and writing—original draft. ZZ: methodology, data analytics, and visualization. TW: writing—review and editing. RS: data collection and curation. KZ, HH, and HZ: data curation and writing—original draft. WL: conceptualization, funding acquisition, and project administration. All authors contributed to the article and approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1118628/full#supplementary-material

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Life-course fertility and multimorbidity among middle-aged and elderly women in China: Evidence from China health and retirement longitudinal study

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Background: Multimorbidity has become an important public health problem in China, especially among middle-aged and elderly women. Few studies have been reported on the association between multimorbidity and female fertility, which is an important stage in the life course. This study aimed to explore the association between multimorbidity and fertility history among middle-aged and elderly women in China.

Methods: Data from 10,182 middle-aged and elderly female participants in the China Health and Retirement Longitudinal Study (CHARLS) in 2018 were used in this study. Multimorbidity was defined as the presence of at least two or more chronic conditions. Logistic regression analysis, negative binomial regression analysis, and restrictive cubic splines (RCSs) were used to analyze the relationship between female fertility history and multimorbidity or the number of chronic conditions. Multivariable linear regression was used to analyze the relationship between female fertility history and multimorbidity pattern factor scores.

Results: The results of this study showed that high parity and early childbearing were significantly associated with an increased risk of multimorbidity and an increased number of chronic conditions among middle-aged and elderly women in China. Late childbearing was significantly associated with reduced risk of multimorbidity and lessened diseases. Parity and age of first childbirth were significantly correlated with the odds of multimorbidity. The association between fertility history and multimorbidity was found to be influenced by age and urban–rural dual structure. Women with high parity tend to have higher factor scores of cardiac-metabolic, visceral-arthritic, and respiratory-psychiatric patterns. Women with early childbearing tended to have higher factor scores of the visceral-arthritic pattern and those with late childbearing tended to have lower factor scores of the cardiac-metabolic pattern.

Conclusion: Fertility history has a significant effect on multimorbidity in the middle and later lives of Chinese women. This study is of great importance for reducing

the prevalence of multimorbidity among Chinese women through their life course and promoting health during their middle and later lives.

KEYWORDS

multimorbidity, life course, women health, aging, fertility history

1. Introduction

Multimorbidity is defined as a simultaneous occurrence of two or more chronic diseases in one person at a certain time, including physical and mental health complications (1). In general, multimorbidity is one of the inevitable outcomes driven by the accumulation of critical events in a longitudinal life course according to life-course theories (2). Studies have consistently linked multimorbidity to lower quality of life (3), higher financial burdens (4, 5), greater psychological stress (6, 7), and higher mortality (8) compared to single diseases. Given the unprecedented aging of the population in China, multimorbidity is regarded as a prominent health problem among Chinese middle-aged and elderly adults, with a prevalence rate of nearly 50% (9, 10). How to effectively and accurately predict the rising prevalence of multimorbidity caused by the rapid aging process has become an important public health challenge in China.

Previous studies have shown sex inequalities in multimorbidity. Women tend to face a higher risk of multiple chronic diseases than men (11). In China, middle-aged and elderly women are more vulnerable to multimorbidity, and they suffer from an increased mental health risk due to their biological characteristics and socioeconomically disadvantageous situations (10, 12). However, the current focus on women's health is still limited to sexual and reproductive health, with no importance attached to their dilemma of facing additional sex-specific risk factors beyond the traditional risk factors of multimorbidity (13).

Female fertility is an important stage in women's life course, including indices such as parity and childbearing age. Some evidence from Western countries has suggested that women's childbearing history has a significant effect on mid-late life health. For instance, women with high parity and those with premature childbearing history are more likely to experience poorer health outcomes and higher mortality in their later life (14–16). On the contrary, late childbearing has been reported to have a significant association with better cognitive function (17). Due to the profound tradition of "family culture" in China, fertility history is particularly important to Chinese women's life course (18). The results of existing reports on the female fertility and health of Chinese women in their middle and later lives are similar to those in Western countries. Elderly women with high parity tend to suffer from activities of daily-living impairment and poorer self-rated health (19). Early age of first childbirth is associated with a higher risk of cardiovascular diseases (20). Women who had been able to have children after the age of 35 years are more likely to have a longer life (21).

The focus must be shifted from single diseases and childbearing events in specific periods to multimorbidity and complete fertility history in the life course to improve the health of women in their middle and later lives. At present, no related literature could be found on the association between fertility history and multimorbidity, not to mention when the subject is middle-aged and elderly women in China.

By using the data from China Health and Retirement Longitudinal Study (CHARLS) conducted in 2018, the study aimed to explore the relationship between life-course fertility and multimorbidity among middle-aged and elderly women in China. Subgroup analyses and tests for interaction were conducted to further evaluate whether the associations were modified by age and region. In addition, the effect of fertility on the multimorbidity pattern factor scores was investigated.

2. Materials and methods

2.1. Data

The data used in this study was from China Health and Retirement Longitudinal Study (CHARLS) conducted in 2018. CHARLS is a nationally representative longitudinal study of the older population of China, covering 28 provinces, 150 counties (districts), and 10,624 families. CHARLS employed stratified probability proportional to size random sampling principles to make sure the representativeness of samples. The baseline survey was conducted in 2011, followed up in 2013 (wave 2), 2015 (wave 3), and 2018 (wave 4).

CHARLS 2018 survey was conducted from February to September 2018 and released in 2020. Of the total 19,816 individuals who participated in the CHARLS 2018 survey, 255 were younger than 45 years, 11,880 were between 45 years and 64 years, and 7,681 were 65 years or older. After excluding male participants, 10,475 female participants remained. After further excluding the participants younger than 45 years of age, and those with missing chronic diseases and fertility history data, 10,228 participants remained. Subsequently, 46 participants without biological children were excluded. Therefore, 10,182 female respondents were identified for analysis. The selection process of participants in this study is shown in Supplementary Figure 1.

2.2. Identification of chronic conditions and multimorbidity

Each participant was asked if they had been diagnosed with any of the following 14 chronic conditions including hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke,

psychiatric disease, arthritis, dyslipidemia, liver disease, kidney disease, digestive disease, asthma, and memory-related disease. When participants have ever been diagnosed with two or more of the 14 aforementioned conditions, they were regarded as having multimorbidity.

2.3. Multimorbidity pattern factor score

Exploratory factor analysis was used to determine how chronic conditions tend to gather together to exhibit multimorbidity patterns among middle-aged and elderly women in China (22). Kaiser–Meyer–Olkin method and Bartlett test of sphericity were used to estimate the adequacy of the sample in factor analysis. Factors were extracted using the principal factor method based on tetrachoric correlation matrices. The number of factors was identified based on their interpretability, eigenvalue, and scree plot shape. Factor interpretation was facilitated with an oblique rotation (Oblimin) of factor-loading matrices. For determining the most appropriate multimorbidity patterns, chronic conditions with a factor loading above 0.20 were selected. Multimorbidity patterns were named according to common features of diseases in the patterns. Factor scores of each multimorbidity pattern were used to assess each participant's multimorbidity status more specifically. To obtain factor scores, the factor loading of each chronic disease was multiplied by 1 (presence of chronic diseases) or 0 (absence of chronic diseases), then each item was summed to calculate each participant's total score, and normalized to the mean value of 0 and standard deviation of 1 (23, 24).

2.4. Female fertility history

Several important variables representing fertility history were collected by interviewing participants in the CHARLS 2018 survey: parity, age of first childbirth, and age of last childbirth. Parity refers to the number of biological children of the respondents, including deceased children. It was divided into three groups: having one child, having two children, and having three or more children. The age of early childbearing was set at 21 years after considering the current fertility status of Chinese women (19). The age of first childbirth was categorized as 21 years or above and younger than 21 years. If a woman gave her first childbirth before the age of 21 years, she was considered as having a history of early childbearing. Similarly, taking into account the fact that the age of 35 years and older were recognized as expectant mothers of older ages in China, the age of last childbirth was categorized as less than 35 years and 35 years or above (21). Women who gave their last birth at the age of 35 years or older were defined as late childbearing.

2.5. Covariates

General demographic characteristics, lifestyle and health behaviors, early physical conditions, and childhood socioeconomic conditions were controlled in this study. General demographic included age, marital status, educational level, socioeconomic status, and place of residence. Taking 65 years old as the standard for the division of middle-aged and elderly people in China, the age groups were divided into middle-aged women aged 45–64 years and elderly women aged 65 years or above. Marital status was categorized as married and other marital statuses, such as single, widowed, divorced, and separated. Educational level was based on the highest educational level achieved and categorized as elementary education or below and secondary education or above. Socioeconomic status was reflected by annual per-capita household expenditure, and defined as four levels based on quartiles of annual per-capita household expenditure. Place of residence, instead of hukou, was used to judge whether participants were from an urban community or rural village because residence could better reflect the socioeconomic environment around the participants. Lifestyle and health behaviors included smoking, drinking, and physical activities. Participants were asked if they had ever smoked cigarettes or drank alcoholic beverages to determine whether they smoked or drank. Physical activities were collected by asking participants whether they regularly engaged in physical activities. Early physical conditions included the age of menarche and childhood health status, collected by asking female participants their age of first menstruated period and health status in childhood compared with peers. The age of menarche was categorized as aged 15 years or younger and aged over 15 years. Childhood health status was categorized as about average, healthier, and less healthy. Childhood socioeconomic conditions were judged by asking participants about their families' financial situation compared to average families in their community or village at that time.

2.6. Statistical analysis

The chi-square test was used to assess differences in sample characteristics between groups. A variance inflation factor (VIF) was used to assess multicollinearity among the covariates adjusted for in our analysis. VIF of covariates in our analysis were all <2, indicating that the assumption of reasonable independence among variables was met.

Multivariable logistic regression models and multivariable negative binomial regression models were used to analyze the relationship between female fertility history with multimorbidity and the number of chronic conditions, respectively. Multivariable negative binomial regression models were chosen instead of multivariable Poisson regression models because the number of chronic conditions was overdispersed (the variance was greater than the mean in the outcome variable). Models were adjusted for age, marital status, educational level, socioeconomic status, place of residence, smoking, drinking, physical activities, age of menarche, childhood health status, and childhood socioeconomic conditions. The results of the logistic regression analyses were presented as odds ratio (OR) and 95% confidence interval (95% CI), and the results of the negative binomial regression analyses were presented as an incidence rate ratio (IRR) and 95% CI. Due to China's obvious age stratification and special urban–rural dual structure, subgroup analyses were performed and stratified by age and residence to determine whether the association between female fertility history and multimorbidity differed among subgroups. A likelihood ratio

test (LRT) was conducted to analyze the interactions by comparing models with interaction terms to those without interaction terms. A cutoff of $P < 0.05$ was used for significance.

Multivariable linear regression models were used to analyze the relationship between female fertility history and multimorbidity pattern factor scores. Models were adjusted for age, marital status, educational level, socioeconomic status, place of residence, smoking, drinking, physical activities, age of menarche, childhood health status, and childhood socioeconomic conditions. The results of the linear regression analyses were presented as β coefficients and a 95% confidence interval (95% CI).

Restrictive cubic splines (RCSs) were used to assess linear or nonlinear associations among female fertility (parity and age of first childbirth), multimorbidity, and factor scores. To better fit models, the node number of RCS is set to four. In the RCS model assessing the association between parity and multimorbidity, having one child was used as a reference. In the RCS model assessing the association between age of first childbirth and multimorbidity, 21 years was used as a reference. RSC models were adjusted for age, marital status, educational level, socioeconomic status, place of residence, smoking, drinking, physical activities, age of menarche, childhood health status, and childhood socioeconomic conditions.

Two sensitivity analyses were performed. First, to identify the effect of missing data on the robustness of the results, a random forest-based multiple imputation method by chained equations (MICE) was performed to fill in missing data and then re-analyze. On the assumption of missing data at random (MAR), the missing data were imputed for covariates with 20 iterations, and five datasets were generated (25). In addition, to evaluate the effect of rural and urban migration, hukou was used as a variable instead of residence to conduct a re-analysis.

Analyses in the study were conducted using SPSS version 26.0 and R version 4.2.1. LRT was performed using the "epicalc" package and RCS was performed using the "rms" package.

3. Results

3.1. Descriptive characteristics of the study participants

The descriptive characteristics of the study participants are shown in Table 1. Of the 10,182 women who participated included in the study, 5,965 (58.6%) had multimorbidity and 4217 (41.4%) were not. Statistical differences were observed in parity, age of first childbirth, age of last childbirth, age, marital status, educational level, hukou, smoking, and age of menarche between women with multimorbidity and those with no multimorbidity ($P < 0.05$).

3.2. Prevalence of multimorbidity and the distribution of chronic diseases

The prevalence of multimorbidity and the distribution of chronic diseases among participants are shown in Figure 1. Of the 14 chronic conditions, the most prevalent chronic conditions were arthritis (44.2%), followed by hypertension (38.8%), and

TABLE 1 Descriptive characteristics of participants in this study.

Variables	Total (N = 10182)	Multimorbidity		P
		No (N = 4217)	Yes (N = 5965)	
Parity, *n* (%)				<0.001
1	1688 (16.6)	870 (20.6)	818 (13.7)	
2	3779 (37.1)	1720 (40.8)	2059 (34.5)	
≥3	4715 (46.3)	1627 (38.6)	3088 (51.8)	
Age of first childbirth, *n* (%)				<0.001
≥21 years old	7892 (77.5)	3399 (80.6)	4493 (75.3)	
<21 years old	2290 (22.5)	818 (19.4)	1472 (24.7)	
Age of last childbirth, *n* (%)				<0.001
<35 years old	8726 (85.7)	3675 (87.1)	5051 (84.7)	
≥35 years old	1456 (14.3)	542 (12.9)	914 (15.3)	
Age, *n* (%)				<0.001
45-64 years old	6275 (61.6)	3101 (73.5)	3174 (53.2)	
≥65 years old	3907 (38.4)	1116 (26.5)	2791 (46.8)	
Marital status, *n* (%)				<0.001
Others	2615 (25.7)	936 (22.2)	1679 (28.1)	
Married	7567 (74.3)	3281 (77.8)	4286 (71.9)	
Educational level, *n* (%)				0.040
Elementary education or below	7890 (77.5)	3225 (76.5)	4665 (78.2)	
Secondary education or above	2292 (22.5)	992 (23.5)	1300 (21.8)	
Socioeconomic status, *n* (%)				0.119
Quartile 1	2105 (25.0)	889 (25.6)	1216 (24.6)	
Quartile 2	2102 (25.0)	900 (25.9)	1202 (24.3)	
Quartile 3	2099 (25.0)	831 (23.9)	1268 (25.7)	
Quartile 4	2104 (25.0)	852 (24.5)	1252 (25.4)	
Place of residence, *n* (%)				0.282
Urban community	4121 (40.5)	1733 (42.1)	2388 (40.0)	
Rural village	6061 (59.5)	2194 (58.9)	3577 (60.0)	
Hukou, *n* (%)				<0.001
Agricultural hukou	7409 (72.8)	2977 (70.6)	4432 (74.3)	
Non-agricultural hukou	2773 (27.2)	1240 (29.4)	1533 (25.7)	
Smoking, *n* (%)				<0.001
No	9374 (92.2)	3980 (94.6)	5394 (90.5)	
Yes	794 (7.8)	227 (5.4)	567 (9.5)	
Drinking, *n* (%)				0.195
No	7842 (77.1)	3273 (77.7)	4569 (76.6)	

(Continued)

TABLE 1 (Continued)

Variables	Total (N = 10182)	Multimorbidity		P
		No (N = 4217)	Yes (N = 5965)	
Yes	2334 (22.9)	939 (23.4)	1395 (23.4)	
Physical activities, *n* (%)				0.673
No	1003 (9.9)	422 (10.0)	581 (9.8)	
Yes	9132 (90.1)	3779 (90.0)	5353 (90.2)	
Age of menarche, *n* (%)				0.001
≤15 years old	3587 (42.1)	1523 (44.2)	2064 (40.7)	
>15 years old	4929 (57.9)	1919 (55.8)	3010 (59.3)	
Childhood health status, *n* (%)				0.672
About average	4550 (51.4)	1891 (51.7)	2659 (51.1)	
Healthier	3169 (35.8)	1309 (35.8)	1860 (35.8)	
Less healthy	1137 (12.8)	456 (12.5)	681 (13.1)	
Childhood socioeconomic conditions, *n* (%)				0.715
About average	4522 (51.0)	1860 (50.8)	2662 (51.1)	
Better	869 (9.8)	370 (10.1)	499 (9.6)	
Worse	3473 (39.2)	1429 (39.1)	2044 (39.3)	

digestive disease (33.1%). Participants had an average of 2.75 chronic conditions; 19.5% of the participants had none of the chronic conditions; 22.0% had only one condition; 20.4% had two conditions, and as high as 38.1% had three or more conditions.

3.3. Association of female fertility history with multimorbidity and number of chronic conditions

The results of multivariable logistic regression and multivariable negative binomial regression on the association of female fertility history with multimorbidity and the number of chronic conditions are shown in Table 2. In the analysis of the association between female fertility history and multimorbidity after adjusting for covariates, the results showed that women with higher parity, including with two children (adjusted OR = 1.221, 95% CI: 1.045–1.427) and with three or more children (adjusted OR = 1.447, 95% CI: 1.215–1.723), were significantly associated with a higher risk of multimorbidity than women with only one child. In brief, women with higher parity were more likely to have multimorbidity. Age of first childbirth < 21 years (adjusted OR = 1.161, 95%CI: 1.015–1.328) was significantly associated with a higher risk of multimorbidity than the age of first childbirth ≥ 21 years. On the contrary, the age of last childbirth ≥ 35 years (adjusted OR = 0.805, 95% CI: 0.681–0.950) was significantly associated with a lower risk of multimorbidity than the age of last childbirth < 35 years.

In the analysis of the association between female fertility history and the number of chronic conditions, the results were consistent with those observed in multivariable logistic regression after adjusting for covariates. Women with two children (adjusted IRR = 1.144, 95% CI: 1.041–1.258) and with three or more children (adjusted IRR = 1.273, 95% CI: 1.147–1.412) were significantly associated with a greater number of chronic conditions than women with only one child. Age of first childbirth <21 years (adjusted IRR = 1.083, 95% CI: 1.005–1.167) was significantly associated with more chronic diseases than the age of first childbirth ≥21 years. Age of last childbirth ≥35 years (adjusted IRR = 0.909, 95% CI: 0.828–0.999) was observed significantly associated with fewer coexisting chronic diseases than the age of last childbirth <35 years. The results of subgroup analyses stratified by age and place of residence are shown in Figures 2–4. The association between fertility history and multimorbidity differed between age groups and urban–rural dual structure. No evidence of interaction was found among female fertility, age, and place of residence.

The results of RCSs on the association among parity, age of first childbirth, and multimorbidity are shown in Figure 5. A significant nonlinear association was found between parity and odds of multimorbidity (P-overall association < 0.001 and P-non-linearity = 0.015). The odds of multimorbidity were found to increase with parity and peak when parity reached four or five. A significant nonlinear association was also observed between the age of first childbirth and odds of multimorbidity (P-overall association < 0.001 and P-non-linearity = 0.011). The odds of multimorbidity decreased with the age of first childbirth being before 26 years and increased with the age of first childbirth being after 27 years, reaching the lowest when the age of first childbirth was 26 or 27 years.

3.4. Association of female fertility history with multimorbidity patterns

The results of the exploratory factor analysis are shown in Table 3. Three multimorbidity patterns were identified: cardiac-metabolic pattern (dyslipidemia, hypertension, diabetes, stroke, and heart disease), visceral-arthritic pattern (digestive disease, arthritis, kidney disease, liver disease, and cancer), and respiratory-psychiatric pattern (memory-related disease, psychiatric disease, asthma, and chronic lung disease).

The results of multivariable linear regression on the relationship between female fertility history and multimorbidity pattern factor scores are shown in Table 4. Having two children (adjusted β = 0.113, 95%CI: 0.038–0.188) and having three or more children (adjusted β = 0.152, 95%CI: 0.069–0.235) were positively associated with the factor scores of cardiac-metabolic pattern compared with women with only one child. Age of last childbirth ≥35 years (adjusted β = −0.136, 95%CI: from −0.212 to −0.059) was negatively associated with the factor scores of cardiac-metabolic pattern compared with the age of last childbirth <35 years. Women with two children (adjusted β = 0.115, 95% CI: 0.038–0.191) and with three or more children (adjusted β = 0.256, 95% CI: 0.171–0.341) tend to have higher factor scores of the visceral-arthritic pattern. Age of first childbirth <21 years (adjusted β = 0.134, 95% CI: 0.071–0.197) was positively associated with the factor scores of visceral-arthritic pattern compared with

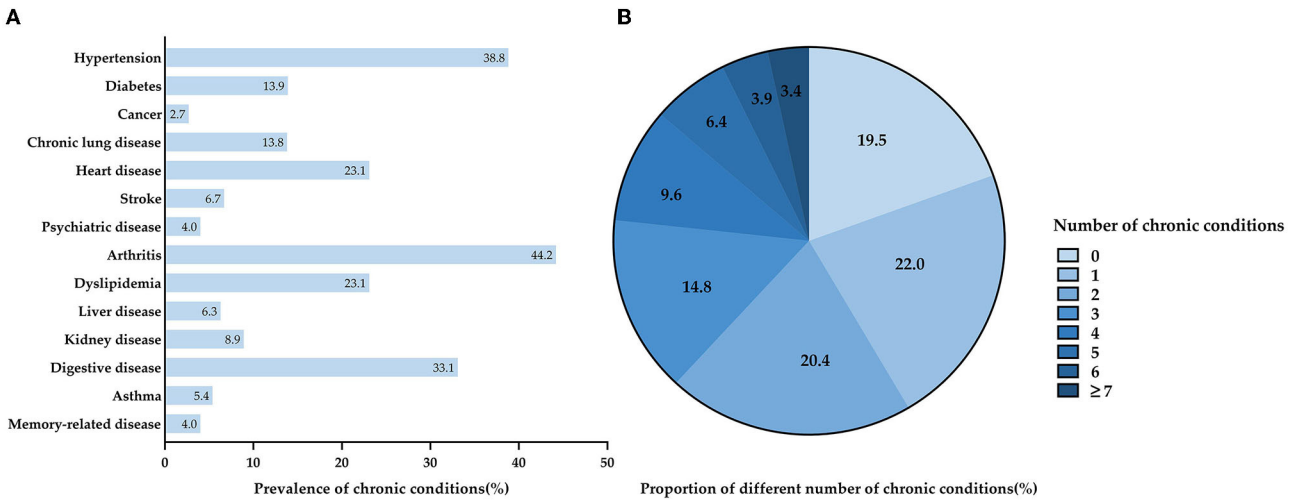

FIGURE 1
Prevalence of multimorbidity and the distribution of chronic diseases of participants. **(A)** Prevalence of chronic conditions among participants in this study. **(B)** The proportion of different numbers of chronic conditions among participants in this study.

TABLE 2 Association of female fertility history with multimorbidity and the number of chronic conditions.

Variables	Multimorbidity		Number of chronic conditions	
	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted IRR (95%CI)	Adjusted IRR (95%CI)
Parity				
1	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
2	**1.257 (1.120, 1.411)**	**1.221 (1.045, 1.427)**	**1.127 (1.049, 1.210)**	**1.144 (1.041, 1.258)**
≥3	**1.940 (1.720, 2.187)**	**1.447 (1.215, 1.723)**	**1.419 (1.320, 1.528)**	**1.273 (1.147, 1.412)**
Age of first childbirth				
≥21 years old	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
<21 years old	**1.143 (1.032, 1.265)**	**1.161 (1.015, 1.328)**	**1.082 (1.021, 1.146)**	**1.083 (1.005, 1.167)**
Age of last childbirth				
<35 years old	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
≥35 years old	1.008 (0.894, 1.138)	**0.805 (0.681, 0.950)**	0.982 (0.917, 1.053)	**0.909 (0.828, 0.999)**

Multivariable logistic regression models and multivariable negative binomial regression models were adjusted for age, marital status, educational level, socioeconomic status, place of residence, smoking, drinking, physical activities, age of menarche, childhood health status, and childhood socioeconomic conditions.

the age of first childbirth ≥21 years. For the respiratory-psychiatric pattern, women with three or more children (adjusted $\beta = 0.132$, 95% CI: 0.050–0.215) tend to have higher factor scores.

The results of RCSs on the association among parity, age of first childbirth, and factor scores are shown in Figure 6. Parity had a significant non-linear association with the factor scores of the cardiac-metabolic pattern (P-overall association = 0.007 and P-non-linearity = 0.021) and visceral-arthritic pattern (P-overall association < 0.001 and P-non-linearity < 0.001) and a significant linear association with factor scores of the respiratory-psychiatric pattern (P-overall association < 0.001 and P-non-linearity = 0.629). Age of first childbirth had a significant linear association with the factor scores of the cardiac-metabolic pattern (P-overall association = 0.048 and P-non-linearity = 0.203) and a significant non-linear association with the factor scores of the visceral-arthritic pattern (P-overall association < 0.001 and P-non-linearity = 0.009) and respiratory-psychiatric pattern (P-overall association = 0.002 and P-non-linearity = 0.010). In general, parity was positively correlated with the factor scores of the three patterns, whereas the age of first childbirth was negatively correlated with the factor scores of the three patterns.

3.5. Sensitivity analysis

The results of the sensitivity analysis are shown in Supplementary Tables 1, 2. MICE was used to impute missing data, and hukou was used as a variable instead of residence. The results of re-analyses were consistent with the main findings of the study, and they showed the same trend.

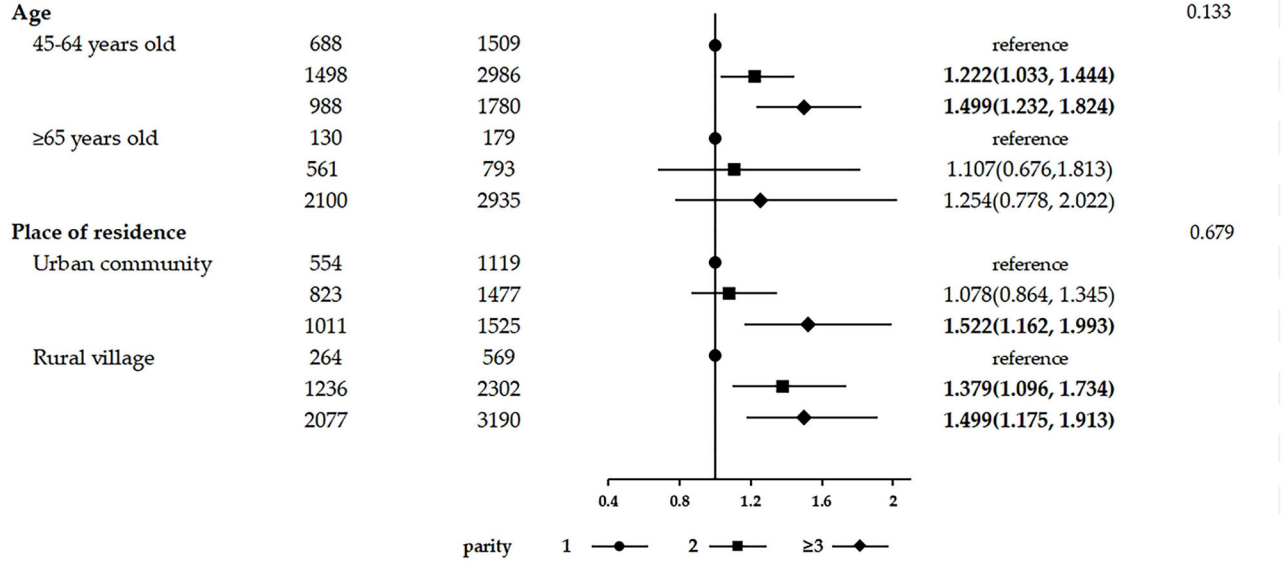

FIGURE 2
Subgroup analyses on the association between parity and multimorbidity stratified by age and place of residence.

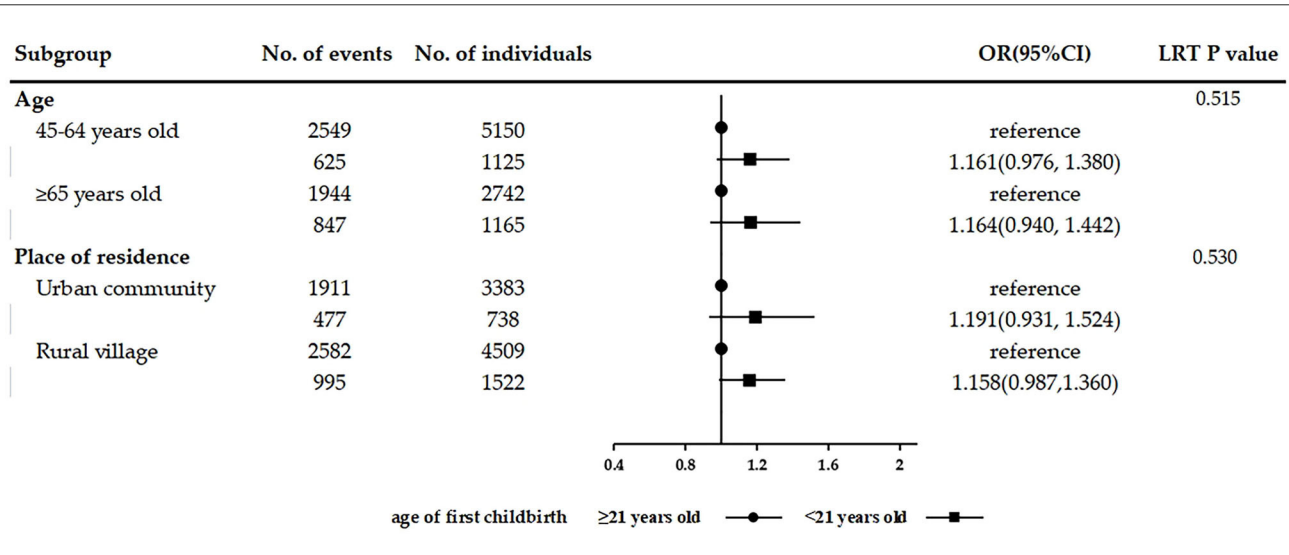

FIGURE 3
Subgroup analyses on the association between age of first childbirth and multimorbidity stratified by age and place of residence.

4. Discussion

To the best of the authors' knowledge, this study was the first to investigate the relationship between fertility history and multimorbidity from the perspective of life courses. It was also the first study focused on the sex-specific risk factors of multimorbidity in middle-aged and elderly women in China. The results showed that high parity and early childbearing were significantly associated with multimorbidity and an increased number of chronic conditions. Late childbearing was a significant protective factor for multimorbidity and the number of chronic conditions. The association between fertility history and multimorbidity was influenced by age and urban–rural dual structure. Significant non-linear associations between parity and odds of multimorbidity and between the age of first childbirth and odds of multimorbidity were observed. Moreover, women with higher parity tended to have higher factor scores of cardiac-metabolic, visceral-arthritic, and respiratory-psychiatric patterns. Early childbearing was positively associated with the factor scores of the visceral-arthritic pattern. Late childbearing was negatively associated with the factor scores of the cardiac-metabolic pattern.

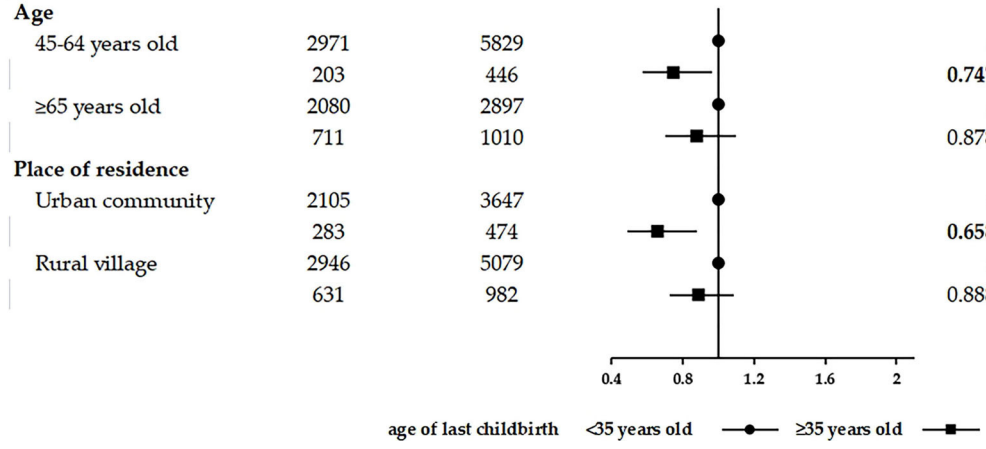

FIGURE 4
Subgroup analyses on the association between age of last childbirth and multimorbidity stratified by age and place of residence.

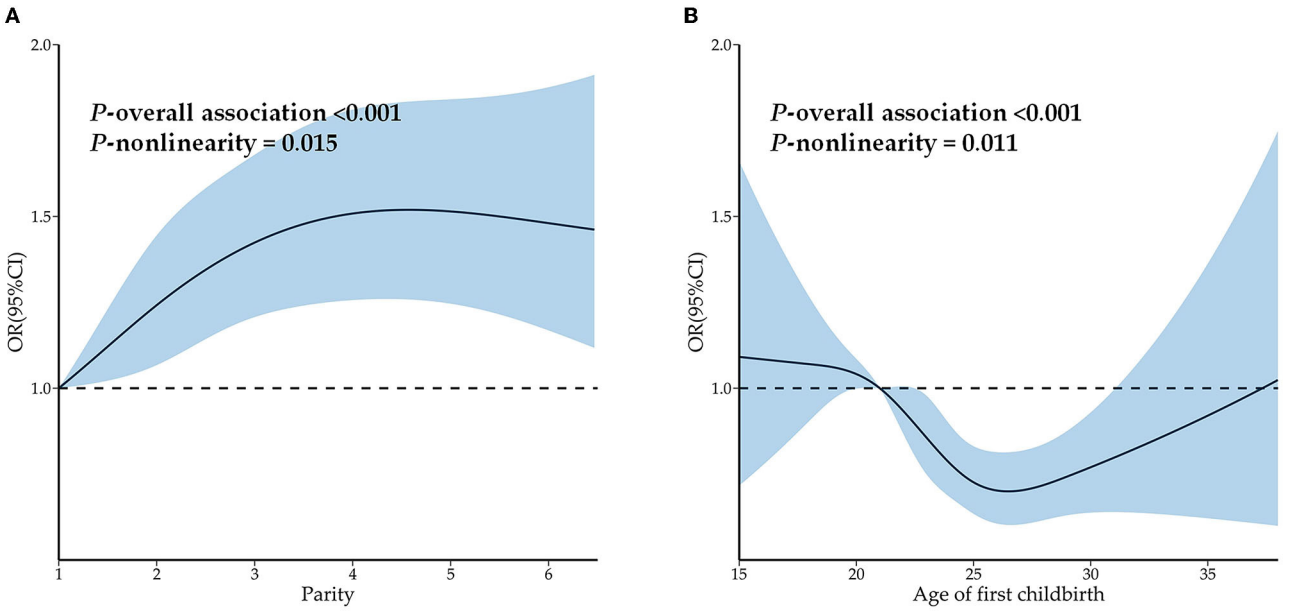

FIGURE 5
Restrictive cubic splines on the association among parity, age of first childbirth, and multimorbidity. **(A)** Restrictive cubic splines on the association between parity and multimorbidity. **(B)** Restrictive cubic splines on the association between age of first childbirth and multimorbidity.

With the acceleration of the aging process, middle-aged and elderly women in China are experiencing an unprecedented burden of multimorbidity, with a prevalence rate of 58.6% in this study. Similar to other studies on the association between life course and multimorbidity (26–28), this study proved that fertility is an important event in the life course of middle-aged and elderly women in China, and its effect on multimorbidity is a promising topic worth exploring. The mechanisms underlying the association between fertility and multimorbidity may be complex including direct physiological and psychological damage and indirect socioeconomic effects (29).

Previous studies have provided evidence for the direct effects of female fertility on multimorbidity in middle and later lives, including the adverse physiological and psychological consequences. Women's abnormal life course fertility, such as high parity and early childbearing, was found to lead to undernutrition (30), frequent immune suppression (31), and metabolic disturbance (32, 33). In addition, fertility events could have a negative effect on women's mental health (34, 35). Accumulated physiological and psychological stress could lead to an increased risk of multimorbidity and an increased number of chronic diseases (36, 37). No consensus was observed on the relationship between late

childbearing and health in middle and later lives (14, 21, 38). However, late childbearing in this study was found to reduce the risk of multimorbidity. This could be explained by increased exposure to endogenous estrogen as a result of a prolonged reproductive period stimulating the women's biological system positively (21). Increased endogenous estrogen was found to reduce the risk of multiple diseases such as cardiovascular diseases (39) and dementia (40). Another mechanism that underlies the relationship between fertility and multimorbidity may be socioeconomic inequalities in Chinese society during female childbearing progress (41, 42). Giving first childbirth at an early age means that young women have to play the role of a mother before they are physically and mentally mature. The lack of economic independence and the inability of Chinese society to timely provide these young mothers with financial aid and psychological counseling results in a huge cost for these women to familiarize themselves with the new roles. Families with many children force women to allocate social and health resources to their husbands or children, easily leading to resource imbalance between families and individuals (43).

