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Association between the systemic immune-inflammation index and metabolic syndrome and its components: results from the multi-ethnic study of atherosclerosis (MESA)

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Abstract

Background The Systemic Immune-Inflammation Index (SII) is a novel biomarker of systemic inflammation. We explored the association between the SII and metabolic syndrome (MetS) and its components in middle-aged and older adults.

Methods We included 2755 participants (1305 men) aged 45–84 years from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort from examination 5 (2010–2012). Logistic regression was employed to assess the relationship between the SII and MetS, as well as its components.

Results A total of 1082 participants (463 men) were diagnosed with MetS. On a continuous scale, the SII was positively associated with MetS (odds ratio (OR): 1.23, 95% confidence interval (CI): 1.05–1.46) and its components including hyperglycemia (1.23: 1.05–1.44) and elevated blood pressure (BP) (1.47: 1.14–1.89). When analyzed on a quartile scale, participants in the quartile 4 of SII had 32% and 63% higher prevalence of hyperglycemia and elevated BP, respectively, compared to those in the quartile 1 (P for trend: 0.021 and < 0.001, respectively). Additionally, we identified 40% higher prevalence of low HDL-C in quartile 2 of the SII compared to quartile 1 (1.40; 1.07–1.83) (P trend = 0.454). In subgroup analysis, general obesity status modified the relationship between SII and abdominal obesity, showing a positive association in obese individuals (1.72: 1.00-2.95) and a negative association (0.80: 0.66–0.97) in non-obese individuals (P for interaction = 0.009).

Conclusions Higher SII scores were associated with an increased likelihood of MetS, hyperglycemia, and high BP among middle-aged and older adults. Longitudinal studies are needed to determine the causal relationships between SII and the development of MetS, as well as to assess the potential role of SII as a screening tool in clinical practice.

Keywords MESA, Systemic immune-inflammation index, Metabolic syndrome

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Background

Metabolic syndrome (MetS) is characterized by a combination of metabolic abnormalities, including hypertension, hyperglycemia, central obesity, and dyslipidemia [1]. MetS is an increasing concern in the United States, affecting a significant proportion of the adult population. The prevalence of MetS in the United States increased from 37.6% in 2011–2012 to 41.8% in 2017–2018, underscoring a significant and growing public health challenge [2].

MetS has been linked to adverse effects on cardiac conduction, as evidenced by prolonged QRS duration and increased QTc dispersion [3], and is associated with a higher recurrence of premature ventricular contractions following catheter ablation in patients without structural heart disease [4]. Furthermore, MetS is a well-established risk factor for the development of cardiovascular disease (CVD) [5, 6], sudden cardiac death [7], and type 2 diabetes mellitus (T2DM) [8].

Recent research has shown that inflammation plays a critical role in the development and progression of the various components of MetS [9, 10]. Elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), have been consistently linked to key components of MetS, including visceral obesity, insulin resistance, and dyslipidemia [11, 12]. These markers indicate a chronic low-grade inflammatory state that contributes to the pathogenesis of T2DM and CVD [11]. In patients with established CVD, this over-inflammatory distress significantly worsens clinical outcomes [13]. A recent study [14] demonstrated that heart failure patients with MetS exhibited higher levels of ST2 protein, as an inflammatory biomarkers, with a poorer prognosis compared to those without MetS. Consequently, researchers in recent years have shifted their focus to identifying appropriate inflammatory biomarkers that could serve as potential indicators of MetS across different populations [15]. Several composite inflammation indices derived from routine complete blood count (CBC) tests, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immunity-inflammation index (SII) have gained attention for their predictive capabilities regarding various diseases, including MetS [16, 17]. These indices are widely recognized as cost-effective and easily accessible biomarkers that effectively reflect the body's inflammatory status. The SII, developed by Hu et al. [18], is a comprehensive biomarker that integrates platelet, neutrophil, and lymphocyte counts to reflect the balance between inflammation and immune status. The SII was initially developed to assess the prognosis of patients with various kinds of cancer [19, 20], but it was later found to be associated with other diseases and conditions such as CVD [21], hypertension [22], hyperlipidemia [23], insulin resistance, prediabetes [24], diabetes [25] and the risk of all-cause and CVD mortality [26]. There are limited studies regarding the association between the SII and MetS, especially in the general population [17, 27–29]. To date, only two studies have directly examined the association between SII and MetS in the general population, both utilizing data from the National Health and Nutrition Examination Survey (NHANES) [27, 28]. In the study by Zhao et al. [28], which analyzed NHANES data from 2011 to 2016, a total of 12,402 participants aged > 18 years (28% diagnosed with MetS) were included. The study demonstrated a positive non-linear association between the SII and MetS in the overall population. However, age-stratified analysis revealed significant association only among younger individuals [18–39], with no significant associations in the 39–59 and > 60 age groups. In contrast, a more recent study by Zeng et al. [27], which included 6999 participants aged > 20 years from NHANES (2015–2018) with a prevalence of MetS at 36%, identified a linear association between the SII and MetS across the overall population. Their age-stratified analysis indicated a significant association only in participants aged < 60 years, while those aged > 60 years showed a non-significant association. Both studies reported a stronger association between SII and MetS in younger individuals compared to older population. This difference may be attributed to the smaller sample sizes of older participants in these studies which included a broad age range (participants aged > 20 years).

Given the growing public health concern surrounding MetS and its associated complications [2], it is crucial to confirm current findings with a specific focus on middle-aged and older adults who are more susceptible to chronic inflammatory and metabolic conditions, and exhibit different lifestyles and physical activity patterns [30]. Our study addresses this gap by examining the association between SII and MetS, as well as its components, within the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. This cohort comprises U.S. adults, aged 45–84 years from diverse racial and ethnic backgrounds.

Methods

The data used for this study were obtained from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), which can be accessed at https://biolincc.nhlbi.nih.gov/.

