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Systemic immunity-inflammation index is associated with body fat distribution among U.S. adults: evidence from national health and nutrition examination survey 2011–2018

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Abstract

Objective The systemic immunity-inflammation index (SII) is a newly developed biomarker that provides an integrated measure of inflammation in the body. We aim to evaluate the relationship between SII and body fat distribution.

Methods Adults from the National Health and Nutrition Examination Survey (NHANES) 2011–2018 were included. The SII was computed using lymphocyte (LC), neutrophil (NC), and platelet (PC) counts as its components. Body fat distribution was assessed by (total, android, gynoid) percentage fat, total abdominal fat area, subcutaneous adipose tissue area, visceral adipose tissue area, and the ratio of visceral to subcutaneous adipose tissue area (V/S ratio). Multivariable weighted linear regression and subgroup analysis were use to examine the relationships between fat distribution and SII. Restricted cubic splines (RCS) and threshold effect analysis were used to examine analyze nonlinear associations.

Results After exclusions, a total of 11,192 adults with a weighted mean age of 38.46 ± 0.26 years were studied. In multivariable weighted linear regression, each level increase in log_2SII was associated with increased of 0.23 SDs total percentage fat (95% CI = 0.03, 0.43) and 0.26 SDs android percentage fat (95% CI = 0.06, 0.47). Besides, the subgroup analysis showed that the positive association between SII and android percentage fat was mainly among obese individuals (BMI > 30 kg/m^2) and non-obese individuals without DM or hypertension. Meanwhile, the relationship between SII and the V/S ratio was found to be significant in the female subgroup, the obese subgroup, individuals with non-alcoholic fatty liver disease (NAFLD), and those without diabetes mellitus. Finally, SII exhibited an inverted U-shaped relationship with total percentage fat, android percent fat and total abdominal fat. Accordingly, threshold effect analysis indicated a positive association between lower SII levels and total percentage fat, android percentage fat and total abdominal fat area.

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Conclusions In the nationwide study, it was observed that the SII exhibited a significant correlation with higher levels of body fat, specifically android fat. This association was particularly noticeable within specific subgroups of the population.

Keywords Systemic immunity-inflammation index, Body fat distribution, Population-based study, NHANES

Introduction

Obesity has emerged as a significant health concern, impacting the overall well-being of individuals worldwide [1, 2]. According to data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of overweight among children and adolescents in the United States was found to be 17.1%, while the rate of obesity among adults was 32.2% [3]. Multiple crucial markers of inflammation have consistently shown associated to obesity, which implied that a persistent, mild inflammatory reaction could be a potentially adjustable risk element [4].

A thorough meta-analysis of 51 independent cross-sectional studies provides strong evidence supporting a significant association between body composition and C-reactive protein (CRP) levels, which are widely recognized as an established marker for systemic inflammation [5]. In addition to C-reactive protein, obesity has been associated with various other inflammatory markers, such as erythrocyte sedimentation rate [6], plasminogen-activator inhibitor [7], and pivotal inflammatory cytokines [8, 9], all of which reinforce the plausible interaction between obesity and inflammation. While these inflammation markers can indeed represent the inflammation status within the body, their disadvantages lied in being individual indicators, potentially unable to provide a comprehensive reflection of the body's inflammatory status.

The systemic immunity-inflammation index (SII) is a novel and reliable biomarker that provides insight into the overall immune and inflammatory status of the human body. It serves as an indicator of systemic inflammation and immune response [10–13], calculating by multiplying the platelet count with the neutrophil count and then dividing it by the lymphocyte count [11, 14]. Previous research has indicated that the SII holds promise in predicting and assessing the prognosis of different types of solid tumors [15–18] and cardiovascular diseases [19–22]. Recently, Xie et al. reported an association between elevated SII levels and the presence of hepatic steatosis [23], which revealed the progression of SII in obesity and metabolic related diseases. A retrospective study indicated body mass index (BMI) is positively correlated with neutrophil, lymphocyte, leukocyte (WBC) counts and SII [24]. However, similar BMI have different fat distributions [25], and different fat compartments may be associated with differential metabolic risk [26]. Moreover, in the 1980s, researchers from Sweden and the United States conducted studies that showed the waist-to-hip circumference ratio to be a more robust indicator of metabolic complications and cardiovascular disease outcomes compared to BMI, highlighting its significance as a straightforward measure of regional body fat distribution [27–31]. Nevertheless, the connection between SII and the distribution of body fat remains unclear and demands additional scrutiny. Drawing upon the previously outlined theoretical framework, this research sought to examine the correlation between SII and body fat distribution in adults aged ≥ 18 years, utilizing data from the NHANES. Concurrently, our hypothesis posited a positive association between SII and body fat distribution.

