Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Association between the C-reactive protein–albumin–lymphocyte index and metabolic syndrome: evidence from the 2003–2010 national health and nutrition examination survey

Lanlan Wu[1†], Dunzheng Han[1†], Yuting Xue[1], Shangfei He[1], Zhuang Ma[1], Shuwen Su[1], Peixin Li[1], Shenrong Liu[1*] and Haobin Zhou[1*]

Abstract

Background Metabolic syndrome (MetS) is a global public health problem that significantly impacts human health and quality of life. The relationship between MetS and the C-reactive protein–albumin–lymphocyte (CALLY) index is uncertain.

Methods This study analyzed the data of 7,534 individuals from the National Health and Nutrition Examination Survey cycles (2003–2010 cycles). Weighted logistic regression and weighted restricted cubic spline (RCS) curve analyses were used to identify the relationships between the CALLY index and MetS, as well as its components.

Results Of the 7,534 participants, 2,086 were diagnosed with MetS. The estimated prevalence of MetS decreased with an increase in the CALLY index ($P < 0.001$). Multivariable logistic regression analysis showed that the odds ratio of MetS was 0.25 (95% confidence interval 0.20–0.32, $P < 0.001$) in the highest CALLY index quartile compared with the lowest quartile after adjusting for confounding variables. The RCS curve analysis revealed non-linear relationships between the CALLY index and MetS or its components.

Conclusions This study revealed an inverse relationship between the CALLY index and MetS risk. The CALLY index might be valuable for identifying individuals who are at a high risk of MetS.

Clinical trial number Not applicable.

Keywords C-reactive protein–albumin–lymphocyte index, Metabolic syndrome

[†]Lanlan Wu and Dunzheng Han contributed equally to this work.

*Correspondence:
Shenrong Liu
2022390056@gzhmu.edu.cn
Haobin Zhou
zhouhaobin021@163.com
[1]Department of Cardiology, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 510120, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Metabolic syndrome (MetS) refers to a group of metabolic abnormalities encompassing elevated fasting plasma glucose (FPG), hypertension, obesity, triglyceride (TG) elevation, and low high-density lipoprotein cholesterol (HDL-C) [1]. As a non-communicable disease, MetS poses a considerable global health risk, and its prevalence continues to increase steadily each year [2]. MetS has a complex pathophysiology, with insulin resistance and dyslipidemia playing central roles in its development [3]. Furthermore, extensive research has demonstrated that MetS significantly increases the risk of type 2 diabetes mellitus, cancer, cardiovascular disease, and all-cause mortality [4–8].

Research has shown that many factors contribute to MetS, including inflammation, immune function, and nutritional status, and the control of inflammation is key to alleviating metabolic disorders. The prevailing perspective is that chronic low-grade inflammation and oxidative stress, which are frequently observed in MetS, play significant roles in the metabolic status and pathophysiology of MetS [9, 10]. Inflammatory factors released from adipose tissue contribute to the onset of metabolic disorders by triggering the systemic inflammatory response [11]. In terms of immune function, immune cell activation is implicated in the progression of diseases associated with metabolic disorders [12, 13]. For instance, Satoshi et al. found that $CD8^+$ T cells activate macrophages in adipose tissue, causing a shift in the immune microenvironment from an anti-inflammatory to a pro-inflammatory state [14, 15]. Furthermore, nutrition has also been associated with MetS risk [16]. Malnutrition can lead to deficiencies in essential nutrients in the body, which affects the metabolic regulation of blood glucose, lipids, and weight. Meanwhile, MetS itself can affect the nutritional state of the body. Insulin resistance and lipid abnormalities may interfere with cellular energy metabolism, affecting nutrient absorption, utilization, and storage. According to the above evidence, the combination of inflammation, immune function, and nutritional status indicators is considered a reliable predictor of patient prognosis [17, 18].

The C-reactive protein–albumin–lymphocyte (CALLY) index developed by Iida et al. [19], is a novel inflammation–nutrition–immunity index based on C-reactive protein (CRP), albumin concentration, and lymphocyte count. The CALLY index has been used for prognostic assessment in patients with various cancers, including gastric cancer, colorectal liver metastases, and non-small-cell lung cancer [20–27]. Additionally, the CALLY index has been found to be effective in selecting cancer treatment regimens, predicting treatment efficacy, and assessing prognosis. Yang et al. revealed that the CALLY index has superior prognostic value in patients with colorectal cancer compared to conventional prognostic factors, including the platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, systemic immune inflammation index, and modified Glasgow prognostic score [28]. The CALLY index reliably predicts the survival of patients with cancer who undergo surgery, with a critical score of ≥ 3. Adjuvant therapies like chemotherapy and targeted treatments can improve the long-term survival of patients with a CALLY index of < 3 and unfavorable postoperative prognoses [29]. The CALLY index is a non-invasive quantitative metric. A low CALLY index may inform the risk of MetS risk due to the associations among inflammation, immunity, and nutrition.

However, the relationship between the CALLY index and MetS is unclear. Thus, we evaluated the association of the CALLY index with MetS among participants included in the National Health and Nutrition Examination Survey (NHANES).

Methods

Study population and design

The NHANES is a cross-sectional study conducted by the National Center for Health Statistics in the United States. The aim of the NHANES is to evaluate the health and nutritional status of the general population. The survey is conducted every 2 years with different participants included in each cycle. Approval is required from the Institutional Review Board of the Centers for Disease Control and Prevention (CDC), and the participants must provide written informed consent to participate. Detailed information on the NHANES study design and data can be found at the official website of the CDC (https://www.cdc.gov/nchs/nhanes/). The present study involved secondary data analysis without personal identifiers; therefore, it did not require institutional review.

The research data were obtained from four NHANES cycles (2003–2010) involving a total of 41,156 participants. We excluded participants aged < 20 years and with incomplete data on the CALLY index, incomplete MetS information, and incomplete covariate data, as well as those who were pregnant. Figure 1 shows the participant selection flowchart.

