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Association between serum chloride and prevalence of metabolic syndrome in the general U.S. adult population: evidence from NHANES 2011–2018

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Abstract

Aim Numerous studies have revealed the decisive role of serum chloride in the outcome of specific patients. However, the potential role of serum chloride in general populations has been rarely investigated. This study aims to assess the association of serum chloride with MetS risk in the general population.

Methods A total of 13,290 adult participants were obtained from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2018. The association between serum chloride and MetS was investigated using weighted logistic regression analyses. The weighted restricted cubic spline (RCS) was constructed based on the fully adjusted model to explore its dose-response relationship. Further stratified analyses were also conducted. All data and analyses were conducted using the "Survey" package in R software (Version 4.4.1).

Results The average age of this population was 48.20 ± 0.35, the average BMI was 29.42 ± 0.12 kg/m^2, included 48.54% males, and the weighted prevalence of MetS was 37.83%. After adjusting full covariates, serum chloride was negatively associated with MetS risk in overweight or obese participants who did not smoke or heavy drink. Meanwhile, serum chloride was significantly inversely correlated with the raised fast glucose (FG), total cholesterol (TG) and blood pressure (BP), and positively related with the reduced high density lipoprotein cholesterol (HDL-C). Consistent results were observed in the RCS analysis.

Conclusion This study suggested a potential inverse relationship between serum chloride levels and MetS risk. Understanding this link may offer fresh perspectives on preventing and treating MetS, presenting new therapeutic targets and strategies for public health improvement.

Keywords Metabolic syndrome, Serum chloride, NHANES, Cross-sectional study

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Introduction

Metabolic syndrome (MetS) is a complex disorder characterized by a combination of metabolic abnormalities. It is typically manifested as a cluster of risk factors, such as hyperglycemia, hypertension, dyslipidemia, and abdominal obesity [1]. Data from the National Health and Nutrition Examination Survey (NHANES) shows that approximately one-third of the American adult population is afflicted with MetS [2]. Multiple studies have reported that patients with MetS have an elevated risk of developing cardiovascular diseases (CVDs) and type 2 diabetes mellitus (T2DM). These two conditions account for two-thirds of deaths from noncommunicable diseases (NCDs) [3]. As a result, MetS places a significant burden on society, clinical practice, and the healthcare system. Thus, identifying additional potential risk factors could play a crucial role in preventing the progression of MetS and its associated cardiovascular complications.

Chloride ions serve as the principal anions in human extracellular fluid. They contribute approximately 30% to plasma tonicity and constitute 70% of all plasma negative charges [4]. These ions play a crucial role in multiple physiological processes, including blood pressure (BP) regulation, maintenance of body osmotic pressure, muscle movement facilitation, and acid-base balance [4, 5]. Homeostasis of chloride ions, although often overlooked, is known to control several key physiological functions both inside and outside the cell. Any disruptions in chloride levels can indicate metabolic disorders. In critical illness, chloride ions are a major determinant of the metabolic acid-base state. For instance, hypochloremic metabolic alkalosis and hyperchloremic metabolic acidosis are associated with abnormal chloride concentrations [5]. A decreased in serum chloride concentration, referred to as hypochloremia (usually falling below the reference range of 97–106 mmol/L), is often linked to metabolic alkalosis [6]. Conversely, when the chloride concentration exceeds the reference range, hyperchloremia occurs.

Changes in serum chloride often coincide with concurrent alterations in serum sodium, potassium, and bicarbonate. As a result, it is difficult to tease apart the independent effects of chloride on various outcomes. Nevertheless, in the 1980s, an independent effect of chloride ions was rediscovered through the use of diets containing citrate or phosphate as the counter anion for Na^+ [7]. Since then, a substantial body of evidence from both animal and human studies has indicated that the BP elevation in response to salt intake might be more specifically attributable to the anionic component namely chloride ion, rather than sodium [8, 9]. Furthermore, a whole host of studies have explored the prognostic value of serum chloride levels in various clinical settings. These studies have reported that the serum chloride level upon admission is a robust and independent predictor of mortality in acute heart failure (HF), chronic kidney disease (CKD), hypertension, CVDs and critically ill patients [10–19]. Intriguingly, it may even have a stronger prognostic value than sodium.

In the general population, analysis of NHANES data have revealed that decreased serum chloride concentrations are independently associated with increased all-cause mortality, CVD mortality, cancer mortality, and respiratory disease mortality [20]. Another population-based cohort study, which aimed to assess the association between the sodium-chloride difference and MetS, found that after adjusting for covariates, the highest quartile of Na^+-Cl^- (≥ 43mmol/L) was associated with an increased risk of developing MetS compared to the lowest quartiles (≤ 38mmol/L) [21]. More recently, a cross-section study reported that, in contrast to healthy controls, patients with T2DM exhibited significant electrolyte imbalances, characterized by reduced sodium and chloride levels and elevated potassium levels [22]. Additionally, another study demonstrated that chloride ions play a pivotal role in the inflammatory process. The inflammatory response induced by tumor necrosis factor-α (TNF-α) and cyclooxygenase − 2 (COX-2) is associated with decreased intracellular chloride ion concentrations [23, 24]. The pathogenesis of MetS involves multiple genetic and acquired factors, all of which are intricately linked to insulin resistance and chronic low-grade inflammation. These evidences prompt us to further explore the potential relationship between chloride levels and the risk of MetS.

Therefore, in current study, we utilized a nationally representative cohort from the NHANES 2011–2018 dataset to investigate whether serum chloride levels were associated with the prevalence of MetS in the general American adult population. Comprehending this potential association in the general population is of utmost importance for identifying individuals at a higher risk of MetS and formulating preventive strategies.

Method

Study population

The NHANES adopted a cross-sectional design. It used stratified, multistage probability sampling of the U.S. population to examine health and nutritional status through household interviews, physical examinations, laboratory tests and health-related questionnaires [25]. The survey was approved by the Ethics Review Board of the National Center for Health Statistics in accordance with the Declaration of Helsinki, the approval details are accessible on the web at: https://www.cdc.gov/nchs/nhanes/. All participants supplied written informed permission.