TABLE 3 Factor loadings of chronic conditions for multimorbidity patterns.

Chronic conditions	Factor		
	Cardiac-Metabolic Pattern	Visceral-Arthritic Pattern	Respiratory-Psychiatric Pattern
Dyslipidemia	0.661	0.174	−0.095
Hypertension	0.628	0.016	0.057
Diabetes	0.626	0.094	−0.114
Stroke	0.434	−0.219	0.327
Heart disease	0.416	0.289	0.169
Digestive disease	−0.013	0.638	−0.052
Arthritis	0.069	0.566	−0.060
Kidney disease	0.166	0.456	−0.027
Liver disease	0.052	0.454	−0.025
Cancer	0.079	0.211	−0.156
Memory-related disease	0.180	−0.240	0.648
Psychiatric disease	0.020	−0.114	0.588
Asthma	−0.168	0.267	0.555
Chronic lung disease	−0.149	0.415	0.470

The multimorbidity patterns of middle-aged and elderly women in China were identified as the cardiac-metabolic pattern, visceral–arthritic pattern, and respiratory-psychiatric pattern. Women with high parity tended to have higher factor scores of the cardiac-metabolic pattern whereas those with late childbearing tended to have lower factor scores of the cardiac-metabolic pattern. Previous studies have found similar results, that is, high parity was associated with diabetes (44), heart disease (45), and stroke (46). Giving birth at a later age was associated with lower vascular risk (47). High parity and early childbearing were positively associated with the factor scores of visceral-arthritic pattern, consistent with previous findings. High parity and early childbearing increased the risk of breast cancer (48), liver disease (49), and arthritis (50). High parity was also associated with higher factor scores of respiratory-psychiatric pattern diseases, such as asthma (51) and depression (52).

In the context of global rapid population growth, the Chinese government introduced the "late, long, few" policy in the early 1970s and an even stricter one-child policy in 1979 (53). Although the one-child policy ended in 2016, the majority of female participants in CHARLS were subjected to it during their childbearing years, which had a significant effect on Chinese women's reproductive behaviors and subsequent health outcomes in their middle and later lives. Subgroup analyses showed that the association between fertility history and multimorbidity differed between age and place of residence groups. High parity and late

TABLE 4 Association between female fertility history and factor scores of multimorbidity patterns.

Variables	Cardiac-Metabolic Pattern	Visceral-Arthritic Pattern	Respiratory-Psychiatric Pattern
	β (95%CI)	β (95%CI)	β (95%CI)
Parity			
1	Reference	Reference	Reference
2	**0.113 (0.038, 0.188)**	**0.115 (0.038, 0.191)**	0.037 (−0.037, 0.111)
≥3	**0.152 (0.069, 0.235)**	**0.256 (0.171, 0.341)**	**0.132 (0.050, 0.215)**
Age of first childbirth			
≥21 years old	Reference	Reference	Reference
<21 years old	0.020 (−0.041, 0.082)	**0.134 (0.071, 0.197)**	0.059 (−0.003, 0.120)
Age of last childbirth			
<35 years old	Reference	Reference	Reference
≥35 years old	**−0.136 (−0.212, −0.059)**	−0.065 (−0.143, 0.013)	0.052 (−0.024, 0.128)

Multivariable linear regression models were adjusted for age, marital status, educational level, socioeconomic status, place of residence, smoking, drinking, physical activities, age of menarche, childhood health status, and childhood socioeconomic conditions.

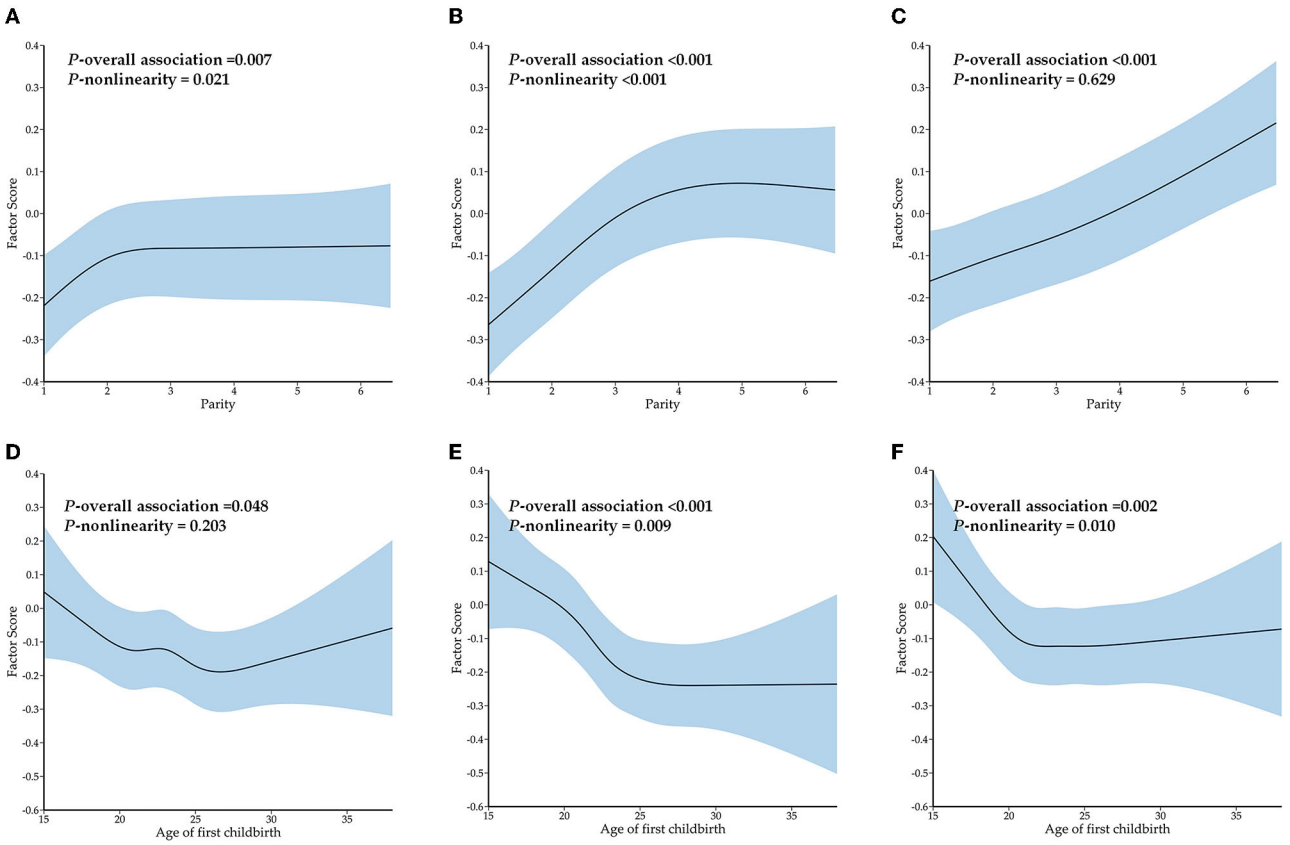

FIGURE 6
The restrictive cubic splines on the association among parity, age of first childbirth, and factor scores of multimorbidity patterns. **(A)** Restrictive cubic splines on the association between parity and factor scores of the cardiac-metabolic pattern. **(B)** Restrictive cubic splines on the association between parity and factor scores of the visceral-arthritic pattern. **(C)** Restrictive cubic splines on the association between parity and factor scores of the respiratory-psychiatric pattern. **(D)** Restrictive cubic splines on the association between age of first childbirth and factor scores of the cardiac-metabolic pattern. **(E)** Restrictive cubic splines on the association between age of first childbirth and factor scores of the visceral-arthritic pattern. **(F)** Restrictive cubic splines on the association between age of first childbirth and factor scores of the respiratory-psychiatric pattern.

childbearing had a significant effect on multimorbidity in women aged 45–64 years, but not in those aged 65 years or above. This could be largely explained by aging, the strongest driver of multimorbidity. It concealed the association between fertility history and multimorbidity in elderly women. However, different childbearing policy contexts also influenced this association (54). Women aged 45–64 years were affected by one-child quotas during their child-bearing years while those aged 65 years or above had children before introducing the strict one-child policy. Under the one-child policy, women with higher parity were subjected to more pressure which adversely affects their health, while those with late childbearing could enjoy more preferential treatment to improve their health.

The dual structure of urban and rural areas in China leads to differences in economic development and fertility concepts, as well as obvious differences in the effect of these fertility restriction policies. Rural women having two or more children faced a higher risk of multimorbidity than those having only one child. However, urban women showed an increase in their risk of multimorbidity when having three or more children. Women in rural areas are not able to afford the penalties for having above-quota births, and a one-time fine could be a considerable portion of their income (55). Under the fertility restriction policy, rural women could not obtain economic support from the government, so the cost of having two children is difficult to bear. In addition, the relatively low level of medical treatment in rural areas and the backward concept of fertility lead to individuals' lower socioeconomic status, resulting in the greater effect of high parity on the multimorbidity of rural women in their middle and later years (56). Late childbearing showed a significant protective effect only among urban women. This finding may be largely explained by the fact that when urban women give birth after the age of 35 years, it is often the result of a shift in fertility decisions with higher education levels (57). Urban women in this age group enjoy better medical conditions and less labor pressure. However, rural women's late childbearing is often due to the traditional idea of "more kids, more blessings" and "preference for sons over daughters." Rural women also suffer from malnutrition and poor reproductive healthcare, and they often perform heavy farm work to supplement family income, thus weakening the protective effect of late childbearing on the middle and later years of these women.

The results of this study are of great importance for formulating effective public health policies and programs from multiple perspectives, reducing the prevalence of multimorbidity, and

improving the health of middle-aged and elderly women in China. The entire society should pay attention to women's reproductive health; strengthen the popularization of women's reproductive knowledge; change the wrong conception of fertility, such as "more kids, more blessings" and encourage women to give birth at the most appropriate age and limit excessive parity. This study showed that women who give their first childbirth at the age of 26–27 years could reduce the risk of multimorbidity in their middle and later lives. At the same time, economic support, medical assistance, and psychological counseling should be provided to women of childbearing age, especially those with a history of high parity and early childbearing. The government should trace the cumulative effect of fertility history on multimorbidity among middle-aged and elderly women, reduce their greater financial burden of coping with multimorbidity, and provide better medical services to improve the poorer clinical outcomes associated with multimorbidity. Due to the imbalance between urban and rural development, rural women should consider the subsequent greater pressure of multimorbidity. The government should redistribute health resources and increase investment in rural medical services.

This study has some limitations, so the interpretation of the results is reserved to a certain extent. First, cross-sectional data were used and not longitudinal data, leading to limitations in demonstrating causal associations between fertility history and multimorbidity. Second, data on the life course was collected mainly by questioning the participants, inevitably leading to recall bias. Finally, other life-course events, such as adverse childhood experience, were not included in this study, which could affect the strength of interpretation of the association between fertility history and multimorbidity.

5. Conclusion

In this study, the association between life course fertility history and multimorbidity among middle-aged and elderly women in China was evaluated. High parity and early childbearing were significantly associated with an increased risk of multimorbidity and an increased number of chronic conditions. Late childbearing was significantly associated with a lower risk of multimorbidity. Age and place of residence had a significant influence on the association between female fertility and multimorbidity. Fertility history had a significant effect on the factor scores of multimorbidity patterns. This study provided data support for exploring the sex-specific risk factors for multimorbidity and assessing the effect of life course on the prevalence of multimorbidity among middle-aged and elderly women in China. Moreover, some suggestions for reducing their burden of multimorbidity were provided.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

MC, JG, and YL contributed to the study design, formal analysis, interpretation, and drafted the manuscript. JX, YH, LY, XX, LZ, JZ, and ZZ performed a formal analysis. HL, SL, and SW contributed to the design of this study, the interpretation of data, and the critical revision of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1090549/full#supplementary-material

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Association between multimorbidity and memory-related diseases among middle-aged and older adults: Evidence from the China Health and Retirement Longitudinal Study

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Objectives: This study aimed to examine the cross-sectional and longitudinal association between multimorbidity and memory-related diseases (MDs) among Chinese middle-aged and older adults.

Methods: This study included 8,338 subjects who participated in the China Health and Retirement Longitudinal Study (CHARLS). Logistic regression and Cox proportional hazards regression models were used to explore the association and effect of multimorbidity on MDs.

Results: The overall prevalence of MDs was 2.52%, and the mean multimorbidity number was 1.87. In a cross-sectional analysis, compared with the no multimorbidity group, groups of multimorbidity with four or more non-communicable diseases (NCDs) were more likely to have MDs (OR: 6.49, 95%CI: 4.35–9.68). Within 2.7 years of follow-up, 82 cases of MDs (1.12%) were reported, and participants with multimorbidity were more likely to have new-onset MDs than participants without multimorbidity (HR: 2.93, 95%CI: 1.74–4.96).

Conclusion: Multimorbidity is associated with MDs among Chinese middle-aged and older adults. This relationship gradually strengthens with the severity of multimorbidity, which indicates that early prevention for people with multimorbidity may reduce the risk of MDs.

KEYWORDS

multimorbidity, dementia, memory-related diseases, non-communicable diseases, Chinese middle-aged and older adults

Introduction

Declining fertility and increasing longevity are the main drivers of population aging globally (1). According to the projection of the WHO, the number of people aged 65 years and above is expected to be 2 billion by 2050 (2). Due to population aging, the prevalence of dementia has increased dramatically from 1990 to 2016, especially after the age of 65 (3). According to the 2022 World Alzheimer Report, approximately 55 million people lived with dementia worldwide in 2019, and it is expected to reach 139 million by 2050, with the majority coming from low-income and middle-income countries (LMICs) (4). A nationwide

cross-sectional study reported that there were 15.07 million Chinese older adults (aged 60 years and over) suffering from dementia (5). The primary causes of dementia are MDs among older adults, including Alzheimer's disease (AD), brain atrophy, and Parkinson's disease. MDs are a multisystemic disease, for which effective treatments are still lacking (6, 7). In addition, dementia is the primary cause of disability and medical care needs among older adults (8, 9). Meanwhile, dementia carries a severe medical burden and economic costs. Specifically, in China, the annual treatment cost of treating patients with AD was 167.74 billion dollars in 2015, and by 2050, the treatment cost is expected to reach 1.8 trillion (10).

Non-communicable diseases (NCDs) are the leading causes of morbidity and mortality worldwide (11). With the increasing aging population, older adults are no longer suffering from only one NCD but two or more NCDs simultaneously, which is conventionally termed multimorbidity (12, 13). A recent study has reported that more than 50% of older adults have multimorbidity in high-income countries (13), and this figure is expected to reach 68% by 2035 (14). Considering the complex needs and high medical costs, multimorbidity poses a significant burden on the healthcare system and could seriously undermine financial protection and universal health coverage (15). Because people are getting older and more exposed to risk factors, the burden of multimorbidity is also rising rapidly in LMICs (16–18). In China, a related study reported that the prevalence of multimorbidity was 61.9% among middle-aged and older adults (age $\geq$ 45) in 2015 (16). Another study found that health expenditure was associated with an increased number of NCDs and that multimorbidity had a great adverse impact on patients' health outcome and healthcare system burden than individual NCDs (19).

Several NCDs, such as diabetes (20), hypertension (21), and cardiovascular diseases (22), have been identified as at-risk conditions for increased dementia incidence. However, older adults often suffer from multimorbidity, and evidence of multimorbidity effects on dementia is relatively scarce (23). Previously, some cross-sectional studies in high-income countries have found that older adults with dementia often concur with multimorbidity (24). As for the longitudinal association, a recent study reported that older adults with multimorbidity had a high risk of dementia (25). Another study also found that multimorbidity had a robust association with subsequent dementia, especially when multimorbidity occurred in middle age (6). There is, however, limited research evidence from LMICs, including China, which suffer from the greater medical and economic burden of dementia and multimorbidity. Accordingly, based on the China Health and Retirement Longitudinal Study (CHARLS), we would investigate whether multimorbidity has an association with MDs and preliminary explore the contribution of each NCD to MDs. In addition, we would also explore whether this association differed between different subgroups.

Methods

Study population

The study data were derived from CHARLS, an ongoing and nationally representative study conducted every 2 years focusing on community-dwelling adults aged $\geq$ 45 years in China. A detailed description of CHARLS has been previously reported elsewhere (26). In brief, CHARLS used a multi-stage stratified probability proportional sampling and uniformly trained investigators to collect high-quality data, including sociodemographic, lifestyle, and health-related information.

This study used the Harmonized CHARLS data, which were more accessible to researchers and facilitated international comparisons (26). The inclusion criteria were as follows: (1) participants in CHARLS 2015 and aged $\geq$ 45 years old; (2) those with information of 11 physical NCDs; and (3) those with information of the MDs status. Exclusion criteria were as follows: (1) participants aged $<$ 45 years in CHARLS 2015; (2) missing data on 11 physical NCDs and MDs status; (3) lack of information on gender, marital status, education level, residence, socioeconomic status, body mass index (BMI), smoking status, and drinking status; and (4) missing data on MDs diagnosed time. There were two analysis datasets included in this study. The first was a cross-sectional analysis with data from CHARLS 2015, in which a total of 21,097 participants were interviewed. The second dataset of the longitudinal study further excluded participants with MDs in CHARLS 2015 (n = 210) and no MDs status (n = 733) and diagnosed time (n = 103) in CHARLS 2018. A detailed inclusion flowchart is shown in Figure 1.

The CHARLS was approved by the Biomedical Ethics Review Committee of Peking University, and informed consent was obtained from all participants (approval number: IRB00001052–11,015).

NCDs and multimorbidity assessment

Similar to a previous study (16), we included 11 physical NCDs to measure multimorbidity, namely, hypertension, dyslipidemia, diabetes, heart disease, stroke, cancer, lung disease, digestive disease, liver disease, kidney disease, and arthritis. During the CHARLS, the status of NCDs was determined by self-report, which was collected by centrally trained staff using face-to-face interviews and structured questionnaires following a standard protocol. Multimorbidity was defined as the presence of two or more NCDs, and the number of NCDs indicated the severity of multimorbidity.

MDs and diagnosed time assessment

The outcome was MDs, which included Alzheimer's disease, atrophy, and Parkinson's disease. Those participants who reported yes were defined as having MDs, and the interviewer would then ask for the first diagnosis or known time. The MDs status was assessed by the question "Have you ever been diagnosed with memory-related diseases (like Alzheimer's disease, atrophy, and Parkinson's disease) by a doctor?". Participants who reported yes were considered to have MDs. The question would then be asked if the participants answered yes, "When was the condition (Alzheimer's disease, atrophy, or Parkinson's disease) first diagnosed or known

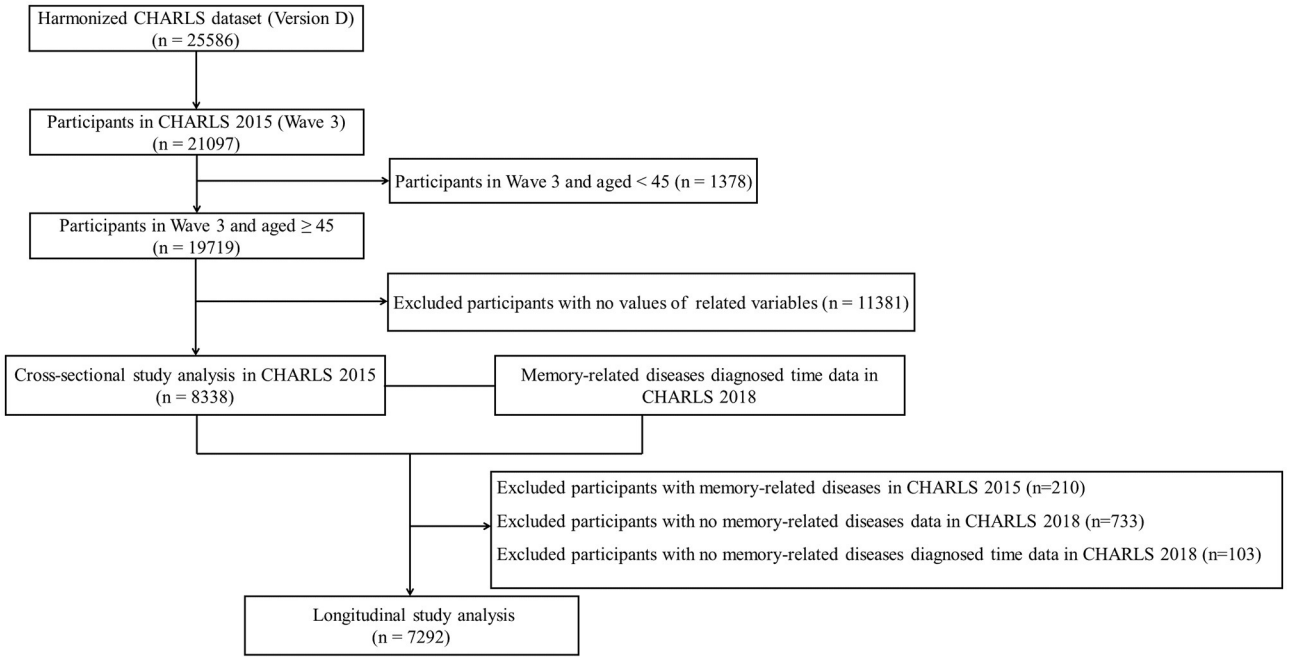

FIGURE 1
Flowchart of participants included in the study.

by yourself?" The answer was taken as the time of diagnosis of MD, and then to calculate the follow-up time.

Covariates

In CHARLS 2015, we added sociodemographic variables that included age, gender, marital status (married and others), education level, residence (urban and rural), and socioeconomic status. Health-related variables included BMI, smoking status, and drinking status. Based on the educational level characteristics of the Chinese older adults, we classified them as illiterate (no formal education illiterate), semi-literate (did not finish primary school but can read and Sishu), elementary school, middle school, high school and above (26). For socioeconomic status, we used annual per capita household consumption expenditure as a proxy (16, 27), and we divided participants into four groups based on the quartiles of annual per capita household consumption expenditure.

Statistical analysis

Continuous variables were presented as means ± standard deviation and percentage for categorical variables. Baseline characteristics were shown as the total population and the status of MDs. The *t*-test and the chi-squared test were used to compare the group difference. In the regression analysis, we not only referred to multimorbidity as a continuous variable but also as a categorical variable and divided it into four groups: non-multimorbidity (NM, participants with no or one NCDs), multimorbidity 1 (M1, participants with two NCDs), multimorbidity 2 (M2, participants with three NCDs), and multimorbidity 3 (M3, participants with four or more NCDs). In the cross-sectional analysis, we used logistic regression analysis to estimate the association between multimorbidity and MDs. In the longitudinal study, we calculated the follow-up time based on the date of the CHARLS 2015 interview, the time of initial diagnosis of MDs, or the date of the CHARLS 2018 interview. Then, we used the Cox proportional hazards model to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) to estimate the relationship between baseline multimorbidity status and incident risk of MDs. Three models were applied: Model 1, crude model; Model 2, adjusted for age, gender, marital status, education level, residence, and socioeconomic status; Model 3 additionally adjusted for BMI, smoking status, and drinking status. Stratified analysis was conducted on age, gender, residence, smoking status, drinking status, and socioeconomic status. The metrics of odds ratio (OR) and hazard ratio (HR) based on the regression models indicated that the percentage increase in the likelihood of MDs as the number of multimorbidity increased, whereas the HR value represented the increased risk of developing MDs with an increasing number of multimorbidity in subjects without baseline MDs. All statistical analyses were performed with SAS 9.4 and plotted with R version 4.1.3. A P-value of < 0.05 was considered statistically significant.

Results

Characteristics of study participants

Among these 8,338 middle-aged and older adults in the cross-sectional analysis, the mean age was 60.43 ± 8.94 and

TABLE 1 Baseline characteristics of participants in the cross-sectional analysis.

Variables	Total	Memory-related diseases	No memory-related diseases	P-value
N	8,338	210	8,128	
Multimorbidity count	1.87 ± 1.60	3.27 ± 1.92	1.83 ± 1.57	P <0.001*
Age, M(SD), years	60.43 ± 8.94	66.62 ± 8.72	60.27 ± 8.89	P <0.001*
Sex (male, %)	4,042 (48.48%)	103 (49.05%)	3,939 (48.46%)	0.87
Marital status, %				0.36
Married and partnered	7,466 (89.54%)	184 (87.62%)	7,282 (89.59%)	
Others	872 (10.46%)	26 (12.38%)	846 (10.41%)	
Education, %				0.43
Illiterate	1,982 (23.77%)	52 (24.76%)	1,930 (23.75%)	
Semi-illiterate	1,524 (18.28%)	44 (20.95%)	1,480 (18.21%)	
Elementary school	1,888 (22.64%)	39 (18.57%)	1,849 (22.75%)	
Middle school	1,898 (22.76%)	53 (2.79%)	1,845 (22.70%)	
High school and above	1,046 (12.54%)	22 (10.48%)	1,024 (12.60%)	
Residence (urban, %)	3,079 (36.93%)	89 (42.38%)	2,990 (36.79%)	0.10
BMI, M(SD), kg/m^2	24.72 ± 18.98	24.74 ± 14.64	24.72 ± 19.08	0.99
Smoking, %	3,729 (44.72%)	100 (52.38%)	3,629 (44.65%)	0.39
Drinking, %	2,985 (35.80%)	59 (28.10%)	2,926 (36.00%)	0.02*
Socioeconomic status				0.12
Quartile 1 (lowest)	2,084 (24.99%)	53 (25.24%)	2,031 (24.99%)	
Quartile 2	2,081 (24.96%)	39 (18.57%)	2,042 (25.12%)	
Quartile 3	2,087 (25.03%)	55 (26.19%)	2,032 (25.00%)	
Quartile 4 (highest)	2,086 (25.02%)	63 (30.00%)	2,023 (24.89%)	

48.48% were men. The average number of multimorbidity was 1.87 ± 1.60, and the prevalence of MDs was 2.52% (210/8338). Compared with the non-MDs group, those with MDs were more likely to be older (mean age, 66.62 vs. 60.27), less likely to drink (28.10 vs. 36.00%), and had a high number of NCDs (average multimorbidity number, 3.27 vs. 1.83) (all $P < 0.05$). The gender, marital status, education, residence, socioeconomic status, BMI, smoking status, and drinking status were not significantly different (Table 1). In longitudinal analysis, we presented the baseline characteristics of 7,292 participants without MDs in CHARLS 2015 (Supplementary Table S1). In addition to drink, similar results were found across MDs groups, and participants with MDs were older (mean age, 64.89 vs. 59.97) and had a higher number of NCDs (average multimorbidity number, 2.54 vs. 1.78) than participants without the incident of MDs. In addition, we compared the prevalence and incidence of MDs between the severity of multimorbidity groups, respectively. In the cross-sectional analysis, the prevalence of MDs increased from the NM group to the M3 group. Similarly, the incidence rate of MDs gradually increased with the severity of multimorbidity in longitudinal analysis (Figure 2).

Association of multimorbidity with MDs in the cross-sectional analysis

Overall, we found that multimorbidity and its severity were significantly associated with MDs (Table 2). Specifically, when multimorbidity was a continuous variable, we observed that the risk of MDs increased by 54% for each unit increase in the number of multimorbidities. After adjusting for sociodemographic and health-related factors, multimorbidity was also significantly associated with MDs [Model 2: OR, 1.50 (1.39–1.61); Model 3: OR, 1.49 (1.39–1.60)]. Similar results were also found when termed multimorbidity as a category variable. After adjusting for the confounding factors, participants in the M1 and M2 groups were more likely to have MDs than those in the NM group [M1 group: OR, 2.42 (1.55–3.76); M2 group: OR, 3.52 (2.23–5.56)]. It was noteworthy that, compared to the NM group, the M3 group had a 6.49-fold odds ratio of MDs [M3 group: OR, 6.49 (4.35–9.68)].

In the stratified analysis, multimorbidity was positively associated with MDs in all subgroups (Figure 3). Particularly, when compared with their counterparts, we found that the positive association was more prominent in the subgroup of individuals

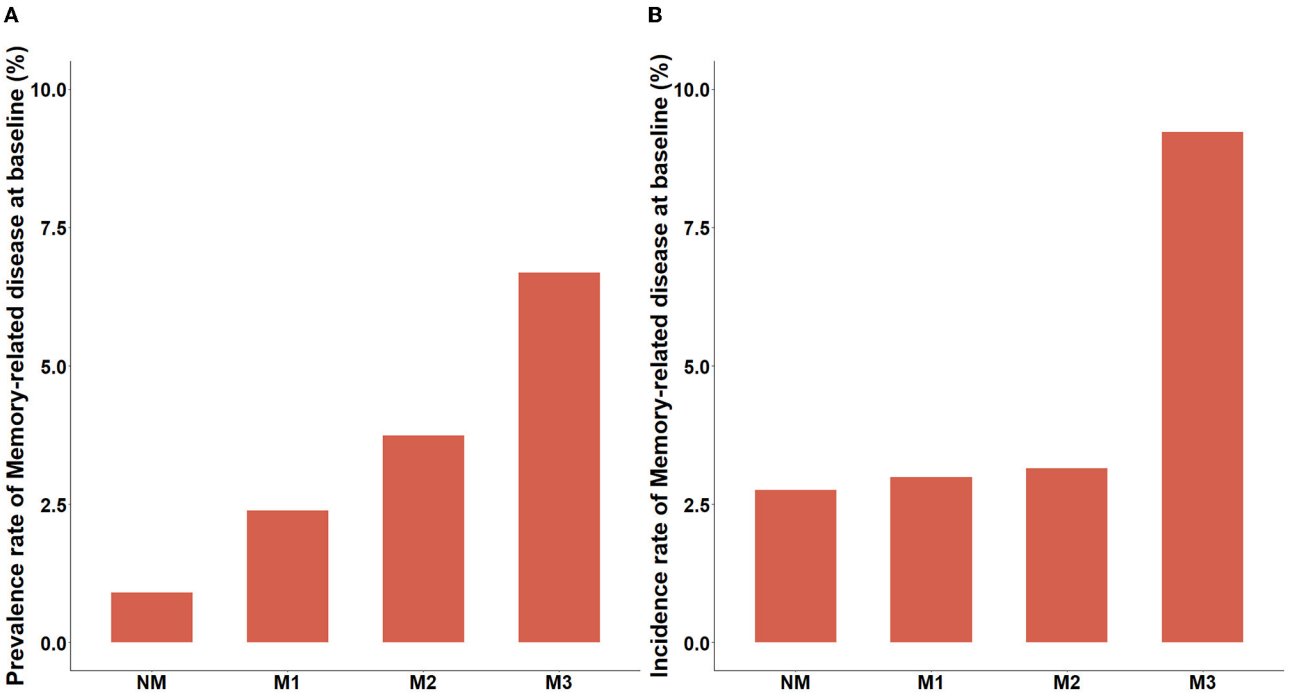

FIGURE 2
Epidemiologic feature of memory-related diseases according to the severity of multimorbidity. **(A)** Prevalence rate of memory-related diseases. **(B)** Incidence rate of memory-related diseases. NM, participants with no or one NCD; M1, participants with two NCDs; M2, participants with three NCDs; M3, participants with four or more NCDs.

TABLE 2 Association between multimorbidity and MDs in the cross-sectional analysis.

	Odds ratio (OR, 95%CI)		
	Model 1	Model 2	Model 3
Multimorbidity count	1.54 (1.44–1.65)	1.50 (1.39–1.61)	1.49 (1.39–1.60)
NM	ref	ref	ref
M1	2.70 (1.74–4.20)	2.44 (1.57–3.80)	2.42 (1.55–3.76)
M2	4.28 (2.73–6.72)	3.56 (2.26–5.62)	3.52 (2.23–5.56)
M3	7.89 (5.32–11.70)	6.57 (4.41–9.81)	6.49 (4.35–9.68)

MDs, memory-related diseases; NM, participants with no or one NCD, M1, participants with two NCDs; M2, participants with three NCDs; M3, participants with four or more NCDs. Model 1 not adjusted; Model 2 adjusted for age, sex, marital status, education, residence, and socioeconomic status; Model 3 additionally adjusted for BMI, smoking status, and drinking status.

aged 45–59 years, women, non-smokers, and those with quartile 2 of socioeconomic status.

Longitudinal association between multimorbidity at baseline and incident MDs

After following up for 2.7 years, 82 cases of MDs (1.12%) were reported. In the longitudinal analysis, the incidence rate of MDs was 3.77 per 1000 person-years among all participants. The incidence rates among the multimorbidity groups were 2.76, 2.99, 3.15, and 9.22 per 1,000 person-years for the NM, M1, M2, and M3 groups, respectively. In Model 1, we found that subjects with multimorbidity were more likely to have an incident of MDs, regardless of whether the multimorbidity was as continuous [HR: 1.30 (1.15–1.46)] or categorical variable [M3 group: HR:3.34 (1.99–5.59)]. Similar results were also found in Models 2 and 3, indicating that participants with multimorbidity were more likely to have new-onset MDs than the NM group [Model 2: HR, 2.90 (1.72–4.87); Model 3: HR, 2.93 (1.74–4.96)] (Table 3).

In the stratified analysis of most of the subgroups, participants with multimorbidity were more likely to have an incidence of MDs (Figure 4). Similar to the cross-sectional analysis, the positive association was more prominent in the group of individuals aged 45–59 years and women, compared with the older (age $\geq$ 60 years old) and men groups, respectively. The longitudinal association was not significant in the subgroup of drink, quartiles 1, 2, and 4 of socioeconomic status.

Cross-sectional and longitudinal associations of each NCD with MDs

To explore the extent to which each of the 11 NCDs that constituted the multimorbidity contributed to the risk of MDs, we analyzed the cross-sectional and longitudinal association between each of the 11 NCDs and MDs separately. As for the cross-sectional association, we found that, except for cancer, the other 10 NCDs all had a significantly positive association with MDs

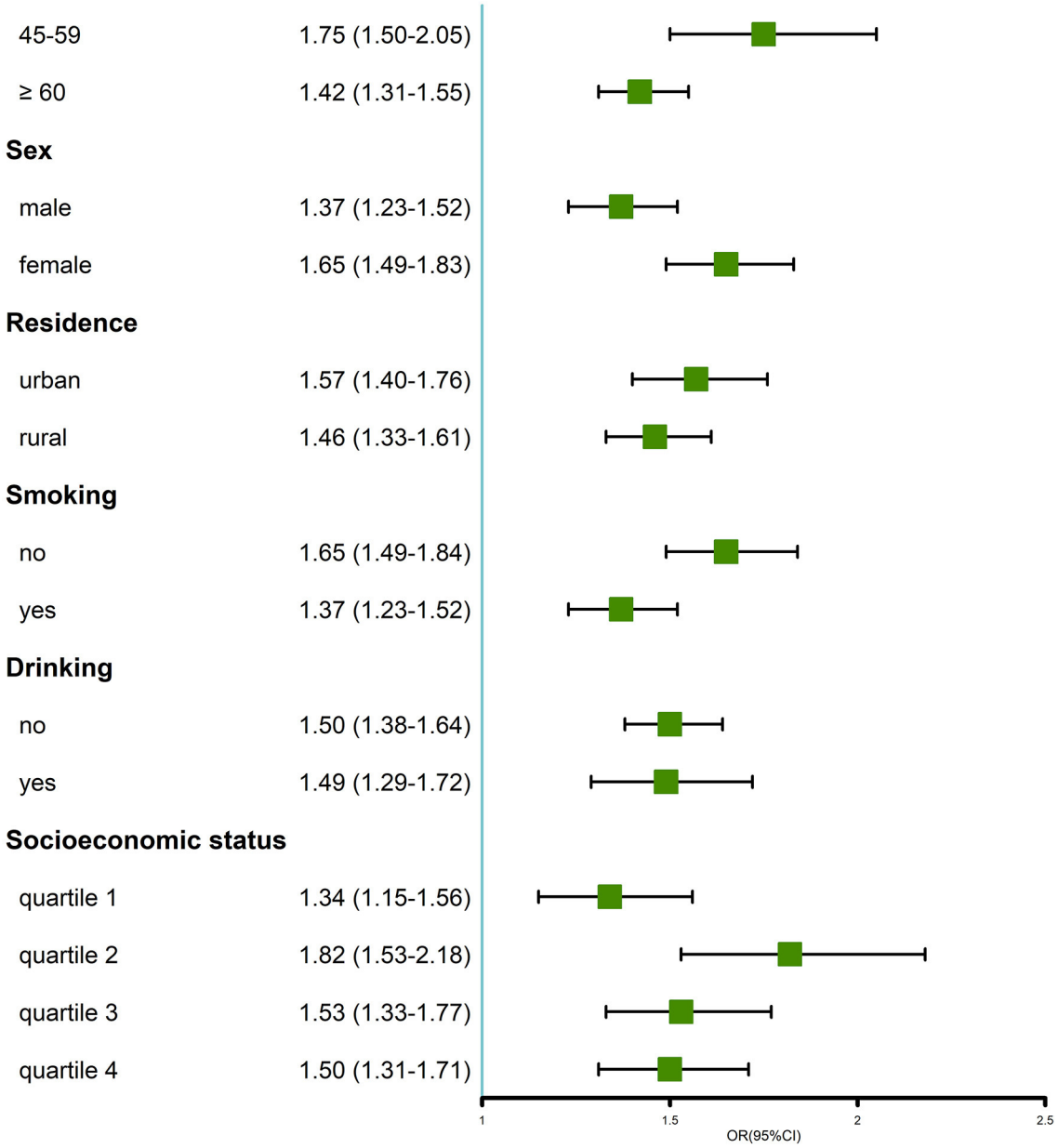

FIGURE 3
Stratified analysis of the ORs between multimorbidity and memory-related diseases.