CALLY index definition

The CALLY index was calculated using the following formula: CALLY index = albumin concentration (g/L) × lymphocyte count (10^9/L) ÷ [CRP concentration (mg/L) × 10]. The CRP concentrations were quantified using latex-enhanced nephelometry on a Behring Nephelometer. Lymphocyte counts were analyzed using the Beckman Coulter MAXM Instrument. Additionally, serum albumin concentration was measured using the Roche modular P and Roche Cobas 6000 chemistry analyzers. For a comprehensive understanding of the laboratory

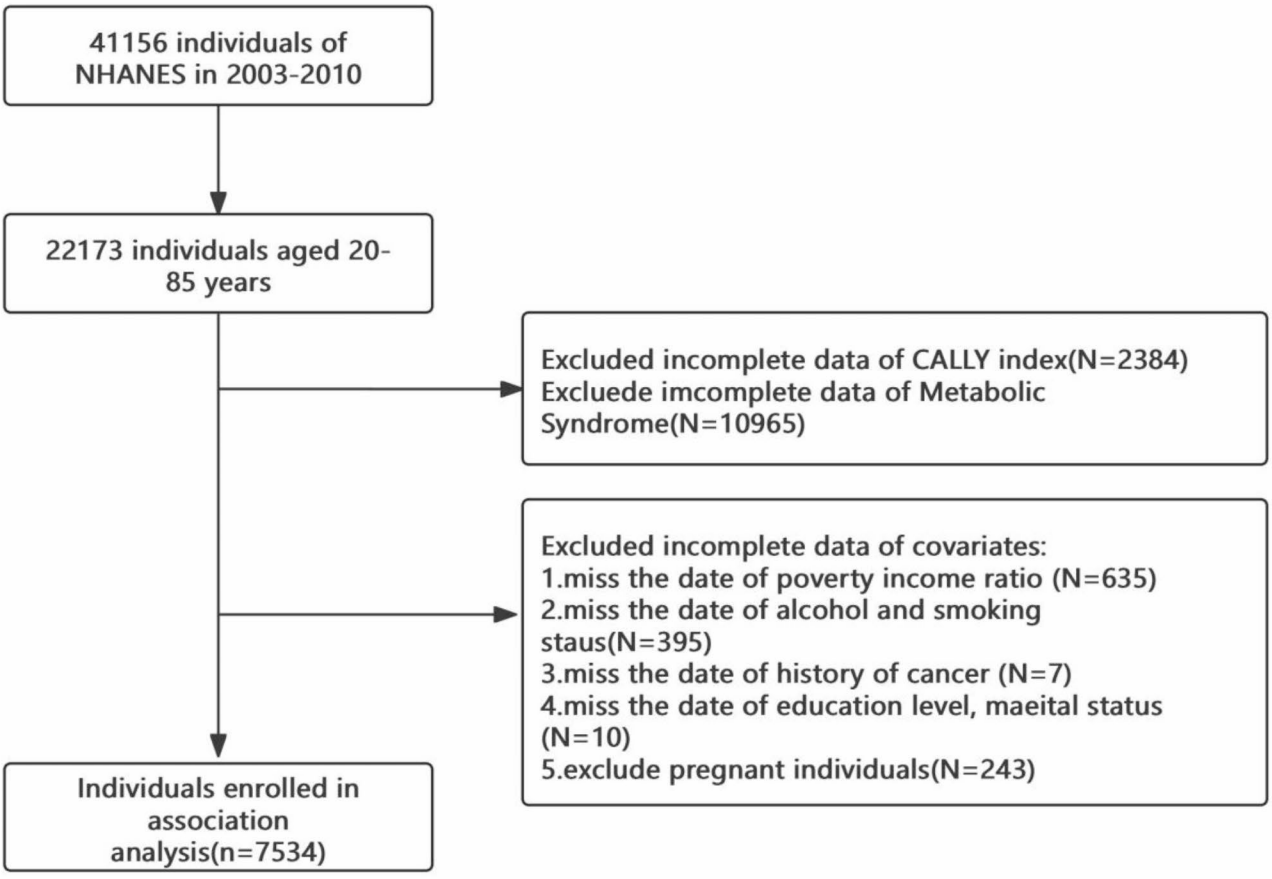

Fig. 1 Flowchart of participant inclusion and exclusion in the current study

processing methodology, please refer to the CDC website [30]. Based on the respective CALLY index values, the participants were stratified into four quartiles: Q1: 0.18 ≤ CALLY index < 1.68, Q2: 1.68 ≤ CALLY index < 4.09, Q3: 4.09 ≤ CALLY index < 9.97, Q4: 9.97 ≤ CALLY index < 139.7.

MetS definition

The definition of MetS involves specific criteria outlined in the Adult Treatment Program III of the National Cholesterol Education Program [31]. The diagnostic criteria for MetS include (1) TG ≥ 150 mg/dL; (2) Low HDL-C (< 40 mg/dL in men and < 50 mg/dL in women); (3) FPG ≥ 6.1 mmol/L; (4) elevated waist circumference (WC), defined as > 102 cm in men and > 88 cm in women; and (5) elevated blood pressure (BP), defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg.

Covariates

The participants completed standardized questionnaires to provide sociodemographic and lifestyle information [32], including sex, age, race (Mexican–American, other Hispanic, Non-Hispanic Black, Non-Hispanic White, other race), poverty-to-income ratio (categorized as ≤ 1, >1 to ≤ 3, and > 3), educational attainment (less than high school, high school, above high school), marital status (married, living alone, or divorced), smoking status (never smoker [< 100 cigarettes prior to the survey], ever smoker [> 100 cigarettes prior to the survey but quit prior to the survey], and current smoker [> 100 cigarettes prior to the survey and smoked during the survey period]), and drinking habits (consumed at least 12 drinks of any type of alcoholic beverage within the last year). Additionally, any self-reported history of cancer and family history of diabetes mellitus were also recorded.

Statistical analysis

Sample weights, clustering, and stratification were integrated into all analyses following the NHANES analytic and reporting guidelines. Continuous variables are summarized as the mean ± standard deviation, while categorical variables are summarized as frequency (percentage). The characteristics of the participants were compared across the CALLY index quartile using one-way analysis of variance for continuous variables and Pearson's

chi-square test for categorical variables. Multivariable logistic regression was used to analyze the associations between the CALLY index and MetS and its components. The crude model was unadjusted; Model 1 was adjusted for age, race, and sex; Model 2 was adjusted for the variables in Model 1, as well as history of cancer, family history of diabetes mellitus, smoking status, alcohol consumption, educational attainment, and poverty-to-income ratio. Tests for a linear trend were performed by entering the CALLY index as a continuous variable. Restricted cubic spline (RCS) regression was used to investigate the non-linear relationships between the CALLY index and MetS and its components. Likelihood ratio tests were used to confirm the relationships. Subgroup analyses of the correlation between the CALLY index and MetS were performed to determine if the predictive ability of the CALLY index varied among subgroups.