This study was based on the demographic, dietary, laboratory, and questionnaire databases of NHANES. A

total of 39,156 participants took part in NHANES from 2011 to 2018. Among them, 24,688 individuals underwent serum chloride testing. We further excluded 218 subjects because of missing information for MetS diagnostic. Additional 3,367 participants were exclude due to age < 18 years, and 7,813 participants were excluded for lacking data on poverty-income ratio (PIR), body mass index (BMI), energy intake, education level, pregnant and information regarding CVDs. Ultimately, 13,290 adult participants were included in the analysis (Fig. 1).

Measurement of serum chloride concentration

Blood samples are collected and processed by certified laboratory professionals at a mobile examination center (MEC), and then stored in a biological bank. As part of the conventional biochemical spectrum, serum chloride concentrations were measured using Beckman Synchron LX20 or Beckman Coulter UniCel DxC800 (Beckman Coulter, Inc), both of which used indirect (or diluted) ion selective electrode methods to determine serum chloride concentrations. The NHANES website provides detailed information about laboratory procedures (https://wwwn.cdc.gov/Nchs/Data/Nhanes/Public/).

Definition of MetS

In the current study, the outcome variable under investigation was MetS, which was diagnosed in accordance with the criteria set by the International Diabetes Federation (2005) [26]. The specific diagnostic requirements were as follows: (1) For waist circumference (WC), it should be ≥ 88 cm in women and ≥ 102 cm in men; (2) hypercholesterolemia (triglycerides (TG) ≥ 1.7 mmol/L or medication for this lipid abnormality), (3) low high density lipoprotein cholesterol (HDL-C < 1.03 mmol/L in men or HDL-C < 1.29 mmol/L in women), (4) elevated BP (SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or both) or antihypertensive drug treatment for hypertension, and (5) elevated fasting glucose (FG) (FG ≥ 5.6 mmol/L, or medication for diabetes). Diagnosis of MetS was established when any three out of these five criteria were met.

Covariates

Through surveys and lab tests, baseline data on participants' ages, sexes, educational levels, race, and BMI were gathered. BMI was computed by measuring the height and weight. The PIR, which is the ratio of family income divided by a set poverty criterion for family size, was used to calculate income. We divided race into White, Black,