Subjects and methods

Study population

NHANES, a program aimed at evaluating the health and nutrition of individuals in the United States, is conducted under the auspices of NCHS, which operates within the Centers for Disease Control and Prevention (CDC). NHANES, which is responsible for generating vital health statistics for the country, obtained approval from the US National Center for Health Statistics Research Ethics Review Board. Prior to participating, all individuals provided written informed consent. Detailed information from NHANES is accessible online at www.cdc.gov/nchs/nhanes/index.htm.

We merged four cycles of NHANES data from 2011 to 2018 for this research (N = 39,156). The exclusion criteria were as follows: (i) adults aged < 18 years, (ii) participants lack of complete SII and body fat distribution data, (iii) participants who were pregnant. In the end, we enrolled a total of 11,192 participants. Figure 1 illustrates the complete process of integrating the data.

Systemic immune-inflammation index

The SII was derived from the complete blood count (CBC) test results, with the laboratory procedure detailed on the NHANES website. Additionally, plate count (PC), neutrophil count (NC), and lymphocyte count (LC) were quantified at 1000 cells/mL, and the SII, used as an exposure variable, was computed as PC * (NC/LC), following established research protocols [10, 11, 23,

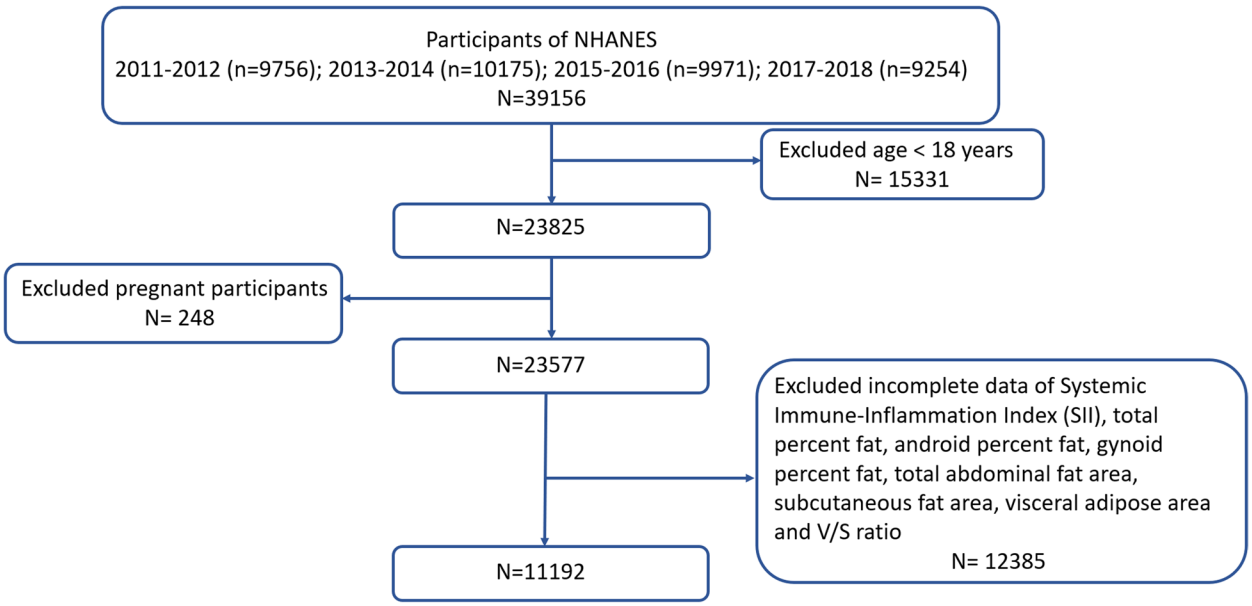

Fig. 1 Study flowchart National Health and Nutrition Examination Survey (NHANES), 2011- 2018

32]. Additionally, when conducting regression analysis, we applied a log2 transformation to SII, taking into consideration that these inflammatory markers exhibited a right-skewed distribution among the adults included in the final analysis (Fig. 2).