Study design and study population

This study utilized data from the MESA, a large, ongoing cohort study that has been collecting longitudinal data to investigate the prevalence, risk factors, and progression of subclinical CVD in a diverse, multiethnic population. Details of the study have been described previously [23]. Briefly, the study recruited 6814 men and women aged

45 to 84 years in examination 1 (2000–2002), representing four different ethnic groups, including non-Hispanic whites, African Americans, Hispanic Americans, and Chinese. These participants were recruited from six different U.S. communities. The participants underwent four follow-up assessments (examinations 2 to 5) over a 10 years period. Of the 6814 participants at baseline examination 1, a total of 4716 participants attended examination 5 (2010–2012), and only 2885 of them had their total white blood cell and subfraction counts measured. After excluding 130 participants due to missing covariate data at examination 5, a total of 2775 participants were included in the final analysis (Fig. 1). The institutional review board of each study center approved the study, and written informed consent was obtained from all study participants at each examination. Approval for the current study was obtained from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

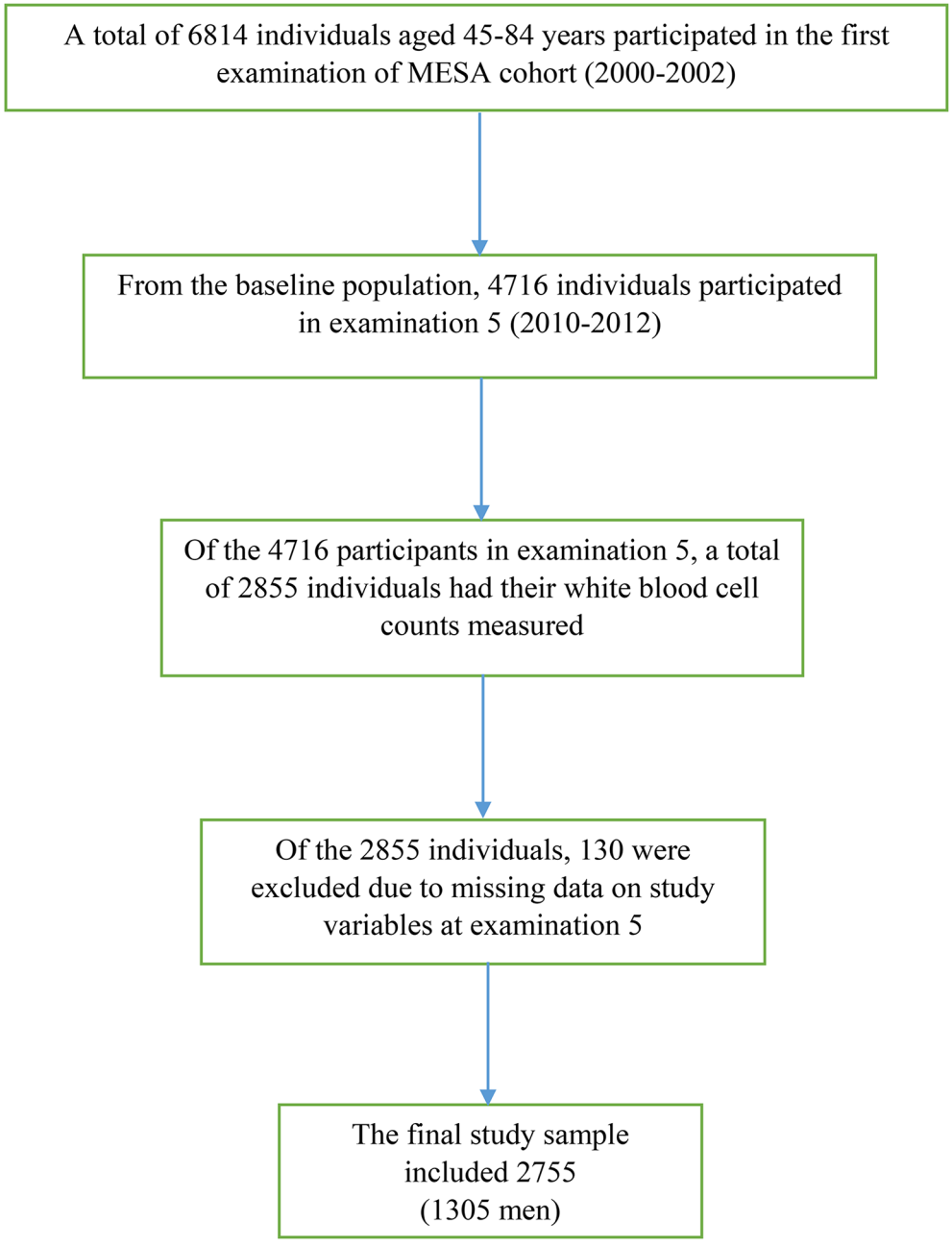

Fig. 1 Flowchart of participants included in the study, MESA cohort (2010–2012). MESA: Multi-Ethnic Study of Atherosclerosis

Data collection

Data on participants' demographics, medical and family history, tobacco use, alcohol consumption, and drug use were collected using self-administered questionnaires and interviews conducted during examination 5. Anthropometric measures of weight, height, and waist circumference (WC) were measured twice using a standardized protocol, and the average of the two measurements was used. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). Three seated resting blood pressure (BP) measurements were taken, and the average of the last two readings was used for analysis. Blood samples were collected after an overnight fast to assess biochemical parameters such as fasting blood glucose (FBG), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) levels using standard laboratory procedures [31]. Platelet, neutrophil, and lymphocyte counts were assessed by CBC measured with an automated cell counter, the Coulter HmX AL Hematology Analyzer (Beckman Coulter), and were expressed as 1000 cells/μL [32]. Physical activity level was evaluated using a semi-quantitative questionnaire that was adapted from the Cross-Cultural Activity Participation Study [33]. This questionnaire assessed the total minutes per week spent on various physical activities performed during a typical week in the past month. The total minutes for each activity was then multiplied by the specific MET (metabolic equivalent of task) value assigned to that activity.

Definition of terms

Covariates

Smoking status was categorized as never, former, or current smoker. Similarly, alcohol consumption was classified into three categories: never-drinkers, current drinkers, and former drinkers. Education levels were categorized as follows: (i) high school or lower, (ii) some college (incomplete college/technical school/ associate degree/ bachelor's degree), and (iii) graduate or professional school. Family history of diabetes (FHD) was defined as the presence of diabetes in first-degree relatives (parents or siblings) and was assessed during the second examination visit for 5382 participants. This information was subsequently used for analysis.