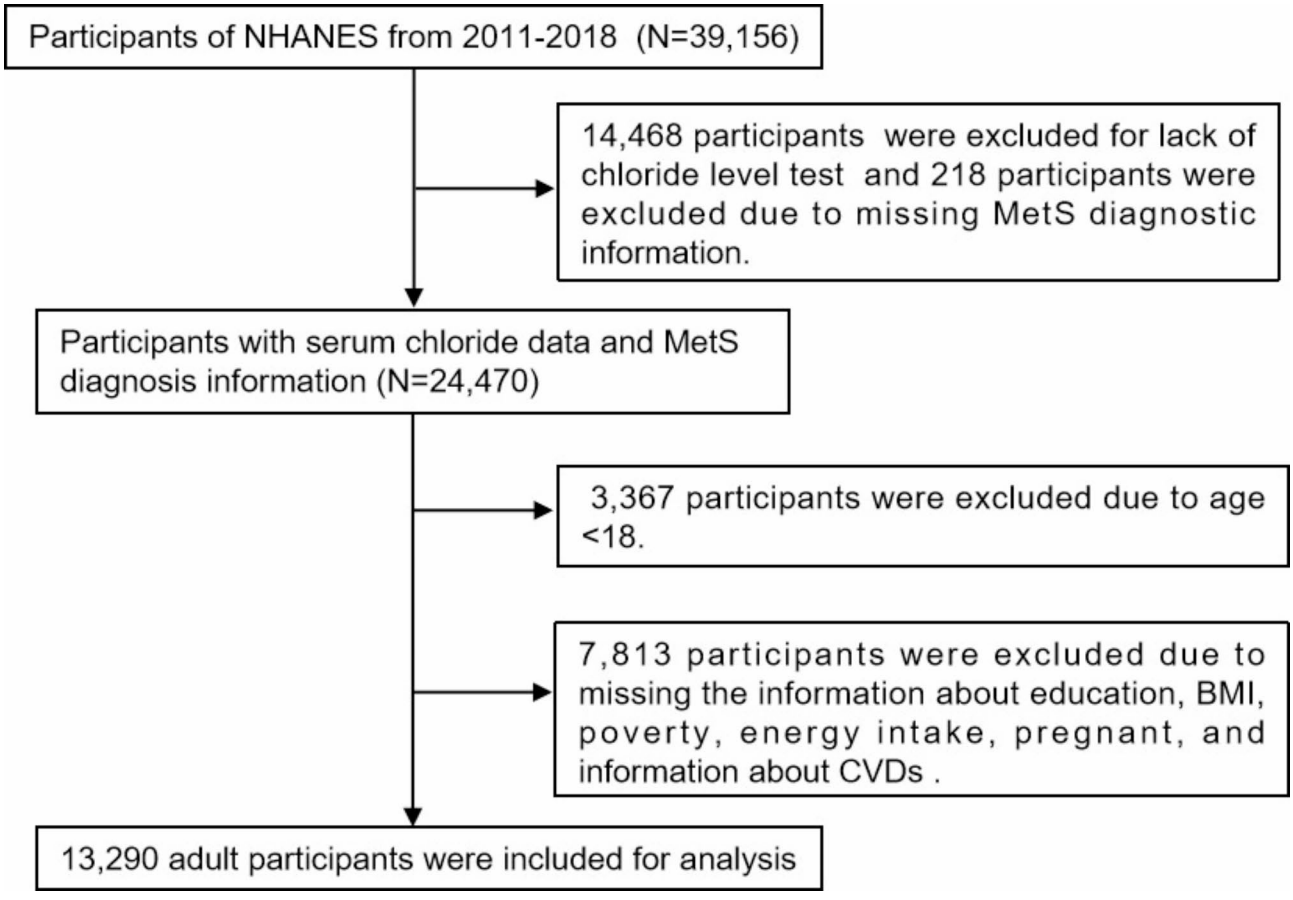

Fig. 1 Work flow

Mexican, and other groups. Educational background was divided into less than high school (less than 9th grade or 9–11th grade [including 12th grade with no diploma]), high school (or equivalent), and more than high school (some college or associate's degree or college graduate or above). Smoking status was classified as never smokers (smoke less than 100 cigarettes in their lifetime), current smokers (smoke more than 100 cigarettes, or had smoked some days), and former smokers (smoke at least 100 cigarettes and had quit smoking). The diagnostic criteria for alcohol consumption and status were heavy drinking (≥ 4 drinks per day for men, ≥ 3 drinks per day for women, or binge drinking ≥ 5 days per month), moderate drinking (≥ 3 drinks per day for men, ≥ 2 drinks per day for women, or binge drinking ≥ 2 days per month), mild drinking (not meeting the above criteria), never (had < 12 drinks in lifetime), or former (had ≥ 12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥ 12 drinks in lifetime). Physical activity was evaluated by self-reported and measured in weekly metabolic equivalent (MET). MET less than 600 was considered inactive, more than 600 was considered active, participants were categorized as inactive and active. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration algorithm. The NHANES collected dietary intake information from participants through two 24-hour dietary recall interviews. The first one was done in-person in the MEC, and the second one was completed by phone between 3 and 10 days later. The United States Department of Agriculture's Food and Nutrient Database for Dietary Studies was employed to calculate total energy, fat and cholesterol intakes. Self-reported questionnaires were used to collect information on the prevalence of CVDs, including myocardial infarction, coronary revascularization or stroke.

Statistical analysis

In this study, the data descriptions and statistical analyses were complexly weighted using the "Survey" package in R software (version 4.4.1). Continuous variables were expressed as the survey-weighted mean and standard errors (SE). Survey-weighted ANOVA analysis was employed to assess the differences between groups for continuous variables of normal distribution. Categorical variables were presented as absolute values (n) and weighted proportions (%), and were analyzed using the survey-weighted chi-square test.

In present study, weighted logistic regression analysis with three models was used to evaluate the odds ratios (OR) and 95% confidence intervals (CIs) between serum chloride level and MetS risk. Model 1 was a crude model; Model 2 adjusted for age and sex; Model 3 was based on Model 2 and included additional factors such as ethnicity, education, PIR, BMI, alcohol and smoke status, dietary energy, fat and cholesterol intake, physical activity, serum bicarbonate level, serum potassium level, serum sodium level, eGFR and CVDs. We investigated the serum chloride level by examining it both as a continuous variable (per standard deviation [SD]) and a categorical variable (Q1, Q2, and Q3). Weighted logistic regression was carried out to examine the association between serum chloride and MetS components. The trend test was used to detect the linear trend in weighted logistic regression. Additionally, we computed variance inflation factors (VIF) to assess the presence of multicollinearity among the independent variables within the multiple regression model. A criterion of VIF < 5 was employed to evaluate the independence of the variables in terms of collinearity.

Furthermore, weighted restricted cubic spline (RCS) logistic regressions were used to examine the potential nonlinear dose-response associations between serum chloride and the risk of MetS and its components in Model 3. Three knots (10th, 50th, and 90th percentiles) were used in our study. A stratified analysis was carried out according to the stratified variables such as age (≤ 45 vs. > 45 years), sex (male vs. female), BMI (normal weight vs. overweight or obese), physical activity level (active vs. inactive), smoking status (never vs. former vs. now), alcohol consumption (never, former, mild, moderate, heavy), and the presence or absence of CVDs (no vs. yes) using the fully adjusted model except for the specific stratification variable. According to the criteria of World Health Organization (WHO), BMI > 25 kg/m^2 is considered as overweight or obese, thus we proposed it as a cut-off value to divide the study population into two groups. The likelihood ratio test also inspected interactions of serum chloride with the stratification variables. In this study, a two-side $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of participants

As presented in Table 1, the average age of this population was 48.20 ± 0.35, with an average BMI of 29.42 ± 0.12 kg/m^2. Males accounted for 48.54% of the population, among whom 69.34% were white. According to the diagnostic criteria, 5375 participants were diagnosed with MetS, and the weighted prevalence of MetS was 37.83%. The concentration of serum chloride in the study population were ranged from 83 to 119 mM. Based on tertiles analysis, serum chloride values were divided into three groups: Q1 (83, 102), Q2 (102, 105) and Q3 (105, 119). Table 1 shows a summary of the baseline characteristics of the included individuals according to the tertiles of serum chloride levels. We observed significant differences in age, sex, ethnicity, PIR, BMI, alcohol consumption, smoking status, and total cholesterol intake among the three groups ($p < 0.01$). Participants with higher serum chloride were more likely to be female, younger and have a higher