(Supplementary Table S2). In terms of effect values, the top five NCDs with the greatest risk effect on MDs were stroke [OR: 5.52 (3.73–8.17)], heart problem [OR: 2.77 (2.07–3.71)], dyslipidemia [OR: 2.60 (1.94–3.49)], kidney disease [OR: 2.28 (1.60–3.26)], and liver disease [OR: 2.06 (1.33–3.18)], whereas, only hypertension, dyslipidemia, diabetes, and kidney diseases were significantly positively associated with MDs in the longitudinal analysis, which might connect with the short follow-up time and a small number of MDs events. From the perspective of effect values, the order of these top four NCDs was diabetes [HR: 2.52 (1.46–4.33)], dyslipidemia [HR: 2.16 (1.33–3.51)], hypertension [HR: 1.99 (1.27–3.12)], and kidney disease [HR: 1.86 (1.02–3.37)] (Supplementary Table S3).

Discussion

Among Chinese middle-aged and older adults, multimorbidity was associated with a higher risk of MDs. As for the cross-sectional association, we found that 49% increased the risk of MDs for each additional NCD and this relationship gradually strengthened with

TABLE 3 Association between multimorbidity and MDs in the longitudinal analysis.

	Incidence Rate, per 1,000 Person-years	Hazard ration (HR, 95%CI)		
		Model 1	Model 2	Model 3
Multimorbidity count	3.77	1.30 (1.15–1.46)	1.26 (1.12–1.42)	1.26 (1.12–1.43)
NM	2.76	ref	ref	ref
M1	2.99	1.08 (0.58–2.01)	0.99 (0.53–1.84)	0.99 (0.53–1.85)
M2	3.15	1.14 (0.54–2.40)	1.01 (0.48–2.14)	1.03 (0.49–2.18)
M3	9.22	3.34 (1.99–5.59)	2.90 (1.72–4.87)	2.93 (1.74–4.96)

MDs, memory-related diseases; NM, participants with no or one NCD, M1, participants with two NCDs; M2, participants with three NCDs; M3, participants with four or more NCDs. Model 1 no adjusted; Model 2 adjusted for age, sex, marital status, education, residence, and socioeconomic status; Model 3 additionally adjusted for BMI, smoking status, and drinking status.

the severity of multimorbidity. Furthermore, we found that the risk of incident MDs was 26% higher for each additional NCD at baseline. Compared with the NM group, the M3 group had a nearly 3-fold higher risk of MDs. Cross-sectional and longitudinal associations remained stable across different subgroups, and this association was more prominent in middle-aged adults. To our best knowledge, this is the first study to explore the association between multimorbidity and MDs in Chinese middle-aged and older adults and found that this association was more notable in middle-aged adults.

Although many studies have focused on the association between multimorbidity and dementia or AD, this study was different and filled some gaps. Previously, cross-sectional studies have found that people with AD or dementia often had a higher proportion of multimorbidity. Regarding AD, a cross-sectional study found that multimorbidity was significantly associated with lower hippocampal volumes and lower fluorodeoxyglucose positron emission tomography standardized uptake values, which were preclinical markers of AD (28). Another related study found that patients with AD had a higher percentage of multimorbidity than controls, and higher multimorbidity was associated with greater impairment in cognition (29, 30). These studies were generally consistent with our results, although the types of MDs of interest and the study populations were different. Moreover, previous studies have focused on older adults and individual MDs. This study examined not only the older adults but also the population aged 45–59 years and found that multimorbidity was positively associated with comprehensive MDs.

In terms of the longitudinal association, a study found that neuropsychiatric, cardiovascular, and sensory impairment/cancer multimorbidity patterns were associated with dementia after followed up for approximately 8.4 years (25). Another study found that older adults with multimorbidity had a higher risk of mild cognitive impairment and dementia than people without multimorbidity (31). A recent study, which included participants aged 35 to 55 at baseline, found that multimorbidity had a robust association with subsequent dementia, and this association was more prominent in multimorbidity onset in midlife (6). These longitudinal studies further supported the relationship between multimorbidity and MDs. The above-mentioned previous studies have shown that multimorbidity was associated with MDs, but these studies were mainly implemented in high-income countries and paid less attention to multimorbidity severity and middle-aged adults. Our study, which included Chinese middle-aged and older adults, examined the cross-sectional and longitudinal associations between multimorbidity and MDs.

For these individual NCDs that constituted the multimorbidity, we found that stroke, cancer, heart problem, dyslipidemia, and kidney diseases had a stronger cross-sectional relationship with MDs. There were some relevant studies in favor of this relationship, and there would be some mechanisms involved (32). A study reported that stroke was associated with cognitive impairment and dementia in older adults, and the six RNA-binding protein (RBP) genes (POLR2F, DYNC1H1, SMAD9, TRIM21, BRCA1, and ERI1) might participate in the process by mediating the hypoxic responses and angiogenesis (33). Regarding cardiovascular diseases and memory function, studies jointly found that better cardiovascular health is associated with lower memory decline and risk of cognitive impairment (34, 35). Another cohort study found that decreased numbers of optimal cardiovascular health metrics were associated with a higher risk of dementia (35). In a meta-analysis study, which included more than 50 000 participants, kidney disease was associated with cognitive impairment (36). In the longitudinal association between individual NCDs and MDs, only diabetes, dyslipidemia, hypertension, and kidney disease remained statistically significant. This might be because the follow-up time was short and there were only a few MDs events. We unified the analysis of 11 NCDs because this situation was closer to the real-world problem of middle-aged and older adults (6). Even though individual NCDs could affect the risk of memory function, studies of multimorbidity suggested that the aggregation of NCDs had a specific cumulative effect that might accelerate cognitive decline and increase dementia risk (31, 37). This was consistent with our study, which showed that participants with four or more NCDs had more significant effect values with MDs. This process might be involved in the inflammatory process (25) and the interaction between and/or cumulative with medications prescribed (31).

Our study has several strengths. First, this study examined the relationship between multimorbidity, rather than individual NCDs, and MDs among Chinese middle-aged and older adults, which was more consistent with the real-world situation. Because the subjects in this study were from a nationally representative study, our findings could be generalized to general adults. Second, the present study further analyzed the longitudinal association and the cross-sectional association. In addition, our findings tentatively suggested that the severity of multimorbidity had a cumulative effect on MDs. There are also some limitations to this study. First,

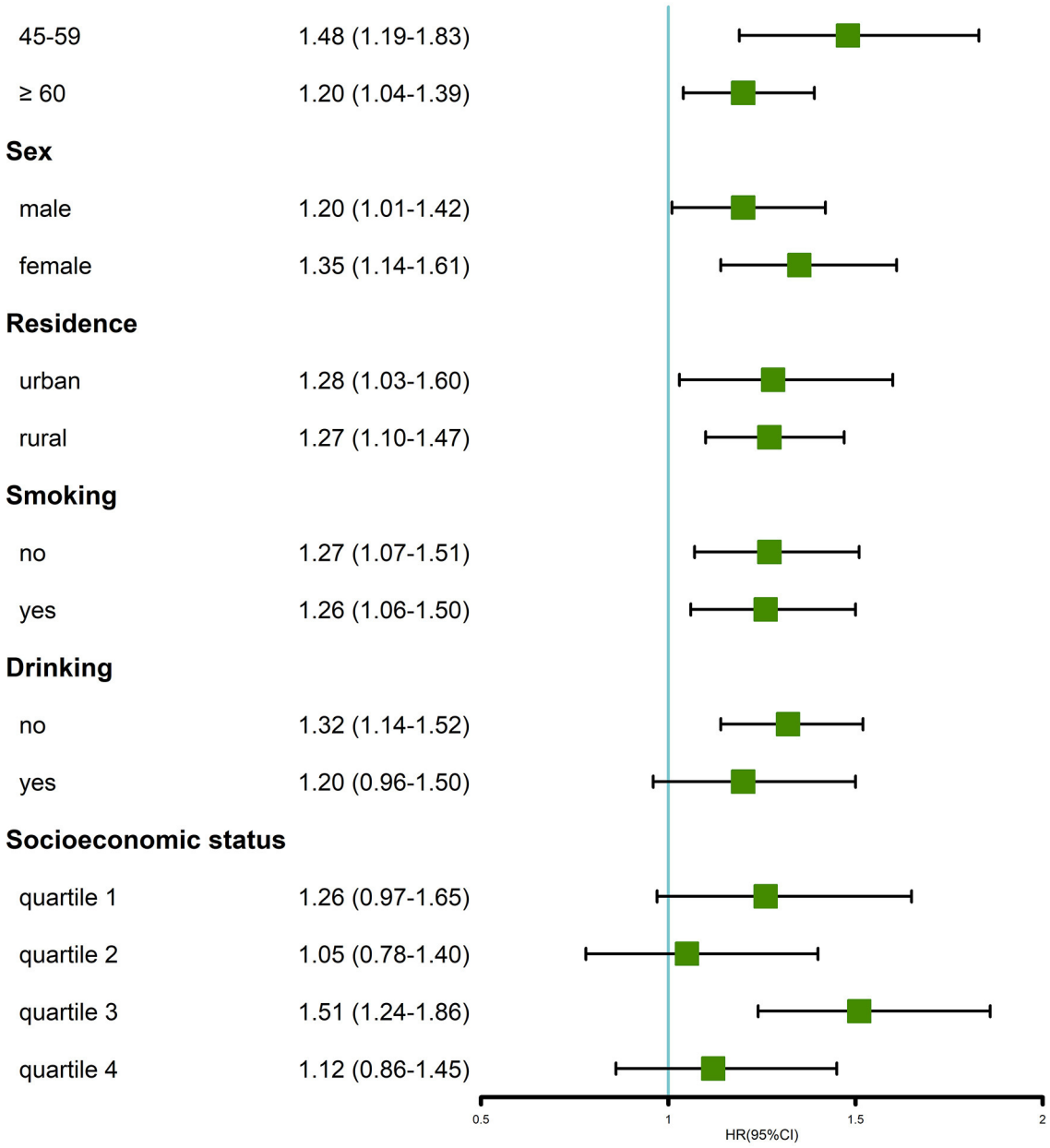

FIGURE 4
Stratified analysis of the HRs between multimorbidity and memory-related diseases.

the diagnosis of NCDs and MDs was self-reported rather than based on medical records, which might produce some misjudgment. A study reported that there was a 75% accuracy in self-reported disease (38). Second, since we lacked data on different MDs types, we were unable to provide a more explicit analysis of the MDs types. Third, this study was a retrospective analysis, so we cannot make causal inferences based on it, and the follow-up time was short. Future long-time cohort studies are needed to pinpoint this causal effect. Despite these limitations, our study found a risk relationship between multimorbidity, a natural condition in middle-aged and older adults, and MDs. This indicated that physicians and the public should pay more attention to multimorbidity patients, especially those who commonly have four or more NCDs, and to prevent the risk of future MDs in advance.

Conclusion

Multimorbidity is becoming more common, and the age of onset is getting younger. Simultaneously, given the lack of effective

treatments for memory decline and its impact on individuals and society, it is imperative to identify the primary risk factors to prevent it in advance. Our study revealed that multimorbidity was associated with MDs among Chinese middle-aged and older adults, and this association was more prominent in middle-aged adults. This relationship gradually strengthened with the severity of multimorbidity. This finding may help reduce the risk of MDs and the medical and financial burden by implementing early prevention strategies for people with a high risk of MDs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1115207/full#supplementary-material

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Multimorbidity patterns and mortality in older adults: Results from the KORA-Age study

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The coexistence of several chronic diseases is very common in older adults, making it crucial to understand multimorbidity (MM) patterns and associated mortality. We aimed to determine the prevalence of MM and common chronic disease combinations, as well as their impact on mortality in men and women aged 65years and older using the population-based KORA-Age study, based in South of Germany. The chronic disease status of the participants was determined in 2008/9, and mortality status was followed up until 2016. MM was defined as having at least two chronic diseases. We used Cox proportional hazard models to calculate the hazard ratios (HRs) and the 95% confidence intervals (CIs) for associations between MM and all-cause mortality. During the study period 495 men (24.6%) and 368 women (17.4%) died. Although the MM prevalence was almost the same in men (57.7%) and women (60.0%), the overall effect of MM on mortality was higher in men (HR: 1.81, 95% CI: 1.47–2.24) than in women (HR: 1.28, 95% CI: 1.01–1.64; *p*-value for interaction <0.001). The type of disease included in the MM patterns had a significant impact on mortality risk. For example, when both heart disease and diabetes were included in the combinations of two and three diseases, the mortality risk was highest. The risk of premature death does not only depend on the number of diseases but also on the specific disease combinations. In this study, life expectancy depended strongly on a few diseases, such as diabetes, hypertension, and heart disease.

KEYWORDS

chronic disease, multimorbidity, mortality, older people, sex differences, hazard ratios

1. Introduction

Even though life expectancy has increased in recent decades as a result of modern medicine, individuals are developing more chronic diseases, resulting in rising multimorbidity (MM) (1). According to the World Health Organization (WHO), MM has been defined as the occurrence of two or more chronic diseases in one person at the same time (2).

Based on a systematic literature review of 41 articles from different countries, the prevalence of MM ranges from 55 to 98% in those aged ≥65 years. In Germany, based on the cross-sectional national telephone health interview survey "German Health Update" (GEDA 2012–2013), the MM prevalence ranged from 61.7% (95% CI: 59.3–64.1) for 60 to 69-year-olds to 72.9% (95%

CI: 70.4–75.2) for 70 to 79-year-old individuals. Others reported a 62% MM prevalence for those aged ≥65 years in the German population. In Augsburg, MM prevalence was 58.6% for individuals aged 65–94 years based on the KORA-Age data in 2008/9 (3).

Investigating chronic illness combinations and their negative consequences on the old people and the health care system is a major concern in countries with growing aging populations nowadays. Many studies showed the association between MM and lower quality of life (4), higher health care use and cost (5), and functional decline in older adults (6).

Moreover, many studies have found a relationship between MM and an increased risk of mortality (7–12), but the value of mortality risk is not similar. One reason for these dissimilarities could be a low sample size in some studies, and another reason for the differences might be the included disease types, age groups, and risk factors (7–12).

To our knowledge, there exists only one recent study (13) in Germany exploring the association of MM patterns and mortality based on health insurance claims data. Therefore, we aimed to identify the prospective association of MM with all-cause mortality controlling for sociodemographic and lifestyle factors in men and women based on the large population-based KORA-Age study. Additionally, we specified the most prevalent combinations of disease in men and women, and their associated mortality risk.

2. Methods

2.1. Data collection and study design

The adult population-based KORA (Cooperative Health Research in the Region of Augsburg) study was conducted between 1984 and 2001 in the Region of Augsburg, Germany. In 2008/9, KORA participants who were aged 65-year-olds or older were invited for the first wave of a specific project on health in old age – the KORA-Age study. Details about the study design and data collection have been explained elsewhere (14). Briefly, 5.991 individuals from the KORA cohort who were still alive, had not moved outside the study area or had not withdrawn their consent to participate met the inclusion criteria born between 1915 and before 1944 (i.e., ≥65 years in 2009). 4,565 individuals returned a postal self-report questionnaire and 4,127 individuals (2015 men and 2,112 women) answered further questions in a 30 min standardized telephone interview. The questionnaire and interview items are based the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project of the World Health Organization or from validated instruments. For instance, the MM instruments chosen were from established questionnaires (15–17). The study was conducted by trained staff at the KORA study Center in Augsburg after an initial pilot phase. Mortality status was assessed until 2016 by official death certificates. 4,127 individuals with questionnaire and interview information were included in this analysis.

Abbreviations: MM, Multimorbidity; BMI, Body mass index; WHR, Waist to hip ratio; KORA, Cooperative Health Research in the Region of Augsburg; WHO, World Health Organization; IQR, Interquartile range; SD, Standard deviation.

2.2. Mortality

All participants of the first wave of the KORA-Age study were followed for all-cause and cause-specific (cardiovascular, cancer, and other disease-related) mortality using official death certificates, coded according to the International Classification of Diseases (ICD-10). Cardiovascular-related mortality consists of diseases of the circulatory system (ICD-9 codes 390–459, ICD-10 codes I00–I99) and sudden death with unknown cause (ICD-9 code 798, ICD-10 code R99). Cancer-related mortality consists of neoplasms (ICD-9 codes 140–208, ICD-10 codes C00–C95). Other disease-related mortality consists of the remaining causes of death, for example, pneumonia (ICD-9 code 486, ICD-10 codes J18.8, J18.9), chronic bronchitis (ICD-9 code 491, ICD-10 Codes J41, J42, J44) and dementias (ICD-9 code 290, ICD-10 Codes F03.90, F05, F01.50, F01.51) (18). Follow-up for participant's mortality status was performed until 07.10.2016 (median follow-up time: 6.97 years, interquartile range; IQR = 75th%–25th%: 7.07–6.74 years).

2.3. Multimorbidity and single chronic diseases

MM has been defined as the presence of two or more chronic diseases in one person simultaneously (2). We considered 14 major chronic diseases, including hypertension, eye disease, heart disease, diabetes, joint disease, lung disease, gastrointestinal disease, stroke, cancer, kidney diseases, liver diseases, neurological diseases, depression, and anxiety. Hypertension, diabetes, cancer (any cancer recognized within the last 3 years), stroke, and heart diseases (myocardial infarction and coronary artery disease) were assessed based on the self-report questionnaire (whether participant currently have disease). All other diseases were identified in a telephone interview based on the Charlson Comorbidity Index (15). Participants were asked whether they suffer from kidney, liver, lung diseases (e.g., asthma, chronic bronchitis, and emphysema), inflammatory joint problems (arthritis or rheumatism), gastrointestinal diseases (e.g., colitis, cholecystic, gastric, or ulcer), heart diseases (e.g., congestive heart failure, coronary heart failure, or angina), eye problems (e.g., cataract, retinitis pigmentosa, glaucoma, macular degeneration, diabetic retinopathy). Neurological diseases were evaluated based on self-reported diseases like epilepsy, Parkinson's disease, or multiple sclerosis. The Geriatric Depression Scale (16) and Generalized Anxiety Disorder Scale-7 (17) screening tools were used to diagnose depression and anxiety. Persons with scores >10 were defined as suffering from depression or anxiety.

2.4. Demographic and lifestyle measures

We considered age, family status, education level, alcohol consumption, physical activity, body mass index (BMI), and smoking behavior as covariates. Family status is a combination of the self-reported marital status and living alone or with a spouse/partner categorized in the two groups "living with a partner/spouse" and "living alone, divorced or widowed." The education level had three categories based on years of education and vocational training: low

level (9 years or less), middle (10 or 11 years), and high (12 years or more).

Alcohol consumption was based on self-reported alcohol intake with the following three groups: "Never, rare or former use," "once a week," or "daily use." Leisure time physical activity was measured from two separate questions about leisure time sports activity per week in winter and summer, including cycling. Possible answers were (1) >2 h, (2) 1–2 h, (3) <1 h, and (4) none. Participants, who had a total score of <5, obtained by summing the numbers (1)–(4) relating to activities in winter and summer, were classified to be "physically active" (19).

The BMI was computed by dividing weight in kilograms by square height in meters. Measurements of height and weight were made by trained investigators while wearing light clothes and without shoes. Based on self-reported information, there are three categories for smoking status: never smokers, former smokers, and active smokers.

2.5. Statistical analysis

We presented categorical data as percentages and continuous data as means (SD) if they were normally distributed or medians (IQR) if non-normally distributed in the descriptive analysis. To examine the differences between outcome groups (alive and dead), *t*-test for continuous variables and the Chi-squared test for categorical variables were performed. Kaplan–Meier curves and log-rank tests were presented graphically to compare the survival distributions of participants with and without MM.

Cox proportional-hazards models were used to investigate the associations between MM and specific combinations of disease with mortality by adjusting for age, education, family status, smoking habits, alcohol use, BMI, and physical activity. The combined model has been used to check the significance of sex differences and then the sex-specific models have been performed. The interaction effect of MM with age and BMI was also checked in the sex specific models. Moreover, the spline Cox proportional hazard model was used for examining the non-linear effect of BMI. The proportional hazard assumption was examined using Schoenfeld residuals. Additionally, the prevalence of every single disease in men and women was calculated. In order to check the patterns of disease combinations, all possible combinations of two and three diseases were identified and the most prevalent combinations were presented in men and women separately. Using those with no disease or just one disease as the reference group, the adjusted hazard ratios of these most common combinations were then calculated.

For sensitivity analysis, we adjusted the model examining the association between MM and mortality for waist-to-hip ratio instead of BMI. Additionally, we fitted the model without MM to check to which degree MM can explain the underlying association between risk factors and mortality. We also ran the model without BMI to evaluate how much BMI could confound the effect of MM on mortality. Statistical relationships were considered significant for *p*-values <0.05. All statistical analyses were performed using R 4.1.2 and RStudio 2021.09.1[1] and the "dplyr," "pspline," "survival" and "survminer" libraries for analysis has been used.

1 https://www.r-project.org

2.6. Ethics statement

The Ethics Committee of the Bavarian Medical Association has approved the KORA-Age study (08094). Written informed consent was obtained from all study participants according to the Helsinki Declaration.

3. Results

3.1. Study population characteristics

The prevalence of MM was 57.7 and 60.0% in men and women, respectively. Baseline characteristics of the 4,127 participants stratified by their mortality status are shown in Table 1. Out of 2015 male participants, 495 (24.5%) died (24.1% cancer related, 44.5% CVD-related and 31.4% other disease-related deaths). Out of 2,112 female participants, 368 (17.5%) died (23.1% cancer-related, 44.8% CVD-related, and 32.1% other disease-related deaths). There were statistically significant differences ($p < 0.001$) between those who survived and those who died for age, family status, education, alcohol use, physical activity, and MM status in both men and women (Table 1). Although associations of BMI and smoking habits with mortality were statistically significant in men, they were not significant in women. Individuals without MM had a significantly longer survival probability compared to those with MM in both men and women (Figure 1).

3.2. Association between multimorbidity and all-cause mortality

Based on a non-linear multivariable-adjusted model, MM status was significantly positively associated with all-cause mortality in men (HR: 1.81, 95% CI: 1.47–2.24) and women (HR: 1.28, 95% CI: 1.01–1.64; Table 2).

3.3. Risk factor profiles of all-cause mortality

Age, family status, educational attainment, physical activity, and smoking were significantly linked to increased mortality risk in males, whereas age, physical activity, and smoking were significantly linked to increased mortality risk in women (Table 2).

Since the interaction effect between age and MM was significant, we stratified our analysis by 5-year age groups.

Among men and women aged 65–79 years, MM was positively associated with all-cause mortality (Table 3; Figure 2). The interaction effect between MM and BMI was not significant, however; there were significant differences in survival probabilities of individuals with and without MM at different levels of BMI in men and women. Additionally, participants with higher BMI (BMI >25 kg/m^2) had a longer survival probability compared to lower BMI (BMI <=25 kg/m^2) both with and without MM (Figure 3). Based on the spline Cox proportional model, a curvilinear association between BMI and all-cause mortality was specified in men and women. The BMI value related to the highest mortality

TABLE 1 Baseline characteristics of the study participants were stratified by sex and mortality status.

Characteristics		Men			Women		
		Died=No	Died=Yes	Value of *p*	Died=No	Died=Yes	Value of *p*
N		1,520	495	…	1744	368	…
Age [mean (SD)]		71.85 (5.34)	77.45 (6.20)	< 0.001	72.3 (5.39)	78.3 (6.66)	<0.001
Multimorbidity (%)	Yes	799 (52.6)	364 (73.5)	< 0.001	993 (56.9)	274 (74.5)	<0.001
	No	721 (47.4)	131 (26.5)		751 (43.1)	94 (25.5)	
Family status (%)	Living alone, divorced, widowed	262 (17.2)	144 (29.1)	< 0.001	965 (55.3)	118 (32.1)	<0.001
	Living with a partner/ spouse	1,258 (82.8)	351 (70.9)		779 (44.7)	250 (67.9)	
Education (%)	Low (8–9 years)	85 (5.6)	52 (10.5)	< 0.001	466 (26.7)	138 (37.5)	< 0.001
	Medium (10–11 years)	800 (52.6)	292 (59.0)		1,012 (58.0)	182 (49.5)	
	High (12 or higher years)	635 (41.8)	151 (30.5)		266 (15.3)	48 (13.0)	
Alcohol (%)	Never, rare or former use	330 (21.7)	142 (28.7)	0.006	977 (56.0)	239 (64.9)	0.004
	Once a week	192 (12.6)	56 (11.3)		251 (14.4)	36.0 (9.8)	
	Daily use	998 (65.7)	297 (60.0)		516 (29.6)	93 (25.3)	
BMI-kg/m^2 (SD)		27.67 (3.59)	27.13 (3.81)	0.004	27.35 (4.55)	26.94 (4.98)	0.122
Smoking (%)	Never Smoker	518 (34.1)	128 (25.9)	0.003	1,231 (70.6)	262 (71.6)	0.637
	Former smoker	900 (59.3)	330 (66.7)		414 (23.7)	80 (21.9)	
	Current smoker	100 (6.6)	37 (7.5)		99 (5.7)	24 (6.6)	
Physical activity (%)	Active	993 (65.3)	201 (39.9)	< 0.001	992 (56.9)	113 (30.3)	<0.001
	Inactive	527 (34.7)	294 (60.1)		752 (43.1)	255 (69.7)	

Arithmetic means (SD) were given for age and BMI as continuous variables and frequency (percentage) for other categorical variables. *T*-test for continuous variables and the chi-squared test for categorical variables were used to check the difference between groups.

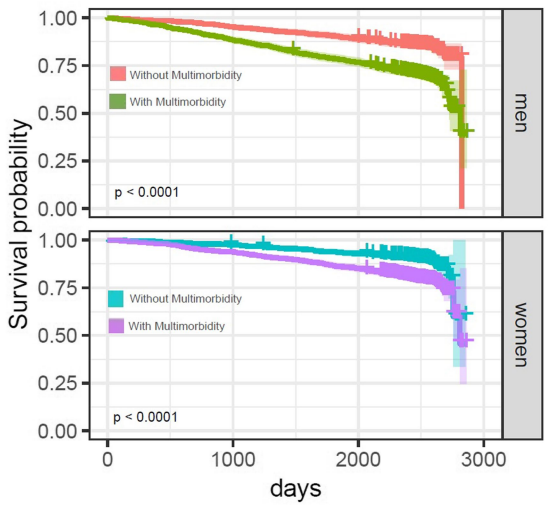

FIGURE 1
Kaplan–Meier survival curves for men and women with and without multimorbidity. Kaplan–Meier curve shows the time to death for individuals with and without MM. Censored data (vertical sign-on lines) denotes participants no longer available in KORA-Age 3 who did not experience death. There were statistically significant (p <0.0001) differences in survival probability between 2 groups in both men and women based on the log-rank test.

was for BMI lower than 25 kg/m^2 (underweight or normal BMI) in both men and women (Figure 4).

3.4. Association between multimorbidity and cause-specific mortality

In the fully adjusted models for cause-specific mortality, the risk of cancer caused mortality was 66% (HR: 1.66, 95% CI: 1.11–2.49) and 76% (HR: 1.76, 95% CI: 1.05–2.95) higher in individuals with MM compared to those without MM in men and women, respectively. In addition, compared with men without MM, the risk of mortality from cardiovascular causes was 83% (HR: 1.83, 95% CI: 1.33–2.51) higher in those who had MM. In women with MM, the hazard ratio for cardiovascular causes was 27% (HR: 1.27, 95% CI: 0.87–1.86) higher than without MM, but the HR was not significantly elevated. For other disease causes, the hazard ratios were (HR: 1.96, 95% CI: 1.32–2.92) and (HR: 1.08, 95% CI: 0.69–1.69) in men and women, respectively, (Figure 5).

3.5. Prevalence of single diseases and disease combinations

The prevalence of single and a combination of two and three diseases are shown in Table 4. The five most prevalent paired diseases

TABLE 2 Multivariate adjusted association of MM and all-cause mortality for men and women.

Characteristics		Men (n=2015)				Women (n=2,112)			
		Model 0	Model 1	Model 2	Model 3 (non-linear BMI)	Model 0	Model 1	Model 2	Model 3 (non-linear BMI)
Multimorbidity (ref: no)		2.32 (1.89,2.85)	1.84 (1.51,2.26)	1.82 (1.48,2.24)	1.81 (1.47, 2.24)	2.10 (1.66,2.66)	1.35 (1.05,1.72)	1.29 (1.01,1.65)	1.28 (1.01,1.64)
Age (per year)			1.13 (1.12,1.15)	1.12 (1.09,1.13)	1.11 (1.09, 1.12)		1.15 (1.13,1.17)	1.12 (1.10,1.15)	1.12 (1.11,1.15)
Family status (ref: Living with a partner/ spouse)	Living alone, divorced, widowed	…	…	1.36 (1.12,1.67)	1.35 (1.11,1.66)	…	…	1.27 (0.99,1.61)	1.25 (0.98,1.59)
Education (ref: 12 years or more)	8–9 years	…		1.50 (1.09,2.07)	1.49 (1.08,2.06)	…		1.15 (0.82,1.62)	1.20 (0.85,1.69)
	10–11 years			1.29 (1.05,1.57)	1.30 (1.06,1.59)			0.93 (0.67,1.28)	0.96 (0.69,1.33)
Alcohol use (ref: once a week)	Never, rare or former use	…		1.29 (1.09,2.07)	1.18 (0.85,1.64)	…		1.25 (0.87,1.79)	1.21 (0.84,1.74)
	Daily use			1.04 (0.77,1.41)	1.04 (0.76,1.40)			1.11 (0.75,1.65)	1.08 (0.73,1.61)
Physical activity (ref: active)		…		1.70 (1.40,2.04)	1.68 (1.39,2.00)	…		1.70 (1.35,2.15)	1.67 (1.32,2.11)
BMI (kg/m^2)		…		0.97 (0.94,0.99)	*	…		0.99 (0.97,1.01)	*
Smoking status (ref: never)	Former smoker	…		1.16 (0.94,1.43)	1.15 (0.93,1.42)	…		1.08 (0.83,1.39)	1.04 (0.880,1.35)
	Current smoker			1.76 (1.21,2.56)	1.73 (1.18,2.51)			1.59 (1.03,2.46)	1.54 (1.00,2.39)
AIC		7070.243	6794.823	6740.871	6730.415	5305.573	5050.834	5032.326	5026.419

Data were presented as hazard ratios with 95% confidence intervals. Model 0, model 1, and model 2 were calculated based on the Cox proportional hazard model. *In model 3, BMI was considered as the spline effect in the spline Cox proportional hazard model.

TABLE 3 Number of men and women in different age groups stratified by mortality status (alive and died).

Age groups	Men			Women		
	Total	Alive	Died	Total	Alive	Died
65–69	709	645	64	720	666	54
70–74	533	433	100	606	548	58
75–79	413	278	135	408	327	81
80–84	262	136	126	250	151	99
85+	98	28	70	128	52	76
Total	2015	1,520	495	2,112	1744	368

Number of men and women in each age groups who were alive or died until end of follow up (07.10.2016).

in men were heart-hypertension, hypertension-eye, diabetes-hypertension, heart-eye, and joint-hypertension. In women, hypertension-eye, heart-hypertension, diabetes-hypertension, joint-hypertension, and heart-eye were the most prevalent pairs.

3.6. Disease combinations and all-cause mortality

The seven most prevalent diseases in men and women (lung, joint, heart, diabetes, hypertension, eye, and anxiety) were selected to check the hazard ratio of the most prevalent combination of two and three diseases. Since the frequencies of quartets and quintets were low, we calculate the HR for the pairs and trios only.

3.6.1. Mortality and combination of two diseases

Men with heart-hypertension, diabetes-hypertension, diabetes-eye, and heart-diabetes had a significantly increased risk of mortality compared with men with one or no disease. Women with heart-hypertension, diabetes-hypertension, heart-eye, joint-hypertension, diabetes-eye, heart-diabetes, lung-hypertension, and hypertension-anxiety had a significantly higher risk of all-cause mortality compared to women with one or no disease. In women, the combination of two diseases resulted in a significantly increased risk of mortality with higher HR value than in men with the same combination (Table 4).

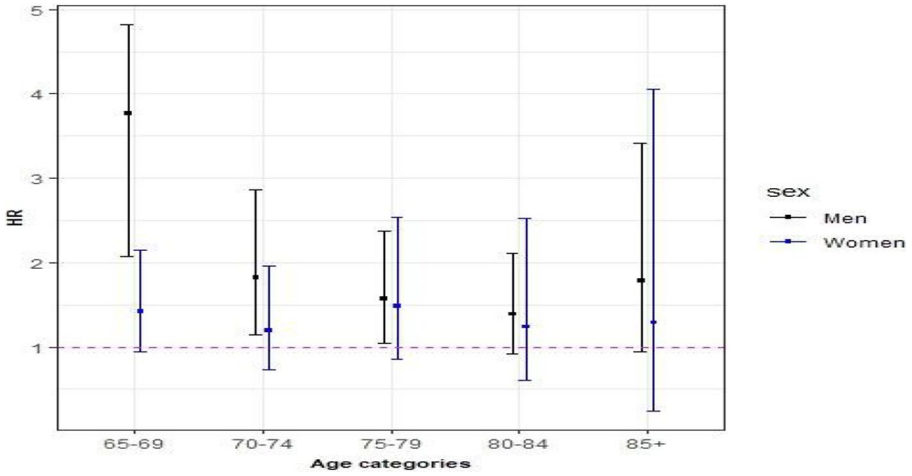

FIGURE 2
Age stratified hazard ratios for the association of multimorbidity with all-cause mortality for men and women. Hazard ratios (95% CIs) for associations of MM with all-cause mortality were calculated for each age group and adjusted for education, family status, smoking habits, alcohol use, BMI, and physical activity.

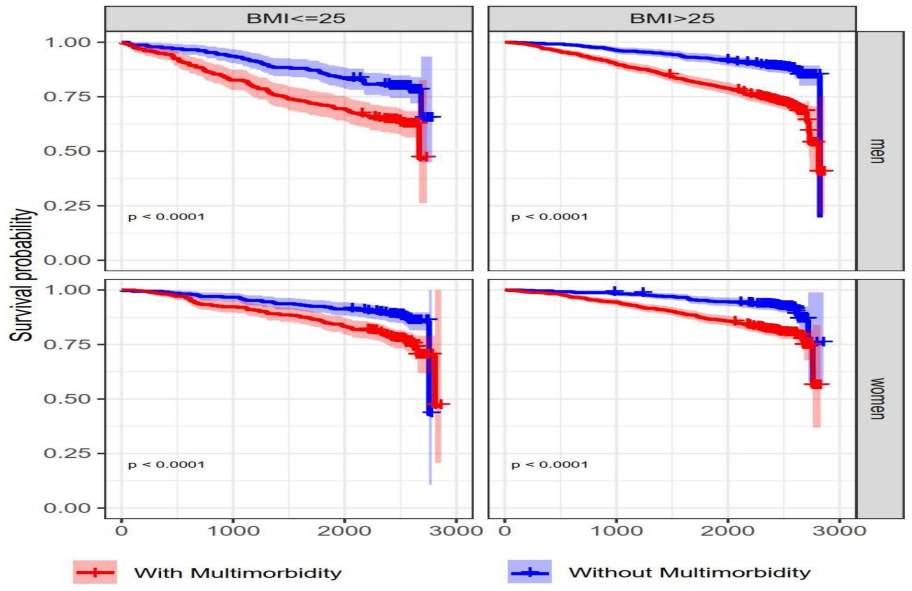

FIGURE 3
Kaplan–Meier survival curves for men and women based on BMI and multimorbidity status. Kaplan–Meier curves show the comparison of survival probability between individuals with and without MM stratified by BMI category (<=25, >25) and sex. *p*-value <0.0001 are presented for the log-rank test.