$P < 0.05$ was considered statistically significant. The statistical analysis was conducted using R version 4.2.1 and the Free Statistics software (version 1.9).

Results

Population characteristics

The data of 7,534 participants were analyzed. The mean age of the participants was 46.68 ± 16.56 years, and 3,876 of the 7534 participants were male (weighted percentage, 50.02%). Among them, 2,086 participants (23.96%) were diagnosed with MetS. The prevalence of MetS was 36.87% in Q1, 31.38% in Q2, 19.85% in Q3, and 10.80% in Q4. Table 1 presents the baseline characteristics of the participants based on the CALLY index quartiles. Individuals in the highest CALLY index quartile were more

Table 1 Weighted baseline characteristics according to the CALLY index quartiles

Variable	Total	Q1	Q2	Q3	Q4	*P* value
Age (years)	46.68(16.56)	49.84(16.22)	48.92 (16.56)	47.05(16.32)	41.85(15.97)	< 0.001
Male, No. (%)	3876 (50.02)	789 (39.15)	911 (45.47)	1074 (55.62)	1102 (57.71)	< 0.001
Race, No. (%)						< 0.001
Mexican American	1390 (7.72)	337 (7.82)	374 (7.86)	372 (8.37)	307 (6.95)	
Other Hispanic	507 (3.63)	103 (2.71)	115 (3.56)	157 (4.71)	132 (3.48)	
Non-Hispanic White	3937 (73.02)	967 (72.51)	981 (73.94)	989 (73.62)	1000 (72.12)	
Non-Hispanic Black	1397 (10.26)	422 (13.15)	357 (10.63)	293 (8.56)	325 (9.12)	
Other Race	303 (5.36)	53 (3.80)	55 (4.01)	74 (4.74)	121 (8.33)	
Poverty income ratio, No. (%)						< 0.001
≤ 1	1384 (11.85)	392 (13.82)	352 (11.52)	314 (11.24)	326(11.08)	
>1, ≤3	3240 (36.28)	850 (39.27)	825(37.66)	820 (36.48)	745 (32.50)	
> 3	2910 (51.87)	640 (46.91)	705 (50.82)	751 (52.28)	814 (56.42)	
Education level, No. (%)						< 0.001
Less than high school	2098 (17.50)	582 (20.57)	531 (17.31)	527 (17.81)	458 (14.87)	
High school diploma	1833 (24.99)	478 (27.26)	476 (26.64)	474 (25.55)	405 (21.22)	
More than high school	3603 (57.51)	822 (52.17)	875 (56.05)	884 (56.64)	1022 (63.90)	
History of cancer, No. (%)	719 (8.65)	227 (11.19)	186 (9.09)	164 (8.02)	142 (6.78)	< 0.001
Family history of diabetes, No. (%)	3219 (40.94)	925 (48.74)	844 (44.1)	723 (36.37)	727 (35.99)	< 0.001
Alcohol consumption, No. (%)	5410 (75.96)	1239 (69.12)	1321 (74.45)	1410 (79.28)	1440 (79.83)	< 0.001
Smoking status, No. (%)						0.012
Never smoker	3857 (51.81)	914 (49.10)	940 (49.68)	974 (52.36)	1029 (55.34)	
Former smoker	2029 (25.64)	550 (28.93)	530 (26.77)	509 (25.34)	440 (22.28)	
Current smoker	1648 (22.55)	418 (21.97)	412 (23.56)	402 (22.3)	416 (22.38)	
Marital status, No. (%)						0.266
Married	4651 (65.89)	1115 (64.94)	1183 (66.58)	1218 (67.38)	1135 (64.72)	
Single or separated	2883 (34.11)	767 (35.06)	699 (33.42)	667 (32.62)	750 (35.28)	
MetS, No. (%)	2086 (23.96)	749 (36.87)	644 (31.38)	445 (19.85)	248 (10.80)	< 0.001
Elevated FPG, No. (%)	1874 (19.18)	620 (27.75)	519 (21.87)	438 (17.14)	297 (11.73)	< 0.001
Low HDL-C, No. (%)	2059 (26.78)	721 (37.37)	563 (32.19)	437 (22.96)	338 (16.98)	< 0.001
Elevated TG, No. (%)	2295 (28.86)	649 (34.13)	697 (36.03)	552 (27.04)	397 (20.08)	< 0.001
Elevated WC, No. (%)	4198 (53.24)	1416 (75.29)	1270 (68.67)	969 (48.39)	543 (26.45)	< 0.001
Elevated BP, No. (%)	2540 (27.48)	730 (33.80)	704 (30.64)	644 (27.81)	462 (19.33)	< 0.001

Abbreviations: Q, quartile; FPG, fasting plasma glucose; BP, blood pressure; WC, waist circumference; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol

Continuous variables were presented as the mean (standard deviation, SD). The *P* value was calculated using a weighted Student's t-test or Mann-Whitney U test. Categorical variables were presented as a percentage (%). The *P* value was calculated using the weighted chi-square test

likely to be male, younger, wealthier, and to have a higher level of education. They were also more likely to have a history of cancer, a family history of diabetes mellitus, to consume alcohol, and to never smoke (all $P < 0.05$).

Association between the CALLY index and MetS

Table 2 presents the results of the weighted logistic regression analysis. In the unadjusted models, higher CALLY index quartiles were associated with a lower risk of MetS ($P_{trend} < 0.001$). This association remained significant after adjusting for age, sex, and race, history of cancer, family history of diabetes mellitus, smoking status, alcohol consumption, educational attainment, and poverty-to-income ratio in Model 2 ($P_{trend} < 0.001$). We next investigated the association between the CALLY index and the specific components of MetS, including elevated WC, elevated FPG, elevated BP, elevated TG, and low HDL-C. We found that higher CALLY index quartiles were negatively associated with elevated WC,

Table 2 Weighted logistic analysis model between CALLY index and MetS and its components