Table 1 Characteristics of study population

Variables	Total (*N* = 13290)	Tertiles of chloride			*P* value
		Q1 (*N* = 5068)	Q2 (*N* = 5298)	Q3 (*N* = 2924)	
Age (Year)	48.20 ± 0.35	49.20 ± 0.49	47.54 ± 0.42	47.54 ± 0.51	0.01
Sex n(%)					< 0.01
Male	6477(48.54)	2699(52.72)	2549(47.50)	1229(42.49)	
Female	6813(51.46)	2369(47.28)	2749(52.50)	1695(57.51)	
Ethnicity n(%)					< 0.01
White	5511(69.34)	2146(70.71)	2206(69.54)	1159(66.28)	
Black	2878(10.01)	1041(9.12)	1134(9.91)	703(11.92)	
Mexican	1695(7.63)	553(6.41)	706(7.98)	436(9.33)	
Other	3206(13.02)	1328(13.76)	1252(12.57)	626(12.47)	
Education n(%)					0.14
Less than high school	2432(11.73)	892(11.01)	946(11.56)	594(13.43)	
High school	2963(22.23)	1106(22.92)	1165(21.50)	692(22.32)	
More than high school	7895(66.04)	3070(66.07)	3187(66.94)	1638(64.24)	
BMI (kg/m^2)	29.42 ± 0.12	29.29 ± 0.20	29.26 ± 0.14	29.99 ± 0.18	< 0.01
PIR	3.08 ± 0.05	3.15 ± 0.05	3.11 ± 0.06	2.88 ± 0.07	< 0.01
Alcohol user					< 0.01
Never	1814(10.18)	665(9.07)	700(10.04)	449(12.59)	
Former	1815(11.14)	568(8.98)	782(12.14)	465(13.40)	
Mild	4902(39.53)	2002(42.22)	1922(39.12)	978(35.13)	
Moderate	2203(18.74)	819(18.42)	900(19.25)	484(18.34)	
Heavy	2556(20.41)	1014(21.32)	994(19.44)	548(20.54)	
Smoking n(%)					0.01
Never	7569(56.90)	2863(56.94)	3096(57.96)	1610(54.75)	
Former	3227(25.51)	1263(26.74)	1273(24.95)	691(24.19)	
Now	2494(17.59)	942(16.32)	929(17.09)	623(21.06)	
Total energy intake (**kCal/day**)	2017.04 ± 12.80	2023.69 ± 19.84	2020.52 ± 16.36	1997.39 ± 26.00	0.64
Total fat intake(g/day)	79.04 ± 0.63	80.39 ± 0.85	78.52 ± 0.81	77.43 ± 1.49	0.09
Total cholesterol(mg/day)	286.07 ± 3.02	296.17 ± 4.34	279.08 ± 3.85	280.09 ± 5.81	0.01
eGFR(ml/min)	93.52 ± 0.41	92.74 ± 0.56	94.21 ± 0.60	93.71 ± 0.60	0.15
Serum chloride level (mM)	103.07 ± 0.10	100.12 ± 0.06	103.96 ± 0.02	107.06 ± 0.04	< 0.01
Serum bicarbonate level(mM)	25.12 ± 0.07	25.80 ± 0.10	25.05 ± 0.08	23.94 ± 0.08	< 0.01
Serum potassium level(mM)	4.00 ± 0.01	3.99 ± 0.02	4.01 ± 0.01	4.02 ± 0.01	0.2
Serum sodium level(mM)	139.35 ± 0.11	138.41 ± 0.15	139.67 ± 0.09	140.56 ± 0.08	< 0.01
Physical activity n(%)					0.11
Inactive	5028(33.41)	1942(33.38)	1959(32.58)	1127(35.09)	
Active	8262(66.59)	3126(66.62)	3339(67.42)	1797(64.91)	
MetS n(%)					< 0.01
No	7915(62.17)	2801(59.37)	3292(63.86)	1822(64.29)	
Yes	5375(37.83)	2267(40.63)	2006(36.14)	1102(35.71)	
CVD n(%)					< 0.01
No	11,864(91.36)	4413(89.89)	4840(92.98)	2611(91.08)	
Yes	1426(8.64)	655(10.11)	458(7.02)	313(8.92)	

Mean ± standard error(SE) for normally distributed continuous variables; n (%) for categorical variables, n reflect the study sample, whereas percentages reflect the survey-weighted data

Chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables

Abbreviation: BMI, body mass index; PIR, ratio of family income to poverty; MetS, metabolic syndrome; CVDs, cardiovascular diseases

BMI. Moreover, the prevalence of MetS was consistently lower in the Q2 and Q3 groups of serum chloride compared to the Q1 group ($p < 0.01$).

Association between serum chloride and MetS

To explore the associations between serum chloride levels, categorized into tertiles, and as a continuous variable (per SD), and the risk of MetS, weighted univariate and multivariate logistic regression analyses were conducted. The findings are presented in Fig. 2. Across three models, continuous serum chloride levels were found to be inversely associated with the risk of MetS. In Model 1, a 14% reduction in the risk of MetS was observed for each SD increase in serum chloride level (OR = 0.86, 95%CI: 0.81–0.92). In Model 2, this reduction was 10% (OR = 0.90, 95% CI: 0.85–0.96), and in Model 3, it was 23% (OR = 0.77, 95% CI: 0.71–0.94) (all $p < 0.01$).