Outcome

MetS was defined by the presence of at least three of the following criteria according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines [1]. The criteria were as follows: [1] TG ≥ 1.69 mmol/L (150 mg/ dL) or treatment for this lipid abnormality; [2] HDL-C < 1.03 mmol/L (40 mg/ dL) in men and < 1.29 mmol/L (50 mg/dL) in women or treatment for this lipid abnormality; [3] FPG ≥ 5.6 mmol/L (100 mg/dL) or treatment for elevated glucose; [4] WC ≥ 102 cm in men and ≥ 88 cm in women; [5] systolic BP (SBP) ≥ 130 mmHg and/or diastolic BP (DBP) ≥ 85 mmHg or treatment for previously diagnosed hypertension.

Exposure

The SII was calculated as platelet count (PC)×neutrophil count (NC)/lymphocyte count (LC) [18].

Statistical analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Since the SII exhibited a right-skewed distribution, we applied a natural logarithm (LnSII) transformation to normalize the data and meet the assumptions required for parametric tests.

Population characteristics are summarized as means with standard deviations (SD) for normally distributed continuous variables, and as medians with interquartile ranges (IQR) for non-normally distributed continuous variables. Categorical variables are presented as frequencies with percentages. Differences between individuals with and without MetS were evaluated using t-tests for continuous variables and chi-square tests for categorical variables. For continuous variables that were not normally distributed, we used Mann-Whitney U test.

We utilized logistic regression model to explore the association between SII and MetS and its components. SII was examined on both continuous and categorical scale. For the continuous scale, LnSII was included in the regression models. For the categorical scale, participants were categorized into four groups based on LnSII quartiles. This approach facilitates the examination of how varying levels of SII relate to MetS and its components and helps identify potential dose-response relationships. In the regression models, the first quartile of LnSII was used as the reference category.

We identified several potential confounding factors related to SII and MetS based on previous studies and clinical relevance [27, 28]. These potential confounders were adjusted for in three distinct regression models to control for their effects: model 1 was unadjusted; model 2 adjusted for demographic confounders including age (continuous), sex, and race/ethnicity (White, Chinese, Black, Hispanic); and model 3 further adjusted for additional confounders such as BMI (continuous), physical activity (continuous), FHD (yes, no), smoking status (never, former, and current), alcohol consumption (never, former, and current), and education level (less than high school/high school, some college, graduate degree/ professional school). For the analysis of each component of MetS, we developed the three aforementioned models along with an additional model (Model 4) that further adjusted for the remaining components of MetS.

To assess the linear trend of the association between the SII and MetS/its components, we included the median of the LnSII quartiles as a continuous variable in the regression models.

The potential nonlinear relationship between the LnSII and MetS and its components was tested using restricted cubic spline (RCS) regression, adjusted for covariates included in model 3. We employed the likelihood ratio test to assess the presence of a nonlinear relationship.

Subgroup analysis of the association between the LnSII and MetS and its components was conducted using stratified factors, including sex, age (< 60 and ≥ 60 years), race, and obesity status (non-obese: BMI < 30 kg/m^2 and obese: BMI ≥ 30 kg/m^2). All analyses were conducted using R version 4.2.1, with two-sided statistical tests considered significant at a threshold of $P < 0.05$.

Results

Participant characteristics

The study sample ($n = 2755$) consisted of 1305 men and 1450 women, with mean (SD) ages of 69.5 (9.2) years for men and 69.4 (9.2) years for women. Table 1 presents the characteristics of participants by MetS status. Approximately 39.2% of the participants were diagnosed with MetS. Among the components of MetS, high BP and high WC exhibited the highest prevalence, affecting 69.7% and 61.6% of participants, respectively. Participants diagnosed with MetS were more likely to be Black or Hispanic, have lower levels of education, engage in less physical activity, and have a lower proportion of current alcohol consumers, compared to those without MetS. Additionally, individuals with MetS exhibited higher BMI, WC, SBP, TG, FBG, NC, LC, and PC, but lower HDL-C than those without MetS.

Association between SII and MetS

Table 2 displays the association between the LnSII and MetS. In the crude model, no significant association was found between the LnSII and MetS. However, in model 2 (adjusted for age, sex, and race), and model 3 (all variables were adjusted), LnSII showed positive correlations with MetS (OR: 1.19; 95% CI: 1.03–1.38, and 1.23; 1.05–1.46, respectively). When LnSII was analyzed as a categorical variable (quartile), after adjusting for all confounders in Model 3, participants in the quartile 3 had a 47% higher prevalence of MetS (1.47; 1.14–1.89), compared to those in the quartile 1 (P trend = 0.041). The RCS curve, based on the Model 3, confirmed a linear relationship between LnSII and MetS (P for nonlinearity = 0.123) (Fig. 2).

Association between SII and components of MetS

Table 3 illustrates the association between the LnSII and the five components of MetS across different models. We found that LnSII was positively associated with high FBG (1.23; 1.05–1.44) and high BP (1.37; 1.15–1.63), but not with the other components. On the categorical scale of LnSII, participants in the highest LnSII quartile (quartile 4) had 32% higher prevalence of elevated FBG compared to those in the lowest quartile (quartile 1) (P trend = 0.021). For high BP, participants in the quartile 4 of SII exhibited a 63% higher prevalence of high BP compared to those in the first quartile (1.63; 1.25–2.14) (P trend < 0.001). Furthermore, we identified 40% higher prevalence of low HDL-C in quartile 2 of the LnSII compared to quartile 1 (1.40; 1.07–1.83) (P trend = 0.454). All the aforementioned associations for each component of MetS were identified after further adjustment for the other components (Model 4). The RCS curve based on the multivariable models (Model 3) did not reveal any non-linear associations between the LnSII and the components of MetS (P for non-linearity > 0.05 for all components).