Body fat distribution

We focused on primary outcomes such as the absolute percentage of fat (total, android, gynoid), as well as secondary outcomes including the total area of abdominal fat, subcutaneous adipose tissue area, and visceral adipose tissue area. To obtain the measurements, we employed a skilled team of technicians who used the dual-energy X-ray absorptiometry (DXA) QDR-4500 Hologic Scanner (Bedford, MA). Total body fat percentage represents the proportion of fat mass relative to total body mass. The android area comprises the lower part of the trunk above the pelvic line and 20% of the length between this line and the neck cut line. The gynoid area is defined as twice the height of the android region below

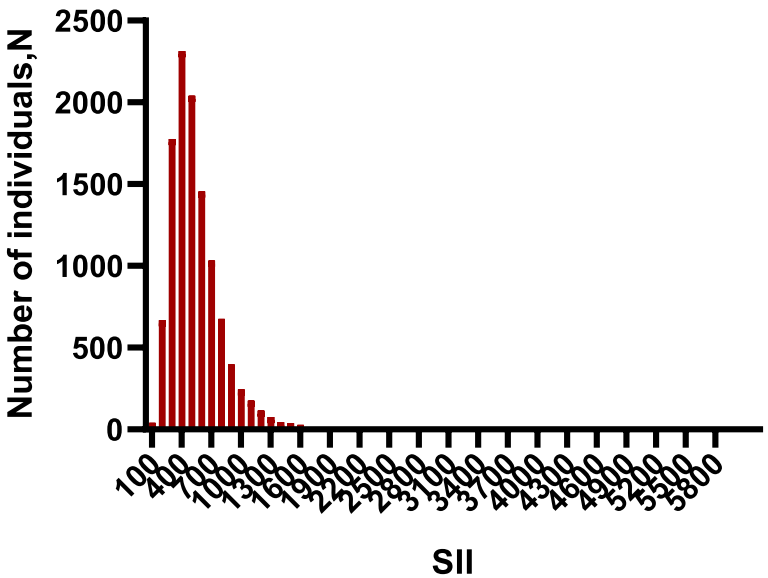

Fig. 2 Distribution of SII among individuals included in the final analysis

the pelvic line. Total abdominal fat area quantifies the total area of fat within the abdominal region. Subcutaneous adipose tissue area refers to the area of fat located just beneath the skin across the abdominal region. Visceral adipose tissue area represents the area of fat located within the abdominal cavity, surrounding internal organs. The V/S ratio is derived by dividing the area of visceral adipose tissue by the area of subcutaneous adipose tissue. This ratio provides insight into the relative distribution of fat between these two compartments.

This scanner allowed for a comprehensive assessment of the entire body. We utilized the Hologic APEX software to estimate the characteristics of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). This software enabled us to measure various parameters, including area, mass, and volume for both SAT and VAT. For SAT measurements, we focused on the area near the space between the fifth and fourth lumbar vertebrae, which is situated outside the abdominal cavity. On the other hand, VAT measurements were taken at the same location but within the abdominal cavity. It is worth noting that total abdominal fat (TAF) encompasses all fat accumulation in the abdominal region, comprising both SAT and VAT.

Covariates

The sociodemographic covariates in our study included age in years, gender, educational levels (categorized as under high school, high school or equivalent, and above high school), race/ethnicity (classified as Mexican American, non-Hispanic black, non-Hispanic white, other Hispanic, and other races). Additionally, we considered the Poverty-Income Ratio (PIR) which is calculated as the ratio of family income to poverty level. Specifically, we categorized PIR into three groups: <1.30, 1.30–3.49, and ≥ 3.50 based on eligibility criteria for the Supplemental Nutrition Assistance Program. This allowed us to examine the potential impact of these sociodemographic factors on our outcomes of interest.