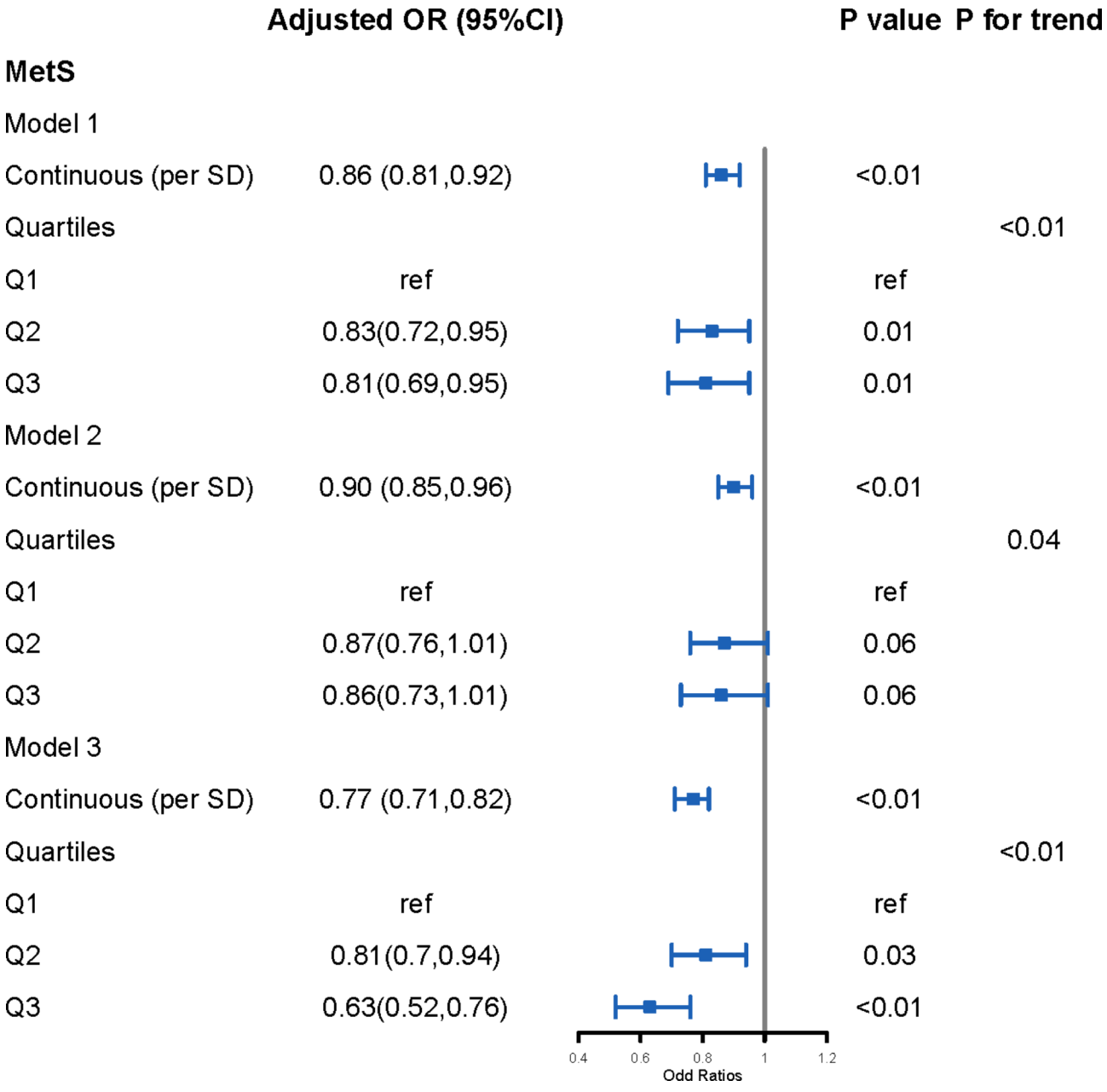

Fig. 2 Weighted logistic regression analysis of the association between serum chloride and MetS risk. Model 1: no covariate adjustment; Model 2: adjusted for age and sex; Model 3 was based on model 2 and plus ethnicity, education, ratio of family income to poverty (PIR), alcohol and smoke status, dietary energy, fat and cholesterol intakes, serum bicarbonate level, serum potassium level, serum sodium level, physical activity, eGFR and CVDs. Abbreviation: NHANES, national health and nutrition examination survey; BMI, body mass index; PIR, ratio of family income to poverty; MetS, metabolic syndrome; CVDs, cardiovascular diseases

We then transformed the continuous serum chloride variable into categorical variables based on tertiles. In model 1, participants in the second tertile of serum chloride had a 17% lower risk of MetS (OR = 0.83, 95% CI: 0.72–0.95, $p = 0.01$), and those in the highest tertile had a 19% lower risk (OR = 0.81, 95% CI: 0.69–0.95, $p = 0.01$), with a significant trend (p for trend < 0.01). Similarly, in model 2, which was adjusted for age and sex, the risk of MetS was marginally lower in the second tertile (OR = 0.87, 95% CI: 0.76–1.01, $p = 0.06$) and the highest tertile (OR = 0.86, 95% CI: 0.73–1.01, $p = 0.06$) compared to the first tertile, with a significant trend (p for trend = 0.04). Moreover, after full adjustment, this association was strengthened. Compared to patients in the first tertile, those in the second and highest tertiles had a significantly lower risk of MetS, with a 19% reduction (OR = 0.81, 95% CI: 0.70–0.94, $p = 0.01$) and a 37% reduction (OR = 0.63, 95% CI: 0.52–0.76, $p < 0.01$), respectively.

Association between serum chloride and the components of MetS

In the present study, we evaluated the relationship between serum chloride levels, both as a continuous variable and categorized into groups, and the risk of components of MetS using three models. The results are presented in Fig. 3. In all three models, each SD increase in serum chloride was associated with a varying degree of decreased risk of elevated FG, TG levels, and BP. Conversely, it was associated with an increased risk of reduced HDL - C and elevated WC (all p for trend < 0.01). After classifying serum chloride into tertiles, in the three models, patients in the highest tertile had a negative association with elevated FG, TG, and BP, and a positive association with reduced HDL - C and WC (all p for trend < 0.01). However, in model 3, for the association with elevated WC, the p for trend was 0.14.

Restricted cubic spline analysis of the relationship between serum chloride levels and MetS and its components

The results of the RCS analysis indicated that serum chloride has a linear negative association with the prevalence of MetS (p for nonlinearity = 0.93, Fig. 4a). It also showed a linear negative correlation with its components, raised FG (p for nonlinearity = 0.49, Fig. 4b) and raised TG (p for nonlinearity = 0.07, Fig. 4c). Conversely, serum chloride presented a linear positive correlation with reduced HDL-C (p for nonlinearity = 0.54, Fig. 4d). In line with the outcomes of the weighted multiple logistic regression, after adjusting for all variables there was no significant relationship between serum chloride and raised WC (p overall = 0.50, Fig. 4e). Moreover, when the serum chloride level exceeded 100 mmol/L, the risk of reduced HDL - C increased markedly (Fig. 4d). Additionally, we discovered a non - linear relationship between serum chloride and elevated BP (p for nonlinearity < 0.01, Fig. 4f).

Stratified analysis

Moreover, we conducted stratified analyses to assess whether the associations varied among participants with different characteristics, including age, sex, BMI, smoking status, alcohol consumption, physical activity levels, and the presence or absence of CVDs. The results, presented in Table 2, demonstrated that the association between serum chloride and MetS was consistent across different age groups, genders, physical activity levels, and regardless of the presence or absence of CVDs (p for trend < 0.05).

We further found that the inverse association was observed specifically among overweight or obese participants who were either non - smokers or former smokers and did not engage in heavy drinking (p for trend < 0.05). Interaction analysis revealed that different levels of BMI and smoking status had distinct impacts on the degree to which serum chloride levels influenced the risk of MetS (p for interaction < 0.05).

Discussion

High - sodium diets, with sodium chloride as the main source of sodium, have been firmly established as a major risk factor for the development of hypertension. Thus, the adoption of a low - sodium diet, including low sodium chloride intake, is highly advocated. However, some studies have disclosed the unfavorable impacts of low serum chloride levels on health. Although these studies were conducted on patients with hypertension, CKD, CVDs, CHF or those who are critically ill [10–19], the evidence regarding its potential role in the general population remains scarce.