Characteristic	Crude model		Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
MetS						
Q1	Ref		Ref		Re	
Q2	0.78 (0.67, 0.91)	0.002	0.78 (0.66,0.91)	0.002	0.81(0.69, 0.95)	0.013
Q3	0.42 (0.35, 0.52)	< 0.001	0.42 (0.35, 0.52)	< 0.001	0.46 (0.37, 0.56)	< 0.001
Q4	0.21 (0.17, 0.26)	< 0.001	0.23 (0.19,0.29)	< 0.001	0.25 (0.20, 0.32)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Elevated WC						
Q1	Ref		Ref		Ref	
Q2	0.72 (0.59,0.88)	0.002	0.76 (0.62,0.93)	0.008	0.78 (0.64,0.96)	0.022
Q3	0.31 (0.26, 0.37)	< 0.001	0.34 (0.28, 0.42)	< 0.001	0.36 (0.30, 0.44)	< 0.001
Q4	0.12 (0.10, 0.14)	< 0.001	0.15 (0.12, 0.17)	< 0.001	0.15 (0.13, 0.18)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Elevated FPG						
Q1	Ref		Ref		Ref	
Q2	0.73 (0.60, 0.89)	0.002	0.69 (0.56, 0.85)	< 0.001	0.72 (0.58, 0.89)	0.003
Q3	0.54 (0.44, 0.66)	< 0.001	0.51 (0.41, 0.64)	< 0.001	0.55 (0.44, 0.69)	< 0.001
Q4	0.35 (0.28, 0.43)	< 0.001	0.40 (0.32, 0.51)	< 0.001	0.44 (0.35, 0.56)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Elevated BP						
Q1	Ref		Ref		Ref	
Q2	0.87 (0.73, 1.02)	0.082	0.87 (0.73, 1.04)	0.137	0.89 (0.74, 1.06)	0.181
Q3	0.75 (0.64, 0.89)	< 0.001	0.81 (0.67, 0.97)	0.025	0.82 (0.68, 1.00)	0.046
Q4	0.47 (0.39, 0.56)	< 0.001	0.61 (0.50, 0.74)	< 0.001	0.63 (0.52, 0.77)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Elevated TG						
Q1	Ref		Ref		Ref	
Q2	1.09 (0.91, 1.29)	0.342	1.05 (0.88, 1.26)	0.581	1.09 (0.90, 1.31)	0.369
Q3	0.72 (0.61, 0.85)	< 0.001	0.66 (0.55, 0.79)	< 0.001	0.70 (0.58, 0.85)	0.001
Q4	0.48 (0.41, 0.58)	< 0.001	0.47 (0.39, 0.57)	< 0.001	0.51 (0.41, 0.62)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001
Low HDL-C						
Q1	Ref		Ref		Ref	
Q2	0.80 (0.68, 0.94)	0.007	0.78 (0.66, 0.92)	0.004	0.81 (0.68, 0.96)	0.014
Q3	0.50 (0.41, 0.62)	< 0.001	0.48 (0.39, 0.59)	< 0.001	0.51 (0.41, 0.64)	< 0.001
Q4	0.34 (0.28, 0.42)	< 0.001	0.31 (0.25, 0.38)	< 0.001	0.33 (0.27, 0.42)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Abbreviations: Q, quartile; FPG, fasting plasma glucose; BP, blood pressure; WC, waist circumference; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol

Crude Model: unadjusted

Model 1: adjustments were made for age, sex, and race

Model 2: In addition to the adjustments made in Model 1, adjustments were also made for history of cancer, family history of diabetes, smoking status, alcohol consumption, educational attainment, and poverty income ratio

BP, FPG, and TG, as well as with reduced HDL-C level in the fully adjusted models (all $P_{trend} < 0.001$).

The weighted RCS curve analysis indicated a significant non-linear relationship between the log-transformed CALLY index and MetS, even after adjusting for multiple covariates in Model 2 ($P < 0.001$, Fig. 2A). The risk of MetS decreased with an increase in the CALLY index. Furthermore, when evaluating the specific components of MetS, significant non-linear associations were observed between the log-transformed CALLY index and elevated WC (Fig. 2B), elevated TG (Fig. 2E), and low HDL-C (Fig. 2F). The relationship between the log-transformed CALLY index and elevated TG exhibited an inverted U-shaped pattern. The risk of TG elevation peaked at a CALLY index close to 0 and then declined sharply, with a significant non-linear relationship ($P < 0.0001$). The analysis also revealed a significant inverse association between the log-transformed CALLY index and both FPG elevation (Fig. 2C) and BP elevation (Fig. 2D), indicating a linear relationship ($P_{non-linearity} > 0.05$).

Subgroup analyses

In the subgroup analyses (Fig. 3), females demonstrated a significantly lower risk of MetS than males ($P_{interaction} = 0.005$). Furthermore, age-stratified subgroups revealed that individuals aged < 60 years exhibited a lower risk of MetS than those aged ≥ 60 years ($P_{interaction} < 0.001$). There were no significant interactions in the other subgroups (all $P_{interaction} > 0.05$).

Discussion

This cross-sectional study of 7,534 adults investigated the associations between the CALLY index and MetS. A lower CALLY index was significantly associated with an increased risk of MetS and its components. Nonlinear associations were observed with MetS, elevated WC, reduced HDL-C, and elevated TG, while linear associations were found with elevated BP and elevated FPG. Subgroup analyses showed that the association between a lower CALLY index and increased risk of MetS was more pronounced in females and individuals under 60 years of age.

MetS is a pathological condition that is characterized by a cluster of metabolic abnormalities, including abdominal obesity, insulin resistance, hypertension, and hyperlipidemia [2]. MetS is considered to be an emerging epidemic. In terms of the prevalence of MetS and individual MetS components, our results were comparable