In our study, we considered several health-related covariates, which included BMI measured in kg/m2, waist circumference (WC) measured in cm, MQI (Muscle Quality Index), smoking status, drinking status, and physical activity level. BMI is calculated by dividing weight in kilograms by the square of height in meters. MQI is a specific measurement that evaluates muscle quality by considering the relationship between muscle strength and muscle mass. To calculate the MQI, the following formula is often utilized: MQI = Muscle Strength/Muscle Mass. Muscle mass is typically assessed through a combination of bioelectrical impedance analysis BIA and dual-energy X-ray absorptiometry DXA to estimate skeletal muscle mass. Muscle strength can be measured using various tests, such as grip strength or leg press strength, depending on the population being studied and the specific protocols used in the NHANES assessments. To classify the smoking status of individuals, we employed the following categorization method. Individuals who had not smoked 100 cigarettes in their lifetimes were labeled as never smokers. Those who had smoked 100 cigarettes in their lifetimes were then categorized as former smokers if they answered "No" to the question "Do you currently smoke?" Alternatively, if they responded "Yes," they were classified as current smokers [33]. The drinking status in our study was categorized into three distinct groups. Individuals who had consumed less than 12 drinks in any one year were classified as "never" drinkers. Those who had consumed at least 12 drinks in any one year but were currently not drinking were categorized as "former" drinkers. Lastly, individuals who had consumed at least 12 drinks in any one year and were currently drinking were classified as "current" drinkers [34]. In terms of current drinking status, we established specific definitions for current heavy alcohol users and current moderate alcohol users. Current heavy alcohol users were identified as individuals who consumed at least 3 drinks per day for females, 4 drinks per day for males, or engaged in binge drinking on 5 or more days per month. On the other hand, current moderate alcohol use was defined as consuming at least 2 drinks per day for females, 3 drinks per day for males, or engaging in binge drinking on at least 2 days per month [35]. In our study, physical activity was measured in terms of metabolic equivalent (MET) minutes of moderate to vigorous physical activity per week. Respondents were categorized into four groups based on their levels of physical activity: No moderate to vigorous physical activity (NMVPA) group: Individuals who reported engaging in 0 MET-minutes/week of moderate to vigorous physical activity; Low moderate to vigorous physical activity (LMVPA) group: Individuals who reported engaging in 1–599 MET-minutes/week of moderate to vigorous physical activity; Moderate to moderately vigorous physical activity (MMVPA) group: Individuals who reported engaging in 600–1199 MET-minutes/week of moderate to vigorous physical activity; High moderate to moderately vigorous physical activity (HMMVPA) group: Individuals who reported engaging in 1200 or more MET-minutes/week of moderate to vigorous physical activity. We collected venous blood samples to measure several biomarkers, which included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. We also measured creatinine levels (Cr) in milligrams per deciliter (mg/dL) and uric acid levels in micromoles per liter (umol/L). To assess insulin resistance, we utilized the Homeostasis Model Assessment of Insulin

Resistance (HOMA-IR). HOMA-IR is calculated based on fasting blood glucose and insulin levels. The formula used to calculate HOMA-IR is as follows: [Insulin (μU/mL) × Glucose (mmol/L)]/22.5 [36]. A higher HOMA-IR value indicates greater insulin resistance, with insulin resistance defined as HOMA-IR > 2.6 [37].

In the medical history section of our study, we assessed the presence of several conditions, including Diabetes Mellitus (DM), Hyperlipidemia, Hypertension, and Nonalcoholic fatty liver disease (NAFLD). DM was diagnosed based on specific criteria. These criteria included having a glycohemoglobin level of ≥ 6.5%, the use of diabetes medication or insulin, or self-reported confirmation of a diabetes diagnosis [38]. In our analysis, we focused on individuals who had elevated lipid levels, specifically triglycerides (TG) ≥ 150 mg/dL, total cholesterol (TC) ≥ 200 mg/dL, LDL-C ≥ 130 mg/dL, and HDL-C < 40 mg/dL for males and < 50 mg/dL for females. Additionally, we included individuals who were taking anti-hyperlipidemic medication, as this can be indicative of a diagnosis of hyperlipidemia [39]. Hypertension was defined based on several criteria. These criteria included having a mean systolic blood pressure of ≥ 140 mmHg, a mean diastolic blood pressure of ≥ 90 mmHg, self-reported hypertension diagnosis, or the use of antihypertensive medication [40]. We defined NAFLD based on the controlled attenuation parameter (CAP) scores. Specifically, individuals with CAP scores of > = 248 dB/m were classified as having NAFLD, given the absence of excessive alcohol use and viral hepatitis [41].