In the human body, the principal sources of chloride are dietary table salt (sodium chloride) and salty foods. However, the regulation of serum chloride concentration isn't merely contingent upon dietary intake and renal mechanisms. Emerging evidence indicates that the immune system plays an extrinsic regulatory role in sodium homeostasis [27]. An intriguing finding is that when this immune mechanism is blocked, there is selective chloride anion accumulation in the skin of individuals with salt - sensitive hypertension.The widely acknowledged normal range of serum chloride for an adult is 96 to 106 mmol/L [20]. In our study, the serum chloride levels within the studied population ranged from 83 to 119 mmol/L. Subjects with higher serum chloride levels also exhibited significantly higher sodium levels and lower bicarbonate levels (Table 1). As Testani et al. have disclosed, although serum sodium and chloride are commonly assumed to

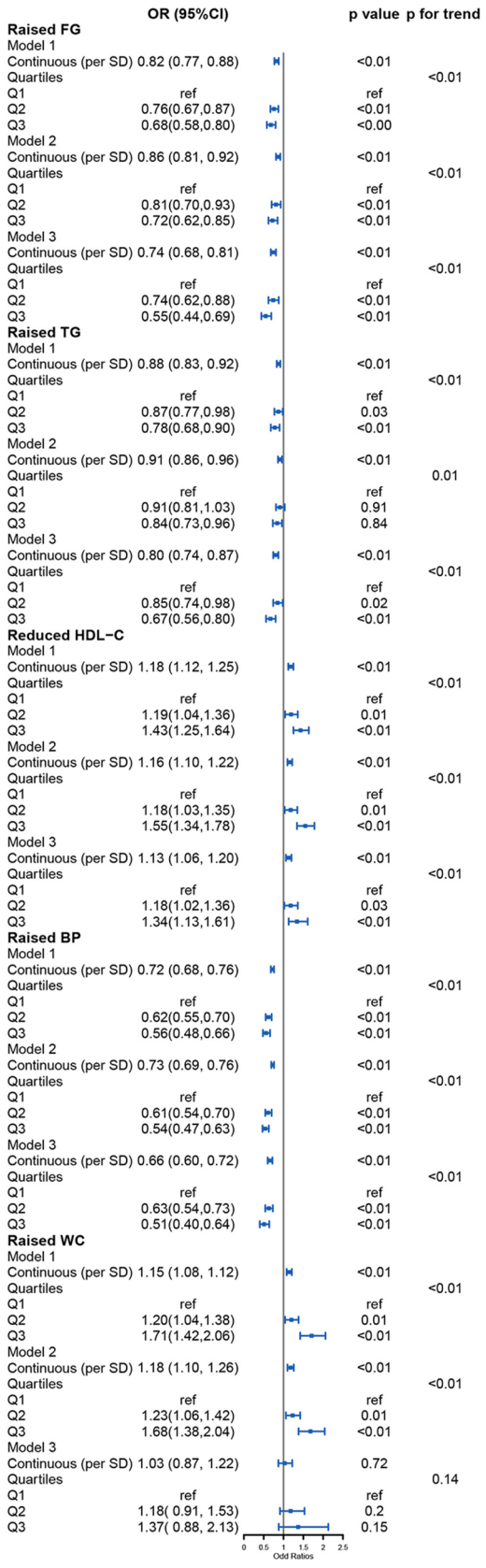

Fig. 3 Weighted logistic regression analysis of the association between serum chloride and the risk of MetS components. Model 1: no covariate adjustment; Model 2: adjusted for age and sex; Model 3 was based on model 2 and plus ethnicity, education, ratio of family income to poverty (PIR), alcohol and smoke status, dietary energy, fat and cholesterol intakes, serum bicarbonate level, serum potassium level, serum sodium level, physical activity, eGFR and CVDs. Abbreviation: CI, confidence interval; MetS, metabolic syndrome; FG, fasting glucose; TG, triglycerides; BP, blood pressure; WC, waist circumference; HDL-C, high density lipoprotein cholesterol

be closely correlated, the serum sodium level can only account for less than 30% of the variability in serum chloride concentration [11]. Significantly, the entire survival setback associated with low serum sodium can be ascribed to the serum chloride concentration. Furthermore, hypochloraemia in the absence of hyponatraemia turns out to be a particularly adverse prognostic indicator [11].

Fluctuation of serum chloride usually occurs with concomitant changes in serum sodium, potassium, and bicarbonate; therefore, we adjusted them in the final models and confirmed the chloride-specific risk independent of hyponatremia or acid-base disturbances. Serum chloride is largely influenced by renal function, therefore, we adjusted eGFR in the model 3. In the three models, weighted logistic regression analysis revealed that, compared with the first tertile, serum chloride levels in the second and third tertiles were significantly associated with a reduced risk of MetS (Fig. 2). The weighted RCS analysis further corroborated the inverse correlation between serum chloride and the risk of MetS (Fig. 4a). A cross-sectional retrospective cohort study reported results consistent with ours, showing that in the crude model, the highest quarter of serum chloride levels was significantly associated with a reduced risk of MetS [21]. However, this association was not significant in the adjusted model. The discrepant results might be attributed to differences in the study populations, sample size and covariates. In that retrospective study, the subjects were mainly from Japan, with a relatively small sample size of 3354. In our study, we included 13,290 adult participants from U.S. We adjusted for more covariates and conducted a more comprehensive analysis to confirm our findings.