3.6.2. Mortality and combination of three diseases

Men presented significantly higher hazard ratios for individuals who had the combination of heart-diabetes-hypertension, heart-diabetes-eye, and joint-diabetes-hypertension compared with men with one or no disease. However, women showed a significantly higher risk for the combination of heart-hypertension-eye, heart-diabetes-hypertension, diabetes-hypertension-eye, lung-hypertension-eye, heart-diabetes-eye, and joint-diabetes-hypertension (Table 4).

3.7. Sensitivity analysis

There is some evidence that the waist-to-hip ratio (WHR) could be a good measure of fat distribution within the body while adjusting for the body shape (20). According to the WHO, a normal WHR range for men is 0.9 or less and 0.85 or less for women, while a WHR of >1.0 can raise the risk of chronic diseases in both male and female. Therefore, we repeated our Cox proportional models using WHR instead of BMI. We only had WHR ratio values for 1,051 participants out of 4,127. Hazard

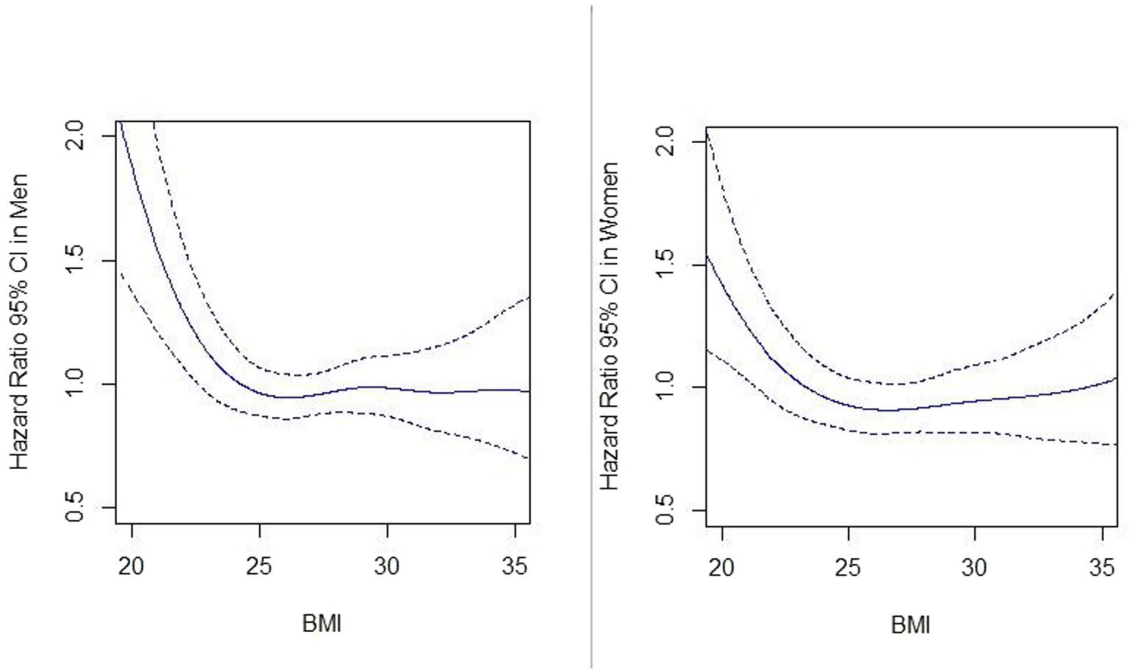

FIGURE 4
Association between BMI (kg/m^2) and all-cause mortality in men and women. Hazard ratios of all-cause mortality are calculated by the spline Cox proportional hazard model. Solid lines and dash lines, respectively, represent the hazard ratios and their 95% confidence intervals after adjusting for MM, age, education, family status, smoking habit, alcohol use, and physical activity.

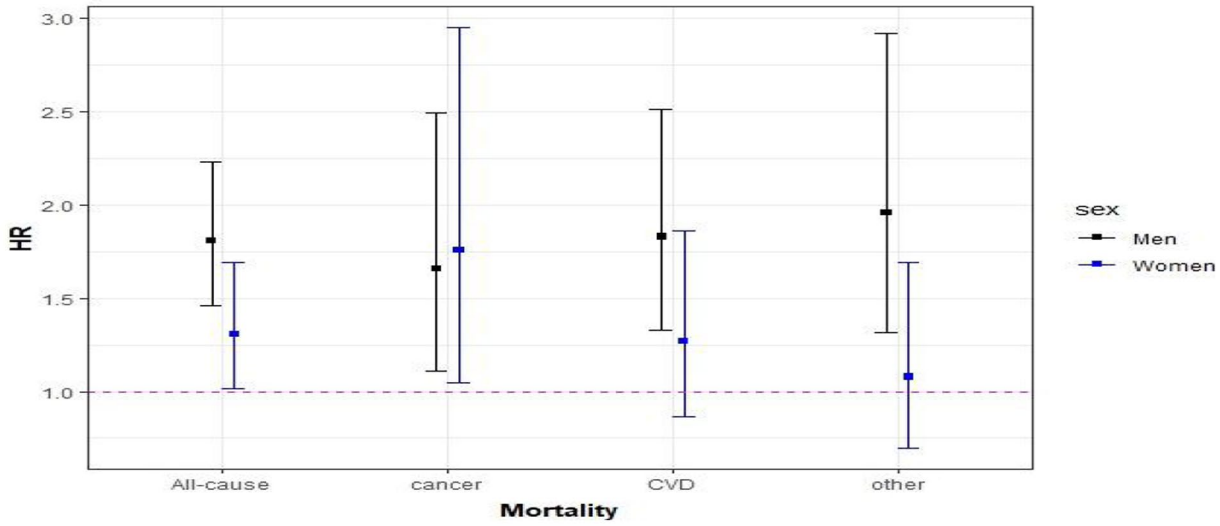

FIGURE 5
Association between multimorbidity and cause-specific mortality. Hazard ratios (95% CIs) of MM were calculated for all-cause and cause-specific mortality and adjusted for education, family status, smoking habit, alcohol use, BMI, and physical activity.

ratios of MM were (HR: 1.89, 95% CI: 1.24–2.78) in men and (HR: 1.12, 95% CI: 0.92–1.69) in women after adjusting the model for WHR instead of BMI. When WHR was used as a continuous variable in the model, a curvilinear (U-shaped) relationship between WHR and all-cause mortality was detected in both men and women (Figure 6). When the cox model was fitted without the MM, the effect estimates for age, particularly in men, increased significantly, but there was no considerable change for the other covariates. Furthermore, only the hazard ratios of MM in men were reduced by roughly 7% after fitting the model without BMI, whereas effect estimates for other covariates did not change significantly (Table 5).

TABLE 4 Frequency of single disease and the most prevalent combination of two and three diseases and their corresponding adjusted hazard ratios (95% confidence interval) for all-cause mortality stratified by sex.

Frequency (Rank) of single diseases			Combination of two diseases	Men (*n* =2015)		Women (*n* =2,112)	
Disease	Men (*n* =2015)	Women (*n* =2,112)		Frequency (Rank*)	HR (95% CIs)	Frequency (Rank)	HR (95% CIs)
Hypertension	1,086 (1)	1,206 (1)	Heart-hypertension	381 (1)	1.47 (1.15,1.71)	323 (2)	1.59 (1.17,2.16)
Eye	630 (2)	862 (2)	Hypertension-eye	378 (2)	0.87 (0.78,1.08)	542 (1)	1.25 (0.94,1.67)
Heart	555 (3)	454 (3)	Diabetes-hypertension	268 (3)	1.63 (1.31,2.04)	258 (3)	2.09 (1.52,2.89)
Diabetes	352 (4)	312 (5)	Heart-eye	203 (4)	1.15 (0.91,1.46)	241 (5)	1.52 (1.11,2.11)
Joint	227 (5)	404 (4)	Joint-hypertension	173 (5)	1.15 (0.87,1.51)	247 (4)	1.42 (1.01,2.02)
Lung	207 (6)	200 (7)	Diabetes-eye	146 (6)	1.34 (1.02,1.74)	163 (7)	1.98 (1.38,2.83)
Gastrointestinal	139 (7)	196 (8)	Heart-diabetes	134 (7)	1.87 (1.43,2.45)	108 (12)	2.87 (1.96,4.20)
Stroke	136 (8)	100 (9)	Lung-hypertension	128 (8)	1.34 (0.99,1.81)	134 (8)	1.67 (1.12,2.51)
Cancer	99 (9)	68 (11)	Joint-eye	116 (9)	1.11 (0.81,1.48)	206 (6)	1.12 (0.77–1.62)
Anxiety	90 (10)	223 (6)	Hypertension-anxiety	60 (16)	1.47 (0.95,2.27)	132 (9)	1.64 (1.06,2.55)
Kidney	81 (11)	70 (10)	Joint-heart	91 (12)	1.32 (0.94,1.85)	129 (10)	1.32 (0.86,2.03)
Neurological	60 (12)	50 (12)	**Combination of three diseases**	**Frequency (Rank)**	**HR (95% CIs)**	**Frequency (Rank)**	**HR (95% CIs)**
Liver	41 (13)	47 (14)	Heart-hypertension-eye	145 (1)	1.08 (0.82,1.43)	177 (1)	1.43 (1.00,2.03)
Depression	23 (14)	49 (13)	Heart-diabetes-hypertension	112 (2)	1.81 (1.36,4.42)	91 (4)	2.87 (1.92,4.28)
			Diabetes-hypertension-eye	111 (3)	1.34 (0.99,1.80)	135 (2)	2.61 (1.65,4.13)
			Lung-hypertension-eye	67 (4)	1.14 (0.76,1.77)	80 (6)	1.69 (1.06,2.72)
			Joint-hypertension-eye	67 (5)	1.23 (0.86,1.75)	129 (3)	1.24 (0.81,1.88)
			Joint-heart-hypertension	66 (6)	1.11 (0.73,1.67)	90 (5)	1.52 (0.95,2.43)
			Heart-diabetes-eye	60 (7)	1.69 (1.18,2.41)	63 (9)	2.61 (1.65,4.12)
			Lung-heart-hypertension	53 (8)	1.46 (0.95,2.23)	50 (13)	1.74 (0.98,3.08)
			Joint-diabetes-hypertension	49 (9)	1.61 (1.07,2.39)	51 (12)	2.09 (1.31,3.36)
			Joint-heart-eye	42 (13)	1.09 (0.69,1.72)	73 (7)	1.17 (0.69,1.98)
			Hypertension-eye-anxiety	27 (23)	1.28 (0.69,2.35)	69 (8)	1.66 (0.99,2.76)

*The Rank of disease combination shows the sorted descending rank based on the prevalence of specific combinations among all possible combinations in men and women separately. The heart-hypertension and the hypertension-eye have the highest frequency and first rank for the diseases pair in men and women, respectively. The Hazard ratios (95% CIs) of the specific combination were calculated after adjusting for age, education, family status, smoking habit, alcohol use, BMI, and physical activity. For each hazard ratio, the reference group was considered as individuals who had no or one disease.

4. Discussion

The KORA-Age study demonstrated a positive association of MM with all-cause mortality. While women had a higher MM prevalence, the HR for the association between MM and all-cause mortality was higher for men than for women. The findings of other studies confirm this finding that women live longer than men but are less healthy (21–24). We could also confirm the finding from a Bavarian Aging Study for individuals older than 65 years old that women with poorer health situations had a lower mortality rate compared to men. They showed that for all ages and morbidity definitions, women had significantly higher life expectancy than men (25).

The sex disparities in MM prevalence and impact of MM on mortality in different parts of the world suggest that there are underlying mechanisms accountable for these differences. One explanation could be that most studies use self-reported information on health status to assess chronic diseases and men prefer to report only severe health conditions. Moreover, women report their chronic diseases and symptoms with more detail and accuracy (26). For instance, a woman suffering from mild angina pectoris might claim that she has a cardiovascular illness, while a man might report it only if he had a heart attack. This reason could also explain the stronger link between MM and CVD mortality among men observed in the present study. Another possible explanation is that the mortality difference between men and women might be influenced by lifestyle factors. Although we performed our analysis after adjusting for socioeconomic factors, the confounder residuals might influence the sex differences in the effect of MM on mortality. While family status was not a significant predictor for women, males who lived alone,

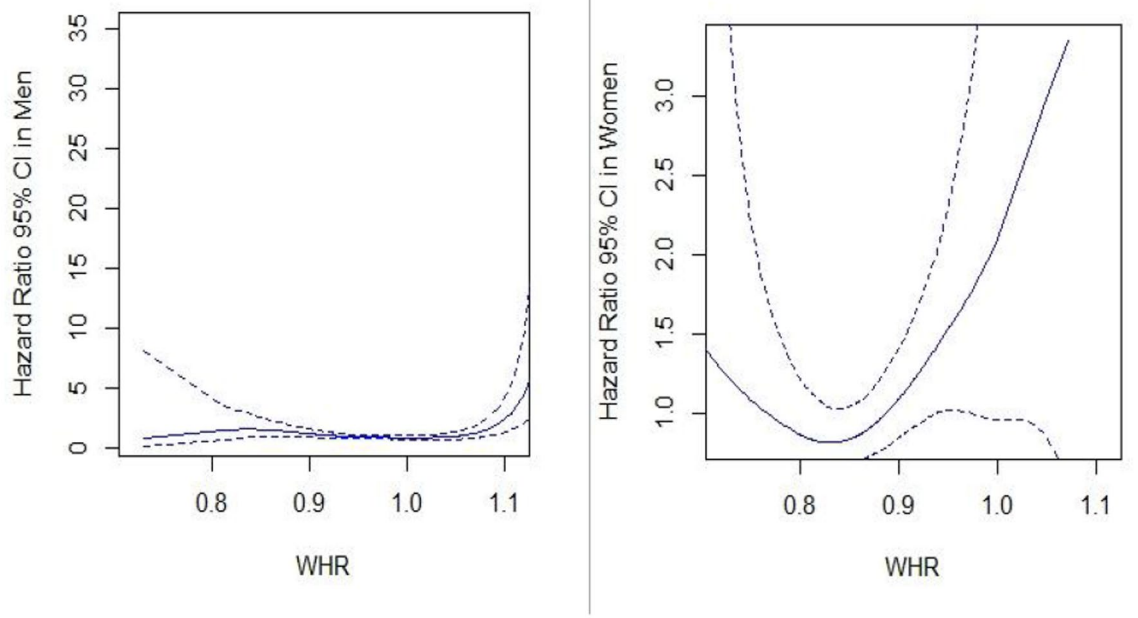

FIGURE 6
Association between waist-hip ratio (WHR) with all-cause mortality in men and women. Hazard ratios of all-cause mortality are calculated by the spline Cox proportional hazard model. Solid lines and dash lines, respectively, represent the hazard ratios and their 95% confidence intervals after adjusting for MM, age, education, family status, smoking habit, alcohol use, and physical activity.

TABLE 5 Association of multimorbidity and covariates with all-cause mortality.

Characteristics		Men			Women		
		Full model	Without MM	Without BMI	Full model	Without MM	Without BMI
Multimorbidity (ref: No)		1.82 (1.48,2.24)	…	1.77 (1.45,2.19)	1.29 (1.01,1.65)	…	1.28 (1.00,1.64)
Age (per year)		1.12 (1.09,1.13)	1.22 (1.14,1.18)	1.12 (1.10,1.13)	1.12 (1.10,1.15)	1.14 (1.11.,1.16)	1.13 (1.11,1.15)
Family status (ref: Living with a partner/spouse)	Living alone, divorced, widowed	1.36 (1.12,1.67)	1.34 (1.10,1.64)	1.27 (0.99,1.61)	1.32 (1.02,1.66)	1.26 (0.99,1.61)	1.27 (0.99,1.61)
Education (ref: 12 years or more)	8–9 years	1.50 (1.09,2.07)	1.46 (1.06,2.01)	1.15 (0.82,1.62)	1.29 (0.88,1.78)	1.16 (0.83,1.64)	1.13 (0.81,1.59)
	10–11 years	1.29 (1.05,1.57)	1.27 (1.04,1.55)	0.93 (0.67,1.28)	1.02 (0.75,1.47)	0.94 (0.68,1.30)	0.93 (0.67,1.28)
Alcohol use (ref: once a week)	Never, rare or former use	1.29 (1.09,2.07)	1.24 (0.89,1.72)	1.25 (0.87,1.79)	1.15 (0.80,1.65)	1.26 (0.88,1.82)	1.27 (0.88,1.82)
	Daily use	1.04 (0.77,1.41)	1.03 (0.76,1.39)	1.11 (0.75,1.65)	1.01 (0.68,1.51)	1.11 (0.75,1.65)	1.13 (0.76,1.67)
Physical activity (ref: active)		1.70 (1.40,2.04)	1.73 (1.43,2.09)	1.66 (1.38,2.00)	1.70 (1.35,2.15)	1.73 (1.37,2.19)	1.69 (1.34,2.14)
BMI (kg/m^2)		0.97 (0.94,0.99)	0.98 (0.95,1.01)	…	0.99 (0.97,1.01)	0.99 (0.97,1.02)	…
Smoking status (ref: never)	Former smoker	1.16 (0.94,1.43)	1.24 (1.01,1.53)	1.15 (0.93,1.42)	1.08 (0.83,1.39)	1.08 (0.84,1.41)	1.08 (0.83,1.40)
	Current smoker	1.76 (1.21,2.56)	1.81 (1.24,2.62)	1.82 (1.25,2.64)	1.59 (1.03,2.46)	1.61 (1.04,2.48)	1.62 (1.05,2.49)
AIC		6740.871	6773.993	6743.304	5032.326	5034.715	5031.005

Data were represented as hazard ratios with a 95% confidence interval. In sensitivity analyses, MM and BMI were, respectively, omitted from the models.

divorced, or widowed had a higher significant mortality risk than those who lived with a partner/spouse. Furthermore, males were more likely to use alcohol daily and less likely to be never smokers than females in our study; therefore, sex-specific differences in MM patterns and mortality could be caused by lifestyle differences. Similar results confirmed in self-reported health status that older men with poorer healthy lifestyles had increased mortality risk compared to women (27).

Our research also found that for older men and women, being overweight or obese (BMI > 25 kg/m^2) is linked to lower mortality risk than having a normal weight (BMI < = 25 kg/m^2). Although some studies showed that individuals in young or middle age who were overweight (25 < BMI < 30) or had obesity (30 > =BMI) could have an increased risk of mortality compared with normal BMI (18.5 < BMI < =25) adults, there are other studies as well which show a BMI paradox particularly for older adults (aged ≥ 65-year-olds) (24). Moreover, BMI cannot always discriminate between body fat mass and lean tissue properly (28). In sensitivity analysis, we discovered a similar relationship using the waist-to-hip ratio instead of BMI. This paradoxical relationship has been shown in various cohort studies and meta-analyses for those aged over 65 years old. They reported less (29–31) or similar (32) mortality risk for overweight or obese individuals compared to normal weight in older persons. There is still a need to explore the effect of central adiposity on MM and then mortality development in older people. Another possible explanation is that the results pointing at a paradox might mostly be a consequence of misclassification bias, reverse causation, or collider bias (33).

Interestingly, although MM is associated with a higher HR of mortality in men compared to women (based on the general definition of having two or more diseases), the risk of all significant combinations of two and three diseases is higher in women compared to men. In our study, the risk of premature mortality for diseasecombination increased with the number of diagnoses, particularly in women, which is consistent with earlier research (7). Participants with three or four chronic diseases had a 25% higher risk of premature death than those who did not have a chronic disease, and the risk jumped to 80% for those with five or more diseases (34).

According to our findings, hypertension is the most common condition, both alone and in combination, which is consistent with past research (2, 35). Hypertension is strongly associated with risk of premature mortality among individuals with diabetes (36), cardiovascular (37), rheumatoid arthritis (38), and eye disease (39). Men's mortality risk decreased or remained constant when hypertension was combined with the pairs of diseases; however, there was no specific pattern in women's risk. Other studies showed that for the old population, hypertension is four times more common in postmenopausal women than in premenopausal women, but only three times more common in age-matched males (40). This sex disparity likely contributes to the lower estrogen level in postmenopausal women since estrogen acts as a protective factor in women (41). Additionally, anxiety and depression in women can increase the risk of hypertension (41). In our study, anxiety appears in the most prevalent combination for women, but these combinations do not show a significantly elevated risk of mortality. Other underlying mechanisms, such as renin-angiotensin, the sympathetic nervous system, the immunological system, lifestyle, and environmental factors could potentially explain sex differences in the presence of hypertension and cardiovascular diseases (42). We also found the heart disease-diabetes combination as the most hazardous in both male and female and it had a higher risk in women compared to men, even when combined with other diseases. Many studies also reported the increased risk of heart failure in the presence of diabetes. This increase might happen because diabetes can raise the risk of atrial fibrillation, and coronary heart disease, which are significant risk factors for heart failure (43). When heart disease-diabetes is combined with hypertension and eye diseases, respectively in trios, the risk decreased in men but remained almost constant in women. In addition, although the joint diseases had the same prevalence in our old men and women, when added into heart-diabetes-hypertension combination, it resulted in significant mortality in women. This finding is in line with other studies that cardiovascular disease is the leading cause of death among rheumatoid arthritis patients, accounting for around 35% of all deaths (44). In contrast to our findings, other studies have found that women suffering from joint disease have less cardiovascular risk compared to men (45, 46). They discovered that, although women are three times more likely than males to have rheumatoid arthritis, they are more protected from coronary artery disease and cardiovascular disease. Different factors such as estrogen level, blood vessel situation, menopausal status, coronary calcium score (46), disability (47) and other lifestyle factors such as alcohol use (48), physical activity (49), BMI (50), and smoking behavior (51) could explain the sex difference risk in diseases combination.

5. Strengths and weaknesses

One of the study's strengths was that it included the most common chronic diseases in the age group 65 and older that might have a significant impact on mortality in older people. Being a very large and informative dataset from the population-based KORA cohort study with older participants and their follow-up information is another strength of our research. We were able to investigate not only the combination of two diseases but also multiple different combinations of diseases due to the large sample size. This database also included data on demographic, sociodemographic, physical, and mental health characteristics, which enabled us to adjust our findings for a variety of MM-related factors.

One potential limitation of this study is that our disease information was collected by questionnaires and telephone interviews, which could result in recall and information biases due to misreporting and non-response in very sick participants. Furthermore, neither the severity of each disease nor geriatric syndromes such as pressure ulcers, incontinence, frailty, falls, functional decline, or delirium were considered in our research. We also did not know which disease occurred first in one individual, which would have allowed for a more exact interpretation. Furthermore, the prevalence of most diseases was relatively low in the KORA-Age population, which could explain the lack of a significant association between some disease combinations and the risk of mortality. Therefore, some of the differences in the strength of associations between MM combinations and mortality between men and women could be explained by the low power induced by the small number of cases in particular combinations of disorders. Furthermore, the data was gathered before the Corona Pandemic and therefore obviously analysis does not take into account the cause-specific mortality by SARS-CoV2.

6. Conclusion

The effects of morbidity patterns on mortality in older men and women are highly heterogeneous and depend on the specific disease combinations. Some diseases affected the MM prevalence, but they had no substantial impact on mortality risk. We suggest that future

research should look at the morbidity patterns in men and women separately, as they showed different patterns of mortality, which might be due to differences in risk factors profileAlthough hypertension, eye, and joint disease appeared in the most common combinations, these conditions were not as strongly associated with the risk of death as other diseases. In conclusion, MM prevalence itself does not predict mortality but depends on the different disease combination. In the KORA-Age population studied here it was heart disease together with diabetes alone or in combination with other diseases was associated with mortality. Future work should however include geriatric syndromes as well as MM prevalence to add to the understanding what factors contribute to a long and healthy life.

Data availability statement

The datasets presented in this article are not readily available because there is no participant consent for public data repositories. Requests to access the datasets should be directed to kora.passt@helmholtz-muenchen.de.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Bavarian Medical Association (08094). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA: conceptualization, methodology, statistical analyses, and original paper draft. AA, AP, BT, and BL: evaluation and interpretation. AA, AP, BT, BL, and MH: revision and editing. AP, BL, BT, MH, and K-HL: main study design, data curation, and quality assurance. AP: supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Health-related patterns and chronic kidney disease in the Brazilian population: National Health Survey, 2019

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Objective: The aim of this study was to identify patterns related to health and their association with chronic kidney disease (CKD) in the Brazilian population.

Methods: We used data from the National Health Survey (PNS), 2019. Participants were interviewed and answered questions related to socioeconomic and demographic information (gender, age, education, race/color), health conditions (presence of hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, overweight and CKD) and lifestyle (smoking, alcohol consumption, physical activity and food consumption). To identify patterns, we used exploratory factor analysis. We performed logistic regression models to describe the association of CKD with each pattern in crude models and adjusted for gender, age group, education level and race/color.

Results: A total of 90,846 individuals were evaluated. The prevalence of CKD was 1.49% (95% CI: 1.3–1.6). Three health-related patterns – metabolic factors, behavioral risk factors and behavioral protective factors – were identified by factor analysis. Metabolic factors were determined by the presence of hypertension, diabetes mellitus, hyperlipidemia and cardiovascular diseases. Behavioral risk factors were determined by smoking, alcohol consumption, regular consumption of soft drinks, sweets and artificial juices, and high salt consumption. The protective behavioral factors were established by the practice of physical activity and regular consumption of vegetables and fruits. Participants of the highest tertile for metabolic factors were more likely to have CKD in the adjusted model (OR=3.61, 95% CI: 2.69–4.85), when compared to those of the lower tertile.

Conclusion: The pattern referring to metabolic factors was associated with a higher chance of presenting CKD.

KEYWORDS

chronic kidney disease, health behavior, risk factors, factor analysis, public health

1. Introduction

Chronic kidney disease (CKD) is a significant global health problem. According to the Global Burden of Disease Study, in 2017, 697.5 million cases of all-stage CKD were recorded, for a global prevalence of 9.1% (8.5–9.8) (1). In a systematic review and meta-analysis of observational studies that estimated the prevalence of CKD in general populations, the global

prevalence was even higher, 11–13% (2). In 2017, the CKD ranked 12th in the ranking of the cause of mortality with 1.2 million deaths (1) and is expected to jump to 5th place in the ranking of the main causes of early death (3). In Brazil, it is estimated that 3–6 million people have CKD and this disease has as aggravating the fact that it is unknown by many people affected (4, 5).

The rate of CKD may increase in future, not only due to the growth and aging of the population, but mainly due to the increasing prevalence of arterial hypertension (AH), diabetes mellitus (DM), obesity and dyslipidemia (4, 6, 7), which are traditional risk factors for CKD (2, 8–10). Other lifestyle factors, such as smoking, sedentary lifestyle, alcohol abuse, excessive salt consumption and inadequate eating habits have been recognized as important predictors of CKD (9).

In addition to being prevalent, health risk factors are highly interrelated (11). Considering that the simultaneous occurrence of risk factors increases the chance of developing negative health conditions, studies have been concerned with determining how much factors and behaviors are aggregated in individuals. Evidence suggests that the concurrency of different risk behaviors may present a synergistic effect, thus resulting in a multiplicative deleterious effect, rather than an additive effect of each behavior (11, 12).

In this sense, some studies investigated multimorbidity patterns including CKD (13–15), other studies have identified dietary patterns related to CKD (16–19), but none of them included behavioral factors such as smoking, alcohol consumption and physical inactivity, which are also known to be more sensitive to interventions than clinical outcomes. In Brazil, some studies have researched the concurrency of risk behaviors for chronic non-communicable diseases (NCDs) in adults (20–22), however, only three studies identified patterns of risk behavior in a Brazilian national sample (12, 23, 24) and none of them associated these standards with CKD.

Besides, most of these studies performed co-occurrence analyses focusing on competing but independent behaviors. Analyses investigating underlying associations between competing behaviors, with clustering identified by divergences in observed and expected prevalence of combinations or by identifying latent or unobservable patterns (25), may be more relevant from the point of view of monitoring and planning of more effective multifactorial interventions (11), which should take into account substitute and complementary relationships between grouped health behaviors.

Thus, the aim of the study was to identify patterns related to health and their association with CKD in the Brazilian population.

2. Methods

2.1. Study population and sampling

The present study used data from the National Health Survey (PNS), a Brazilian household survey conducted in 2019 by the Brazilian Institute of Geography and Statistics (IBGE) in partnership with the Health Surveillance Secretariat of the Ministry of Health and the Oswaldo Cruz Foundation.

The sampling plan was defined by conglomerate in three stages of selection. In the first stage, the primary sampling units were stratified, consisting of sectors or groups of census tracts. The second stage consisted of households, and residents 15 years of age or older corresponded to the units of the third stage. The selection of a subsample of the primary sampling units was made by simple random sampling (26).

The estimated sample size was based on 108,525 households, and 94,114 individuals aged 15 years or older were interviewed. More details about the research are available in the publication of STOPA et al. (26)

2.2. Data collection and studied variables

Participants were interviewed and answered questions related to socioeconomic, demographic information, health conditions and lifestyle. The socioeconomic and demographic variables evaluated were: gender (male and female); age categorized into groups (15–29; 30–44; 45–59; 60 or more); education (without incomplete education/elementary school; complete elementary school/incomplete high school; complete high school/incomplete higher education; complete higher education) and race/color [white; black; brown and others (yellow and indigenous)].

Information on AH, DM, CKD, hypercholesterolemia and cardiovascular disease was based on self-reported previous medical diagnosis. In the identification of overweight, body mass index (BMI) was calculated according to self-reported weight and height. The cutoff point for overweight was BMI $\geq$ 25.0 kg/m^2 for adults (27) and BMI $\geq$ 27.0 kg/m^2 for the elderly (28).

Among the risk and protection factors related to lifestyle, we analyzed smoking (non-smoker, former smoker and smoker), alcohol consumption (heavy episodic drinking), physical activity and food consumption. Alcohol consumption, considering heavy episodic drinking, was defined as the intake of 60 g or more of alcohol (five or more doses of alcohol) on at least one occasion in the last 30 days (29). Two questions were used: "How often do you usually consume an alcoholic beverage? (I never drink, less than once a month and once or more a month)" and "In the last 30 days, did you consume five or more doses of alcoholic beverages on a single occasion? (yes and no)." A dose of drink was defined as the equivalent of a dose of cachaça, a glass of wine, a can of beer, a dose of whiskey or any other distilled alcoholic beverage. Heavy episodic drinking was considered when individuals answered "once or more a month" in the first question and "yes" in the last question. For physical activity, individuals who practiced at least 150 min of physical activity per week were considered active, considering four domains: leisure, work, commuting and domestic activities (30). Regarding food consumption, the frequency of weekly consumption of soft drinks, artificial juices, sweets (such as biscuit/stuffed cookie, chocolate, gelatin, candies and others), fruits or vegetables (such as lettuce, tomato, cabbage, carrot, chayote, eggplant, zucchini, excluding potatoes, cassava or yams) and beans were analyzed. Food consumption was considered regular when it occurred five or more times a week (6).

The perception of salt consumption was obtained considering the following question: "Considering freshly prepared food and processed foods, you think your salt intake is": very high, high, adequate, low and very low. Salt intake was categorized as adequate (adequate, low and very low) and high (high and very high).

2.3. Statistical analysis

For descriptive analysis, the following variables were considered, according to the presence of CKD: gender, age group, education level, race/color, AH, DM, hypercholesterolemia, cardiovascular disease,

overweight, physical activity, smoking, alcohol consumption, regular consumption of beans, regular consumption of vegetables, regular consumption of fruits, regular consumption of soft drinks, regular consumption of artificial juices, regular consumption of sweets and high salt consumption. The chi-square test was used to verify whether there is a statistically significant difference between individuals with and without CKD.

To identify patterns, we used exploratory factor analysis to reduce the initial number of variables in a smaller set of factors that represent, in a synthetic way, the information contained in the larger set of variables (31).

The adequacy of the data for factor analysis was initially evaluated with the Kaiser-Meyer-Olkin (KMO) sample adequacy measure. KMO assumes values between 0 and 1, and the lower values indicate that the variables have very little in common. A value of KMO = 0.62 was obtained, which means good adequacy (32).

The principal component analysis was used to extract the factors and the oblique promax rotation was performed to facilitate the interpretation of the factors. The determination of the number of factors to be retained considered the following criteria: the evaluation of the scree plot, the factor structure with loads of items above 0.30 (33), the lowest number of cross-loads of possible items, no factor with less than three items and a reasonable interpretation of the emerging factors.

Then, we identified three health-related patterns, named metabolic, risk behavior and protective behavior. Each individual had values assigned to each of the patterns, through regression models, according to their higher or lower adhering to the pattern. The values of each pattern were categorized into tertiles (the lowest category and the highest category represent the lowest and highest adhesion to a specific pattern, respectively). The first tertile of each pattern was used as a reference group.

Subsequently, we performed logistic regression models to describe the association of CKD with each pattern in crude models and adjusted for gender, age group, education level and race/color.

The analyses were performed in Stata software version 14.2, considering significance level of 5% and the effects of complex PNS sampling.

2.4. Ethical aspects

The PNS project was approved by the National Research Ethics Commission (CONEP) of the National Health Council (CNS) (opinion n. 3529376). The invited individuals who agreed to participate in the research signed the Free and Informed Consent Form.

3. Results

A total of 90,846 individuals were evaluated. The prevalence of CKD was 1.49% (CI 95%: 1.3–1.6). Regarding the characterization of the population studied, it is noteworthy that the majority of the study participants were women, aged between 30 and 44 years, brown and had completed high school education. A higher prevalence of CKD was found in older individuals ($p < 0.001$), with lower education level ($p < 0.001$) and white ($p = 0.015$; Table 1).

Among individuals with CKD, it was possible to observe a higher prevalence of AH (53.7%), DM (21.3%), hypercholesterolemia (33.4%), cardiovascular disease (20.5%) and lower physical activity (34.6%; Table 1).

Alcohol consumption and regular consumption of beans were more prevalent in the group of participants without CKD, while regular consumption of vegetables was higher in the group of people with CKD (Table 1).

Three health-related patterns – metabolic factors, behavioral risk factors and behavioral protective factors – were identified by factor analysis. These patterns explained 11.25, 9.34 and 9.33% of variance, respectively (Table 2). Together, they explained ~30% of the variance.

Regarding the characterization of these patterns, metabolic factors were determined by the presence of AH, DM, hyperlipidemia and cardiovascular diseases. Behavioral risk factors were determined by smoking, alcohol consumption, regular consumption of soda, regular consumption of sweets, regular consumption of artificial juices and high salt consumption. The behavioral factors of protection were established by the practice of physical activity, regular consumption of vegetables and regular consumption of fruits. The highest factorial loads were found in the metabolic pattern for AH, DM and hypercholesterolemia and in the behavior protective pattern for regular consumption of vegetables and fruits (Table 2). Higher factor loadings indicate greater adherence to the respective pattern.

The association of the patterns identified with CKD, stratified by tertiles, were presented in Table 3. Participants of the highest tertile for metabolic factors were more likely to have CKD in the crude model (OR = 4.39, 95% CI 3.33–5.79) and adjusted (OR = 3.61, 95% CI 2.69–4.85), when compared to those of the lower tertile. No significant association was observed between behavioral risk and protection factors and the presence of CKD.

4. Discussion

The findings of the present study showed a prevalence of CKD of 1.49%. In the factor analysis, three health-related patterns were identified, labeled as: metabolic factors, behavioral risk factors and behavioral protective factors. Only metabolic factors were associated with the chance of presenting CKD.

The prevalence of CKD in the Brazilian population is still uncertain (5). According to PNS data, the prevalence of self-reported CKD was 1.4% (34), as described in the present study. In a subsample of the PNS, in which laboratory tests were performed, the prevalence of CKD was 6.48% (35). The prevalence of CKD among participants of the Longitudinal Study of Adult Health (ELSA), in six research institutions in Brazilian capitals, was 8.9% (36). The difference in self-reported prevalence and that assessed by laboratory tests shows the high percentage of unknown cases of the disease. The hidden cases of the disease can be explained by the lack of screening for the disease and by the insidious and asymptomatic loss of renal function, being a major public health problem.

About the health-related patterns, Corsonello et al. (13) reported that CKD is associated with multimorbidity and was rarely observed without any concomitant disease, and AH and DM were among the co-ocurrent pairs of greater significance involving CKD. In addition, it is known that these factors are the main causes

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TABLE 1 Sociodemographic characteristics and prevalence of metabolic and behavioral factors, according to the presence of CKD. PNS, 2019.