Subgroup analyses

The results of the subgroup analysis revealed a significant positive correlation between LnSII and MetS (Fig. 3) in specific subgroups, including men, individuals aged ≥ 60 years, Black individuals, and those who were obese. Regarding MetS components (Supplementary Table 1), a positive relationship between LnSII and high BP was found in various subgroups, including both men and women, individuals under 60 and over 60 years, as well as White and Black individuals, and in both obese and non-obese groups ($P < 0.05$). However, the interaction test indicated that these subgroups did not significantly modify the association between LnSII and MetS, high FBG, and elevated BP (all P for interaction > 0.05). Regarding the other components of MetS, obesity status significantly influenced the association between LnSII and elevated WC. Specifically, in obese individuals, LnSII was positively associated with higher prevalence of elevated WC (1.72: 1.00-2.95), whereas a negative association was observed in non-obese individuals (0.80: 0.66–0.97) (P for interaction = 0.009) (Supplementary Table 1).

Discussion

In this study, we identified a significant linear relationship between SII and MetS, as well as its components, including elevated FBG and high BP, even after controlling for relevant confounding variables. These findings were consistent when analyzing SII in categorical scale. In subgroup analysis, obesity status acted as an effect modifier in the relationship between SII and elevated WC, revealing the positive association in obese individuals, whereas a negative association was observed in non-obese individuals.

SII is a well-recognized index for predicting cancer treatment efficacy and prognosis in various malignancies,

Table 1 Demographic, clinical, and lifestyle characteristics of participants stratified by metabolic syndrome status: MESA cohort (2010–2012)

Characteristic	Total population *n* = 2755	Metabolic Syndrome		*P* value
		No *n* = 1673	Yes *n* = 1082	
Age (year) (mean, SD)	69.4 (9.3)	69.2 (9.3)	69.6 (9.1)	0.265
Male (%)	1305 (47.4)	842 (50.3)	463 (42.8)	< 0.001
Race/ethnicity (%)				
White	1189 (43.2)	818 (48.9)	371 (34.3)	< 0.001
Chinese	27 (1.0)	25 (1.5)	2 (0.2)	
Black	749 (27.2)	420 (25.1)	329 (30.4)	
Hispanic	790 (28.7)	410 (24.5)	380 (35.1)	
Education (%)				
Less than high school/ High school	934 (33.9)	504 (30.1)	430 (39.7)	< 0.001
Some college	1337 (48.5)	816 (48.8)	521 (48.2)	
Graduate degree or professional school	484 (17.6)	353 (21.1)	131 (12.1)	
Smoking status (%)				
Never	1118 (40.6)	682 (40.8)	436 (40.3)	0.832
Former	1391 (50.5)	846 (50.6)	545 (50.4)	
Current	246 (8.9)	145 (8.7)	101 (9.3)	
Alcohol consumption (%)				
Never	371 (13.5)	201 (12.0)	170 (15.7)	< 0.001
Former	1145 (41.6)	655 (39.2)	490 (45.3)	
Current	1239 (45.0)	817 (48.8)	422 (39.0)	
Physical activity (MET.min/wk) (mean, SD)	9701.5 (7863.1)	10058.2 (8220.5)	9150.1 (7245.3)	0.002
BMI (kg/m^2) (mean, SD)	29.2 (5.5)	27.3 (4.9)	32.4 (5.2)	< 0.001
WC (cm) (mean, SD)	100.9 (14.1)	95.7 (12.7)	109.1 (12.3)	< 0.001
SBP (mm Hg) (mean, SD)	124.0 (20.5)	121.4 (20.5)	128.1 (20.1)	< 0.001
DBP (mm Hg) (mean, SD)	68.1 (10.1)	68.0 (10.2)	68.3 (10.1)	0.518
HDL-C (mmol/L) (mean, SD)	1.4 (0.4)	1.6 (0.4)	1.2 (0.3)	< 0.001
***TG (mmol/L) (median, IQR)**	1.1 (0.7)	0.9 (0.5)	1.4 (0.9)	< 0.001
FBG (mmol/L) (mean, SD)	5.7 (1.7)	5.2 (1.0)	6.5 (2.2)	< 0.001
Mets components				
High FBG (%)	1123 (40.8)	298 (17.8)	825 (76.2)	< 0.001
Low HDL-C (%)	719 (26.1)	139 (8.3)	580 (53.6)	< 0.001
High TG (%)	489 (17.7)	73 (4.4)	416 (38.4)	< 0.001
High WC (%)	1697 (61.6)	707 (42.3)	990 (91.5)	< 0.001
High BP (%)	1919 (69.7)	941 (56.2)	978 (90.4)	< 0.001
Family history of diabetes (%)	1124 (40.8)	601 (35.9)	523 (48.3)	< 0.001
SII (mean, SD)	513.0 (331.9)	507.1 (322.6)	522.5 (345.8)	0.233
***SII (median, IQR)**	447.5 (315.4)	438.0 (320.8)	457.3 (305.9)	0.167
NC ($\times 10^9$ L) **(mean, SD)**	3.6 (1.4)	3.5 (1.4)	3.9 (1.5)	< 0.001
LC ($\times 10^9$ L) **(mean, SD)**	1.8 (1.1)	1.7 (1.1)	1.9 (1.2)	< 0.001
PC ($\times 10^9$ L) **(mean, SD)**	228.3 (62.4)	224.5 (61.3)	234.2 (63.9)	< 0.001

MET: metabolic equivalent of task; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; FBG: fasting blood glucose; BP: blood pressure; SII: systemic immune-inflammation; LC: lymphocyte count, NC: neutrophil count, PC: platelet count; SD: standard deviation; IQR: interquartile range; MESA: Multi-Ethnic Study of Atherosclerosis

The SII was calculated using the formula: SII = platelet count × neutrophil count / lymphocyte count

*The Mann-Whitney U test was used to compare variable between the two groups

including gastric, cervical, and breast cancers [34]. Previous studies have also demonstrated its predictive value in the context of other metabolism-related diseases, such as CVD [21], obesity [35], hyperlipidemia [23], hypertension [36], and diabetes [25].