Most studies did not further clarify which mechanism was responsible for the associations between serum chloride and the risks of MetS components. However, these researchers obtained results consistent with ours that higher level of serum chloride was associated with a reduced risk of raised FG, and TG (Fig. 3 and Fig, 4b, c). For example, a more recent study showed that, compared to subjects without T2DM, T2DM patients had lower serum chloride levels [22]. Although the researchers

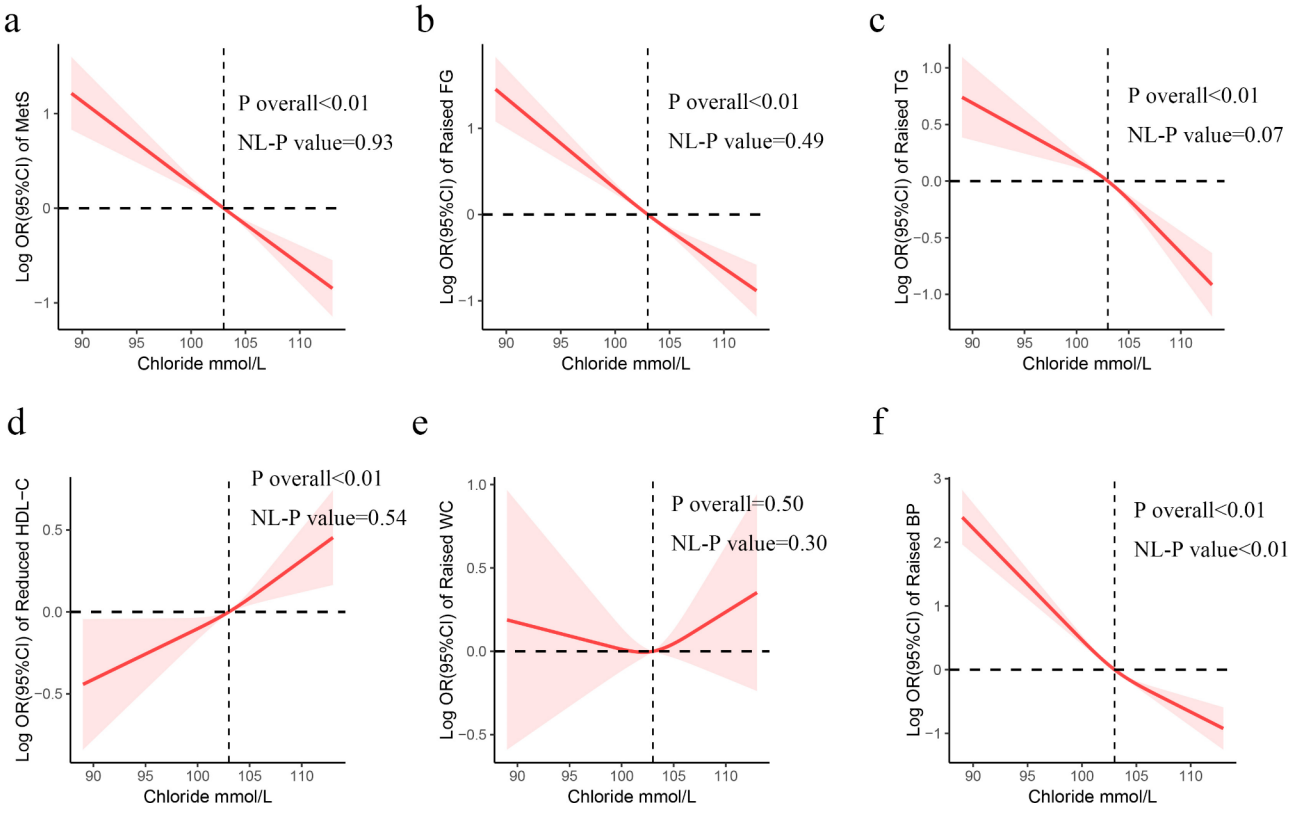

Fig. 4 The dose-response relationship between serum chloride and the risk of MetS and its components. Serum chloride was observed to non-linear negative correlated with MetS (**a**), raised FG (**b**), and TG (**c**), non-linear positive linked with reduced HDL-C (**d**), and linear inversely related with raised BP (**f**), but has no significantly association with raised WC (**e**). Abbreviation: MetS, metabolic syndrome; FG, fasting glucose; TG, triglycerides; BP, blood pressure; WC, waist circumference; HDL-C, high density lipoprotein cholesterol

attributed this electrolyte imbalance to the use of specific glycemic - control medications, it still indicated a subtle association between glycemic control and serum electrolyte imbalance. As shown in Table 1, compared with participants in the Q1 group, subjects in the Q2 and Q3 groups had much lower total cholesterol intake. In our study, total cholesterol intake was included as a covariate in Model 3, and the significant positive association between serum chloride and reduced risk of HDL-C remained (Figs. 3 and 4d), indicating that the association was not caused by cholesterol intake.

The negative association of serum chloride with BP observed in this study (Figs. 3 and 4f) was differ from the the effects of dietary chloride on BP. Although the direct relationships between serum chloride and BP, blood glucose, and blood lipids have been rarely studied, several hypotheses have been proposed regarding the underlying mechanisms. It has been proposed that changes in intracellular chloride anion concentration affect various cellular functions, including reactive oxygen species levels [28], Additionally, halide binding to the bromide - binding site inhibits myeloperoxidase by effectively competing with H_2O_2 for access to the distal histidine [29]. Oxidative stress in metabolic disorders can induce diabetes and CVDs [30]. Chronic low - grade inflammation is commonly observed in obesity, diabetes, CVD, and other chronic diseases related to MetS [31]. More importantly, animal experiment discovered that reduction of chloride concentration activates IKKβ-IκBα-NF-κB signaling pathway and promotes endothelial cell inflammatory response, which contributes to the development of hypertension and hypertension-associated cardiovascular diseases [23]. These pieces of evidence may explain the correlation of serum chloride levels with the risk of MetS and its components.

We discovered that in the crude model and model 2 (which was adjusted for age and sex), patients in the highest tertile had a positive association with elevated WC (all p for trend < 0.01)(Fig. 3). However, after adjusting for all covariates in model 3, this association become non - significance (Figs. 3 and 4e). Evidently, when BMI, dietary energy and fat intake, and physical activity level were included as covariates in the model, serum chloride was not an independent risk factor of elevated WC.