	Variables	Total	CKD		Value of *p*
			No	Yes	
		% (CI 95%)	% (CI 95%)	% (CI 95%)	
Gender	Male	47.1 (46.8–47.4)	47.1 (46.8–47.5)	45.4 (42.7–48.1)	0.2
	Female	52.9 (52.6–53.2)	52.9 (52.5–53.2)	54.6 (51.9–57.3)	
Age group	15–29 years	19.5 (19.2–19.7)	19.6 (19.4–19.9)	7.4 (6.1–9.0)	**<0.001**
	30–44 years	29.4 (29.1–29.7)	29.6 (29.3–29.9)	19.3 (17.2–21.5)	
	45–59 years	26.0 (25.7–26.3)	25.9 (25.7–26.2)	32.2 (29.7–34.8)	
	60 years or more	25.0 (24.7–25.3)	24.8 (24.5–25.1)	41.1 (38.4–43.8)	
Education level	Uneducated/incomplete elementary school	33.1. (32.5–33.8)	34.1 (33.5–34.8)	46.7 (42.2–51.3)	**<0.001**
	Complete elementary school/incomplete high school	17.1 (16.6–17.6)	17.4 (17.0–17.9)	17.8 (14.3–22.0)	
	Complete high school/incomplete higher education	34.1 (33.5–34.6)	33.4 (32.8–33.9)	25.1 (21.4–29.2)	
	Complete higher education	15.7 (15.1–16.3)	15.0 (14.4–15.6)	10.4 (7.9–13.5)	
Race/color	White	43.6 (42.8–44.3)	42.9 (42.1–43.6)	48.2 (43.6–52.8)	**0.015**
	Black	11.2 (10.8–11.6)	11.4 (11.0–11.8)	10.0 (7.4–13.4)	
	Brown	43.7 (43.0–44.3)	44.2 (43.6–44.9)	40.4 (36.1–44.8)	
	Others (indigene or yellow)	1.5 (1.3–1.7)	1.5 (1.3–1.7)	1.4 (0.8–2.3)	
Arterial hypertension		24.8 (24.3–25.2)	23.9 (23.4–24.3)	53.7 (49.1–58.3)	**<0.001**
Diabetes mellitus		8.0 (7.7–8.3)	7.7 (7.5–8.0)	21.3 (17.8–25.2)	**<0.001**
Hypercholesterolemia		14.8 (14.4–15.2)	14.5 (14.1–14.9)	33.4 (29.0–38.1)	**<0.001**
Cardiovascular disease		5.2 (5.0–5.5)	4.8 (4.6–5.1)	20.5 (16.8–24.7)	**<0.001**
Overweight		61.6 (61.0–62.2)	61.6 (61.0–62.2)	64.7 (60.2–69.0)	0.174
Physically active		46.3 (45.6–47.0)	46.2 (45.6–46.8)	34.6 (30.4–39.2)	**<0.001**
Smoking		11.4 (11.0–11.8)	12.1 (11.8–12.5)	12.1 (9.3–15.6)	0.976
Alcohol consumption		14.2 (13.8–14.6)	14.6 (14.1–15.0)	9.4 (6.8–12.7)	**0.004**
Regular consumption of beans		68.0 (67.4–68.7)	68.2 (67.6–68.9)	63.5 (58.9–68.0)	**0.039**
Regular consumption of vegetables		55.1 (54.4–55.7)	54.0 (53.4–54.7)	59.2 (54.7–63.6)	**0.026**
Regular consumption of fruits		45.4 (44.7–46.0)	44.2 (43.6–44.8)	48.1 (43.6–52.6)	0.087
Regular consumption of soda		9.2 (8.9–9.6)	9.6 (9.2–10.0)	7.8 (5.4–11.2)	0.265
Regular consumption of artificial juices		13.3 (12.8–13.7)	13.8 (13.4–14.3)	11.0 (8.2–14.5)	0.11
Regular consumption of sweets		15.4 (14.9–15.9)	15.7 (15.2–16.2)	13.1 (10.1–16.8)	0.164
High salt consumption		12.5 (12.0–13.0)	12.9 (12.4–13.4)	11.2 (8.6–14.4)	0.279

Bold data reflect statistical significance ($p < 0.05$).

of CKD worldwide (37). In agreement, this study showed the importance of metabolic factors, which include AH and DM, in the development of CKD.

AH may be the cause or consequence of CKD. In hypertensive patients, chronically increased systemic arterial pressures cause remodeling of the aferent arteriola and reduce its capacity for contraction and dilation. Over time, increased blood pressure and pressure transmitted to the kidney lead to nephrosclerosis and progressive loss of renal function (38).

With regard to DM, chronic hyperglycemia leads to metabolic dysregulation due to increased glycolysis, which regulates several distinct pathways and leads to glomerular hyperfiltration and proteinuria. In addition, hyperglycemia causes hemodynamic changes in the kidney, oxidative stress, inflammation, hypoxia and deregulation of the Renin-Angiotensin-Aldosterone system (RAAS), which causes adverse changes in the kidney vessels, such as thickening of the glomerular basement membrane (39–42).

In the study by Liu et al. (43), the relationship between cardiovascular diseases and CKD was demonstrated, evidencing a deep association between them, and the disease of one organ causes dysfunction in the other. Thus, it is assumed that two main mechanisms can explain this association. The kidney can release hormones (44, 45), enzymes and cytokines (44, 46) in response to kidney injury, which leads to changes in blood vessels. In addition, CKD mediators and hemodynamic changes contribute to heart damage (44, 47).

Likewise, in the study by Chang et al. (48) it has been reported that older adults with hyperlipidemia and cardiovascular diseases were at higher risk of developing CKD. This association is due to the fact that patients with CKD tend to present physiological and biochemical

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alterations that lead to imbalance in lipid profile. In addition, triglyceride levels are increased by 30–50%, which is related to the reduction of hepatic lipase and lipoprotein lipase activity. There is a decrease in HDL-cholesterol, increased lipoprotein A and the accumulation of LDL-cholesterol. Thus, there is a prevalence of oxidized LDL molecules, which are captured by immune system cells, with consequent contribution in the formation of atherosclerotic plaque. Another mechanism related to dyslipidemia is its ability to damage mesangial and endothelial cells, which facilitates the progression of kidney injury. The mechanisms involving dyslipidemia and CKD are not yet fully understood, but it is possible to highlight some more relevant factors such as insulin resistance and increased oxidative stress (49, 50).

TABLE 2 Factor structure of metabolic, behavior risk and behavior protective in the Brazilian population. PNS, 2019.

Factors	Metabolic	Behavior risk	Behavior protective
Arterial hypertension	**0.7166**	−0.0271	0.0364
Diabetes mellitus	**0.6091**	−0.0362	0.0254
Hypercholesterolemia	**0.6186**	0.0565	0.1010
Cardiovascular disease	**0.4982**	0.0746	0.0688
Overweight	0.2473	0.0132	−0.1935
Smoking	0.0136	**0.3949**	−0.1658
Alcohol consumption	−0.1092	**0.4516**	−0.0188
Regular consumption of soda	0.0097	**0.5671**	−0.0515
Regular consumption of sweets	0.0184	**0.4868**	0.1856
Regular consumption of artificial juices	0.0218	**0.4354**	−0.0086
High salt consumption	0.0431	**0.4762**	−0.0731
Regular consumption of beans	0.0230	0.0462	0.1012
Regular consumption of vegetables	0.0605	0.0385	**0.7417**
Regular consumption of fruits	0.1034	−0.0956	**0.7392**
Physically active	−0.2609	0.1064	**0.4056**
Variance explained (%)	11.25	9.34	9.33
Cumulative variance (%)	11.25	20.59	29.92

Bold data reflect that the variable has loaded in the pattern.

The findings of this study allowed the identification of a higher chance of having CKD for those individuals in the highest tertile of the pattern called metabolic factors. Therefore, the importance of evaluating these factors simultaneously is highlighted, because the individual hardly has only one isolated factor and this demonstrates the role of multimorbidity in this disease (51, 52).

In relation to the other patterns analyzed, it is noteworthy that this study did not observe a significant association of behavioral risk factors and behavioral factors of protection with CKD, similar to the results presented by Foster et al. (53), who found no association between CKD and physical activity, smoking and alcohol consumption. In the Brazilian context, study with a representative sample of the population, in univariate analysis, found an association between CKD and some behavioral factors, such as smoking, excessive alcohol consumption and physical activity, but also found no association between CKD and regular intake of fruits and vegetables, consumption of red meat with fat and excessive consumption of salt. In an adjusted analysis, considering behavioral factors, only smoking remained associated with CKD (35).

However, other studies have shown that behavioral factors may influence the presence and development of CKD (13, 16, 18, 24, 48, 54). Regarding the association of dietary patterns with CKD, studies conducted with the populations of Iran (16), United Kingdom (55) and China (19, 56) found that dietary patterns high in fat and sugar were associated with higher chances of incidence of CKD, while plant-rich dietary patterns were associated with reduced risk of CKD. However, due to the diversity of eating habits in the world, the results found in these studies cannot be extrapolated to other populations (17). In addition, the absence of association of behavioral factors with CKD in the present study may be due to cross-sectional design and reverse causality, as lifestyle risk and protection behaviors may be altered due to the diagnosis and guidance given by health professionals to delay the progression of CKD.

Although patterns related to risk and protective factors have not been associated with CKD, it can be inferred as a practical application the encouragement of protective behaviors and the reduction of risk behaviors. Thus, investing in NCD prevention actions can be a good strategy to prevent the development and progression of CKD. In this sense, another practical application is the strengthening and

TABLE 3 Association of the three health-related patterns with CKD, by tertile. PNS, 2019.

	Crude model			Adjusted model[a]		
	OR (CI 95%)			OR (CI 95%)		
	1st tertile	2nd tertile	3rd tertile	1st tertile	2nd tertile	3rd tertile
Metabolic factors	1	1.18	4.39	1	1.11	3.61
		(0.84–1.66)	(3.33–5.79)		(0.79–1.56)	(2.69–4.85)
Behavioral risk factors	1	0.98	0.8	1	1.03	0.98
		(0.78–1.22)	(0.63–1.02)		(0.82–1.29)	(0.77–1.24)
Behavioral protective factors	1	1.01	1	1	0.96	0.89
		(0.80–1.28)	(0.79–1.27)		(0.76–1.22)	(0.70–1.14)

[a]Adjusted for gender, age group, education level and race/color.

implementation public policies aimed at CKD with the objective of encouraging the promotion of healthy habits, which makes it possible to prevent the occurrence of NCDs, such as AH and DM, and, consequently, CKD.

In Brazil, the implementation of public policies for the prevention and management of kidney diseases is recent and incipient (57). In 2004, the *National Policy for Attention to Patients with Kidney Disease* was instituted by Ordinance n° 1.168/2004. In 2006, the Ministry of Health published guidelines for the *Clinical Prevention of Cardiovascular, Cerebrovascular and Chronic Kidney Disease*, which recommended early screening in primary care in risk groups, such as AH, DM and family history of CKD. In 2014, the Ministry of Health published Ordinance n° 389/2014, which defined the criteria for the organization of the line of care for people with CKD and published the *Clinical Guidelines for the Care of Patients with Chronic Kidney Disease in the Sistema Único de Saúde (SUS)*. In addition, reinforcing that the main action in the prevention of CKD cases is the reduction and treatment of the main risk factors for the development of kidney disease, in 2011, the Federal Government prepared the *Strategic Action Plan to Combat Chronic Noncommunicable Diseases in Brazil 2011–2022*, which was recently updated, considering the period 2021–2030 (57).

Despite all the efforts made toward the reduction of chronic conditions, it is observed that challenges still need to be overcome to ensure improved care for people with CKD. A recent study shows flaws in the screening of people at risk for CKD in primary health care in Brazil (58) and worldwide (59). It also highlights the need for actions to improve the control of the most prevalent conditions in the adult population, that is, AH, DM and dyslipidemia (58, 59). Therefore, it is necessary to implement CKD control and prevention strategies, which consist of the quality and effectiveness of existing programs in primary care, as well as the degree of motivation, training and continuing education of health professionals (57).

This study has strengths and limitations. Regarding the strengths, the sample size of the study stands out, being representative of the Brazilian population. In addition, different factors were analyzed: metabolic, risk and protective behavior. Moreover, this study used factor analysis, a statistical analysis technique that allows grouping the variables, according to the correlations between them, that is, with this analysis the pattern of the variables and the adhering to this pattern by the individuals is better represented, surpassing the analysis of the occurrence of isolated factors or the co-occurrence of factors.

As for limitations, it is found that the design of the cross-sectional study does not allow establishing a causal relationship. Consequently, the possibility of reverse causality also exists. Future studies using prospective cohorts are needed to explain and confirm a causal relationship between health-related patterns and CKD. In addition, there may have been interviewer bias and participants' memory bias, since the data were self-reported. Also noteworthy is the possibility of underdiagnosis, especially of metabolic factors, leading to underestimated prevalence. Regarding the excessive salt consumption variable, the results of the present study cannot be seen as an approximation of the real salt consumption by the Brazilian adult population, since the agreement between the perceived and actual level of salt consumption is distorted (Brazilian consume, on average, almost twice the World Health Organization recommendations, yet a small fraction acknowledge their excessive intake) (60). Finally, it was not possible to stratify the severity of the disease.

Accordingly, our study made it possible to identify that the pattern referring to metabolic factors was associated with a higher chance of presenting CKD, while patterns related to behavioral risk factors and behavioral protective factors were not significantly associated. This suggests that underlying diseases, such as AH and DM, may be more strongly linked to the chance of CKD than behavioral factors such as diet and physical activity.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.ibge.gov.br/estatisticas/sociais/saude/9160-pesquisa-nacional-de-saude.html?=&t=downloads.

Ethics statement

The 2019 National Health Survey project was forwarded to the National Research Ethics Committee (CONEP)/National Health Council (CNS) and approved under Opinion No. 3,529,376, issued on 23 August 2019. The participants provided their written informed consent to participate in this study.

Author contributions

LCMS and NRS contributed to the formal analysis of the data. CMA, AEMR, and LSS contributed to conceptualization and visualization, formal analysis of the data. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Identifying lifestyle factors associated to co-morbidity of obesity and psychiatric disorders, a pilot study

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Obesity and psychiatric disorders are linked through a bidirectional association. Obesity rates have tripled globally in the past decades, and it is predicted that by 2025, one billion people will be affected by obesity, often with a co-morbidity such as depression. While this co-morbidity seems to be a global health issue, lifestyle factors associated to it differ between countries and are often attributed to more than one factor. Prior obesity studies were performed in Western populations; this is the first study that investigates lifestyle factors relating to obesity and mental health of the diverse population in Qatar, a country that has witnessed tremendous lifestyle change in a short time. In this pilot study, we surveyed 379 respondents to assess and compare the lifestyles of Qatar residents to the global population. However due to the high proportion of responses from the United Kingdom (UK) residents, we have made comparisons between Qatar residents and UK residents. We used chi-square analysis, spearman rank correlation and logistic regression to compare the lifestyle factors of individuals suffering from both increased BMI and mental health conditions. The types of food consumed, stress, exercise frequency and duration, alcohol and tobacco consumption, and sleep duration, were explored and results argue that different lifestyle factors can contribute to the same health condition, suggesting different mechanisms involved. We found that both groups reported similar sleep durations (p=0.800), but that perception of sleep (p=0.011), consumption of alcohol (p=0.001), consumption of takeaway food (p=0.007), and physical activity significantly varied between the groups (p=0.0001). The study examined the predictors of comorbidity in Qatar as well as UK populations using multivariate logistic regression analysis. The result of the study showed no statistical association between comorbidity and the predictors drinking habit, smoking, physical activity, vegetable consumption, eat outs, and sleep perception for the Qatar population, and for the combined population. This study, however showed a significant association (p=0.033) between sleep perception and comorbidity for the UK population. We conclude that further analysis is needed to understand the relationship between specific lifestyle factors and multimorbidity in each country.

KEYWORDS

obesity, overweight, Qatar, UK, nutrition, depression

1. Introduction

Over the last three decades, Qatar has witnessed an increase in citizens that are either overweight or obese (1). Simultaneously, anxiety and depressive disorders are the most common psychiatric disorders in Qatar, with prevalence being comparable to the rest of the world (2).

Many co-morbidities have been associated with practicing an unhealthy lifestyle, including obesity, psychiatric disorders, diabetes type 2, an increased risk of developing certain cancers, osteoarthritis, and cardiovascular disease (3–7). Notably, psychiatric disorders have been associated with having a BMI greater than 25 (8). Individuals with low self-esteem and distorted body image suffer from poor mental health, and those with poor mental health have displayed a tendency to over-eat. Both of these factors, overeating and psychiatric disorders impact an individual's quality of life and morbidity (9).

While the co-morbidity between psychiatric disorders and BMI greater than 25 has been observed in various countries, we inquire on whether the lifestyle factors associated to it are the same. Is there a "one-size-fits-all" approach to targeting this co-morbidity in terms of behavioral changes? The following pilot study aims at exploring this question by comparing the lifestyle between Qatar and a western country.

Originally, the survey was distributed through social media, and the country from which we received most answers beside Qatar was UK. This is not surprising as around 22,000 UK citizens are currently residing in Qatar, whilst Qatar citizens and businesses have over £40 billion in investments in the UK, and around 100,000 Qataris regularly visit the UK for travel and education (10). Despite differences such as climate, population, and culture, the two countries are connected on multiple levels.

To shed more light on the role of each lifestyle factor and their interactions, this paper looks to analyze the cultural and environmental lifestyle factors of those with a psychiatric disorder and BMI greater than 25 residing in Qatar and compare it to those residing in the UK to see if there are any similarities or differences in their lifestyles.

Qatar is a small peninsula located in the Persian Gulf. It has a population of approximately 2.6 million people as of 2021 (11), while the UK has a much larger population than Qatar at over 67 million in 2020 (12). Life expectancy in both Qatar and the UK is 79 years old for males and 82 and 83 years old, respectively, for females. Both countries despite the geographical distance have very similar national dishes, both being based around rice and spices. A consensus by Cloud Based Human Resource Software (CIPHR) found that 39% of people resident in the UK list money worries as a main stressor, whilst a study from Qatar concluded that work pressure was the root cause of stress in Qatar (13, 14).

Food is an important part of Qatari and Arabic culture, with countries in the Gulf region known for their hospitality. Qatar has also become a melting pot of culture whereby it is easy to access a variety of cuisines, contributing to Qatar residents consuming more animal proteins, fat, and refined carbohydrates. Currently, it is difficult to compare nutrition in Qatar vs. UK because most studies completed in Qatar focus specifically on Qatar nationals and not Qatar residents, which does not represent a true statistic since the large expatriate population is thus excluded. A previous study has shown that 70.1% of Qatar citizens had a BMI over 25 (15). Another study investigated rates of overweight and obesity in school-age children who were both citizens and residents and found that Qatari nationals were 1.4 times more likely to be obese than non-Qataris (16). Indeed, the types and volume of food consumed between the two groups has been showed to be different, Qatari individuals consuming around 4,275 kcal daily, substantially more than non-Qatari households, which consume around 2,424 Kcal daily (17). Dining out and purchasing takeaway food is common in Qatar, unlike in the UK (15). In comparison, the average daily intake in the UK is still lower at 1764 Kcal, with 56.8% of the calories coming from ultra-processed foods (18).

The consistently high temperatures in Qatar, which average 45 degrees Celsius and humidity of up to 94% in the summer months, constrain most outdoor activities and sports to the winter months. Thus, the temperature not only affects people's ability to exercise but also their daily routines. During the summer months, it is common for people to wait until later in the evening to socialize, meaning that they go to bed later and potentially sleep less, as work and school hours tend to start relatively early in the morning. Whilst in the UK 38% of men and 23% of women regularly take part in aerobic exercise and strength training (19).

The combination of low physical activity levels, less sleep, and a diet high in processed foods has been shown to negatively impact individuals' mental health (20). To gain insight into the local impact of a country's culture on the lifestyle of its residents, this study aimed to compare the lifestyle and health of residents of Qatar and the UK. We designed an observational cross-sectional study that was conducted between August 2021 and March 2022 to find answer the following questions: How different is diet and nutrition in Qatar and UK? How different is alcohol consumption in Qatar and UK? How different is tobacco use in Qatar and UK? How different is sleep in Qatar and UK? How different is physical activity in Qatar and UK? What correlations between lifestyle factors, BMI and neuropsychiatric disorders can be revealed by this comparison?

2. Methods

2.1. Sample population

We designed a questionnaire for the general public according to the protocol approved by the institutional review board. The questionnaire was prepared using Qualtrics software in the English language, and links were generated for distribution via internal email and relied on social media sharing, via Instagram, Twitter, and Facebook. The questionnaire was open to participants globally who were over the age of 18 years old and were able to read English. In total, 384 responses were recorded from participants all over the world, most of which were collected during the first few weeks of the release (August 2021). Table 1 represents the number of respondents and their country of residence.

For the sake of this present analysis, only respondents who filled both criteria of BMI > 25 and a psychiatric disorder have been considered for the comparison. Respondents having a BMI > 25 and a psychiatric disorder is an example of co-morbidity, which is a condition of having two or more diseases at the same time.

2.1.1. Questionnaire

The lifestyle questionnaire included 40 questions on social demographic variables, exercise, sleep, diagnosed diseases, nutrition,

TABLE 1 Country and number of respondents to the questionnaire.

Country of residence	Number of respondents	Relative frequency %
Qatar	294	77.57%
UK	63	16.62%
France	5	1.31%
Saudi Arabia	3	0.79%
UAE	3	0.79%
Oman	2	0.52%
Egypt	2	0.52%
United States of America	2	0.52%
South Korea	1	0.26%
Bahrain	1	0.26%
Spain	1	0.26%
Russia	1	0.26%
Philippines	1	0.26%
Total	379	100%

stress and depression, alcohol and tobacco consumption. We constructed the questions so that evidence-based feedback was provided to the participants based upon their answers. The subsections below detail the questions and answers used for this paper. A table of all the questions asked and the scoring assigned to answers can be found in Supplementary File (S1). We also obtained approval from the American College of Lifestyle Medicine to feature ACLM's flyers in between question blocks as a means to advocate for healthy lifestyle choices.

2.1.2. Social demographic variables

The questions used to assess the social demographic variables for this data set were not scored and were collected in the following format: Height (Answer recorded in cm), Weight (Answer recorded in kg) Country of residence (Qatar, Other. If other is selected prompted to answer with country name)

2.1.3. Exercise

A disclaimer was given at the start of the subset of questions: Medical disclaimer: This quiz does not provide medical advice. It is intended for informational purposes only. According to the American College of Sport Medicine guidelines and the American College of Lifestyle Medicine, if you have symptoms of metabolic disease, cardiovascular disease or renal disease, or if you have been diagnosed with one of these diseases, you must obtain medical clearance before engaging in any exercise. A single question was used from the data set to assess exercise between the two groups. Answers were scored and feedback given dependent on the participants answer. The exercise variable was collected in the following format: Days exercised in a week (0, 1–3, 4–6, 7). For the logistic regression analysis, we grouped the results into two groups, those who did 0 days exercise and those who 1 day or more.

2.1.4. Sleep

Two questions from the data set were used for the sleep section. Sleep duration was scored, and feedback given dependent on the participants answer. Perception of enough sleep was not scored. Sleep variables were collected in the following format: Hours slept in an average night (Less than 4, 4–6 h, 7–9 h, 10+ hours), perception of having enough sleep (Yes, no). For the logistic regression analysis, we grouped the results of sleep duration into two groups, those who slept less than 4 h and those who slept 4 or more hours.

2.1.5. Diseases

A single question was used to assess the diagnosed diseases for this data set and was not scored. The diagnosed disease variable was collected in the following format: Have you ever been diagnosed with any of the following medical conditions by a GP/physician? Diabetes type 1, Diabetes type 2, Cardiovascular disease, Anxiety, Obesity, Cancer (if selected prompted to name which type), Inflammatory bowel disease, Rheumatoid arthritis, Autoimmune disease, Autism, Depression, Schizophrenia, Bipolar, Alzheimer's, Parkinson's, Arthritis.

Two questions from the data set were used for self-reported stress and depression, both were scored, and feedback given dependent on the participants answer. The variables were collected in the following way: Depression scale- Over the last 2 weeks, how often have you been bothered by any of the following problems? 1. Little interest or pleasure in doing things, 2. Feeling down, depressed, or hopeless, 3. Trouble falling or staying asleep, or sleeping too much, 4. Feeling tired or having little energy, 5. Poor appetite or overeating, 6. Feeling bad about yourself or that you are a failure or have let yourself or your family down, 7. Trouble concentrating on things, such as reading the newspaper or watching television, 8. Moving or speaking so slowly that other people could have noticed. Or the opposite being so fidgety or restless that you have been moving around a lot more than usual, 9. Thoughts that you would be better off dead, or of hurting yourself (Not at all, Several days, More than half the days, Nearly every day). The depression scale used is from the American Psychological Association and total scores of 1–4 were classed as minimal depression and not counted. Perceived stress scale- In the last month, how often have you felt that you were unable to control important things in your life? In the last month, how often have you felt confident about your ability to handle your personal problems? In the last month, how often have you felt that things were going your way?

In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? (Never, almost never, sometimes, fairly often, very often). The stress scale used is from the American College of Lifestyle Medicine and scored of 0–4 were classed as low stress and not counted.

2.1.6. Nutrition

Three questions from the data set were used for the nutritional comparison, two were scored, and feedback given dependent on the participants answer. The nutrition variables were collected in the following format: Vegetables consumed daily (1, 2, 3, 4+), Takeaways/ times dined out in a week (0,1,2,3, 4+), Food type most eaten 1 = most eaten, 8 = least eaten (red meat, poultry pasta, cheese, pizza/ sandwich/ hamburger, vegetable, pastries/sweets). For the logistic regression analysis, we grouped the results into two groups, for vegetable consumption those who ate less than 4 servings of vegetable and those who ate four or more servings of vegetables. For takeaways/dining out the results were grouped into those who dine out/ eat takeaway less

than 3 times a week and those who dine out/ eat takeaway 3 or more times a week.

2.1.7. Alcohol and tobacco consumption

Two questions from the data set were used for alcohol and tobacco consumption, both were scored, and feedback given dependent on the participants answer. The variables were collected in the following format: Consumption of alcohol (yes, no), use of nicotine products (yes, no).

2.2. BMI calculation

The formula used to calculate BMI is: (person's weight in kilograms) divided by their squared height in meters.

2.3. Psychiatric disorder assessment

The Patient Health Questionnaire (PHQ-9) of the American Psychological Association was used to assess depression. The assessment includes DSM-IV depression criteria and other leading major depressive symptoms into a brief self-report set of nine questions commonly used for screening and diagnosis (21). The second scale used is the perceived stress scale- 4 (PSS-4) (22). For both scales, participants who scored 5 and above (at least mild depression) were counted as having a psychiatric disorder.

2.4. Statistical analysis

SPSS 26 software was used for descriptive and statistical analysis. The frequency and percentages for nominal variables were described. Pearson's Chi-square test for categorical variables was used to analyze the lifestyle variables of the respondents from Qatar and UK. All Chi-square tests used were two sided at the level $\alpha = 0.05$. A Spearman rank correlation was done to analyse the correlations between independent variables. Multivariate logistic regression analysis was used to determine if the independent variable has any effect on the dependent variable, co-morbidity. A second logistic regression test was conducted with country of residence entered as an independent variable. The results of the logistic regression analysis were presented as value of p, odds ratio (OR) and 95% confidence interval (95%CI). The case processing summary for Qatar (Supplementary Table 1) and the UK (Supplementary Table 2) and parameter estimates for Qatar (Supplementary Table 12) and the UK (Supplementary Table 13) containing the descriptive data output from the logistic regression analysis can be found in the supplementary file to reduce the number of tables in the body if the paper.

3. Results

3.1. Co-morbidity assessment

Of the respondents to the questionnaire, 294 were resident in Qatar and 63 were resident in the UK. Of those respondents, 104 (35.37%) from Qatar and 28 (40.57%) from the UK had the co-morbidities of a BMI >25 and psychiatric disorder. The percentages of respondents from Qatar and UK with the co-morbidity are displayed in Figure 1. The respondents were then separated into groups dependent on country of residence, the number of diagnosed morbidities (Table 2) and types of diseases (Table 3). The condition most frequently reported by participants was "Psychiatric disorders" (Table 3). In total, 22 respondents from Qatar and 11 from the UK were diagnosed by a doctor as having a psychiatric disorder (Table 4), the remaining 99 did not report it but were scored with at least a mild depression or mild perceived stress using our validated scales. A chi-square test was used to assess if there was a statistical difference between those diagnosed by a doctor and was found to be significantly different between countries with a p-value = 0.013. Eleven respondents from Qatar and zero respondents from the UK were diagnosed as being obese by a doctor (Table 4), the remaining 121 were concluded by the calculation of reported height and weight as per the formula described in the methods section.

3.2. Sleep assessment

The number of responses received for the sleep assessment questions were n = 28 for the UK, while Qatar had $n = 102$ responses for hours slept and $n = 103$ responses for perception of having enough sleep (Table 5). A chi-square test was used to assess average hours slept per night by country of residence. The chi-square test was not statistically significant, x^2 (1, $N = 130$). =0.924, p-value = 0.670.

Among the UK residents, 25% had the perception they had enough sleep, whilst 75% felt they did not get enough sleep in an average night. For Qatar residents, 52.4% felt they had enough sleep, and 47.6% felt they did not get enough sleep in an average night. A chi-square test was used to assess whether country of residence was related to the perception of having enough sleep. The Pearson chi-square test was statistically significant, x^2 (1, $N = 131$) =6.656, p-value = 0.011, with Phi (φ) coefficient of −0.225, indicating a small relationship.

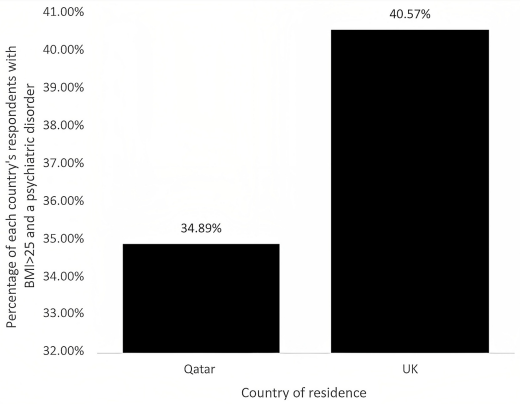

FIGURE 1
Co-morbidity of psychiatric disorder and BMI>25 in Qatar's and UK's respondents. Percentages correspond to the percentage of respondents from respective country who had both a BMI>25 and a psychiatric disorder.

TABLE 2 Number of morbidities diagnosed by a doctor in all the respondents.

Number of morbidities	Number of respondents[a]	Relative frequency %
1 disease	86	66.66%
2+ diseases	43	33.33%
Total	129	100%

[a]Number of respondents who answered this question in the questionnaire, $n = 129$.

TABLE 3 Morbidities diagnosed by a doctor in all respondents.

Diagnosed morbidity type	Number of respondents[a]	Relative frequency %
Psychiatric disorders	92	53.17%
Obesity	25	14.45%
Autoimmune	19	8.09%
Type 2 diabetes	11	6.35%
IBD	7	4.04%
Arthritis	7	4.04%
Cardiovascular disease	5	2.89%
Rheumatoid arthritis	4	2.31%
Type 1 diabetes	3	1.73%
Total	173	100%

[a]Number of respondents who answered this question in the questionnaire, $n = 173$.

3.3. Nutrition and exercise assessment

The number of UK respondents who answered the nutrition and exercise assessment questions was $n = 28$, and for Qatar $n = 104$ for take away and dine out and for daily vegetable consumption, and $n = 103$ for days of exercise per week (Table 5). A chi-square test was used to assess whether weekly take away/ dining out consumption was related to country of residence. The chi-square test was statistically significant, x^2 (1, $N = 132$) =13.353, p-value = 0.007, with Phi (φ) coefficient of 0.326, indicating a small to medium relationship.

The percentage of Qatar residents who consume less than the recommended two portions of vegetables per day is 49%, while the percentage of UK residents is 28.6%. A chi-square test was used to assess whether daily vegetable consumption was related to country of residence. The chi-square test was not statistically significant, x^2 (1, $N = 134$) =8.604, p-value = 0.058.

The top five most eaten foods in Qatar were poultry, vegetables, rice, red meat, and pasta (Supplementary Table 14). This information was collected as part of the questionnaire; however, respondents were not asked how these foods were cooked and consumed (i.e., fried, baked, part of a dish, as an individual item, etc.).

The percentage of respondents with the co-morbidity who exercised 0 times a week was 30.1% for Qatar vs. 7.1% for UK. A chi-square test was used to assess whether days of exercise per week was related to country of residence. The chi-square test was statistically significant, x^2 (1, $N = 131$) =20.409, p-value = 0.0001, with Phi (φ) coefficient of 0.405, indicating a small to medium relationship between the country of residence and the number of days exercising per week.

3.4. Risky substances

The number of respondents with the co-morbidity from UK who provided data on risky substances was $n = 28$ and Qatar $n = 103$ (Table 5). Meanwhile, 22.3%. of Qatar respondents reported that they consume alcohol, vs. 53.6% of UK respondents. A chi-square test was used to assess whether alcohol consumption was related to country of residence. The chi-square test was statistically significant, x^2 (1, $N = 131$) =10.434, p-value = 0.001, with Phi (φ) coefficient of 0.282, indicating a small to medium relationship between the country of residence and alcohol consumption.

The percentage of Qatar respondents with the co-morbidity that use tobacco products was 13.6%. The percentage of UK residents that use tobacco products was 6.7%. A chi-square test was used to assess whether tobacco use was related to country of residence. The chi-square test was not statistically significant, x^2 (1, $N = 118$), p-value = 0.689.

3.5. Logistic regression

Spearman's correlation test (Table 6) was conducted to see the correlation between the predictor variables as an assumption check for the logistic regression and found no significant correlation between the independent variables (None of the correlation coefficients are more than 0.6 or less than −06).A multivariate logistic regression model (Table 7) analyzed the effect of drinking habit (alcohol consumption), smoking (use of nicotine or tobacco products), physical activity (do you exercise regularly?), vegetable consumption (daily vegetable servings), eat outs (dine outs or take aways per week), hours slept per night and perception of having enough sleep on comorbidity in Qatar population ($N = 294$) and UK ($N = 63$) separately, and also for the combined population. The logistic regression model showed no statistical significance when all the predictor variables were considered and comorbidity for Qatar population and the population as a whole, however for UK population, significance at $p < 0.05$ level demonstrated a statistical association for sleep perception (do you feel you are getting enough sleep?) and comorbidity, OR. 3.415 (95% CI = 1.105, 10.552), $p = 0.033$ (Table 8).

4. Discussion

4.1. A silent co-morbidity: the problem of awareness

An important proportion of respondents from Qatar (89.42%) was found with BMI greater than 25. Our survey noted that only 25% of those who had a BMI greater than 25 and a psychiatric disorder had been diagnosed by a doctor. The remaining 75% self-identified via the questionnaire. This has been previously highlighted in a study that found that only 6.7% of men and 22.2% of woman correctly identified themselves as being obese (23).

Having a BMI greater than 25 has been linked to co-morbidities, such as metabolic syndrome, type 2 diabetes, and cardiovascular disease (24) which are now the leading causes of deaths in the world (25). In this study, we have observed that at least half of those with

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TABLE 4 Respondents with the co-morbidity (BMI>25+psychiatric disorder) and their diagnosis status.

		Qatar	UK	Chi-square	*p*-value
Psychiatric disorder diagnosed by scale scoring	Yes	82 (82.8%)	212 (82.2%)	0.021	0.884
	No	17 (17.2%)	46 (17.8%)		
Psychiatric disorder diagnosed by physician	Yes	22 (66.7%)	272 (84%)	6.156	0.013
	No	11 (33.3%)	52 (16%)		
BMI25 > diagnosed by a physician	Yes	12 (100%)	282 (81.7%)	2.661	0.136
	No	0 (0%)	63 (18.3%)		
BMI25 > diagnosed by BMI calculator	Yes	92 (76.7%)	202 (85.2%)	4.022	0.045
	No	28 (23.3%)	35 (14.8)		

TABLE 5 A comparative analysis of lifestyle factors between Qatar and UK residents.

	Qatar	UK	Chi-square	*p*-value
Hours slept				
<4	3 (2.9%)	1 (3.6%)	0.924	0.800
4–6	43 (42.2%)	14 (50%)		
7+	56 (54.9%)	13 (46.4%)		
Perception of having enough sleep				
Yes	54 (52.4%)	7 (25%)	6.656	0.011
No	49 (47.6%)	21 (75%)		
Alcohol consumption				
Yes	23 (22.3%)	15 (53.6%)	10.434	0.001
No	80 (77.7%)	13 (46.4)		
Tobacco consumption				
Yes	14 (13.6%)	1 (6.7%)	.	0.689
No	89 (86.4%)	14 (93.3%)		
Takeaways/ dining out in a week				
0	10 (9.6%)	5 (17.9%)	13.353	0.007
1	22 (21.2%)	14 (50%)		
2	31 (29.8%)	6 (21.4%)		
3	28 (26.9%)	2 (7.1%)		
4+	13 (12.5%)	1 (3.6%)		
Daily vegetable serving				
0	8 (7.5%)	1 (3.6%)	8.604	0.058
1	42 (40.38%)	7 (25%)		
2	36 (34%)	8 (28.6%)		
3	11 (10.4%)	6 (21.4%)		
4+	7 (6.6%)	6 (21.4%)		
Days of exercise per week				
0	31 (30.1%)	2 (7.1%)	20.409	0.0001
1–3	43 (41.7%)	5 (17.9%)		
4–6	26 (25.2%)	20 (71.4%)		
7	3 (2.9%)	1 (3.6%)		

psychiatric disorders were also suffering from increased BMI, both in Qatar and UK. Interestingly, the majority of respondents were also undiagnosed in their psychiatric disorders, with 79.8% of Qatar respondents and 60.7% of UK respondents being classified as having a psychiatric disorder based on the answers given in the survey as opposed to being diagnosed by a doctor. This is far higher than a

TABLE 6 Spearman's rank correlations between the predictor variables.