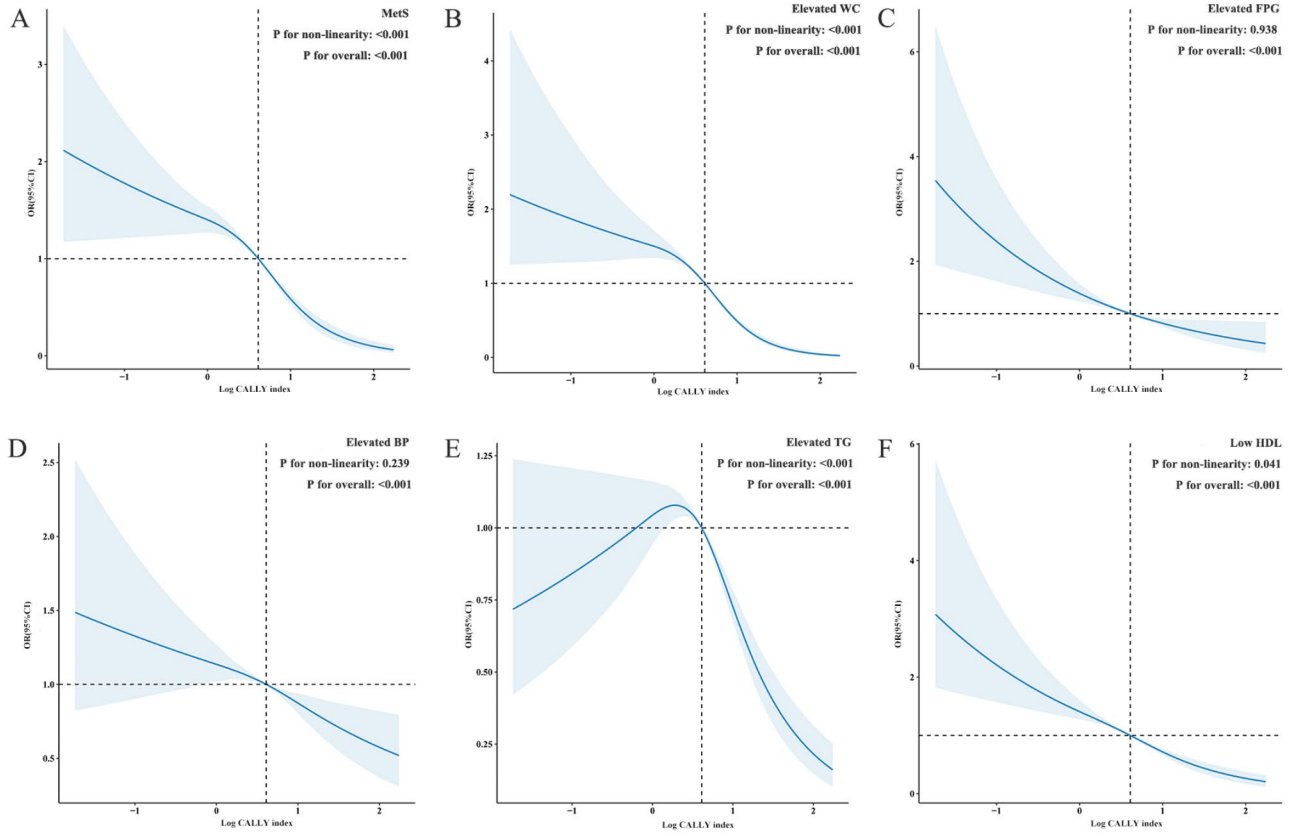

Fig. 2 Dose-response relationships between MetS (**A**), elevated WC (**B**), elevated FPG (**C**), elevated BP (**D**), elevated TG (**E**), low HDL (**F**) and the CALLY index