Generally, when compared to individuals with normal weights, overweight or obese people typically exhibit higher levels of inflammation and oxidative stress. Existing evidence indicates that a decrease in extracellular

Table 2 Stratified analysis

Variables	Tertiles of chloride			*p* for trend	*p* for interaction
	Q1	Q2	Q3		
Age					0.15
≤45 year	ref	0.87 (0.70, 1.09)	0.71 (0.53, 0.96)	0.02	
>45 year	ref	0.76 (0.63, 0.93)	0.57 (0.45, 0.71)	< 0.01	
Sex					0.07
Male	ref	0.96 (0.77, 1.20)	0.66 (0.51, 0.85)	0.01	
Female	ref	0.69 (0.56, 0.85)	0.59 (0.46, 0.77)	< 0.01	
BMI					0.03
Normal weight	ref	0.61 (0.43, 0.87)	0.68 (0.39, 1.17)	0.07	
Overweight/Obese	ref	0.82 (0.70, 0.97)	0.61 (0.50, 0.75)	< 0.01	
Smoking					< 0.01
Never	ref	0.83 (0.69,1.00)	0.69 (0.56,0.86)	< 0.01	
Former	ref	0.71 (0.52,0.95)	0.39 (0.28,0.56)	0.11	
Now	ref	1.02 (0.75,1.39)	0.94 (0.61,1.47)	0.82	
Alcohol user					0.12
Never	ref	0.61 (0.40, 0.91)	0.58 (0.34, 0.97)	0.04	
Former	ref	0.55 (0.36, 0.85)	0.37 (0.23, 0.57)	< 0.01	
Mild	ref	0.95 (0.76, 1.20)	0.67 (0.49, 0.92)	0.02	
Moderate	ref	0.66 (0.46, 0.95)	0.55 (0.34, 0.91)	0.01	
Heavy	ref	1.02 (0.74, 1.41)	0.86 (0.59,1.26)	0.49	
Physical activity					0.21
Inactive	ref	0.72 (0.58, 0.88)	0.61 (0.46, 0.83)	< 0.01	
Active	ref	0.86 (0.71, 1.05)	0.62 (0.50, 0.78)	< 0.01	
CVD					0.67
No	ref	0.81 (0.69, 0.95)	0.63 (0.52, 0.77)	< 0.01	
Yes	ref	0.81 (0.53, 1.22)	0.56 (0.33, 0.96)	0.04	

Stratified analyses of the association between serum chloride and MetS risk stratified by age, sex, BMI, smoking status, alcohol consumption, physical activity level, and CVDs. Adjusted for age, sex, ethnicity, education, PIR, alcohol and smoke status, physical activity, dietary energy, fat and cholesterol intakes, serum bicarbonate level, serum potassium level, serum sodium level, eGFR and CVDs. The interaction effect was evaluated using the likelihood ratio test

Abbreviation: BMI, body mass index; CVDs, cardiovascular diseases

chloride levels results in increased COX-2 expression. This, in turn, mediates the production and secretion of renin [23, 24]. This finding may explain the inverse relationship between serum chloride levels and the risk of MetS and its components, a relationship that is only significant among overweight or obese participants. Unhealthy lifestyle habits, such as smoking and excessive alcohol consumption, have the potential to disrupt endocrine function and trigger related metabolic disorders [32, 33]. Therefore, these unhealthy behaviors may be directly associated with the risk of MetS. As a result, the impact of serum chloride on the risk of MetS could be overlooked. In this study, this correlation was not significant.

Limitations

However, it is essential to acknowledge several limitations of this study. Firstly, due to the observational study design, causality cannot be determined. Randomized controlled studies are required to confirm the causal relationship. Secondly, serum chloride levels can be affected by short - term factors. Detecting serum chloride levels only once at baseline fails to accurately reflect an individual's true serum chloride level. Thus, in future research, repeated measurements are highly desirable. Thirdly, in this study, the cutoff point for low serum chloride was set as the first quartile of the chloride distribution in the population (102 mmol/L). This differs from the criteria commonly used in other studies, which typically define low serum chloride as ≤ 96 mmol/L [10], or some researchers choose 100 mmol/L as the cutoff point [17]. Therefore, when interpreting the inverse effect of low serum chloride on the risk of MetS, the differences in definition criteria should be carefully considered. Fourthly, the study participants were adult civilians in the United States. When attempting to generalize the results to other populations, the associations and effect sizes need to be further confirmed. Fifth, the approach to handling missing values can also influence the research results. In this study, we excluded subjects with missing values. Finally, the possibility of residual and unknown confounding factors, such as the use of diuretics, cannot be completely excluded. Additionally, certain information was acquired through self - reporting.

Despite these limitations, this study also had several strengths. The relatively large sample size and the nationally representative sample design enhanced the generalizability of our findings. Moreover, we accounted for a wide range of potential confounding factors, including sociodemographic factors, lifestyle factors, laboratory test results, drug use, and comorbidities, through extensive statistical methods. This comprehensive approach ensured the robustness of our research conclusions.

Conclusion

In conclusion, our analysis of the general U.S. adult population indicates a potential inverse relationship between serum chloride levels and the risk of MetS, especially in overweight or obese participants who did not smoke or heavy drink. Further in - depth research is warranted. Well - designed prospective cohort studies and interventional trials are needed to establish a causal relationship and to clarify the underlying mechanisms. Understanding this relationship could potentially provide new insights into the prevention and treatment of MetS, offering new therapeutic targets and strategies for improving public health. More importantly, in the clinical practise, changes in serum chloride levels should also be monitored when on a low - sodium diet.

Abbreviations

NHANES	National health and nutrition examination surveys
BMI	Body mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
MetS	Metabolic syndrome
TG	Triglycerides
WC	Waist circumference
HDL-C	High density lipoprotein cholesterol
FG	Fasting glucose
BP	Blood pressure
RCS	Restricted cubic spline

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Author contributions

L.Z. and HP.L.prepared Figs. 1 and 4; Table 1. XL.L., JM.Z. and RF.Z. prepared Figs. 2 and 3; Table 2, WM.X. and Q.W. wrote the main manuscript text. All authors reviewed the manuscript.

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Data availability

The datasets generated during the current study are available in database (https://www.cdc.gov/nchs/nhanes/).

Declarations

Ethical approval and consent to participate

The protocol was approved by the Institutional Review Board of National Center for Health Statistics in accordance with the Declaration of Helsinki, and no new data was added.

Consent to participate

Not applicable

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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