Recently, a growing number of studies have focused on the significance of hematological parameters in diagnosing and preventing metabolic conditions such as MetS. For instance, it has been shown that LC [37], PC [38], and NC [39], were significantly higher in individuals with MetS compared to those without MetS, as demonstrated

Table 2 Association between systemic immune-inflammation and metabolic syndrome in whole population; MESA cohort (2010–2012)

	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
LnSII	1.12 (0.98–1.28)	1.19 (1.03–1.38)	1.23 (1.05–1.46)
LnSII quartiles			
Q1	Ref	Ref	Ref
Q2	1.18 (0.95–1.46)	1.21 (0.97–1.52)	1.25 (0.97–1.61)
Q3	1.27 (1.02–1.58)	1.38 (1.10–1.73)	1.47 (1.14–1.89)
Q4	1.15 (0.92–1.43)	1.26 (1.00-1.58)	1.26 (0.97–1.64)
P for trend	0.147	0.025	0.041

Q1-Q4: quartile 1- quartile 4; SII: systemic immune-inflammation; LnSII: natural logarithm-transformed SII; OR: odds ratio; CI: confidence interval; Ref: reference; BMI: body mass index; MESA: Multi-Ethnic Study of Atherosclerosis

The SII was calculated using the formula: SII = platelet count × neutrophil count / lymphocyte count

Model 1: non-adjusted

Model 2: adjusted for age (continuous), sex, and race (White, Chinese, Black, and Hispanic)

Model 3: adjusted for model 1 and BMI (continuous), total physical activity level (continuous), family history of diabetes (yes/no), alcohol consumption (never, former and current), education (less than high school/ high school, some college and graduate degree or professional school), smoking (never, former and current)

in our study. Some studies have also investigated the ratios of various types of blood cells in relation to MetS and have reported inconsistent findings [40]. Results from previous studies generally indicate that hematological parameters, whether assessed individually or in combination as ratios, can serve as useful predictors for MetS. However, the SII provides a more comprehensive assessment of the inflammatory state [18] by incorporating the balance between pro-inflammatory (neutrophils) [41] and anti-inflammatory (lymphocytes) responses [42], along with the role of platelets in inflammation and thrombosis [43].

Conditions such as MetS, characterized by chronic inflammation [9] and insulin resistance [44], may benefit from the inclusion of SII in risk assessment and management strategies. Two recent studies have underscored the predictive role of the SII as an inflammatory marker in relation to MetS in the general adult population. Zhao et al. [28], analyzed data from the NHANES (2011–2016) and found a non-linear association between elevated SII scores and MetS. In contrast, a study by Zeng et al. [27], using NHANES data (2015–2018), identified a linear association between SII scores and MetS. Notably, both studies were conducted in the U.S. population, focused on adults aged ≥ 20 years, and utilized NHANES data [27, 28], yet they reported differing results. The inconsistent findings regarding the shape and nature of the association between the SII and MetS and its components from two previous studies underscore the complexity of this association and highlight the need for further research to clarify these relationships.

In this study, we also observed a linear association between the LnSII and MetS. The significant positive relation between the SII and MetS, observed in our study as well as previous studies, suggests that SII plays a key role in the diagnosis of MetS across different age groups. Importantly, our findings extended prior research by demonstrating that this significant relationship may also apply to older populations, who are at higher risk for cardiometabolic disorders.

Regarding the components of MetS, our study further identified a significant linear association between the SII and elevated FBG, both on continuous and categorical scale of SII, even after adjusting for other components. This finding contrasts with two existing studies [27, 28] where the association between SII and elevated FBG disappeared upon adjusting for multiple confounders. This discrepancy may be attributed to differences in the characteristics of the study populations, such as age, prevalence of hyperglycemia, and baseline SII levels. In our study, the mean age was 69 years compared to 47 years in the two previous studies [27, 28]. Older adults are more likely to have higher levels of inflammation and a greater prevalence of MetS components. For instance, the prevalence of MetS was 36% and 27% in two previous studies [27, 28], compared to 39.2% in our study. Additionally, the mean SII was 448.8 and 242.5 in two previous studies [27, 28], compared to 513.0 in our study. Moreover, the prevalence of elevated FBG in our study was approximately 41%, compared to 26% and 30% in two previous studies [27, 28]. To our knowledge, no other studies have investigated the association between SII and hyperglycemia. However, a study utilizing data from the NHANES (2017–2020), which analyzed 7877 participants over the age of 20, indicated a positive association between SII and diabetes (1.04; 1.02–1.06) after adjusting for multiple confounders [25].

The association between inflammation, as indicated by elevated SII, and high FBG involves a complex interplay of multiple biological mechanisms. Chronic inflammation triggers the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) from immune cells, including macrophages and adipocytes. These cytokines disrupt insulin signaling pathways by inducing serine phosphorylation of insulin receptor substrates (IRS), leading to insulin resistance [45]. Insulin resistance impairs glucose uptake in peripheral tissues, such as skeletal muscle and adipose tissue, resulting in elevated FBG. Additionally, inflammation promotes hepatic insulin resistance, causing increased gluconeogenesis and reduced glycogen synthesis, further contributing to hyperglycemia [49]. Inflammatory mediators also activate stress-sensitive signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun

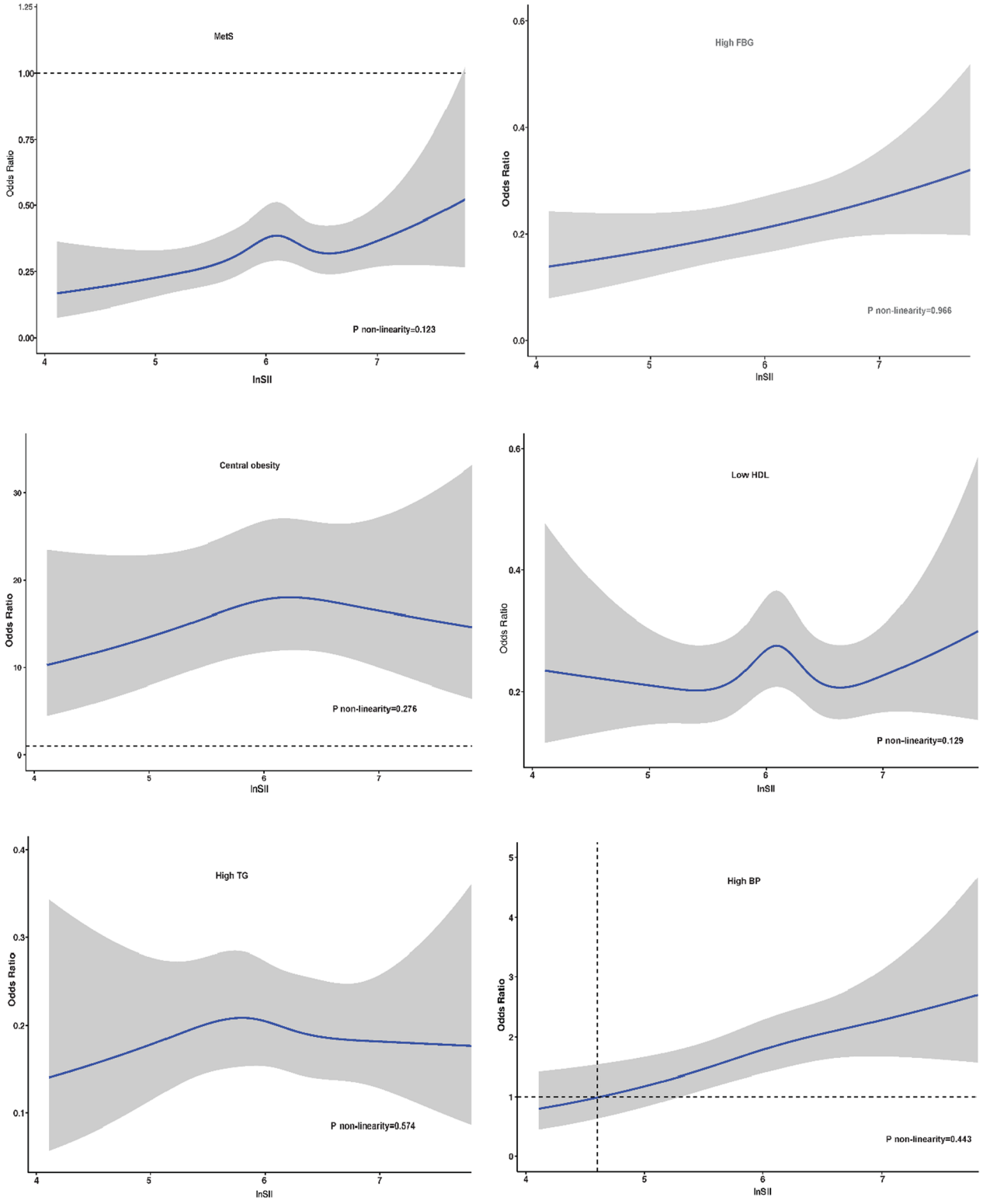

Fig. 2 Restricted cubic spline curve depicting the association (with 95% CI) between LnSII and MetS and its components; MESA cohort (2010–2012). The solid line represents the OR, and the gray shaded area indicates the 95% CI. The horizontal dashed line represents the null value (OR = 1), and the vertical dashed line marks the threshold of LnSII at which the OR changes direction. OR: odds ratio; 95% CI: 95% confidence interval; SII: systemic immune-inflammation; LnSII: natural logarithm-transformed SII; MetS: metabolic syndrome; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; BP: blood pressure; FBG: fasting blood glucose; TG: triglycerides; MESA: Multi-Ethnic Study of Atherosclerosis. The models were adjusted for age, sex, race, BMI, total physical activity level, family history of diabetes, alcohol consumption, education and smoking

Table 3 Association between systemic immune-inflammation and components of metabolic syndrome in whole population: MESA cohort (2010–2012)

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
High FBG				
LnSII	1.10 (0.96–1.26)	1.23 (1.06–1.42)	1.25 (1.07–1.46)	1.23 (1.05–1.44)
LnSII quartiles				
Q1	Ref	Ref	Ref	Ref
Q2	0.97 (0.78–1.20)	1.06 (0.85–1.33)	1.08 (0.85–1.37)	1.02 (0.80–1.29)
Q3	1.01 (0.81–1.24)	1.14 (0.91–1.43)	1.15 (0.90–1.46)	1.10 (0.86–1.40)
Q4	1.15 (0.92–1.42)	1.34 (1.06–1.68)	1.35 (1.06–1.72)	1.32 (1.03–1.69)
P for trend	0.186	0.009	0.013	0.021
Low HDL-C				
LnSII	1.05 (0.90–1.22)	1.05 (0.90–1.22)	1.03 (0.87–1.22)	1.03 (0.87–1.23)
LnSII quartiles				
Q1	Ref	Ref	Ref	Ref
Q2	1.39 (1.09–1.77)	1.35 (1.05–1.73)	1.40 (1.09–1.81)	1.40 (1.07–1.83)
Q3	1.23 (0.96–1.57)	1.21 (0.94–1.55)	1.20 (0.93–1.56)	1.22 (0.92–1.60)
Q4	1.17 (0.91–1.50)	1.18 (0.91–1.53)	1.15 (0.88–1.50)	1.18 (0.89–1.57)
P for trend	0.396	0.382	0.585	0.454
High TG				
LnSII	1.08 (0.91–1.29)	0.99 (0.82–1.20)	0.97 (0.80–1.17)	0.95 (0.78–1.17)
LnSII quartiles				
Q1	Ref	Ref	Ref	Ref
Q2	1.28 (0.97–1.69)	1.13 (0.85–1.51)	1.12 (0.84–1.50)	0.98 (0.71–1.33)
Q3	1.17 (0.88–1.56)	1.02 (0.76–1.36)	0.99 (0.74–1.34)	0.93 (0.68–1.27)
Q4	1.10 (0.82–1.44)	0.96 (0.71–1.29)	0.91 (0.67–1.23)	0.85 (0.61–1.17)
P for trend	0.696	0.633	0.404	0.327
High WC				
LnSII	2.58 (1.12–5.99)	0.91 (0.78–1.06)	1.11 (0.87–1.41)	1.07 (0.84–1.36)
LnSII quartiles				
Q1	Ref	Ref	Ref	Ref
Q2	1.60 (1.37–1.86)	1.09 (0.86–1.38)	1.22 (0.85–1.75)	1.21 (0.84–1.74)
Q3	1.13 (0.91–1.41)	1.03 (0.82–1.31)	1.29 (0.90–1.86)	1.26 (0.87–1.81)
Q4	0.87 (0.70–1.08)	0.87 (0.69–1.10)	1.13 (0.78–1.65)	1.08 (0.74–1.59)
P for trend	0.155	0.219	0.445	0.625
High BP				
LnSII	1.20 (1.04–1.38)	1.36 (1.16–1.61)	1.39 (1.17–1.65)	1.37 (1.15–1.63)
LnSII quartiles				
Q1	Ref	Ref	Ref	Ref
Q2	1.15 (0.91–1.44)	1.39 (1.09–1.79)	1.43 (1.10–1.85)	1.41 (1.08–1.83)
Q3	1.18 (0.94–1.48)	1.53 (1.19–1.97)	1.56 (1.20–2.02)	1.55 (1.19–2.02)
Q4	1.37 (1.08–1.72)	1.61 (1.25–2.09)	1.66 (1.27–2.17)	1.63 (1.25–2.14)
P for trend	0.008	< 0.001	< 0.001	< 0.001