Spearman's rho correlations									
		Alcohol consumption	Tobacco consumption	Sleep perception	Dine outs/ takeaways	Daily Vegetable	Exercise frequency	Country	Sleep hours
Alcohol consumption	Correlation Coefficient	1.000	0.099	0.002	−0.108*	−0.102	−0.185**	0.295**	−0.091
	Sig. (2-tailed)	.	0.074	0.977	0.050	0.063	0.001	0.000	0.100
	N	329	329	329	329	329	329	329	329
Tobacco consumption	Correlation Coefficient	0.099	1.000	−0.069	0.068	0.001	−0.015	−0.099	−0.046
	Sig. (2-tailed)	0.074	.	0.210	0.221	0.986	0.780	0.072	0.403
	N	329	329	329	329	329	329	329	329
Sleep perception	Correlation Coefficient	0.002	−0.069	1.000	−0.044	0.038	0.131*	0.106	0.133*
	Sig. (2-tailed)	0.977	0.210	.	0.423	0.489	0.018	0.054	0.016
	N	329	329	329	329	329	329	329	329
Dine outs/ takeaways	Correlation Coefficient	−0.108*	0.068	−0.044	1.000	0.127*	0.222**	−0.208**	−0.038
	Sig. (2-tailed)	0.050	0.221	0.423	.	0.020	0.000	0.000	0.498
	N	329	329	329	338	338	332	338	329
Daily Vegetable serving	Correlation Coefficient	−0.0102	0.001	0.038	0.127*	1.000	0.110*	−0.185**	−0.0091
	Sig. (2-tailed)	0.063	0.986	0.489	0.020	.	0.046	0.001	0.101
	N	329	329	329	338	338	332	338	329
Exercise frequency	Correlation Coefficient	−0.185**	−0.015	0.131*	0.222**	0.110*	1.000	−0.170**	−0.019
	Sig. (2-tailed)	0.001	0.780	0.018	0.000	0.046	.	0.002	0.731
	N	329	329	329	332	332	332	332	329
Country	Correlation Coefficient	0.295**	−0.099	0.106	−0.208**	−0.185**	−0.170**	1.000	−0.013
	Sig. (2-tailed)	0.000	0.072	0.054	0.000	0.001	0.002	.	0.808
	N	329	329	329	338	338	332	357	329
Sleep hours	Correlation Coefficient	−0.091	−0.046	0.133*	−0.038	−0.091	−0.019	−0.013	1.000
	Sig. (2-tailed)	0.100	0.403	0.016	0.498	0.101	0.731	0.808	.
	N	329	329	329	329	329	329	329	329

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

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TABLE 7 Multivariate sesults for the combined sample Qatar and UK.

Characteristics	*p*-value	OR (95% CI)
Alcohol consumption (ref: No)	0.164	0.688 (0.406, 1.165)
Tobacco consumption (ref: No)	0.669	1.176 (0.559, 2.475)
Sleep perception (ref: Yes, to the question, do you feel you get enough sleep?)	0.889	1.033 (0.655, 1.630)
Dine out/take away (ref: <3 per week)	0.202	1.395 (0.837, 2.326)
Daily Vegetable Servings (ref: ≥4 servings daily)	0.433	1.340 (0.645, 2.787)
Exercise frequency (ref: Yes)	0.424	1.256 (0.718, 2.196)
Country (ref: Qatar)	0.088	1.691 (0.924, 3.093)

TABLE 8 Multivariate logistic regression results for each country separately.

Characteristics	*p*-value	OR (95% CI)
Qatar		
Alcohol consumption (ref: No)	0.344	0.739 (0.394, 1.384)
Tobacco consumption (ref: No)	0.604	1.232 (0.560, 2.708)
Sleep perception (ref: Yes, to the question, do you feel you get enough sleep?)	0.236	0.728 (0.431, 1.231)
Dine out/take away (ref: <3 per week)	0.289	1.341 (0.779, 2.308)
Daily Vegetable serving (ref: ≥4 servings daily)	0.487	1.401 (0.541, 3.624)
Exercise frequency (ref: Yes)	0.252	1.417 (0.781, 2.571)
UK		
Alcohol consumption (ref: No)	0.203	0.494 (0.167, 1.461)
Tobacco consumption (ref: No)	0.987	1.021 (0.074, 14.071)
Sleep perception (ref: Yes, to the question, do you feel you get enough sleep?)	0.033	3.415 (1.105, 10.552)
Dine out/take away (ref: <3 per week)	0.807	1.237 (0.224, 6.832)
Daily Vegetable serving (ref: ≥4 servings daily)	0.436	1.668 (0.460, 6.044)
Exercise frequency (ref: Yes)	0.891	(0.131, 5.842)

previous study conducted in 2014, which noted that 36% of common psychiatric disorders in the UK are undiagnosed (26).

This pilot study suggests that for larger cohorts labelled as "healthy" as the ones provided by Qatar Biobank, it will be important to look for the existence of this co-morbidity. This also highlights the importance of raising awareness on both conditions, and help them move out of the "pre-contemplation" stage of the transtheoretical model of behavior change (27). Indeed, if a person is unaware that they have a health condition such as a BMI greater than 25 or a psychiatric disorder, they are unable to make the changes needed to improve their health and lifestyle factors associated to their condition.

4.2. Lifestyle factor 1: exercise

According to the questionnaire results, around 30.1% of Qatar's respondents with the co-morbidity did no weekly exercise, with only 25.6% exercising 4–6 times per week. This is not surprising since the weather condition in the desertic climate of Qatar is relatively hot all year long and might be discouraging people to exercise outdoor. In the past few years, Qatar has launched several initiatives to promote and facilitate outdoor physical activities such as public parks, the National Sport Day, health campaigns such as the "Step into health." It would be interesting to observe this specific lifestyle factor over the coming years on a larger cohort.

In comparison, 71.4% of UK residents with the co-morbidity exercised 4–6 times a week, with only 7.1% reporting that they did not partake in any weekly exercise. This suggest that exercise might play a heavier role in the co-morbidity found in Qatar than in UK and might therefore be the preferred lifestyle factor to target in Qatar for managing the co-morbidity, but not in UK.

Using exercise as an alternative to medication for treating psychiatric disorders has only recently been investigated, but findings indicate that exercise can have a positive effect on an individual's mood through the increase in endorphins and a decrease in cortisol (28). Exercise has also been shown to stimulate the growth of new nerve cells and the release of proteins such as brain-derived neurotrophic factor, which is essential to growing and maintaining neurons involved in emotion, as well as increasing the size of the hippocampus and enhancing cognitive function (29–32). Studies have shown that observing the recommended guidelines of 150 min moderate or 75 min vigorous physical activity/exercise is not enough to promote significant weight loss (33, 34). Instead, it was suggested that 200–300 min per week of exercise is an optimal amount of physical activity to accomplish significant weight loss (35). This recommendation, however, does not take into account training methods such as resistance training or weight training, which are often effective in reducing fat mass and the associated

negative health implications even if no weight loss is observed (36). Nonetheless, it is recognized that exercise alone cannot solely contribute to weight loss, especially when diet is not healthy and balanced.

4.3. Lifestyle factor 2: nutrition

Between 2009–2015, Qatari children between the ages of 12–17 had the highest levels of fast-food consumption in the region, on average consuming fast food over 2.5 times per week (37). This correlates to the findings from the questionnaire, which show that 69.2% of Qatar residents with the co-morbidity dine out or consume take away food 2 or more times per week. This is doubled in comparison to the 32.1% of UK residents with the co-morbidity who dined out or consumed takeaway food 2 or more times per week. This suggests that nutrition is a second lifestyle factor that can be preferably considered as a target for change.

Stress-induced overeating leads to obesity, which has a direct impact on neurotransmitters and inflammatory markers that are present and affect mood, with a high-fat diet thought to cause mood disorders (38). On the other hand, psychiatric disorders are known to cause over-eating and binge-eating and curtail participation in exercise, which leads to increased levels of body fat (39). We are here in the presence of a bidirectional communication between gut and brain, commonly called as the gut-brain axis (40). This is supported by a study that found that eating fruit and vegetables containing dietary fiber was associated with better mental health (41). A review that evaluated 61 observational studies asserted that adults who had a higher consumption of fruit, vegetables, and dietary fiber were protected against depressive symptoms (42). It has long been known that vegetables contain many of the antioxidants, vitamins and dietary fiber that our bodies need (43). Low grade inflammation has been found in individuals who are obese and overweight, this has been linked to causing metabolic changes and an accumulation of adipose tissue which plant peptides have been shown to have an impact on reducing (44). As well as the reduction of inflammatory cytokines, vegetables have been shown to be protective against cardiovascular disease, colon and rectal cancers and depression (44–46).

An increase in obesity levels is correlated with the increased consumption of a Western style diet, which tends to have more omega-6 and processed carbohydrates (47). For those with a BMI >25, there is a 44% increase in the risk of myocardial infarction, hypertension, fatty liver disease, type 2 diabetes, and some cancers (38, 48). Our results showed that in both Qatar and UK, the top consumed food was poultry, not vegetables. A study has shown that consuming a high amount of protein can enhance body composition and help to reduce body weight (49). However, many studies have proven that a diet predominantly composed of meat has a higher risk of diabetes, heart disease and stroke (50–52).

Nutrition itself affects lifestyle behavior and can influence of other lifestyle factors such as sleep.

4.4. Lifestyle factor 3: sleep

Nutrition affects sleep. Indeed, consumption of foods with a high glycemic index approximately 4 hours before bedtime increases REM sleep and reduces the onset of sleep latency (53, 54). However, a different study showed that individuals who consumed high fat and carbohydrate foods before bedtime had an increased sleep latency and decreased REM (55). Those with shortened sleep have shown to have a higher snack intake in the day, diets high in carbohydrates have been shown to cause an increase in REM sleep but the types of carbohydrates consumed cause different outcomes (56). This could be an explanation as to why only 52.4% of Qatar residents who responded felt that they had enough sleep in an average night.

Insufficient sleep has many negative effects on an individual's health, including the development of many non-communicable diseases due to impairment of immune system and cardiovascular health as well as being linked to the development and worsening of psychiatric disorders (57).

Alcohol consumed before bedtime has been found to cause a decrease in the REM in the first half of the night, as the alcohol levels drop in the second half of the night sleep becomes disrupted at the time when REM duration is at its greatest causing an increase in waking leading to fatigue during the day (58). In our survey, a larger proportion of the UK residents (75%) felt that they did not get enough sleep. It is possible that this could be linked to alcohol consumption, with 53.6% of UK respondents confirming that they consume alcohol. Many people turn to alcohol to facilitate the sleep process, which is counterproductive, as alcohol causes an individual to have faster sleep onset but a poorer quality of sleep, with REM sleep being suppressed (59). This is due to the effects that alcohol has on many of the neurotransmitters, such as the GABAergic system, which is involved in sleep–wake regulation (59). Alcohol consumption can also disrupt sleep by disturbing the respiratory system (60). Further, alcohol consumption affects physical activity and exercise by decreasing strength output through inhibiting certain Ca2+ channels, decreasing muscle synthesis, peripheral vasodilation, and diuretic actions (61–63). In addition, the link between obesity and alcohol was highlighted back in 2014, when it was found that those who consumed alcohol had a 70% risk of obesity via the development of alcoholic fatty liver (64). Even though most obese individuals in Qatar do not drink alcohol, the metabolic syndrome is believed to arise from a combination of all other lifestyle factors, especially nutrition, sleep, and lack of physical activity.

4.5. Lifestyle factor 4: tobacco

Our study did not find any statistical difference in tobacco use between Qatar and UK respondents, but a significant difference in alcohol consumption. Tobacco and alcohol consumptions have been shown to be involved in with weight gain, by acting on sleep and modulated by the level of physical activity (64). It was found that cigarette smokers have a poorer sleep quality possibly due to nicotine being a stimulant; however, sleep quality was improved with a daily increase in exercise (65, 66). Physical exercise was found to deter adolescent girls from using tobacco products; however, the same result was not seen in adolescent boys (67).

The case of tobacco use is interesting as it relates to anxiety and weight gain at the same time, and its use is involved in the top causes for morbidity and mortality in the Western world (65). Our results show that a higher percentage of respondents from Qatar used tobacco products (13.6%) as compared to UK (6.7%). There is some conflict as to whether there is an association between people with a BMI >25 and

people who smoke. Some people, especially females, believe that smoking will help in preventing weight gain (66). However, we are wondering whether respondents considered "shisha" as part of tobacco use, since the use of "shisha" is culturally more acceptable for women in the region. The amount of tobacco consumed were suggested to have an impact on the weight of an individual, with smokers less likely to be obese than non-smokers but only up to a certain level, heavy smokers are more likely to be obese than those who had never smoked (67). Research has also shown that people who quit smoking gain between 2.6 to 5.kg of weight which could be a decisive factor for people when considering stopping the use of tobacco products (68). An association was found between people with psychiatric disorders, heavy smoking, and difficulties in cessation of smoking (69). A barrier to stopping smoking for those with psychiatric disorders is the perception that it may worsen their symptoms due to many using smoking as a coping mechanism (70).

Other studies have suggested a strong link between alcohol and tobacco use, with up to 86% of smokers drinking alcohol, caused by environmental cues and genes that are involved in regulating some brain chemical systems such as cross tolerance; however those studies certainly did not account for countries such as Qatar were alcohol consumption is reduced (71, 72).

4.6. Correlation study: toward a paradigm shift

Surprisingly, the logistic regression analysis between lifestyle factors for UK, only found one factor to significantly correlate with the comorbidity: the question "Do you feel you get enough sleep?." This question relates to quality of sleep rather than the number of hours slept. None of the other factor such as nutrition, exercise or alcohol consumption significantly correlated to the comorbidity. The small sample size for this group is an evident limitation, and the investigation need to be done for a larger group. However, when looking at the Qatar group, which had a bigger sample size, none of the lifestyle factors significantly correlated with the comorbidity, suggesting that in addition to the sample size factor, another reason might explain this observation. Our hypothesis is that two main factors might have contributed to this. The first one is that Qatar's population is high in expatriates and includes many different cultural practices such as Indian, Asian, African, Arab, American, European, Eastern, which could result in large variations in answers. For example: eating three servings of vegetables a day might be critical for a group that does not include enough physical activity in their daily lifestyle but might be less critical for another group which exercises daily. Similarly, when the logistic regression analysis was conducted including both Qatar and UK participants, by including the country as an independent variable, the significance found for sleep perception was also lost. This might be due to large variations in lifestyles and the rather small sample size.

The second reason that could explain the failure to identify one of those lifestyle factors as significantly correlating to the co-morbidity may be that the lifestyle factors investigated in this study might be confounding factors to a different factor that was not investigated. In the light of previous studies on the gut-brain axis (73–76), we believe that this factor is the gut dysbiosis. Indeed, a growing body of evidence has shown that gut dysbiosis, or the sustained imbalance of gut microbes, is associated to nutrition (77) exercise (78), alcohol consumption (79) smoking (79), and sleep (80). In addition, gut dysbiosis has been association to obesity (81) and mental health (82). Indeed, gut dysbiosis has also been linked to mental health issues. A systematic review published in the journal Nutrients found that gut dysbiosis was associated with depressive symptoms in humans (83). In another study, mice with gut dysbiosis exhibited anxiety-like behaviors (84). These studies suggest that gut dysbiosis can have significant effects on mental health.

Emerging evidence suggests that an unhealthy gut microbiome can contribute to sleep disturbances, which can in turn lead to metabolic and mental disorders. Several studies have shown that gut dysbiosis can disrupt circadian rhythms and reduce the production of melatonin, leading to poor sleep quality and duration (85, 86). In a study of Leone et al. (87), mice fed a high-fat diet exhibited gut dysbiosis, which led to altered sleep patterns, increased food intake, and weight gain. These findings suggest that gut dysbiosis can result in sleep disturbances that contribute to metabolic dysfunction resulting in weight gain. Nevertheless, the gut dysbiosis can be caused by other factors such as nutrition, antibiotic courses history, substance use (88). A study published in the journal Frontiers in Psychiatry found that probiotics may improve sleep quality and reduce depressive symptoms in humans (89). These studies suggest that promoting gut health through dietary interventions may help improve sleep and reduce the risk of developing metabolic and mental disorders (90, 91). Studies on the role of the gut microbiome and metabolome in health and diseases have proposed a paradigm shift in health sciences (20, 78, 80, 81, 92). While our pilot study was only looking at lifestyle variables, the results suggest that the relationship of each variable to the comorbidity is complex and suggests that one or more pieces of the puzzle are missing. The development of a tailored strategies for the prevention and treatment of obesity and psychiatric disorders in Qatar and UK is needed in order to help reduce pressure on health services, ensure better quality of life and lower associated mortality rates.

5. Limitations

The data collected from the questionnaire include its reliance on individuals self-reporting, which can sometimes not be completely accurate. By making the questionnaire anonymous, we hoped that people would feel they could answer openly, this might have however helped in assessing depression and perceived stress disorders. With regards to using BMI as a measure for the different categories, we are aware that it is imperfect as it does not consider muscle mass, which can cause an individual to be classed as overweight or obese whilst they are in fact a healthy weight. Another issue with using BMI is that there are variations for different ethnic groups. The UK and Qatar groups were not equal in number, and the results of this study need to be confirmed by further explorations. We acknowledge the sample might not be representative of those who do not have access to Instagram, Facebook, twitter, WhatsApp or emails. As well as being limited by the method of data collection used.

The results cannot be generalized to the entire Qatar and UK population and this study is only a pilot study that aimed at providing preliminary data for further explorations. It was the first of its kind performed in the country, and the first to use this type of interactive survey. Testing the method was also an objective of this pilot study and

we concluded that the survey was effective in recruiting a significant sample since 282 participants were recruited on the first week after the release of the advertisement on social media. Further exploration on larger cohort could get more insight by comparing the comorbid vs. total population.

6. Conclusion

The co-morbidity of psychiatric disorders with BMI over 25 has been observed in both Qatar and UK. Yet, the lifestyles are different. Diet, exercise frequency and substance use have been shown to be significantly different between respondents of the two countries. Therefore, we conclude that this co-morbidity cannot be attributed to the same factors for all over the world, and further studies need to be done to understand the mechanisms involved in every situation. The results from this questionnaire address the necessity of developing more precision medicine approaches that consider the different lifestyles in population. The global problem of growing waistlines and psychiatric disorders can be better addressed by targeting a population's specific needs to facilitate behavioral changes required to improve physical and mental health. We are proposing the idea that lifestyle factors can be involved in different manners and with different weights in resulting with such co-morbidity (Figure 2). In Qatar, the cause could be first attributed to a lack of exercise, and a diet which has shifted from the more traditional Arabic cuisine to that of the many cultures it now houses, including the high fat, processed Western diet. Although no difference in use of tobacco was found, it would be interesting to investigate on the role of Shisha smoking in this co-morbidity. For UK residents, the consumption of alcohol is more worrying, as many do not factor into their diet, but contributes 7 Kcal/g.

When addressing weight loss, the most effective way for an individual to maintain weight loss is to combine an exercise routine with a balanced diet and a change in overall lifestyle behaviors, which in turn will benefit overall quality of life and help to lessen the burden of psychiatric disorders. Most importantly, this survey allowed us to raise a concern that an important proportion of individuals seemed unaware of their BMI greater than 25 and/or of their psychiatric condition, and we would like to remind the importance of awareness as being the initial step to engage behavioral change.

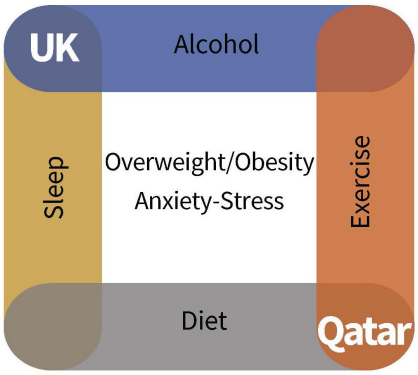

FIGURE 2
The need for precision medicine in lifestyle medicine.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by WCMQ-IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GB conceived and designed the study and recruited participants. CG and GB developed the questionnaire and drafted the initial manuscript. GB, CG, and PS conducted data analysis. GB, PS, and EA made critical revisions of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1132994/full#supplementary-material

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Prevalence of common chronic disease and multimorbidity patterns in Guangdong province with three typical cultures: analysis of data from the Diverse Life-Course Cohort study

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Background: Variations in the prevalence and pattern of multimorbidity might be attributable to lifestyle and environmental factors. This study was performed to determine the prevalence of common chronic diseases and to reveal multimorbidity patterns among adults in Guangdong province with Chaoshan, Hakka, and island cultures.

Methods: We used data collected at the baseline survey (April–May 2021) of the Diverse Life-Course Cohort study and included 5,655 participants aged ≥20 years. Multimorbidity was defined as the presence of two or more of the 14 chronic diseases collected by self-reports, physical examinations, and blood tests. Multimorbidity patterns were explored by association rule mining (ARM).

Results: Overall, 40.69% of participants had multimorbidity, and the prevalence among coastland (42.37%) and mountain residents (40.36%) was higher than that among island residents (37.97%). The prevalence of multimorbidity increased rapidly with higher age groups and showed an inflection point at 50 years, beyond which >50% of the middle-aged and older adults had multimorbidity. The proportion of people with two chronic diseases accounted for most cases of multimorbidity, and the strongest association was found between hyperuricemia and gout (lift of 3.26). The most prevalent multimorbidity pattern was dyslipidemia and hyperuricemia in the coastland areas and dyslipidemia combined with hypertension in the mountain and island areas. Furthermore, the most common triad combination consisted of cardiovascular diseases, gout, and hyperuricemia, which was verified in the mountain and coastal areas.

Conclusion: These observations of multimorbidity patterns, including the most frequent multimorbidity and associations, will help healthcare providers develop healthcare plans that improve the effectiveness of multimorbidity management.

KEYWORDS

prevalence, multimorbidity pattern, different kinds of culture, aging, Guangdong province

1. Introduction

The number of people with multiple chronic health conditions has been rising with the global population aging and the growing prevalence of non-communicable diseases (NCDs) (1–3). An estimated one-third of adults worldwide have two or more coexisting chronic diseases (4). Multimorbidity, an emerging and prominent public health issue globally, has been associated with poorer patient outcomes and poses a challenge to the increased difficulty for health systems to optimize personalized care, furthermore translating into a substantial economic burden for health systems (1, 5, 6).

A large body of literature has revealed the prevalence and patterns of multimorbidity among adults in China. The prevalence of multimorbidity ranges widely from 4.8 to 90.5% (7–10) because of variance in aspects such as geographical environments and the definitions and measurements of disease (11, 12). In general, people who are older, female, or living in northern areas have a higher prevalence of multimorbidity (12–14). As the number of older adults has grown, there has been a dramatic increase in the prevalence of multimorbidity during the past decade. According to the China Health and Retirement Longitudinal Study (CHARLS), the prevalence of multimorbidity increased from 38.6 in 2011 to 53.9% in 2018 among middle-aged and older adults, respectively (15, 16). Additionally, multimorbidity is not exclusive to older people, and it appears to affect a much broader cross-section of the population (3). A systematic review of 39 observational studies across 12 high-income countries illustrated a strong positive association between increasing age and the prevalence of multimorbidity [odds ratio (OR), 1.26–227.46] (17). Studies also have shown different multimorbidity patterns in people of different ages: multimorbidity is likely to involve mixed digestive system diseases (such as hepatobiliary disease) and other physical health conditions (such as hypertension and diabetes) in younger age groups, whereas older adults are more prone to multiple physical health conditions (18, 19). Currently, evidence on multimorbidity in younger populations is limited in China. Moreover, some studies have revealed that variations in the prevalence and pattern of multimorbidity might be attributable to lifestyle and environmental factors. However, most studies on lifestyle factors and multimorbidity have been conducted in Western countries, where the multimorbidity pattern may differ from that in the Chinese population (7, 20).

Guangdong province, a typical representative coastal area with many platforms, is located in the south of China, and its inhabitants exhibit many kinds of dietary behaviors. Chaoshan, Hakka, and Island, as typical intriguing cultures in Guangdong province, have great differences in inhabitants and lifestyle, which may lead to differences in health status (21, 22). Chaoshanese mainly reside in the Chaoshan area along the southeast coast of Guangdong province and commonly consume meats from seafood and drink hot red tea. Hakka mainly inhabit the mountains of Eastern Guangdong province, commonly consuming meats from pork and chicken and drinking green tea. Nan-Ao Island in Shantou city, which is selected as the representation of island culture, is a relatively isolated place with native residents living with unchanged customs and having porridge for three meals and fish as seasoning. Therefore, the present study was performed to determine the prevalence of common chronic diseases and reveal multimorbidity patterns among adults in Guangdong province, as well as to examine the diversity of common chronic diseases and multimorbidity patterns by different age groups and across different cultures.

2. Materials and methods

2.1. Data source

This study utilized the baseline data from the Diverse Life-Course Cohort (DLCC) study (23), which is a population-based prospective cohort study. The survey was conducted in Shantou and Meizhou cities in Guangdong province from April 2021 to May 2021. The locations of the study sites are shown in Figure 1. Considering the three cultures "Chaoshan", island, and "Hakka", we divided the study sites into coastland (including the Chenghai and Jinping districts in Shantou city), island (including Nan-Ao county in Shantou city), and mountain areas (including Meijiang district and Jiaoling county in Meizhou city).

Using a cluster random sampling method, participants aged ≥20 years who had lived in their current residence for at least 1 year were recruited in this study using the sampled units mentioned above. Individuals with severe mental or physical illness, pregnant females, and military personnel on active service were excluded. In total, 5,655 participants completed the survey; they comprised 2,419 (42.8%) coastland residents, 1,259 (22.2%) island residents, and 1,977 (35.0%) mountain area residents. All participants gave written informed consent to participate in this study. The study was approved by the Ethics Committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

2.2. Data collection

Participants were invited to take a face-to-face questionnaire survey that included demographic and socioeconomic information, personal medical history, and health-related lifestyle factors such as smoking status, alcohol consumption, physical activity, and dietary patterns. The completeness and correctness of each questionnaire were examined by an epidemiologist through face-to-face re-check with the participant. This study was implemented in accordance with a previously published study (24). The participants underwent physical examinations including measurement of weight, height, blood pressure, electrocardiography, and bone mineral density. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times after at least 5 min of rest in a seated position, using a digital sphygmomanometer (Omron HEM-907, Japan). In addition, a 10-ml fasting blood sample (≥8 h) was drawn from each participant. Fasting plasma glucose (FPG, mmol/L), serum uric acid concentration (SUA, μmol/L), and serum-lipid including triglyceride (TG, mmol/L), total cholesterol (TC, mmol/L), high-density lipoprotein cholesterol (HDL-C, mmol/L), and low-density lipoprotein cholesterol (LDL-C, mmol/L) were tested in Bejing Hepingli Hospital.

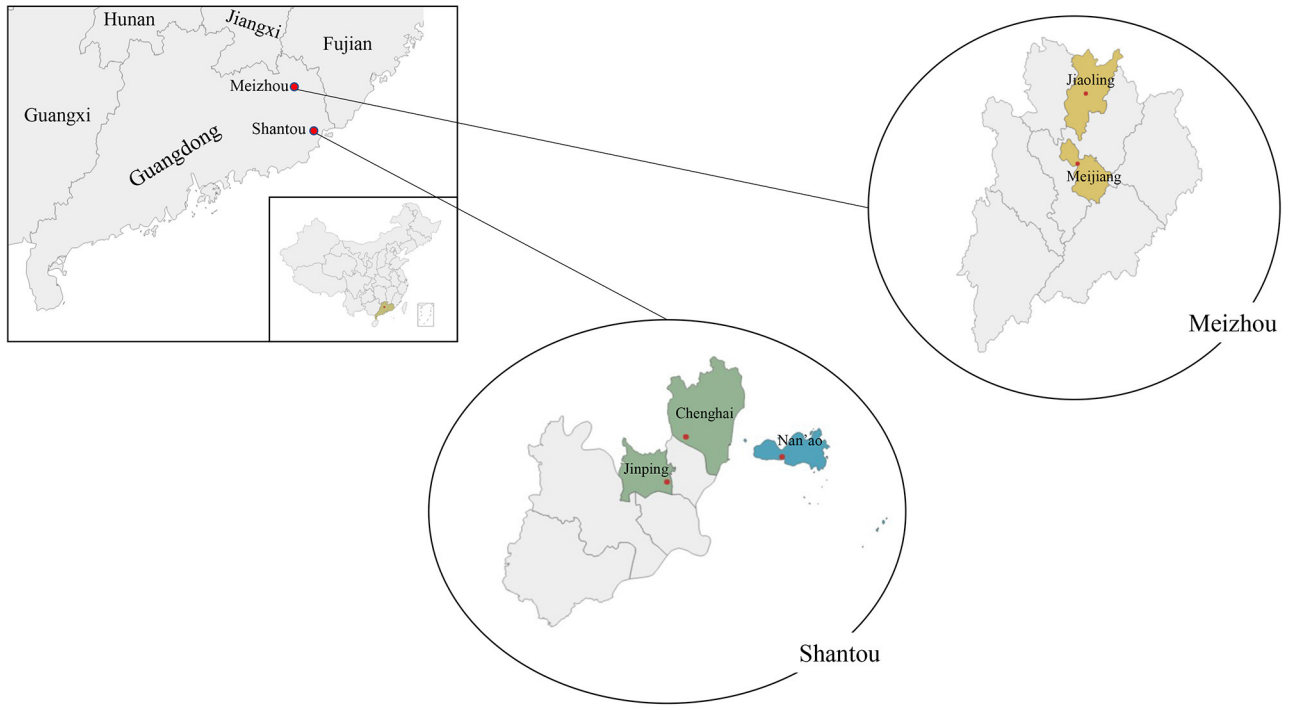

FIGURE 1
Locations of study sites in Guangdong province in the DLCC.

2.3. Definition and measurement of multimorbidity

In this study, we identified 14 common chronic diseases based on the most frequently mentioned diseases for multimorbidity measures in previous studies (7, 9–11). Hypertension was defined as an average SBP of ≥140 mmHg and/or an average DBP of ≥ 90 mmHg, or self-reported hypertension history. Diabetes was defined as FPG ≥7.0 mmol/L or self-reported diabetes history. Dyslipidemia was defined as total cholesterol > 6.2 mmol/L, triglycerides ≥2.3 mmol/L, LDL-C ≥4.1 mmol/L, or HDL-C <1.0 mmol/L or self-reported dyslipidemia history (25). Hyperuricemia was defined as SUA >420 μmol/L or self-reported hyperuricemia history (26). Other chronic diseases, such as gout, gastroenteritis/ulcer diseases (gastroenteritis, reflux esophagitis, gastric perforation, peptic ulcer disease, colitis, and rectitis), urinary system diseases (kidney stones, nephritis, renal cysts, renal insufficiency, diabetic nephropathy, and urinary tract calculi), gallbladder diseases (gallstones, cholecystitis, and gallbladder polyps), coronary heart disease, respiratory diseases (chronic obstructive pulmonary disease, asthma, bronchitis, emphysema, and pulmonary nodules), cancer, stroke, arthritis or rheumatism, and liver diseases (hepatitis, cirrhosis, and hepatic cysts) were identified according to self-reported physician professional diagnosis. All diseases were defined as a binary variable (yes or no). Multimorbidity was defined as two or more coexisting chronic conditions within one person.

2.4. Statistical analysis

Age as a continuous variable is presented as mean ± standard deviation and median (P_{25}, P_{75}). Overall prevalence was calculated as the number of cases divided by all included participants in the sample and age-specific prevalence; the Wilson method was used to estimate the prevalence of multimorbidity and its 95% confidence interval (CI). Other categorical variables are summarized as count (percentage), and the chi-square test was performed to compare these characteristics. Direct standardization was performed using China's population age structure from the China Statistical Yearbook 2021.

Association rule mining (ARM) was used to determine common multimorbidity patterns. Association rules were relationships between sets of diseases from itemset1 (called "Conditions") to itemset2 (called "Outcomes"). Support, confidence, and lift in particular were used as measurement indicators in ARM, in which the support is equivalent to the prevalence of disease combinations; the confidence is the conditional probability of occurrence of itemset2, given itemset1; a higher value of lift (>1) indicates that the relationship between itemset1 and itemset2 is more significant than expected if the two were independent. This further suggests that itemset1 is positively associated with itemset2 (27). For this study, we first used an *a priori* algorithm with a threshold of support of 0.001 (confidence was not limited) to identify all critical association rules, in which the percentage in the whole dataset that contains both conditions and outcomes is no <0.1%. Then, to identify more frequent and

potentially important patterns, the minimum thresholds of the parameters in ARM were defined as follows: support >0.5%, confidence >30%, and lift >1. The function "apriori" in the R package "arules" was used in the clustering analysis. All the analyses were performed using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and R4.1.2 (R Development Core Team).

3. Results

3.1. Sample description

The general characteristics of the 5,655 study participants are shown in Table 1. The mean age was 52.9 ± 12.91 years, the majority of participants were in the 40–69 age group (74.45%), and 1,660 (29.35%) were men. Significant differences among the three groups were seen in all characteristics except alcohol drinking. Coastland residents showed higher education and personal annual income, island residents were older and comprised more women, and mountain residents had a higher body mass index and physical activity and a lower incidence of smoking behavior.

3.2. Prevalence of chronic diseases

Figure 2 shows the prevalence of chronic diseases among the survey participants. Dyslipidemia was the most frequent disease, with a prevalence as high as 44.76%, far higher than the other chronic diseases. The prevalence of other chronic diseases, in descending order, was 30.40% for hypertension, 28.70% for hyperuricemia, 13.56% for diabetes, and 4.86% for gout. The pattern was similar between coastland and island residents, except that the fifth disease was urinary system diseases in the mountain area residents. Furthermore, significant differences among the three areas were seen in hyperuricemia, diabetes, urinary system diseases, gallbladder diseases, and respiratory diseases. Hyperuricemia was significantly higher among coastland and island residents (>30.0%) than among mountain residents (21.75%), island residents had the lowest prevalence rate of diabetes (10.17%), the rate of urinary system diseases in mountain area residents was higher than that in coastland and island residents (5.46 vs. 2.40 and 0.95%, respectively), and coastland residents had a higher prevalence of gallbladder diseases and respiratory diseases.

3.3. Prevalence and pattern of chronic multimorbidity

The burden of multimorbidity is presented in Figure 3. The prevalence of multimorbidity among the population was 40.69%, which significantly increased with age from 12.09% in the 20–29 years age group to 69.58% in the ≥70-year age group. Of participants aged >60 years, 60% had multimorbidity. Similar trends were found in different areas; there was a significant difference in the distribution of multimorbidity among the three regions (37.97, 40.36, and 42.37% in island, mountain, and coastland areas, respectively). Moreover, the age-standardized rate was 41.90% (95% confidence interval: 39.66–44.13%) using the population census data of China in 2020 as the reference population. The standardized rates were different in the coastland [43.40% (40.23–46.57%)], mountain [41.56% (37.31–45.81%)], and island areas [36.47% (31.41–41.53%)].

Among the 2,301 participants with multimorbidity, 1,247 (54.2%) had two diseases. The top three binary multimorbidity combinations were dyslipidemia and hyperuricemia (26.22%, 327/1247), dyslipidemia and hypertension (24.86%, 310/1247), and hyperuricemia and hypertension (9.46%, 118/1247). A total of 713 (31.0%) participants had three diseases. The top ternary multimorbidity combinations were dyslipidemia, hyperuricemia, and hypertension; dyslipidemia, hypertension, and diabetes; and dyslipidemia, hyperuricemia, and diabetes. In addition, 256 (11.1%) and 85 (3.7%) participants had four diseases and five or more diseases, respectively. Figure 3 shows the top binary and ternary multimorbidity combinations by age and region. For the binary multimorbidity groups, dyslipidemia and hyperuricemia were the most common combination in young and middle-aged participants (<50 years of age), and dyslipidemia and hypertension were the most common combination in the older groups. Unlike in the mountain area (20.7%, 90/435), dyslipidemia combined with hyperuricemia was the most common binary combination in the coastland (29.4%, 157/534) and island regions (28.8%, 80/278). For the ternary multimorbidity combination groups, dyslipidemia, hyperuricemia, and hypertension were the most common disease combination, especially in middle-aged and older participants. Furthermore, the combination of dyslipidemia, hypertension, and diabetes was more common in older groups.