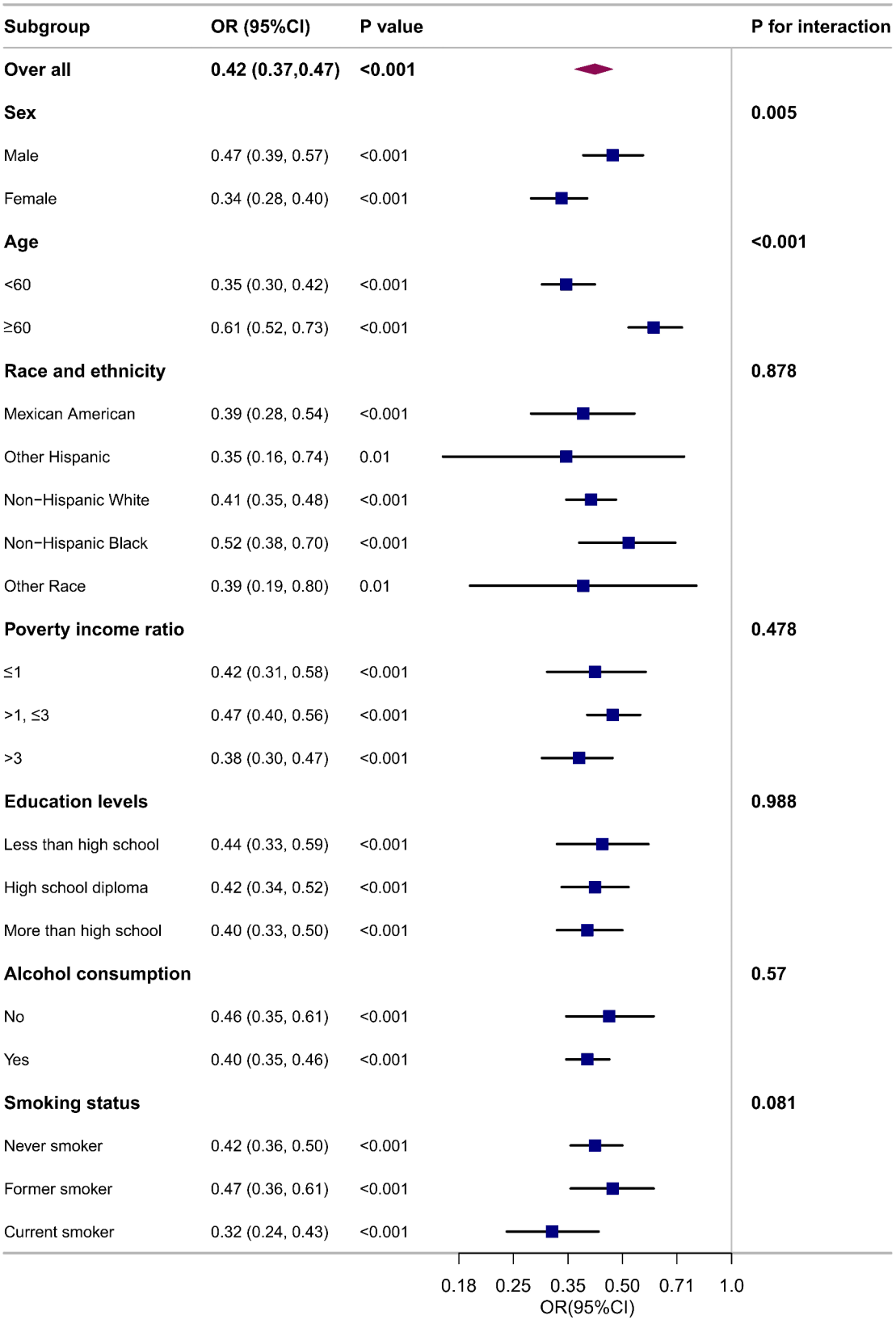

Fig. 3 Subgroup analysis of the associations between MetS and the CALLY index

to those previously reported in the literature, with obesity being the most common (91.86%) and hyperglycemia the least common (23.96%) type of MetS. The prevalence of each MetS component was much higher for participants who met the criteria for MetS. The CALLY index is a predictor of cancer treatment efficacy and prognosis. In addition to cancer, the predictive value of the CALLY index for MetS has attracted our attention. We observed a significant correlation between the CALLY index and different MetS components. In particular, the CALLY index demonstrated a correlation with obesity, hypertension, hyperglycemia, high TG, and low HDL-C. This finding suggests that MetS may not only be associated with the CALLY index as a whole, but that it may also be closely associated with its constituent factors. Consequently, it may be hypothesized that the components of the CALLY index play an important roles in the pathogenesis of MetS.

MetS is associated with various risk factors and plays a crucial role in disease progression [16, 33]. There is mounting evidence illustrating an association between MetS and inflammation, nutritional status [34–36], and immune function. MetS causes modifications in cell signaling pathways, resulting in elevated inflammatory markers, lipid peroxides, and free radicals [37]. The use of CRP as an inflammatory biomarker is becoming more common in the assessment of cardiovascular risk [38–41], with CRP elevation linked to key MetS risk factors, such as insulin resistance, hyperglycemia, and abdominal adiposity [42, 43]. A previous study showed that CRP was significantly elevated in patients with MetS [44], highlighting the inflammatory state of the body and underscoring the importance of chronic inflammation in the pathogenesis of MetS, which is consistent with the findings of the present study.

T lymphocytes, which are crucial players in the adaptive immune response, intricately contribute to inflammation in patients with obesity [45]. Individuals with obesity and those with MetS exhibit elevated T lymphocyte counts, disrupting the delicate balance between proinflammation and anti-inflammation [15, 31, 46]. Some studies have associated heightened lymphocyte counts with an increased risk of diabetes mellitus due to insulin resistance. Although some studies have suggested compromised lymphocyte function, evidenced by increased apoptosis or decreased immune response capacity, conflicting findings have emerged. The present study confirmed that individuals with MetS had significantly higher peripheral blood lymphocyte counts than healthy controls, supporting their role in MetS pathogenesis. This finding is consistent with emerging evidence illustrating the crucial role of the immune system in MetS development and highlighting the complex relationship between immune dysregulation and metabolic disturbances.

The serum albumin concentration is linked to the severity of malnutrition and plays a crucial role as an antioxidant by scavenging hydroxyl radicals and reducing reactive oxygen species production [47, 48]. Albumin also regulates inflammation by suppressing pro-inflammatory cytokines [49, 50] and activating the nuclear factor-κB pathway [51], which can impact cellular signaling pathways and MetS development. Low albumin is associated with heightened inflammation [52, 53]. The interaction of inflammatory markers, such as the CRP/albumin ratio, has been shown to play a significant role in disease progression and outcomes, as demonstrated in studies on cardiovascular conditions [54, 55]. Furthermore, there are negative correlations between the albumin concentration and obesity, lipid metabolism abnormalities [51, 56], and insulin sensitivity [57, 58]. A previous study suggested that increasing the serum albumin concentration over time may prevent MetS development [59]. However, excessive dietary protein intake may exacerbate hyperinsulinemia, hyperglycemia, hypertension, and lipid abnormalities, potentially contributing to MetS [60]. Other studies have suggested that there is a positive correlation between the increase in baseline serum albumin and the prevalence of MetS [61–63]. In the present study, we observed a lower albumin concentration in patients with MetS than in those without MetS. This finding supports the results of a previous study on blood changes in patients with MetS. For example, lower serum albumin is linked to coronary heart disease risk [64]. Xu et al. showed that microalbuminuria and high 24-hour urinary albumin excretion are risk factors for MetS, indicating lower albumin levels in these patients [65].

This study takes full advantage of the independent predictive value of these three indicators, as well as their interactions. The findings suggest that the combination of these three common indices within the CALLY index may have greater potential to investigate the association between the baseline CALLY index and MetS risk. The CALLY index may influence the occurrence and progression of MetS through various pathways. First, serving as a comprehensive indicator of metabolic health, the CALLY index likely reflects an individual's nutritional status and lifestyle habits. These factors are closely associated with the pathophysiological mechanisms of MetS. For instance, a diet high in fat, sugar, and salt may lead to weight gain, insulin resistance, and elevated BP, thereby promoting MetS development. Second, the CALLY index may be linked to metabolic activity, influencing energy and lipid metabolism within the body. Inappropriate energy metabolism and lipid storage patterns can result in fat accumulation, insulin resistance, and metabolic dysregulation, consequently increasing MetS risk. Additionally, the CALLY index may reflect the level of inflammation and immune function within the body.

Inflammation and immune dysfunction are crucial components in the pathogenesis of MetS, leading to metabolic disturbances and tissue damage, thereby facilitating MetS progression.

The subgroup analyses showed that a stronger association between the CALLY index and MetS was observed in females ($P_{interaction}$ = 0.005) and participants aged < 60 years ($P_{interaction}$ < 0.001). Differential responses to sex hormones may explain the sex difference in the relationship between the CALLY index and MetS [66]. A meta-analysis discovered that reduced sex hormone-binding globulin and elevated estradiol concentrations increased the risk of diabetes mellitus in women [67]. In those aged ≥ 60 years, the association between the CALLY index and MetS was present, but it was relatively weak. This may be related to the decline in immune cell function and immune cell proliferation [68], and the reduction in the number of pattern recognition receptors in the elderly. Moreover, chronic diseases in the elderly also inhibit normal immune system function [69].