Q1-Q4: quartile 1- quartile 4; SII: systemic immune-inflammation; LnSII: natural logarithm-transformed SII;

OR: odds ratio; CI: confidence interval; Ref: reference; BMI: body mass index; WC: waist circumference; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; FBG: fasting blood glucose; BP: blood pressure; MetS: metabolic syndrome; MESA: Multi-Ethnic Study of Atherosclerosis

The SII was calculated using the formula: SII = platelet count × neutrophil count / lymphocyte count

Model 1 non-adjusted.

Model 2 adjusted for age (continuous), sex, and race (White, Chinese, Black and Hispanic).

Model 3 adjusted for model 2 and BMI, total physical activity level, family history of diabetes, alcohol consumption, education and smoking.

Model 4 adjusted for model 3 and other components of MetS.

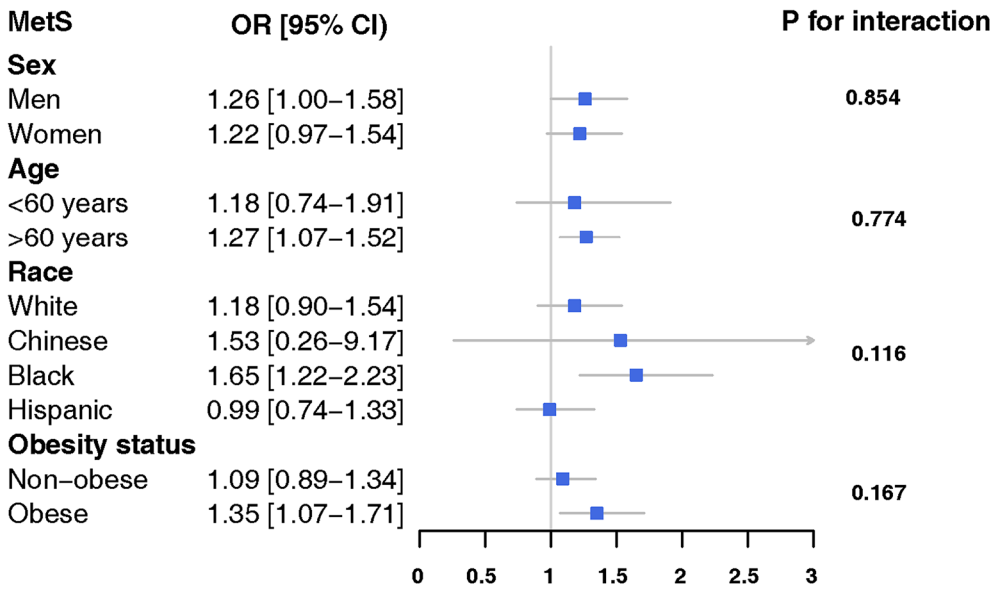

Fig. 3 The association between systemic immune-inflammation and metabolic syndrome in subgroups based on sex, age, race, and obesity status; MESA cohort (2010–2012). The association between LnSII and MetS was estimated using logistic regression model fitted separately for each subgroup, adjusting for age, sex, race, BMI, total physical activity level, family history of diabetes, alcohol consumption, education level, and smoking status. MESA: Multi-Ethnic Study of Atherosclerosis; OR: odds ratio; CI: confidence interval; SII: systemic immune-inflammation; LnSII: natural logarithm-transformed SII; MetS: metabolic syndrome; BMI: body mass index; non-obese: BMI < 30 kg/m^2; obese: BMI ≥ 30 kg/m^2

N-terminal kinase (JNK), which exacerbate insulin resistance and impair pancreatic β-cell function [50].

We further identified a positive association between the SII and high BP, which aligns with findings from two previous studies in this field [27, 28]. However, the shape of this association was linear in both Zhao et al. [28] and our study, while it was found to be non-linear J-shaped in Zeng et al. [27] study. Research on the association between the SII and hypertension is increasingly common. A recent cross-sectional analysis of 13,742 adults from the NHANES (2017–2020) study noted a U-shaped relationship between SII and hypertension risk in American adults, with a threshold point at SII = 501.2 [36]. Additionally, another study utilizing a larger population from NHANES (1999–2018), which included 44,070 participants aged ≥ 20 years, also found a U-shaped association between the SII and hypertension, with an inflection point at SII = 363.1 [51]. The linear association between the SII and high BP in our study may be attributed to several age-related factors such as chronic low-grade inflammation, often referred to as "inflammaging" which contributes to increased cardiovascular risk and reduced physiological resilience in older adults [11, 12]. As individuals age, they tend to have higher baseline levels of SII due to cumulative exposure to various risk factors [12], leading to a more pronounced and continuous association between inflammation and BP. Further research is necessary to explore these dynamics comprehensively and validate these findings across diverse populations. The mechanisms linking the SII to hypertension involve several interconnected pathways influenced by inflammation. Research has shown that inflammation can lead to endothelial damage and dysfunction, resulting in increased vascular resistance and elevated BP [52]. Additionally, inflammation increases the production of ROS, which further impair endothelial function, promote vascular remodeling, and activate signaling pathways such as PKC and NF-κB. These pathways contribute to vascular inflammation and stiffness [45, 53]. Moreover, chronic inflammation contributes to insulin resistance, which is associated with increased sympathetic nervous system activity and sodium retention, both of which elevate BP [54]. A study by Araos et al. [55] has also demonstrated that neutrophils may play a role in the infiltration of immune cells into tissues, releasing chemokines and cytokines that promote pro-inflammatory states, contributing to the onset of arterial hypertension. Another mechanism is that inflammation can activate angiotensin II, a key component of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II promotes vasoconstriction and sodium retention, further exacerbating hypertension. Additionally, angiotensin II enhances the expression of adhesion molecules and chemokines, facilitating the recruitment of inflammatory cells to tissues and perpetuating a cycle of inflammation that exacerbates hypertensive conditions [56].