3.4. ARM results

The associations among the included diseases were illustrated by ARM. To avoid missing any critical association rules, 434 rules were generated after running the *a priori* algorithm based on the threshold of support of 0.001 at the beginning (confidence was not limited). A total of 72 patterns were finally kept through threshold filtering. The top 10 association rules among these diseases according to lift are presented in Tables 2A, B. For the binary multimorbidity groups, the strongest association was found between the combination of hyperuricemia and gout, for which the lift was 3.26. That means gout is positively associated with hyperuricemia. Meanwhile, the rule "gout"-> "hyperuricemia" showed that individuals who have gout are most likely to experience hyperuricemia (93.45% probability). The support indicated that these two diseases co-exist in 4.54% of the participants within a certain period. Even if the lift values were different, a similar pattern of hyperuricemia and gout was shown in three areas. Among the coastland area participants, the second strongest association was observed between diabetes and coronary heart disease, for which the lift was 2.64, whereas the second lift for the island and mountain areas was 2.40 and 2.43 for the combination of hypertension and coronary heart disease and the combination of diabetes and gout, respectively. Moreover, hypertension tended to be comorbid with other diseases that occurred in coastland participants; dyslipidemia tended to be comorbid with other diseases that occurred in island participants; and patients with stroke or coronary heart disease

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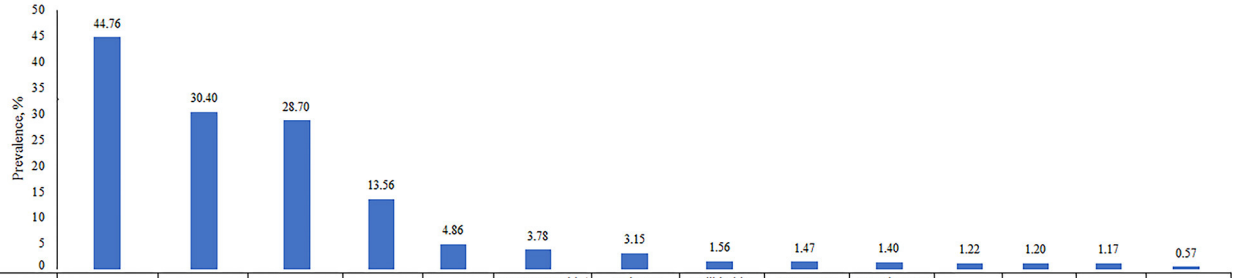
TABLE 1 Characteristics of participants recruited from different regions.

	Total	Island	Mountain	Coastland	*P*-value for three different regions
N	5,655	1,259	1,977	2,419	
Age, yr					
Mean (sd)	52.9 (12.91)	54.0 (11.92)	53.7 (12.19)	51.7 (13.83)	<0.0001
Medium (P_{25}, P_{75})	54 (45, 62)	55 (48, 63)	54 (46, 62)	54 (41, 62)	<0.0001
Age group, yr, *n* (%)					<0.0001
20–29	306 (5.41)	59 (4.69)	58 (2.93)	189 (7.81)	
30–39	636 (11.25)	87 (6.91)	212 (10.72)	337 (13.93)	
40–49	1,128 (19.95)	247 (19.62)	415 (20.99)	466 (19.26)	
50–59	1,799 (31.81)	476 (37.81)	665 (33.64)	658 (27.20)	
60–69	1,283 (22.69)	281 (22.32)	438 (22.15)	564 (23.32)	
≥70	503 (8.89)	109 (8.66)	189 (9.56)	205 (8.47)	
Sex, *n* (%)					<0.0001
Male	1,660 (29.35)	297 (23.59)	577 (29.19)	786 (32.49)	
Female	3,995 (70.65)	962 (76.41)	1,400 (70.81)	1,633 (67.51)	
BMI group[a], *n* (%)					0.0002
Underweight	291 (5.16)	64 (5.09)	77 (3.90)	150 (6.24)	
Normal	2,964 (52.59)	674 (53.62)	990 (50.15)	1,300 (54.05)	
Overweight	1,861 (33.02)	415 (33.02)	704 (35.66)	742 (30.85)	
Obesity	520 (9.23)	104 (8.27)	203 (10.28)	213 (8.86)	
Education attainment, *n* (%)					<0.0001
Primary school or below	1,370 (24.26)	588 (46.85)	265 (13.42)	517 (21.39)	
Middle school	2,966 (52.53)	457 (36.41)	1,268 (64.24)	1,241 (51.34)	
High school and above	1,310 (23.20)	210 (16.73)	441 (22.34)	659 (27.27)	
Personal annual income (RMB), *n* (%)					<0.0001
<10,000	434 (7.78)	124 (9.86)	165 (8.38)	145 (6.16)	
10,000–29,999	2,122 (38.04)	584 (46.46)	847 (43.02)	691 (29.38)	
30,000–49,999	1,555 (27.88)	286 (22.75)	426 (21.64)	843 (35.84)	
≥50,000	1,467 (26.30)	263 (20.92)	531 (26.97)	673 (28.61)	
Smoking, *n* (%)					<0.0001
Never	4,624 (81.78)	1,044 (82.92)	1,733 (87.66)	1,847 (76.39)	
Ever	211 (3.73)	25 (1.99)	84 (4.25)	102 (4.22)	
Current	819 (14.49)	190 (15.09)	160 (8.09)	469 (19.40)	
Drinking, *n* (%)					0.1363
Never	4,717 (83.44)	1,073 (85.23)	1,620 (81.94)	2,024 (83.74)	
Ever	98 (1.73)	22 (1.75)	34 (1.72)	42 (1.74)	
Current	838 (14.82)	164 (13.03)	323 (16.34)	351 (14.52)	
Physical activity[b], *n* (%)					<0.0001
Low	1,517 (26.84)	509 (40.43)	303 (15.33)	705 (29.17)	
Moderate	681 (12.05)	160 (12.71)	210 (10.62)	311 (12.87)	
High	3,455 (61.12)	590 (46.86)	1,464 (74.05)	1,401 (57.96)	

BMI, body mass index.

[a]Underweight was defined as a BMI of <18.5 kg/m^2, normal weight as a BMI of 18.5 to <24.0 kg/m^2, overweight as a BMI of 24.0 to <28.0 kg/m^2, and obesity as a BMI of ≥28.0 kg/m^2.

[b]The level of physical activity, considered both occupational and leisure-time physical activity, was classified as low (light level of both occupational and leisure-time physical activity), moderate (moderate or high level of either occupational or leisure-time physical activity), or high (moderate or high level of both occupational and leisure-time physical activity).



Area	Dyslipidemia	Hypertension	Hyperuricemia	Diabetes	Gout	Gastroenteritis/ ulcer disease	Urinary system	Gallbladder diseases	Coronary heart disease	Respiratory disease	Cancer	Stroke	Arthritis	Liver disease
Island	550 (43.69)	370 (29.39)	381 (30.26)	128 (10.17)	55 (4.37)	46 (3.65)	12 (0.95)	12 (0.95)	17 (1.35)	9 (0.71)	10 (0.79)	9 (0.71)	18 (1.43)	5 (0.40)
Mountain	925 (46.79)	615 (31.11)	430 (21.75)	289 (14.62)	93 (4.70)	85 (4.30)	108 (5.46)	25 (1.26)	32 (1.62)	23 (1.16)	30 (1.52)	30 (1.52)	23 (1.16)	15 (0.76)
Coastland	1056 (43.65)	734 (30.34)	812 (33.57)	350 (14.47)	127 (5.25)	83 (3.43)	58 (2.40)	51 (2.11)	34 (1.41)	47 (1.94)	29 (1.20)	29 (1.20)	25 (1.03)	12 (0.50)
P value	0.0792	0.5826	<.0001	0.0003	0.4592	0.3122	<.0001	0.0117	0.7804	0.0059	0.1870	0.1242	0.5691	0.3407

FIGURE 2
The observed prevalence of chronic diseases by region.

tended to have a higher risk of hypertension, hyperuricemia, and diabetes among mountain areas.

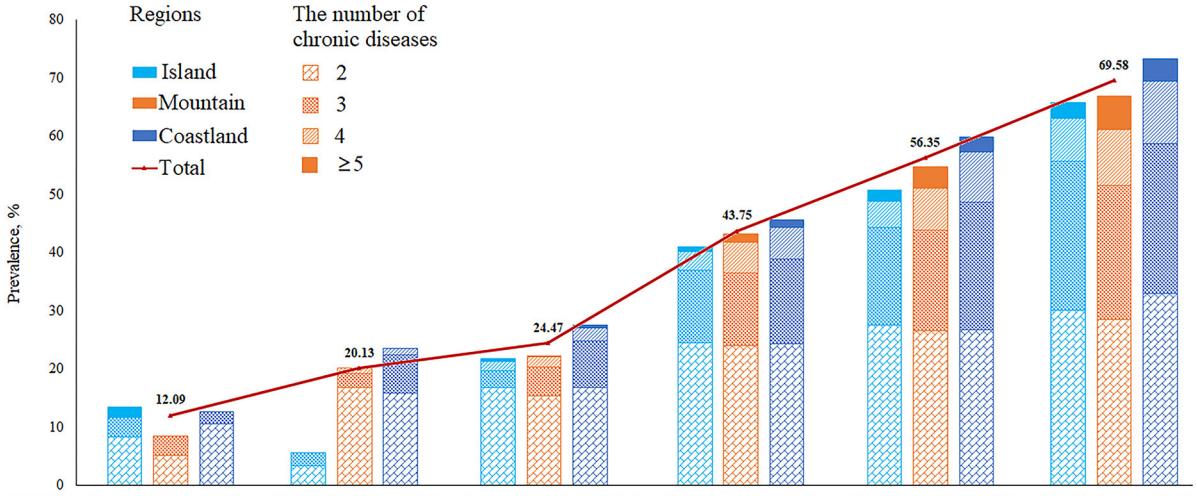
Among ternary multimorbidity (shown in Table 2B), the strongest association was found for the combination of diabetes, hyperuricemia, and gout, for which the lift was 3.37. This means that the chance of these diseases occurring together was 3.37 times higher than would be expected if they were independent. Furthermore, diabetes and gout appeared most in the six rules as conditions and seemed to have a strong relationship with hyperuricemia, hypertension, and dyslipidemia. Among different areas, the highest lift of 6.60 was observed for the combination of diabetes, hyperuricemia, and gout in the mountain area; the combination of dyslipidemia, hyperuricemia, and gout in the coastland area (lift = 2.95); and the combination of hypertension, hyperuricemia, and coronary heart disease in the island area (lift = 3.40). Dyslipidemia, hyperuricemia, gout, diabetes, and hypertension were the most common multimorbidity.

4. Discussion

In this study, we showed that multimorbidity was prevalent in Guangdong province. There was a significant difference in the distribution of multimorbidity among three different regions: coastland residents (42.37%) had a higher prevalence than mountain residents (40.36%) and island residents (37.97%). Hyperuricemia and gout, in addition to dyslipidemia, hypertension, and diabetes, were identified as the most prevalent diseases. We also showed that the prevalence of multimorbidity increased in populations of higher age groups, showing an inflection point at 50 years, beyond which >50% of the middle-aged and older adults had multimorbidity. The multimorbidity pattern involving two chronic diseases changed from dyslipidemia and hyperuricemia to dyslipidemia combined with hypertension with increasing age. Furthermore, the most common triad combination consisted of cardiovascular diseases, gout, and hyperuricemia, which was verified in the mountain and coastal areas.

We found that the prevalence of multimorbidity was 40.69% in our sample from three survey areas in Guangdong province, which is consistent with the range of the overall prevalence in Guangdong province (9, 28, 29). One finding in this study that is worthy of particular attention is the regional difference: the prevalences among coastland and mountain residents were higher than those among island residents. An explanation is that information regarding the participants' medical history was obtained through self-reports and supplemented by physical examinations or blood tests. Considering the long-term traffic blockages and insufficient medical resources, health literacy is inadequate in the island population. For example, the awareness of hypertension was only 50% in the island region, <58% in the coastland area, and 60% in the mountain area. The current study findings may have important implications that government should strengthen medical resource allocation for island areas, which may be closely related to multimorbidity prevention and control. With respect to the number of morbidities, the proportion of people with two chronic diseases accounted for most participants with multimorbidity, and the proportion was highest in the island area (58%). Regarding specific compositions of multimorbidity, the most prevalent multimorbidity pattern was dyslipidemia and hyperuricemia in the coastland area and dyslipidemia and hypertension in the mountain and island areas. One alternative explanation might be that hypertension was more common than hyperuricemia in the mountain areas (31.11 vs. 21.75%); the population surveyed in isolated island areas was older, and age is reportedly the major risk factor for cardiovascular diseases (30). Additionally, differences in population and socioeconomic status may have interfered with the comparison of regional effects among different studies. Thus, the strategies for the prevention and control of chronic diseases should be tailored to different regions. Previous studies have shown that residents of the coastal area have poor dietary habits (such as excessive alcohol drinking, seafood intake, and midnight snack), which can lead to metabolic disorders (31). The government should increase the promotion of health education. For island areas with a large proportion of the older adults population, the control level of chronic diseases should be actively monitored to improve residents' compliance with follow-up visits.

We found that the prevalence of multimorbidity was as low as 12.09% for young people aged 20–29 years and as



		n1/N1	20-29yr	n2/N2	30-39yr	n3/N3	40-49yr	n4/N4	50-59yr	n5/N5	60-69yr	n6/N6	≥ 70yr
Binary comorbidities													
Total	Rank1	28/306	Dyslipidemia+Hyperuricemia 20	93/636	Dyslipidemia+Hyperuricemia 60	185/1128	Dyslipidemia+Hyperuricemia 70	439/1799	Dyslipidemia+Hypertension 129	347/1283	Dyslipidemia+Hypertension 101	155/503	Dyslipidemia+Hypertension 42
	Rank2		Dyslipidemia+Diabetes 3		Hyperuricemia+Hypertension 9		Dyslipidemia+Hypertension 33		Dyslipidemia+Hyperuricemia 105		Dyslipidemia+Hyperuricemia 58		Hypertension+Diabetes 29
	Rank3		Hyperuricemia+Liver disease 1		Dyslipidemia+Hypertension 5		Dyslipidemia+Diabetes 12		Dyslipidemia+Diabetes 48		Hyperuricemia+Hypertension 38		Dyslipidemia+Diabetes 20
Island	Rank1	5/59	Dyslipidemia+Hyperuricemia 3	3/87	Dyslipidemia+Hyperuricemia 3	42/247	Dyslipidemia+Hyperuricemia 20	117/476	Dyslipidemia+Hyperuricemia 37	78/281	Dyslipidemia+Hypertension 26	33/109	Dyslipidemia+Hypertension 14
	Rank2		Hyperuricemia+Hypertension 1		-		Dyslipidemia+Hypertension 8		Dyslipidemia+Hypertension 32		Dyslipidemia+Hyperuricemia 16		Hypertension+Diabetes 5
	Rank3		Dyslipidemia+Gout 1		-		Hyperuricemia+Gout 4		Hyperuricemia+Hypertension 15		Hyperuricemia+Hypertension 7		Hyperuricemia+Hypertension 5
Mountain	Rank1	3/58	Dyslipidemia+Hyperuricemia 3	36/212	Dyslipidemia+Hyperuricemia 25	64/415	Dyslipidemia+Hyperuricemia 20	161/665	Dyslipidemia+Hypertension 63	117/438	Dyslipidemia+Hypertension 39	54/189	Dyslipidemia+Hypertension 11
	Rank2		-		Dyslipidemia+Gastroenteritis/ ulcer disease 3		Dyslipidemia+Hypertension 15		Dyslipidemia+Diabetes 21		Dyslipidemia+Diabetes 16		Hypertension+Diabetes 10
	Rank3		-		Dyslipidemia+Hypertension 3		Dyslipidemia+Urinary system diseases 5		Dyslipidemia+Hyperuricemia 21		Dyslipidemia+Hyperuricemia 14		Dyslipidemia+Diabetes 8
Coastland	Rank1	20/189	Dyslipidemia+Hyperuricemia 14	54/337	Dyslipidemia+Hyperuricemia 32	79/466	Dyslipidemia+Hyperuricemia 30	161/658	Dyslipidemia+Hyperuricemia 47	152/564	Dyslipidemia+Hypertension 36	68/205	Dyslipidemia+Hypertension 17
	Rank2		Dyslipidemia+Diabetes 3		Hyperuricemia+Hypertension 8		Dyslipidemia+Hypertension 10		Dyslipidemia+Hypertension 34		Dyslipidemia+Hyperuricemia 28		Hypertension+Diabetes 14
	Rank3		Hyperuricemia+Liver disease 1		Hyperuricemia+Gout 3		Hyperuricemia+Hypertension 8		Hyperuricemia+Hypertension 22		Hyperuricemia+Hypertension 24		Dyslipidemia+Diabetes 10
Three comorbidities													
Total	Rank1	8/306	Dyslipidemia+Hyperuricemia +Gout 4	29/636	Dyslipidemia+Hyperuricemia +Gout 11	65/1128	Dyslipidemia+Hyperuricemia+ Hypertension 26	239/1799	Dyslipidemia+Hyperuricemia +Hypertension 79	247/1283	Dyslipidemia+Hyperuricemia+ Hypertension 61	125/503	Dyslipidemia+Hyperuricemia+ Hypertension 38
	Rank2		Hyperuricemia+Hypertension +Gout 2		Dyslipidemia+Hyperuricemia +Hypertension 7		Dyslipidemia+Hyperuricemia+ Gout 10		Dyslipidemia+Hypertension+ Diabetes 34		Dyslipidemia+Hypertension+ Diabetes 59		Dyslipidemia+Hypertension+ Diabetes 24
	Rank3		Dyslipidemia+Hyperuricemia +Respiratory disease 1		Dyslipidemia+Hyperuricemia +Respiratory disease 2		Dyslipidemia+Hypertension+ Urinary system diseases 6		Dyslipidemia+Hyperuricemia +Diabetes 28		Dyslipidemia+Hyperuricemia+ Diabetes 19		Dyslipidemia+Hyperuricemia+ Gout 8
Island	Rank1	2/59	Hyperuricemia+Hypertension +Gout 1	2/87	Hyperuricemia+Hypertension +Gout 1	7/247	Dyslipidemia+Hyperuricemia+ Hypertension 4	60/476	Dyslipidemia+Hyperuricemia +Hypertension 23	47/281	Dyslipidemia+Hyperuricemia+ Hypertension 15	28/109	Dyslipidemia+Hyperuricemia+ Hypertension 10
	Rank2		Dyslipidemia+Hyperuricemia +Hypertension 1		Dyslipidemia+Hyperuricemia +Gout 1		Dyslipidemia+Hyperuricemia+ Gout 2		Dyslipidemia+Hyperuricemia +Diabetes 9		Dyslipidemia+Hypertension+ Diabetes 7		Dyslipidemia+Hypertension+ Diabetes 6
	Rank3		-		-		Dyslipidemia+Hyperuricemia+ Diabetes 1		Dyslipidemia+Hyperuricemia +Gout 6		Dyslipidemia+Hyperuricemia+ Diabetes 6		Dyslipidemia+Hypertension+ Coronary heart disease 2
Mountain	Rank1	2/58	Dyslipidemia+Hyperuricemia +Gout 2	5/212	Dyslipidemia+Hyperuricemia +Hypertension 3	21/415	Dyslipidemia+Hyperuricemia+ Hypertension 6	83/665	Dyslipidemia+Hyperuricemia +Hypertension 25	76/438	Dyslipidemia+Hypertension+ Diabetes 23	44/189	Dyslipidemia+Hypertension+ Diabetes 10
	Rank2		-		Dyslipidemia+Hyperuricemia +Gout 1		Dyslipidemia+Hypertension+ Urinary system diseases 5		Dyslipidemia+Hypertension+ Diabetes 14		Dyslipidemia+Hyperuricemia+ Hypertension 16		Dyslipidemia+Hyperuricemia+ Hypertension 10
	Rank3		-		Hypertension+Hyperuricemia +Gallbladder diseases 1		Dyslipidemia+Hypertension+D iabetes 3		Dyslipidemia+Hyperuricemia +Gout 8		Dyslipidemia+Hypertension+ Urinary system diseases 6		Dyslipidemia+Hyperuricemia+ Diabetes 4
Coastland	Rank1	4/189	Dyslipidemia+Hyperuricemia +Gout 2	22/337	Dyslipidemia+Hyperuricemia +Gout 9	37/466	Dyslipidemia+Hyperuricemia+ Hypertension 16	96/658	Dyslipidemia+Hyperuricemia +Hypertension 31	124/564	Dyslipidemia+Hyperuricemia+ Hypertension 30	53/205	Dyslipidemia+Hyperuricemia+ Hypertension 18
	Rank2		Dyslipidemia+Hyperuricemia +Respiratory disease 1		Dyslipidemia+Hyperuricemia +Hypertension 4		Dyslipidemia+Hyperuricemia+ Gout 7		Dyslipidemia+Hypertension+ Diabetes 15		Dyslipidemia+Hypertension+ Diabetes 29		Dyslipidemia+Hypertension+ Diabetes 8
	Rank3		Hyperuricemia+Hypertension +Gout 1		Dyslipidemia+Hyperuricemia +Respiratory disease 2		Dyslipidemia+Hyperuricemia+ Diabetes 2		Dyslipidemia+Hyperuricemia +Diabetes 13		Hypertension+Hyperuricemia +Diabetes 10		Dyslipidemia+Hyperuricemia+ Gout 6

FIGURE 3
The top binary and ternary multimorbidity combinations by age and region.

high as 69.58% for older adults aged ≥70 years. Although older adults had a higher prevalence of multimorbidity, which is consistent with previous studies, multimorbidity was not unique to older adults (6, 18). Our results suggest an inflection point in the prevalence of multimorbidity at 50 years, beyond which more than 50% of the middle-aged and older adults had multimorbidity. This is consistent with the result from the CHARLS in 2018 (16). Furthermore, the prevalence found in our study is commensurate with the ranges found in other countries: the index among adults aged ≥65 years was 63.7% in the United States (32) and 62.8% in Japan (33). For the multimorbidity patterns, dyslipidemia combined with hyperuricemia was the most common pattern among young people, while dyslipidemia combined with hypertension or diabetes was identified among the advanced-age population; this is consistent with natural aging-related changes (30). This phenomenon indicates that the management of multimorbidity should be age-specific. In particular, young people are more likely to have modifiable lifestyle factors preventing the incidence of metabolic disorders, (20, 34) whereas older persons with long-existing multimorbidity should receive increased resources and policy input, and the focus of health system services should be adjusted to improve the effectiveness of multimorbidity management (5, 35, 36).

TABLE 2A Top 10 association rules in order of lift with dyads of morbidities.

Total					Island				
Conditions	Outcomes	Support, %	Confidence, %	Lift	Conditions	Outcomes	Support, %	Confidence, %	Lift
Gout	Hyperuricemia	4.54	93.45	3.26	Gout	Hyperuricemia	3.89	89.09	2.94
Coronary heart disease	Hypertension	1.01	68.67	2.26	Coronary heart disease	Hypertension	0.95	70.59	2.40
Stroke	Hypertension	0.78	64.71	2.13	Urinary system diseases	Hyperuricemia	0.56	58.33	1.93
Diabetes	Hypertension	7.64	56.32	1.85	Diabetes	Hypertension	5.00	49.22	1.67
Stroke	Hyperuricemia	0.57	47.06	1.64	Coronary heart disease	Dyslipidemia	0.95	70.59	1.62
Gout	Dyslipidemia	3.34	68.73	1.54	Gout	Hypertension	1.99	45.45	1.55
Gout	Hypertension	2.23	45.82	1.51	Urinary system diseases	Dyslipidemia	0.64	66.67	1.53
Coronary heart disease	Hyperuricemia	0.62	42.17	1.47	Gout	Dyslipidemia	2.86	65.45	1.50
Diabetes	Dyslipidemia	8.79	64.8	1.45	Arthritis	Hyperuricemia	0.64	44.44	1.47
Coronary heart disease	Dyslipidemia	0.94	63.86	1.43	Diabetes	Dyslipidemia	6.43	63.28	1.45
Mountain					**Coastland**				
Conditions	Outcomes	Support, %	Confidence, %	Lift	Conditions	Outcomes	Support, %	Confidence, %	Lift
Gout	Hyperuricemia	4.35	92.47	4.25	Gout	Hyperuricemia	5.04	96.06	2.86
Gout	Diabetes	1.67	35.48	2.43	Coronary heart disease	Diabetes	0.54	38.23	2.64
Stroke	Diabetes	0.51	33.33	2.28	Stroke	Hypertension	0.83	68.97	2.27
Coronary heart disease	Hypertension	1.11	68.75	2.21	Coronary heart disease	Hypertension	0.95	67.65	2.23
Coronary heart disease	Diabetes	0.51	31.25	2.14	Diabetes	Hypertension	8.52	58.86	1.94
Stroke	Hypertension	0.96	63.33	2.04	Stroke	Hyperuricemia	0.66	55.17	1.64
Stroke	Hyperuricemia	0.66	43.33	1.99	Gout	Dyslipidemia	3.72	70.87	1.62
Diabetes	Hypertension	8.24	56.4	1.81	Gout	Hypertension	2.32	44.09	1.45
Coronary heart disease	Hyperuricemia	0.61	37.5	1.72	Diabetes	Dyslipidemia	9.01	62.29	1.43
Respiratory disease	Hypertension	0.61	52.17	1.68	Urinary system diseases	Hypertension	1.03	43.1	1.42

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TABLE 2B Top 10 association rules in order of lift with triads of morbidities.

Total					Island				
Conditions	Outcomes	Support, %	Confidence, %	Lift	Conditions	Outcomes	Support, %	Confidence, %	Lift
Hypertension + Gout	Hyperuricemia	2.16	96.83	3.37	Hyperuricemia + Coronary heart disease	Hypertension	0.56	100.00	3.40
Dyslipidemia + Gout	Hyperuricemia	3.22	96.3	3.36	Hypertension + Gout	Hyperuricemia	1.91	96.00	3.17
Diabetes + Gout	Hyperuricemia	1.06	95.24	3.32	Dyslipidemia + Gout	Hyperuricemia	2.70	94.44	3.12
Coronary heart disease + Dyslipidemia	Hypertension	0.64	67.92	2.23	Dyslipidemia + Coronary heart disease	Hypertension	0.64	66.67	2.26
Hypertension + Gout	Diabetes	0.67	30.16	2.22	Hypertension + Gastroenteritis/ulcer disease	Hyperuricemia	0.56	63.64	2.10
Diabetes + Gout	Hypertension	0.67	60.32	1.98	Hypertension + Coronary heart disease	Hyperuricemia	0.56	58.33	1.93
Diabetes + Hyperuricemia	Hypertension	3.06	59.66	1.96	Hypertension + Gastroenteritis/ulcer disease	Dyslipidemia	0.71	81.82	1.87
Diabetes + Dyslipidemia	Hypertension	4.97	56.54	1.86	Diabetes + Hyperuricemia	Dyslipidemia	3.10	79.59	1.82
Diabetes + Gout	Dyslipidemia	0.87	77.78	1.74	Diabetes + Hyperuricemia	Hypertension	2.07	53.06	1.81
Diabetes + Hyperuricemia	Dyslipidemia	3.93	76.55	1.71	Diabetes + Dyslipidemia	Hypertension	3.18	49.38	1.68
Mountain					**Coastland**				
Conditions	Outcomes	Support,%	Confidence, %	Lift	Conditions	Outcomes	Support,%	Confidence, %	Lift
Diabetes + Hyperuricemia	Gout	1.62	31.07	6.60	Dyslipidemia + Gout	Hyperuricemia	3.68	98.89	2.95
Diabetes + Gout	Hyperuricemia	1.62	96.97	4.46	Hypertension + Gout	Hyperuricemia	2.27	98.21	2.93
Hypertension + Gout	Hyperuricemia	2.18	95.56	4.39	Diabetes + Gout	Hyperuricemia	0.95	95.83	2.85
Dyslipidemia + Gout	Hyperuricemia	2.98	93.65	4.31	Hypertension + Dyslipidemia	Diabetes	5.17	32.05	2.22
Dyslipidemia + Stroke	Hyperuricemia	0.51	66.67	3.07	Diabetes + Hyperuricemia	Hypertension	3.35	58.70	1.93
Hypertension + Gout	Diabetes	1.01	44.44	3.04	Diabetes + Dyslipidemia	Hypertension	5.17	57.34	1.89
Dyslipidemia + Gout	Diabetes	1.32	41.27	2.82	Diabetes + Gout	Hypertension	0.54	54.17	1.79
Hyperuricemia + Coronary heart disease	Hypertension	0.51	83.33	2.68	Diabetes + Hyperuricemia	Dyslipidemia	4.34	76.09	1.74
Hyperuricemia + Urinary system diseases	Diabetes	0.61	37.5	2.57	Diabetes + Gout	Dyslipidemia	0.74	75.00	1.72
Hyperuricemia + Gout	Diabetes	1.62	37.21	2.55	Hyperuricemia + Gout	Dyslipidemia	3.68	72.95	1.67

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At present, there is no international consensus regarding the best way to define and measure multimorbidity (37). Hyperuricemia and gout, the most prevalent diseases in Guangdong province, were included. Our study showed that the prevalences of hyperuricemia and gout were 28.70 and 4.86%, respectively, which were higher than the pooled prevalences of gout in the adult population in China (13.3 and 1.1%, respectively) (38) and consistent with previous studies in Guangdong province (39). The main reasons for this phenomenon are closely related to the local characteristics of residents' eating habits. Residents prefer broth in hot and humid weather, which would contain too many purines. For example, nearly 25% of people eat the local special food "Saam Kap Dai" every week, which consists of pork, chitterlings, and belly. In addition, the prevalence of hyperuricemia was higher in the island (30.26%) and coastal regions (33.57%) with $p < 0.0001$, which may be due to the consumption of seafood, and the frequency of weekly seafood consumption was much higher in the coastland (95%) and island (97%) areas than in the mountain areas (47%). Furthermore, a strong association between hyperuricemia and gout was detected by ARM in all regions, which is in accordance with the fact that hyperuricemia is the most dominant factor in gout development (26, 40). Moreover, our study showed that patients with coronary heart disease and/or stroke were prone to occur hyperuricemia, and the connections between diseases have been recognized by mass epidemiological data (41–43).

We found that the most prevalent disease pair was dyslipidemia combined with hyperuricemia and that the most common triad combination was dyslipidemia, hyperuricemia, and hypertension. Considering the differences in the definitions and measurements of multimorbidity, this multimorbidity pattern was initially revealed based on the specificity of the study population. Moreover, the lift in ARM revealed interesting combinations of multimorbidity that occurred more frequently than expected (27, 44). In our study, the ranked lift indicated strong associations between cardiovascular disease and metabolic diseases, including coronary heart disease, stroke, and hypertension with hyperuricemia, diabetes, and dyslipidemia. In agreement with our findings, the pathophysiological connections between diseases in these chronic disease pairs are well-recognized (45–47). Through the above analysis, the frequency of different diseases in different multimorbidities can be identified, and the focus of community multimorbidity prevention and control can be clarified. The level of chronic disease multimorbidity in the community can be significantly reduced through the prevention and control of such key chronic diseases, which will greatly improve the efficiency of community-level chronic disease prevention.

Multimorbidity is common in the surveyed areas, thus clinicians, especially family doctors, need to take into consideration the overall health conditions of patients with multiple chronic diseases to satisfy patient-specific needs regarding disease diagnosis and treatment. They should actively explore multiple approaches to implement polypharmacy management for adults with multimorbidity, particularly problems of polypharmacy in older adults. Considering the importance of primary care in addressing multimorbidity, strengthened training of primary-level medical workers is required to better prevent and control NCDs and to deliver multimorbidity care in a coordinated and continuous manner. Our findings on the multimorbidity patterns in different areas could help formulate more reasonable public health policies to maximize the benefits of medical services.

The main strength of this study was the large sample size of the population-based data used to illustrate the multimorbidity prevalence and patterns among three areas in Guangdong province. However, the study also had some limitations. First, self-report bias might exist because we included self-reported information. Therefore, the prevalence of multimorbidity might be underestimated, and factors associated with multimorbidity patterns should be interpreted with caution because of the problem of underdiagnosis. Second, selection bias might exist because we did not include individuals who were unable or unwilling to participate in this survey. Third, although the survey was based on the DCLL study, the cross-sectional data of the current study made it impossible to confidently draw causal conclusions. Fourth, the definition of multimorbidity should be further improved considering the limited number and types of diseases included. Our list was not exhaustive and included 14 common NCDs, and we may have overlooked some other higher-burden conditions. This may have led to an underestimation of the prevalence and impact of multiple diseases. In addition, the areas included in our study have unique cultures, dietary habits, and geography, thus the results may not be extrapolated to other areas in China.

In conclusion, with a prevalence approaching 40%, multimorbidities were common among adults aged ≥20 years in Guangdong province, and the prevalence increased with age. Coastland residents with "Chaoshan" culture had a higher prevalence than other areas. The most prevalent disease pair was dyslipidemia combined with hyperuricemia. The most common triad combination was dyslipidemia, hyperuricemia, and hypertension. Cardiovascular diseases and metabolic diseases were more likely to co-occur. These findings in our study, including the most frequent multimorbidity, associations, and clusters, will help healthcare providers to develop healthcare plans that will improve the effectiveness of multimorbidity management.

Data availability statement

The raw data supporting the conclusions of this article will be made available by reasonable request by sending email to the corresponding author. Requests to access the datasets should be directed to GS, guangliang_shan@163.com.

Ethics statement

The study was approved by the Ethics Committee of Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GS, QO, LP, XZ, and XC contributed to the study conception and design. YH and HH performed the data analysis. The first draft of the manuscript was written by YH. All authors contributed to

the material preparation, data collection, interpreted the results, revised, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Synergistic effects of overweight/obesity and high hemoglobin A1c status on elevated high-sensitivity C-reactive protein in Chinese adults: a cross-sectional study

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Background: High-sensitivity C-reactive protein (hs-CRP) is an inflammatory marker that has been suggested as a predictor of cardiovascular diseases. High glycated hemoglobin (HbA1c) levels and overweight/obesity are independently associated with elevated hs-CRP; meanwhile, high HbA1c levels are frequently accompanied by overweight or obesity. However, their joint effect on elevated hs-CRP levels has not been well-established. Therefore, we evaluated whether overweight/obesity modified the association between high HbA1c levels and elevated hs-CRP.

Methods: Based on cross-sectional data from the Chinese Urban Adults Diet and Health Study (CUADHS) in 2016, we included 1,630 adults aged 18–75 years (mean age 50.16 years and 33.6% male). Elevated hs-CRP was defined as serum hs-CRP $\geq$ 3 and <10 mg/L. The interactive effects of BMI and HbA1c levels on the risk of elevated hs-CRP levels were calculated by using multiple logistic regression models, followed by strata-specific analyses.

Results: Individuals with elevated hs-CRP had a higher rate of HbA1c level than those without elevated (25.3 vs. 11.3%, $P < 0.001$), as well as a higher rate of overweight/obesity (67.1 vs. 43.5%, $P < 0.001$). Higher HbA1c levels were independently associated with an increased risk of elevated hs-CRP [adjusted odds ratio (aOR) = 2.31, 95% confidence interval (CI): 1.47, 3.65], as well as overweight/obesity with the risk of elevated hs-CRP (aOR = .31, 95% confidenc–3.73). Furthermore, overweight/obesity showed a significant synergistic effect on high HbA1c levels with a higher aOR of 5.25 (2.77, 9.95) ($P_{interaction} < 0.001$). This synergistic effect was more prominent when stratified by age (in 18–44 years old, aOR, 95% CI = 30.90, 4.40–236.47 for interaction vs. 6.46, 1.38–30.23 for high HbA1c only) and gender (in women, aOR, 95% CI = 8.33, 3.80–18.23 for interaction vs. 2.46,1.38–4.40 for high HbA1c only).

Conclusion: There are synergistic effects of high HbA1c levels and overweight/obesity on the risk of elevated hs-CRP in Chinese adults, with more significant effects in adults aged 18–44 years or females. Intervention strategies for preventing high blood glucose levels and body weight simultaneously may be important for reducing hs-CRP-related diseases. Further studies are needed to confirm this finding in other populations, and its molecular mechanisms need to be elucidated.

KEYWORDS

interaction, hs-CRP, HbA1c, BMI, Chinese adults

Introduction

High-sensitivity C-reactive protein (hs-CRP) is an acute-phase reactant and a biomarker of systemic inflammation. Chronic elevated hs-CRP may have biological effects on endothelial function, coagulation, fibrinolysis, oxidation of low-density lipoproteins (LDL), and stability of atherosclerotic plaque (1). Hs-CRP is considered an optimal predictor for the assessment of future cardiovascular events according to the recommendation of the American Heart Association (AHA) (2). It is well-known that cardiovascular disease (CVD) is the leading cause of death globally, which places a substantial burden on health and economy. A meta-analysis of 22 studies indicated that the concentrations of hs-CRP greater than or equal to 3 mg/L were associated with a 60% increased risk of CVD (3), and other studies (4–6) reached similar conclusions including the Chinese population (7). In addition, elevated hs-CRP levels have also been shown to be a risk factor for other diseases. For example, high hs-CRP was significantly associated with a 40% increased risk of depression in younger adults (8, 9) and a 60% increased risk of fractures in elderly men (10). As a result, there is an urgent need to take measures to prevent and control the elevation of hs-CRP to reduce the risk of related diseases.