Strengths of this study include the use of NHANES database, which ensures a nationally representative sample and broad generalizability, as well as the identification of the CALLY index as a novel, non-invasive biomarker with potential to enhance MetS risk assessment. However, this study also has several limitations that should be considered. First, the NHANES design only allowed for certain counts to be measured at a single time point, potentially affecting the accuracy of the results. Moreover, the exclusion of participants with incomplete data may have introduced selection bias. Second, the retrospective cross-sectional nature of this study rendered our observations susceptible to inherent bias, and causality could not be established, allowing for only an interpretation of the associations [70]. Despite these limitations, the findings of this study are clinically relevant. By utilizing routine laboratory markers, the CALLY index could serve as a practical and cost-effective tool for primary care physicians to identify individuals at high risk for MetS. Its potential clinical application may facilitate early detection and timely intervention, thereby potentially slowing or even preventing the progression of MetS. Given the inverse relationship between the CALLY index and MetS, patients with a lower index may benefit from individualized treatment approaches focused on reducing inflammation and improving nutritional status. Interventions such as anti-inflammatory therapies and dietary modifications could enhance metabolic health, thereby preventing the progression of MetS. However, further studies are needed to validate these hypotheses.

Conclusion

Our analysis showed that a higher CALLY index was associated with a lower risk of MetS among adults from the United States. The CALLY index may provide additive value for identifying individuals who are at a higher risk of developing MetS. Further prospective studies are needed to validate our findings.

Acknowledgements

The authors thank the NHANES 2003-2010 participants for their invaluable contributions.

Author contributions

Study concept and design: HB Zhou, SR Liu and DZ Han; Acquisition of data: LL Wu, SW Su, and Z Ma; Analysis and interpretation of data: YT Xue and SF He; Drafting of the manuscript: LL Wu, PX Li and SW Su; Critical revision of the manuscript: HB Zhou, SR Liu and DZ Han. All authors have reviewed and approved the final version of the manuscript.

Funding

This project was supported by the National Outstanding Youth Science Fund Project of National Natural Science Foundation of China. (No.82100263).

Data availability

Publicly available datasets were analyzed in this study. These data are accessible at the following website: www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The National Center for Health Statistics and the Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent. The authors have disclosed no conflicts of interest.

Consent for publication

All authors have reviewed and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Received: 21 August 2024 / Accepted: 22 January 2025
Published online: 31 January 2025

References

1. Alberti KG, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.
2. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20(2):12.
3. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14(3):173–94.
4. Wu SH, Liu Z, Ho SC. Metabolic syndrome and all-cause mortality: a meta-analysis of prospective cohort studies. Eur J Epidemiol. 2010;25(6):375–84.
5. Mottillo S, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56(14):1113–32.
6. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care. 2005;28(7):1769–78.
7. Sin S et al. Metabolic syndrome and risk of Lung Cancer: an Analysis of Korean National Health Insurance Corporation Database. J Clin Endocrinol Metab, 2020;105(11).