In summary, the current evidence demonstrates bidirectional relationships between inflammation and Mets components. For example, while inflammation may drive metabolic dysfunction, metabolic abnormalities per se

(e.g., hyperglycemia, hypertension) can also exacerbate inflammation, creating a vicious cycle [55, 56].

We did not find a significant association between the LnSII and three other components of Mets: high TG, elevated WC, and low HDL-C in total population. However, in categorical scale, we identified 40% higher prevalence of low HDL-C in quartile 2 of the LnSII compared to quartile 1 (Model 4). We did not observe a significant association between the SII and elevated WC or TG. However, two previous studies reported a significant positive correlation between SII and high WC [28] as well as high TG [27]. The discrepancy between our findings and those of the mentioned studies could be attributed to the differences in adjustment methods. In our analysis, we further adjusted for the other components of MetS to examine the independent relationship between SII and specific MetS components, free from the influence of the other remaining components. This adjustment is crucial, as MetS components are often interrelated. In contrast, the previous studies [27, 28] did not account for these interrelationships. Without such adjustments, the association observed between a specific MetS component and SII may be confounded by the presence of other interrelated components. For instance, insulin resistance can contribute to both hypertension and dyslipidemia [57]. When assessing the relationship between SII and elevated TG, this association may be influenced by the presence of high BP, or insulin resistance. Failure to adjust for these components could obscure the true association between SII and elevated TG.

The independence associations of the SII with MetS components, particularly high FBG and high BP, free from other components of MetS in our study, highlight the potential of SII as a comprehensive marker for metabolic disturbances and underscores its relevance in understanding glucose and BP regulation within the context of MetS. This finding suggests that monitoring SII levels may help identify individuals at risk for hyperglycemia and hypertension, even before the full manifestation of MetS.

Subgroup analysis in this study revealed a positive relationship between SII and high WC in obese individuals, while a negative association was observed in non-obese participants. The contrasting associations between SII and elevated WC in obese versus non-obese participants could be attributed to differences in body composition, as obese individuals typically have a higher proportion of visceral fat associated with increased inflammation [58], leading to a stronger positive correlation between SII and elevated WC. Additionally, non-obese individuals may exhibit a healthier metabolic profile, where inflammation does not translate to increased abdominal fat. Further investigation using longitudinal studies is necessary to elucidate the underlying mechanisms.

The strengths of our study lie in its utilization of the MESA data, which provides a large, diverse, and well-characterized cohort with detailed information on cardiovascular and metabolic risk factors. Additionally, our study addresses a critical gap in the literature by focusing on middle-aged and older adults, a population at heightened risk for cardiometabolic disorders. This focus contributes valuable insights to the field and enhances the relevance of our findings for public health strategies aimed at improving metabolic health in this vulnerable demographic. Furthermore, in our investigation of the association between SII and each MetS component, we made additional adjustments for other components that were not considered in previous studies [27, 28]. Finally, we achieved a statistical power of over 99% to detect a significant OR of at least 1.20 for MetS and its components, including elevated FPG and high BP, per one-unit increase in lnSII. This robust statistical power enhances the reliability of our findings and underscores the validity of the observed associations.

However, it is important to acknowledge the limitations of our study. First, the cross-sectional design restricts our ability to draw causal inferences regarding the examined associations. Second, there may be unmeasured confounding factors, such as dietary intake or lifestyle variables, that could influence the results. Third, our study was conducted within a U.S. population with participants aged over 45 years. This focus on a specific demographic may limit the applicability of our findings to younger populations.

Conclusion

This study indicated a significant positive association between the SII and the presence of MetS and its components, including elevated FBG and high BP. Our results suggest that SII may serve as a simple and cost-effective method for identifying individuals with MetS in middle age and older adults. This is particularly relevant for individuals at risk of diabetes and hypertension, even before the full manifestation of MetS. The findings from our study highlight the need for further investigation into the mechanisms underlying the observed associations.

Abbreviations

MetS	Metabolic syndrome
CVD	Cardiovascular disease
CBC	Complete blood count
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
SII	Systemic immunity-inflammation index
NHANES	National Health and Nutrition Examination Survey
MESA	Multi-Ethnic Study of Atherosclerosis
WC	Waist circumference
BMI	Body mass index
BP	Blood pressure
FBG	Fasting blood glucose
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol

MET	Metabolic equivalent of task
FHD	Family history of diabetes
NCEP	National Cholesterol Education Program
ATP III	Adult Treatment Panel III
PC	Platelet count
NC	Neutrophil count
LC	Lymphocyte count
SD	Standard deviation
Ln	Natural logarithm
ANOVA	Analysis of variance
RCS	Restricted cubic spline
Systolic BP	Systolic blood pressure
DBP	Diastolic blood pressure
Q	Quartile
OR	Odds ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
F.H. and A.R. contributed to conceptualizing the study and design; A.R. analyzed and interpreted the data; A.R. wrote the initial manuscript. M.T. and A.A. contributed to the interpretation of results and discussion. All authors reviewed the manuscript and provided final approval of the manuscript.

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

Declarations

Ethics approval and consent to participate
The institutional review board of each study center approved the study, and written informed consent was obtained from all study participants at each examination. Approval for the current study was obtained from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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