Glycated hemoglobin (HbA1c) is the amount of hemoglobin in the blood that binds to glucose, reflecting the average blood glucose level over the last 2–3 months. Diabetes is diagnosed the level of HbA1c is 6.5% or higher, according to current guidelines (11, 12). HbA1c above 7% puts diabetics at risk of developing macrovascular and microvascular complications (13–15). Recently, an increasing number of studies have shown that higher HbA1c levels are associated with a greater risk of cardiovascular-related disorders even in non-diabetic subjects (16–19). Elevated HbA1c level is an established risk factor for cardiovascular (CV) complications (20, 21). Therefore, maintaining HbA1c within the normal range could reduce the risk of cardiovascular events. However, there is little evidence to suggest that could confirm the association between the levels of HbA1c and inflammatory biomarkers of CVD, such as hs-CRP.

High HbA1c status is frequently accompanied by being overweight or obese (22), while some studies have observed a relationship between high HbA1c status and higher hs-CRP levels, it is still unclear whether this relationship exists after adjusting for adiposity. Obesity is a chronic metabolic condition that is related to a high risk of CVD, hypertension, insulin resistance and other comorbidities. The latest reported data showed that more than 34.3 and 16.4% of Chinese adults (≥18 years) were overweight and obese, respectively; meanwhile the global prevalence of obesity continues to grow slowly and remains at a high level (23, 24). Studies have shown that inflammatory cytokines produced by adipose tissue, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), promote the production of hs-CRP in the liver (25, 26). Consequently, there is a strong positive correlation between obesity indicators, such as waist circumference (WC) and body mass index (BMI), and hs-CRP (27, 28).

Several researchers suggested that inflammation may be a link between obesity, type 2 diabetes and CVD. However, as far as we know, little is known about their combined effects of HbA1c level and overweight/obesity on increased risk of hs-CRP, especially in Chinese adults. In this study, we hypothesized that high HbA1c levels and overweight/obesity, both individually and jointly, are associated with elevated hs-CRP in Chinese adults. If this connection can be proven, lifestyle interventions such as the control of body weight and blood sugar levels can play a primary preventive role in the occurrence of CVD-related diseases by reducing the level of hs-CRP.

Therefore, to evaluate this hypothesis, we conducted this study to explore the interaction between overweight/obesity and high HbA1c status on elevated hs-CRP in adults of the Chinese population.

Methods

Study design and population

The data used in the research were drawn from the Chinese Urban Adults Diet and Health Study (CUADHS), which was a cross-sectional study that covered eight cities, representing different economic development and public resources regions in China. From March to July 2016, this survey used a multistage sampling method to randomly recruit 1739 urban adults between 18 and 75 years old from Beijing, Guangzhou, Xuchang, Jilin, Wuhan, Lanzhou, Chenzhou and Chengdu [details have been described elsewhere (29)]. Those with mental illness, memory problems, physical disabilities, or women who were pregnant or lactating were excluded. A series of questionnaires, physical

examinations, and blood samples were collected on the day of enrollment. This study was conducted by the biomedical ethics committee of Peking University (No. IRB00001052-15059) and obtain the informed written consent of all participants.

In the current analysis, participants were excluded if they had missing data on high-sensitivity C-reactive protein (hs-CRP) (n = 16), glycated hemoglobin (HbA1c) (n = 28), or body mass index (BMI) (n = 5). Moreover, participants with hs-CRP levels equal to or higher than 10 mg/L were excluded from the analysis (n = 33), as those values are indicative of current acute infection (30). Accordingly, 1,630 individuals were included in the final analysis.

Data collection and definition

Data on sociodemographic characteristics, lifestyle behaviors and individual health status were self-reported and recorded by uniformly trained interviewers, including age, gender, race, marital status, education, income, tobacco smoking, alcohol consumption, physical activities and disease history. Physical examination was performed simultaneously. Height and body weight were measured following standard protocols using SECA877, and BMI was calculated as the weight in kilograms divided by height in meters squared. Then, it was divided into two groups ($<$24 or $\geq$24 kg/m^2) based on the Working Group on Obesity in China criteria (24). Using Omron HEM-7124 electronic blood pressure (BP) monitor, BP was measured twice after sitting for 5 min. The criterion for hypertension was average systolic BP $\geq$140 mmHg and/or average diastolic BP $\geq$90 mmHg or having a history of hypertension or having taken prescription drugs to treat hypertension.

Blood samples were collected in the morning after overnight fasting to detect serum Hs-CRP and HbA1c. All samples were analyzed by the Lawke Health Laboratory with strict quality control. The concentration of serum hs-CRP was determined by immunoturbidimetry (Roche Diagnostic). When the serum hs-CRP is above 3 mg/L and below 10 mg/L, it is considered that the individual is in a state of chronic inflammation and has a high risk of CVD. For the present study, serum hs-CRP level was stratified into two degrees ($<$3 or $\geq$3 mg/L), and hs-CRP $\geq$3 mg/L was defined as elevated according to the American Heart Association and Centers for Disease Control and Prevention (30). HbA1c was measured with high-performance liquid chromatography (Tosoh, Tokyo, Japan). We defined higher HbA1c levels as HbA1c $\geq$ 6.5% and lower HbA1c levels as $<$ 6.5% (31). Individual with TC $\geq$ 6.22 and/or TG $\geq$ 2.26 mmol/L, and/or HDL-D $<$ 1.04 and/or LDL-D $\geq$ 4.14 mmol/L or previous diagnosis with dyslipidemia were identified as dyslipidemia (32).

Statistical analysis

Data were tested for normality before statistical analysis. If continuous variables didn't follow a normal distribution, median and interquartile ranges were presented and compared using Mann-Whitney U tests; otherwise, mean ± standard deviation (SD) and Student's t-tests were utilized. Categorical variables are presented as frequencies and percentages and were compared using chi-squared tests.

Multivariable logistic regression was performed and odds ratios [OR, with 95% confidence intervals (CI)] were calculated to analyze the individual and joint associations of BMI and HbA1c with elevated hs-CRP levels in this population. In multivariate logistic regressions, model 1 adjusted for age, gender, race, education level, marital status, and monthly household income, and model 2 further adjusted for city grade, hypertension, dyslipidemia, alcohol use, and smoking status. We tested for interaction effects on a multiplicative scale. For multiplicative interaction, we calculated two-sided P-values to evaluate the significance of each product term in the logistic regression models and compared the ORs for HbA1c and elevated hs-CRP in different BMI layers (33).

To further clarify the association, we performed stratified analyses according to age and sex to explore potential disparities in the association between the interaction of BMI and HbA1c on hs-CRP in model 2. All analyses were performed in SPSS Statistics version 24. Two-sided p-values less than 0.05 were considered significant.

Results

Basic characteristics

The demographic characteristics of study participants by elevated hs-CRP are summarized in **Table 1**. Among the 1,630 participants [547 men (33.6%)], the mean (± SD) age was 50.16 ± 17.33 years, most were of Han nationality (97.4%), 26.0% had a university education or above and 38.1% of the participants were living in first-tier developed cities. The prevalence of elevated hs-CRP was 8.96% (n = 146). Individuals with elevated hs-CRP had higher HbA1c levels than those without elevated hs-CRP (25.3 vs. 11.3%, $P < 0.001$), as well as a higher rate of overweight/obesity (67.1 vs. 43.5%, $P < 0.001$). Additionally, compared with participants with normal hs-CRP levels, those with elevated hs-CRP tended to be older, had poorer educational backgrounds and had a higher level of blood pressure ($P < 0.05$).

Individual associations of BMI and HbA1c with elevated hs-CRP

Table 2 shows the relationship between BMI and HbA1c and the risk of elevated hs-CRP levels in the overall population, respectively. In the binary logistic regression analyses, by comparison to the lower HbA1c levels, the crude OR (95% CI) of elevated hs-CRP in the higher HbA1c group was 2.66 (1.77, 3.99) ($P < 0.001$). When adjusted for age, sex, race, educational level, marital status, monthly household income, city grade, hypertension, dyslipidemia, alcohol use and smoking status, higher HbA1c levels were still significantly associated with an increased risk of elevated hs-CRP [adjusted OR 2.31 (1.47, 3.65), $P_{adjusted} \leq 0.001$]. Similarly, compared to those who were normal/underweight, those overweight/obese had a crude OR (95% CI) of 2.66 (1.85, 3.81) ($P < 0.001$) for elevated hs-CRP. After adjusting for potential confounding factors, a higher BMI level remained significantly associated with the risk of elevated hs-CRP (aOR = 2.51; 95% CI: 1.68–3.73, $P_{adjusted} < 0.001$).

TABLE 1 Basic demographic characteristics of high-sensitivity C-reactive protein (hs-CRP) elevated[1] and normal[2] (*N* = 1,630).

Characteristics	Total	Elevated hs-CRP	Normal hs-CRP	*P*-value
n (%)	1,630	146 (8.96)	1,484 (91.04)	–
Age, years	52.09 (34.82, 65.86)	63.47 (43.98, 68.75)	51.34 (33.94, 65.45)	<**0.001**
18–44	611 (37.5)	39 (26.7)	572 (38.5)	–
45–64	556 (34.1)	40 (27.4)	516 (34.8)	–
≥65	463 (28.4)	67 (45.9)	396 (26.7)	–
Gender (%)				0.714
Male	547 (33.6)	47 (32.2)	500 (33.7)	–
Female	1083 (66.4)	99 (67.8)	984 (66.3)	–
City grade (%)				0.883
First-tier city[3]	621 (38.1)	54 (37.0)	567 (38.2)	–
Second-tier city[4]	332 (20.4)	32 (21.9)	300 (20.2)	–
Third-tier city[5]	677 (41.5)	60 (41.1)	617 (41.6)	–
Race (%)				0.316
Han Chinese	1587 (97.4)	144 (98.6)	1443 (97.2)	–
Ethnic minorities	43 (2.6)	2 (1.4)	41 (2.8)	–
Educational level (%)				**0.001**
Junior high school and below	530 (32.6)	67 (45.9)	463 (31.3)	–
High school or equivalent	672 (41.4)	51 (34.9)	621 (42.0)	–
University graduate or above	422 (26.0)	28 (19.2)	394 (26.7)	–
Marital status (%)				**0.022**
Unmarried	266 (16.4)	12 (8.3)	254 (17.2)	–
Married	1250 (76.9)	123 (84.8)	1127 (76.1)	–
Divorced or widowed	110 (6.8)	10 (6.9)	100 (6.8)	–
Monthly household income, ¥				0.589
<5,000	815 (50.3)	76 (52.1)	739 (50.1)	–
5,000–9,999	511 (31.5)	48 (32.9)	463 (31.4)	–
≥10,000	295 (18.2)	22 (15.1)	273 (18.5)	–
Smoking status (%)				0.479
Never	1243 (76.8)	118 (80.8)	1125 (76.4)	–
Former	174 (10.7)	13 (8.9)	161 (10.9)	–
Current	202 (12.5)	15 (10.3)	187 (12.7)	–
Alcohol drinking (%)	453 (27.8)	36 (24.7)	417 (28.1)	0.376
Physical activity, mets/week	1386.0 (693.0, 2772.0)	1567.5 (693.0, 3186.0)	1386.0 (693.0, 2754.0)	0.221
Dyslipidemia (%)	256 (15.8)	30 (20.7)	226 (15.3)	0.090
Hypertension (%)	419 (26.2)	57 (40.1)	362 (24.8)	<**0.001**
SBP, mmHg	122.0 (110.0, 136.0)	130.0 (120.0, 145.3)	120.0 (110.0, 135.0)	<**0.001**
DBP, mmHg	78 (70.0, 85.0)	81.5 (73.0, 88.0)	78.0 (70.0, 85.0)	<**0.001**
Metabolic syndrome (%)	506 (31.0)	89 (51.1)	417 (28.6)	<**0.001**
BMI, kg/m^2 (%)	23.55 (21.37, 26.01)	25.73 (23.20, 28.02)	23.40 (21.23, 25.81)	<**0.001**
<24	887 (54.4)	48 (32.9)	839 (56.5)	–
≥24	743 (45.6)	98 (67.1)	645 (43.5)	–
Fasting blood glucose, mmol/L	5.22 (4.78, 5.76)	5.58 (5.02, 6.35)	5.19 (4.77, 5.70)	<**0.001**
HbA1c (%)	5.80 (5.50, 6.10)	6.10 (5.60, 6.50)	5.70 (5.50, 6.10)	<**0.001**
<6.5	1425 (87.4)	109 (74.7)	1316 (88.7)	–
≥6.5	205 (12.6)	37 (25.3)	168 (11.3)	–

Data are expressed as the median (interquartile range, IQR) for non-normally distributed continuous variables, as the means ± SDs for normally distributed continuous variables or as counts (percentages) for categorical variables. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

[1]Elevated hs-CRP group: hs-CRP ≥ 3 mg/L.

[2]Normal hs-CRP group: <3 mg/L.

[3]Beijing, Guangzhou.

[4]Chengdu, Lanzhou.

[5]Xuchang, Jilin, Wuhu, Chenzhou. The bold values mean that the differences are statistically significant.

TABLE 2 Odds ratios [ORs, 95% confidence intervals (CIs)] for the individual associations of body mass index (BMI) and hemoglobin A1c (HbA1c) status with elevated high-sensitivity C-reactive protein (hs-CRP) (*N* = 1,630).

Variables	*n* (%)	Crude OR, 95% CI	*P*-value	Model 1 OR, 95% CI	*P*-value	Model 2 OR, 95% CI	*P*-value
BMI, kg/m^2							
<24	48 (5.41)	Ref.	–	Ref.	–	Ref.	–
≥24	98 (13.19)	**2.66 (1.85, 3.81)**	**<0.001**	**2.45 (1.67, 3.60)**	**<0.001**	**2.51 (1.68, 3.73)**	**<0.001**
HbA1c, %							
<6.5	109 (7.65)	Ref.	–	Ref.	–	Ref.	–
≥6.5	37 (18.05)	**2.66 (1.77, 3.99)**	**<0.001**	**2.19 (1.41, 3.38)**	**<0.001**	**2.31 (1.47, 3.65)**	**<0.001**

BMI, body mass index. Model 1: age, gender, race, educational level, marital status, monthly household income; Model 2: model 1+ city grade, hypertension, dyslipidemia, alcohol use and smoking status. *n* (%): numbers and prevalence rates of high high-sensitivity C-reactive protein (hs-CRP) of each layer. The bold values mean that the differences are statistically significant.

TABLE 3 Odds ratios [ORs, 95% confidence intervals (CIs)] for the interaction associations of body mass index (BMI) and hemoglobin A1c (HbA1c) status with elevated high-sensitivity C-reactive protein (hs-CRP) (*N* = 1,630).

Interaction	*n* (%)	Crude OR, 95% CI	*P*-value	Model 1 OR, 95% CI	*P*-value	Model 2 OR, 95% CI	*P*-value
N-weight* N-HbA1c	36 (4.45)	Ref.	–	Ref.	–	Ref.	–
N-weight* H-HbA1c	12 (15.38)	**3.90 (1.94, 7.86)**	**<0.001**	**3.43 (1.63, 7.24)**	**0.001**	**4.07 (1.90, 8.72)**	**<0.001**
O-weight* N-HbA1c	73 (11.85)	**2.89 (1.91, 4.37)**	**<0.001**	**2.82 (1.81, 4.39)**	**<0.001**	**3.01 (1.90, 4.77)**	**<0.001**
O-weight* H-HbA1c	25 (19.69)	**5.26 (3.03, 9.13)**	**<0.001**	**4.77 (2.62, 8.68)**	**<0.001**	**5.25 (2.77, 9.95)**	**<0.001**

N, normal (<24 kg/m^2 for BMI or <6.5% for HbA1c); H, high (≥6.5% for HbA1c); O, overweight or obesity (≥24 kg/m^2 for BMI); Model 1, age, gender, race, educational level, marital status, monthly household income; Model 2, model 1 + city grade, hypertension, dyslipidemia, alcohol use and smoking status; *n* (%), numbers and prevalence rates of high high-sensitivity C-reactive protein (hs-CRP) of each layer. The bold values mean that the differences are statistically significant.

Synergistic interaction of BMI and HbA1c on elevated hs-CRP

Furthermore, to investigate the effect of the coexistence of BMI and HbA1c levels on elevated hs-CRP, participants were divided into four groups based on the levels of BMI and HbA1c: Group 1 (Normal-weight and Normal-HbA1c), Group 2 (Normal-weight and High-HbA1c), Group 3 (Overweight/Obesity-weight and Normal-HbA1c), and Group 4 (Overweight/Obesity-weight and High-HbA1c). Compared with individuals in Group 1, there were significantly increased risks of elevated hs-CRP for individuals in Groups 2, 3, and 4 ($P_{interaction} < 0.001$). Compared with Group 1, the adjusted OR (95% CI) for Group 4 was 5.25 (2.77, 9.95) in the entire population, in contrast with 4.07 (1.90, 8.72) for Group 2 and 3.01 (1.90, 4.77) for Group 3. That is, when analyzed jointly, overweight/obesity and high HbA1c levels were synergistically associated with an increased risk of hs-CRP, and the interactive effect was approximately twice as significant as the individual effect. Results are displayed in detail in Table 3.

Subgroup analyses

Next, the above analysis was repeated in two subgroups: age (18–44, 45–64 vs. ≥65 years) and sex (female vs. male). In model 2, the interactions of BMI and HbA1c level with hs-CRP were evaluated to determine whether the joint effect was the same in each subgroup. Stratified analysis by age and gender in model 2 is shown in Figure 1 (age) and Figure 2 (gender). Among those aged 18–44, the interaction effects of overweight/obesity and high HbA1c level on elevated hs-CRP were nearly 6 times more likely than the total population (aOR = 30.90, 95% CI: 4.04–236,47, $P_{interaction} = 0.001$) (Supplementary Table 1). It is worth noting that the 95% CI was wide, indicating that the excess risk may be an accidental finding due to the small number of cases in this age range. Interestingly, there were no significant interactions in the population aged 45–64 (aOR = 3.27, 95% CI: 0.95–11.20, $P = 0.060$). Among those over 65 years old, the interaction was weaker (aOR = 3.30, 95% CI: 1.44–7.56, $P = 0.049$). In the stratified analysis by sex, after adjustment for potential confounders, women with high HbA1c levels and overweight/obesity were nearly twice as likely to have elevated hs-CRP than the total population (aOR = 8.33, 95% CI: 3.80–18.23, $P_{interaction} < 0.001$) (Supplementary Table 2). However, this association became non-significant in men (aOR = 1.89, 95% CI: 0.57–6.27, $P_{interaction} = 0.301$). After stratification by age and sex, the unadjusted and adjusted ORs (95% CIs) according to models 1 and 2 for each layer are attached in the Supplementary material.

Discussion

In our study of 1,630 Chinese adults, we found that high HbA1c levels and overweight/obesity were independent predictors of hs-CRP elevation, even after

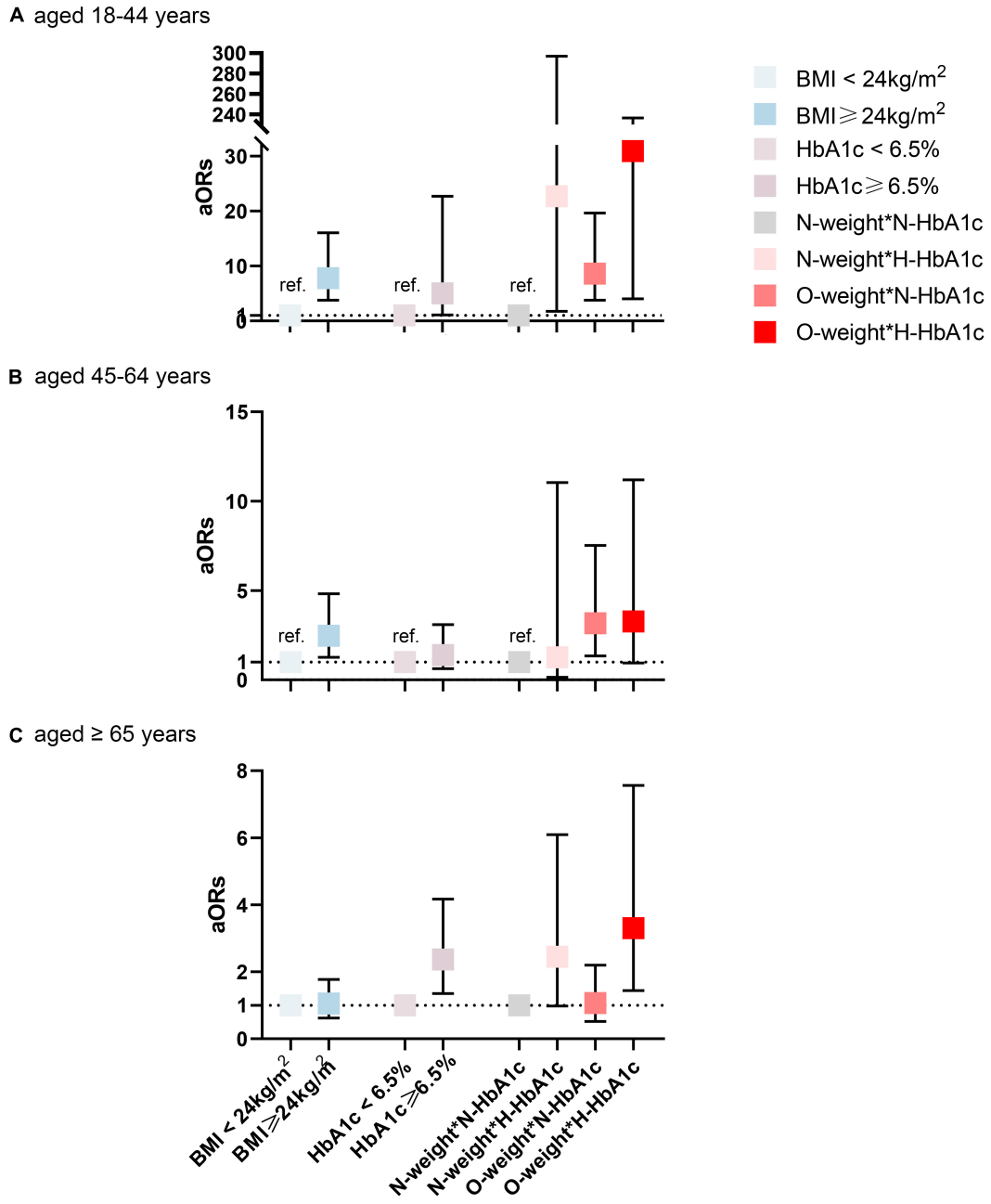

FIGURE 1
Interaction and independent effect of BMI and hemoglobin A1c (HbA1c) status on elevated high-sensitivity C-reactive protein (hs-CRP), stratified by age. **(A)** aged 18–44 years **(B)** aged 45–64 years **(C)** aged ≥ 65 years. N, normal (<24 kg/m^2 for BMI or <6.5% for HbA1c); H, high (≥6.5% for HbA1c); O, overweight or obesity (≥24 kg/m^2 for BMI); BMI, body mass index. Adjusted for gender, race, educational levels, marital status, monthly household income (CNY), city grade, hypertension, dyslipidemia, alcohol use, and smoking status.

considering several traditional confounding factors. Significant interaction effects were observed in the joint analyses, approximately twice as much as the single effect, and the combined effects were stronger in female and younger individuals (aged 18–44 years) for hs-CRP elevation prediction.

Many previous studies have reported a high association between HbA1c and hs-CRP levels. The increase in hs-CRP level is a predictor of a higher risk of cardiovascular events and cardiovascular mortality in the future. A recent study confirmed that HbA1c was favorable for predicting arterial stiffness in the general Chinese population, regardless of whether or not it was in those with a normal glucose status (34). A previous study demonstrated that the serum hs-CRP level was high in patients with diabetes, and the only statistically significant determinants of hs-CRP in this study were gender, BMI, WHR, and concurrent HbA1c (35). Similar to these findings, Wei et al. (36) found that the level of HbA1c was positively correlated with the level of hs-CRP in patients with diabetes according to Pearson correlation analysis. These results suggested an association between HbA1c

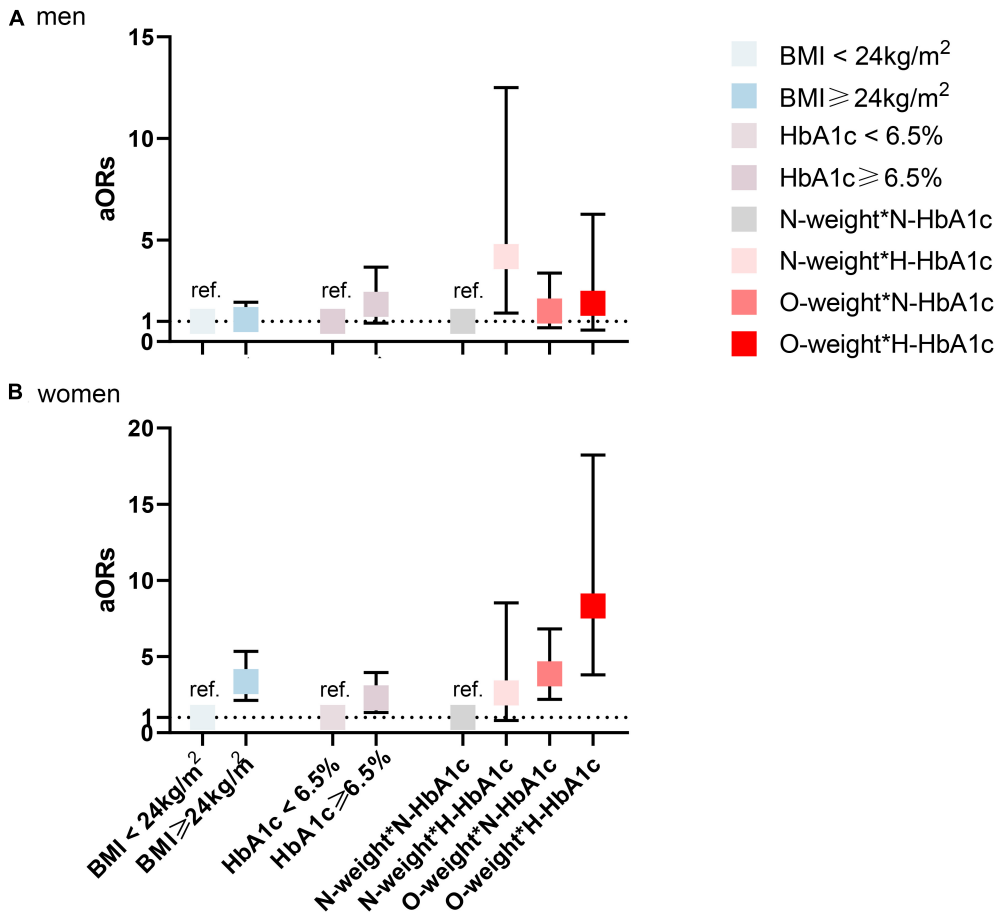

FIGURE 2
Interaction and independent effect of body mass index (BMI) and hemoglobin A1c (HbA1c) status on elevated high-sensitivity C-reactive protein (hs-CRP), stratified by gender. **(A)** men **(B)** women. N, normal (<24 kg/m^2 for BMI or <6.5% for HbA1c); H, high (≥6.5% for HbA1c); O, overweight or obesity (≥24 kg/m^2 for BMI); BMI, body mass index. Adjusted for age, race, educational level, marital status, monthly household income, city grade, hypertension, dyslipidemia, alcohol use, and smoking status.

levels and inflammatory levels in diabetic patients. Meanwhile, in 3,537 Korean adults not diagnosed with diabetes (aged 19–80 years), increases in HbA1c correlated with hs-CRP levels (β = 0.185, p = 0.001, and R^2 = 0.087). In this study, after adjusting for confounders, there was a correlation between fasting glucose and hs-CRP levels in females. However, similar to our research, there was no statistical significance in males (37). Among 1,723 Korean teenagers (aged 10–18 years), in multiple regression analysis, HbA1c levels were significantly associated with hs-CRP (β = 0.036, p = 0.012) (38). However, we note that some other studies had contrary results. One study with older adults aged 65–95 in Portugal found that HbA1c was not associated with hs-CRP (39). However, only 118 older adults were enrolled in this study.

Previous studies have demonstrated that higher BMI levels were associated with higher CRP levels, which is consistent with our findings. In a cross-sectional study reported in Chinese adults, after adjusting for confounders, the risk of elevated hs-CRP in overweight group was 1.27 times greater than in normal weight group, and that in the obese group was 1.70 times greater than in normal body weight group (40). Khoo et al. (41) found that BMI was directly related to hs-CRP in all evaluated ethnic groups. The increase in hs-CRP associated with each unit increase in BMI was greater in the Chinese population than in other ethnic groups. Another study suggested that Asians had higher body fat content and a higher risk of diabetes, hypertension, and heart disease than people with the same BMI of other races (42). In other races and populations, the results are similar. Among middle-aged and olderly African-Americans enrolled in the Jackson Heart Study, hs-CRP was used as a measure of inflammation, and there was a strong correlation between BMI and hs-CRP. In a case–control study conducted in Australia, MacKenzie et al. (43) found that hs-CRP was related to BMI z- score (r = 0.47, p < 0.001) in children with type 1 diabetes mellitus (T1DM). In Cuban Americans, Huffman et al. (44) showed that BMI was significantly associated with ln hs-CRP whether with type 2 diabetes or not. The slope for the relationship between BMI and ln hs-CRP was stronger in people without diabetes was greater than that in people with diabetes (β = 0.099 and β = 0.055, respectively), but both slopes were significantly different than zero (p < 0.001). That is, there is an interaction between BMI and diabetes status on the risk of elevated hs-CRP in this population. This study seems to show that their

relationship is stronger in women than in men, which is similar to our findings.

To our knowledge, this is the first study to examine the interactions between HbA1c levels, BMI and their interaction on the risk of hs-CRP elevation among adults in China. Therefore, the current analysis is largely exploratory in nature but serves to add clinical insight into the inflammatory burden of Asian populations.

Obesity induces adipocyte dysfunction, with adipokine secretion and macrophage activation leading to proinflammatory cytokine such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) production and the release of anti-inflammatory adipokines such as adiponectin reduction (45). Inflammatory adipocytokines TNF-α and IL-6 are associated with elevated levels of circulating hs-CRP (26). These changes in the release of adipocytokines, especially from visceral adipose tissue, induce a state of systemic insulin resistance and low-grade inflammation (45). Being overweight and obese is known to be associated with insulin resistance and increased glycemia. Previous studies have explored the association between serum glucose and inflammation. Some studies have suggested that reactive oxidative species from glycation end products are a pro-inflammatory effect of increased glucose levels (46). Another plausible mechanism is that hyperglycemia affects NF-κb, a key mediator that regulates multiple proinflammatory and proatherosclerotic target genes in endothelial cells, vascular smooth muscle cells, and macrophages (47). When the overweight/obesity and high HbA1c levels exist at the same time, they have a synergistic effect on the increase in hs-CRP.

Our investigation also revealed the effect of their interaction on hs-CRP after stratification by sex and age. Our results show that the interaction between overweight/obesity and high HbA1c levels was significant in females. However, this effect was not observed in males. Our findings are similar to those of Nari et al. (48). Two mechanisms have been suggested. First, estrogen secretion in female individuals may play a role in the etiology of inflammation (49), resulting in a more pronounced effect on hs-CRP levels. Second, females generally have higher levels of the body and visceral fat than males (50), with a consequent increase in hs-CRP levels and CVD risk. Moreover, this joint effect was not attenuated in the age-specific analysis and was observed in both younger and older individuals. Interestingly, this effect was not observed in middle-aged people. In future research, the sample size can be expanded for further analysis.

Overall, our study has important clinical and public health implications. The gate for the prevention and control of CVD-related diseases moved forward from controlling the occurrence of CVD to controlling the level of hs-CRP. It is clear from our study that reducing HbA1c levels and controlling body weight are important for reducing the risk of hs-CRP-related diseases in the future. Rossello et al. (16) clarified the clinical significance of routine detection of HbA1c levels in non-diabetic subjects, which can not only prevent the development of diabetes, but also estimate the risk of subclinical atherosclerosis (SA) and subsequent CVD, and monitor the effectiveness of therapeutic interventions to address this risk. In routine clinical practice, measurement of HbA1c levels is not always performed in subjects without diabetes, while levels below the diabetic range are also often left untreated. Our study provides a scientific basis for paying attention to and controlling HbA1c levels and body weight in non-diabetic patients to help reduce inflammation. For individuals, simultaneous control of body weight and blood sugar levels can reduce inflammation better than a single indicator, especially for women and people aged between 18 and 44 years old. Individuals with excess body weight or high HbA1c status are believed to benefit from early diet and lifestyle intervention. For health professionals, to improve the early identification of CVD-related diseases, more attention should be given to the body weight and HbA1c level of this population simultaneously in clinical practice, which may have greater clinical significance for the prevention and treatment of these diseases.

The primary strength of this study was that our study quantitatively shows for the first time the effects of overweight/obesity and high levels of HbA1c on inflammation, and provides scientific evidence for the prevention and treatment of related diseases caused by hs-CRP. Second, stratified analysis by age and sex was performed to clarify different effects between the combined BMI and HbA1c and elevated hs-CRP levels. Third, this study was carried out among the general population in eight cities in China, and multistage stratified cluster sampling was conducted, which is a nationally representative survey, improving the representativeness of the findings for the Chinese population.

The current study nevertheless had several limitations. First, as this was a cross-sectional study, we could not infer causality and temporality relationship between overweight/obesity, high HbA1c levels and elevated hs-CRP, and there might be recall bias. Second, the sample size of this study is relatively small, and the extrapolation of the research results is affected to a certain extent. Third, despite extensive adjustment for potential confounders, residual confounding factors cannot be completely ruled out, such as a history of CVD-related disease and a family history of the disease. Finally, this study was conducted in the general population of China, without distinguishing whether diabetes was present, and the results may be easily affected by diabetes status. In the future, separate studies can be conducted specifically in diabetic and non-diabetic people to better determine whether there is interaction and the size of the effect in different diabetic states.

Conclusion

In conclusion, high HbA1c levels and overweight/obesity, both individually and jointly, were associated with elevated hs-CRP risks in Chinese adults, especially in female and younger individuals. Hs-CRP-related disease prevention strategies aimed at reducing HbA1c levels and reducing body weight simultaneously may exceed the expected benefits based on targeting either risk factor alone. Further studies are required to expand the sample size and validate these findings in different populations. The potential mechanism underlying the joint effect of high HbA1c levels and overweight/obesity needs to be clarified.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedical Ethics Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QS and YZ contributed to the design of this study. SM, WZ, and PL contributed to the data collation of the manuscript. TH, TL, and IS were responsible for quality control. QS analyzed the data and drafted the manuscript. HJ and YZ contributed to revising this manuscript. All authors read and approved the final manuscript.

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Conflict of interest

TH, TL, and IS were employed by Inner Mongolia Dairy Technology Research Institute Co., Ltd. TH and TL were employed by Inner Mongolia Yili Industrial Group Co., Ltd.

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1156404/full#supplementary-material

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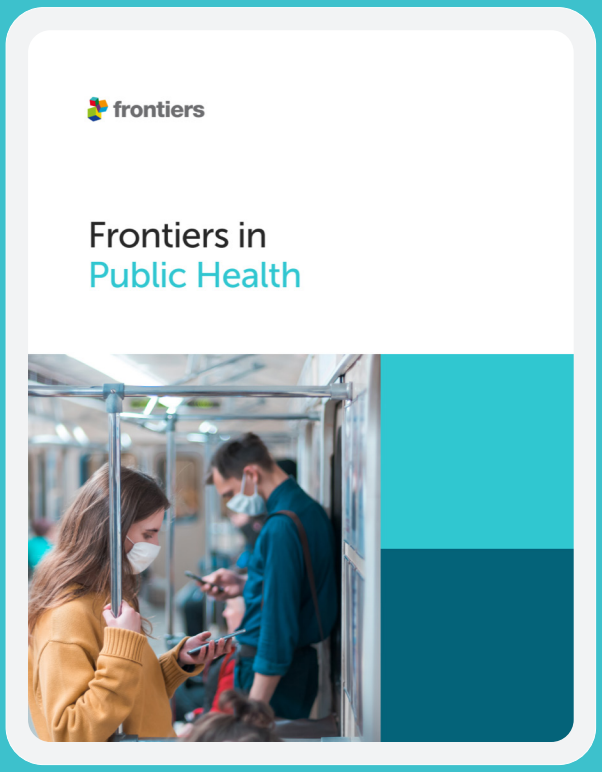

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