8. Lee MK, et al. Changes in metabolic syndrome and its components and the risk of type 2 diabetes: a nationwide cohort study. Sci Rep. 2020;10(1):2313.
9. Fahed G et al. Metabolic syndrome: updates on pathophysiology and management in 2021. Int J Mol Sci, 2022;23(2).
10. Xue Q, et al. Association between baseline and changes in high-sensitive C-reactive protein and metabolic syndrome: a nationwide cohort study and meta-analysis. Nutr Metab (Lond). 2022;19(1):2.
11. Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med. 2008;14(3–4):222–31.
12. Hotamisligil GS. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. Immunity. 2017;47(3):406–20.
13. Berbudi A, et al. Type 2 diabetes and its impact on the Immune System. Curr Diabetes Rev. 2020;16(5):442–9.
14. Nishimura S, et al. CD8 + effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat Med. 2009;15(8):914–20.
15. Chawla A, Nguyen KD, Goh YP. Macrophage-mediated inflammation in metabolic disease. Nat Rev Immunol. 2011;11(11):738–49.
16. Martin CA, et al. Systematic review of the Effect of Lifestyle interventions on the components of the metabolic syndrome in south Asian migrants. J Immigr Minor Health. 2018;20(1):231–44.
17. Karakayali M, et al. The relationship between the systemic Immune-inflammation index and ischemia with non-obstructive coronary arteries in patients undergoing coronary angiography. Arq Bras Cardiol. 2024;121(2):e20230540.
18. Karakayali M, et al. The prognostic value of HALP score in predicting in-hospital mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis. 2023;34(7):483–8.
19. Iida H, et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. HPB (Oxford). 2022;24(1):101–15.
20. Tsunematsu M, et al. The impact of C-reactive protein-albumin-lymphocyte (CALLY) index on the prognosis of patients with distal cholangiocarcinoma following pancreaticoduodenectomy. Ann Gastroenterol Surg. 2023;7(3):503–11.
21. Furukawa K, et al. Impact of C-reactive protein-albumin-lymphocyte (CALLY) index on prognosis after hepatectomy for colorectal liver metastasis. Surg Oncol. 2023;47:101911.
22. Takeda Y et al. Prognostic usefulness of the C-reactive protein-albumin-lymphocyte (CALLY) index as a novel biomarker in patients undergoing colorectal cancer surgery. Asian J Surg. 2024;47(8):3492–8.
23. Ma R, et al. Clinical implications of C-reactive protein-albumin-lymphocyte (CALLY) index in patients with esophageal cancer. Surg Oncol. 2024;53:102044.
24. Hashimoto I, et al. Clinical impact of the C-reactive protein-albumin-lymphocyte index in post-gastrectomy patients with gastric Cancer. Vivo. 2024;38(2):911–6.
25. Fukushima N et al. Prognostic significance of the preoperative C-reactive protein-albumin-lymphocyte (CALLY) index on outcomes after gastrectomy for gastric cancer. Surg Today. 2024;54(8):943–52.
26. Liu XY, et al. The value of CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker in patients with non-small cell lung cancer. Support Care Cancer. 2023;31(9):533.
27. Feng J, et al. Clinical significance of preoperative CALLY index for prognostication in patients with esophageal squamous cell carcinoma undergoing surgery. Sci Rep. 2024;14(1):713.
28. Yang M, et al. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: from the investigation on nutrition status and clinical outcome of common cancers study. Front Immunol. 2023;14:1131496.
29. Wang W, et al. Pre-treatment CRP-Albumin-lymphocyte index (CALLY Index) as a Prognostic Biomarker of Survival in patients with epithelial ovarian Cancer. Cancer Manag Res. 2022;14:2803–12.
30. McQuillan GM, et al. National Health and Nutrition Examination Survey Biospecimen Program: NHANES III (1988–1994) and NHANES 1999–2014. Vital Health Stat. 2015;2(170):1–14.
31. Esser N, et al. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141–50.
32. Zhao Y, et al. Association between systemic immune-inflammation index and metabolic syndrome and its components: results from the National Health and Nutrition Examination Survey 2011–2016. J Transl Med. 2023;21(1):691.
33. Russo S, et al. Meta-inflammation and metabolic reprogramming of macrophages in diabetes and obesity: the importance of metabolites. Front Immunol. 2021;12:746151.
34. Jin HS et al. Association between Use of Nutritional labeling and the metabolic syndrome and its components. Int J Environ Res Public Health, 2019;16(22).
35. Zujko ME, Rożniata M, Zujko K. Individual Diet modification reduces the metabolic syndrome in patients before pharmacological treatment. Nutrients, 2021;13(6).
36. Xu X, et al. Increase in the prevalence of arthritis in adulthood among adults exposed to Chinese famine of 1959 to 1961 during childhood: a cross-sectional survey. Med (Baltim). 2017;96(13):e6496.
37. Guldiken S, et al. The levels of circulating markers of atherosclerosis and inflammation in subjects with different degrees of body mass index: Soluble CD40 ligand and high-sensitivity C-reactive protein. Thromb Res. 2007;119(1):79–84.
38. Cesari M, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation. 2003;108(19):2317–22.
39. Koenig W, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring trends and determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999;99(2):237–42.
40. Ridker PM, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002;347(20):1557–65.
41. Tracy RP, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997;17(6):1121–7.
42. González AS, et al. Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin. Eur J Clin Nutr. 2006;60(6):802–9.
43. Deepa R, et al. Serum levels of interleukin 6, C-reactive protein, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1 in relation to insulin resistance and glucose intolerance--the Chennai Urban Rural Epidemiology Study (CURES). Metabolism. 2006;55(9):1232–8.
44. Rein P, et al. Roles of the metabolic syndrome, HDL cholesterol, and coronary atherosclerosis in subclinical inflammation. Diabetes Care. 2010;33(8):1853–5.
45. Kiran S, et al. High Fat Diet-Induced CD8(+) T cells in adipose tissue mediate macrophages to sustain low-Grade chronic inflammation. Front Immunol. 2021;12:680944.
46. Rodríguez CP, et al. Peripheral lymphocytes, obesity, and metabolic syndrome in young adults: an Immunometabolism Study. Metab Syndr Relat Disord. 2018;16(7):342–9.
47. Gutteridge JM. Antioxidant properties of the proteins caeruloplasmin, albumin and transferrin. A study of their activity in serum and synovial fluid from patients with rheumatoid arthritis. Biochim Biophys Acta. 1986;869(2):119–27.
48. Peng YF, Wei YS. The relationships between serum fructosamine concentrations and lipid profiles in community-dwelling adults. Sci Rep. 2017;7(1):6886.
49. Cooper BA, et al. Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. Am J Kidney Dis. 2004;43(1):61–6.
50. Rodiño-Janeiro BK, et al. Glycated human serum albumin induces NF-κB activation and endothelial nitric oxide synthase uncoupling in human umbilical vein endothelial cells. J Diabetes Complications. 2015;29(8):984–92.
51. Si M et al. Triglycerides as Biomarker for Predicting systemic lupus Erythematosus related kidney Injury of negative Proteinuria. Biomolecules, 2022;12(7).
52. Bologa RM, et al. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis. 1998;32(1):107–14.
53. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340(6):448–54.
54. Rencuzogullari I, et al. Assessment of the relationship between preprocedural C-reactive protein/albumin ratio and stent restenosis in patients with ST-segment elevation myocardial infarction. Rev Port Cardiol (Engl Ed). 2019;38(4):269–77.
55. Karabağ Y, et al. Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris. J Clin Lab Anal. 2018;32(7):e22457.
56. Yan C, et al. Therapeutic effects of Batoclimab in Chinese patients with generalized Myasthenia gravis: a Double-Blinded, randomized, placebo-controlled phase II study. Neurol Ther. 2022;11(2):815–34.

57. Liu H, et al. Young and undamaged recombinant albumin alleviates T2DM by improving hepatic glycolysis through EGFR and protecting islet β cells in mice. J Transl Med. 2023;21(1):89.
58. Farhangi MA, et al. Mediterranean dietary quality index and dietary phytochemical index among patients candidate for coronary artery bypass grafting (CABG) surgery. BMC Cardiovasc Disord. 2017;17(1):114.
59. Jin SM, et al. Change in serum albumin concentration is inversely and independently associated with risk of incident metabolic syndrome. Metabolism. 2016;65(11):1629–35.
60. Vasbinder A, et al. Risk of metabolic syndrome and metabolic phenotypes in relation to biomarker-calibrated estimates of energy and protein intakes: an investigation from the women's Health Initiative. Am J Clin Nutr. 2021;113(3):706–15.
61. Ishizaka N, et al. Association between serum albumin, carotid atherosclerosis, and metabolic syndrome in Japanese individuals. Atherosclerosis. 2007;193(2):373–9.
62. Cho HM, et al. The association between serum albumin levels and metabolic syndrome in a rural population of Korea. J Prev Med Public Health. 2012;45(2):98–104.
63. Kadono M, et al. Serum albumin levels predict vascular dysfunction with paradoxical pathogenesis in healthy individuals. Atherosclerosis. 2010;209(1):266–70.
64. Djoussé L, et al. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham offspring study. Circulation. 2002;106(23):2919–24.
65. Xu J, et al. Association of microalbuminuria and high-normal 24-hour urinary albumin excretion with metabolic syndrome and its components in the general Chinese population: cross-sectional study. BMJ Open. 2019;9(11):e031443.
66. Ding EL, et al. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia. 2007;50(10):2076–84.
67. Ding EL, et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006;295(11):1288–99.
68. Wu C, et al. Risk factors Associated with Acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–43.
69. Costagliola G, Spada E, Consolini R. Age-related differences in the immune response could contribute to determine the spectrum of severity of COVID-19. Immun Inflamm Dis. 2021;9(2):331–9.
70. Nicoară DM et al. Assessing the relationship between systemic Immune-inflammation index and metabolic syndrome in children with obesity. Int J Mol Sci, 2023;24(9).

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.