Statistical analysis

To address missing covariate data, we employed a multiple imputation approach using the "mice" package. Specifically, we created five imputed datasets using chained equations. By conducting multiple imputations, we aimed to reduce the impact of missing data on our analysis. Once the covariates were imputed, we performed a sensitivity analysis to assess the robustness of the results. This involved analyzing the outcomes using each of the five imputed datasets to evaluate potential variations in the findings (Supplementary Table 1–2). To minimize duplicate information, several steps were taken in our study. First, when presenting the baseline characteristics, we used weighted means and standard errors for continuous variables and weighted proportions for categorical variables. This approach accounts for any sampling weights and provides a more accurate representation of the population. Second, we employed multivariable weighted linear regression models to assess the association between the SII and body fat distribution. This helps us determine the impact of the SII on body fat distribution while controlling for other relevant variables. Third, we conducted subgroup analyses by stratifying the data based on various factors such as age, sex, BMI, insulin resistance, DM, hypertension, hyperlipidemia, and NAFLD. This allows us to examine how the association between the SII and body fat distribution varies across different subgroups. Lastly, to explore any potential non-linear relationship between the SII and body fat distribution, we used restricted cubic splines. This flexible modeling technique helps capture complex relationships that may not be linear. Additionally, threshold effect analysis was performed to identify any cut-off points or thresholds that may exist. By implementing these steps, we aimed to provide a comprehensive analysis while avoiding redundancies and capturing important nuances in the relationship between the SII and body fat distribution.

$P < 0.05$ was considered statistically significant. All analyses were performed using the R software (version 4.3.1; https://www.R-project.org).

Results

Baseline characteristics of participants

The baseline characteristics of the participants were presented by SII quartiles as follows: Q1: < 312.99; Q2: 312.99–437.18; Q3: 437.18–608.00; Q4: > 608.00. All adults included in the final analysis had a weighted mean age of 38.46 ± 0.26 years. The mean percent fat (total, android, gynoid), total abdominal area, subcutaneous adipose tissue area, visceral adipose tissue area and V/S ratio were 32.70 ± 0.15%, 34.71 ± 0.18%, 35.30 ± 0.13%, 432.44 ± 4.14 cm^2, 331.31 ± 3.26 cm^2, 101.13 ± 1.14 cm^2, 0.34 ± 0.00, respectively. There are significant differences in age, sex, race, education level, smoke status, alcohol status, physical activity level, BMI, WC, MQI, DM or not, hypertension or not, hyperlipidemia or not, ALT, creatinine, total percentage fat, android percentage fat, gynoid percentage fat, total abdominal fat area, subcutaneous fat area, visceral adipose tissue area, V/S ratio across SII quartiles (Table 1). Moreover, there were significant differences in SII between adults among quartiles of all body fat distributions. The results are listed in Fig. 3.

Weighted multivariate linear regression between SII and body fat distribution

The associations of SII and body fat distribution are listed in Table 2. When age, sex, race, education levels, PIR, PA, smoke status, alcohol status, BMI, WC, MQI, ALT, AST, creatinine, uric acid, hypertension or not, diabetes or not, hyperlipidemia or not, NAFLD or not, insulin resistance or not were adjusted (Model 3), log2-SII was positively associated with total percentage fat (β, 95%CI: 0.23, 0.03–0.43), android percentage fat (β, 95%CI: 0.26, 0.06–0.47), total abdominal fat area (β, 95%CI: 4.38, 1.65–7.11), subcutaneous fat area (β, 95%CI: 2.47, 0.07–4.86), visceral

Table 1 Baseline characteristics of adults included in the final analysis according SII quartiles

Total	Total	Q1	Q2	Q3	Q4	*P* value
Age [year]	38.46(0.26)	37.82(0.41)	37.83(0.39)	38.86(0.34)	39.25(0.44)	**0.002**
Sex						**< 0.0001**
Male	5603(50.06)	1652(59.56)	1452(53.62)	1365(49.42)	1134(41.44)	
Female	5589(49.94)	1146(40.44)	1346(46.38)	1437(50.58)	1660(58.56)	
Race						**< 0.0001**
Mexican American	1735(15.5)	372(10.09)	454(11.12)	443(10.35)	466(11.17)	
Non-Hispanic Black	2308(20.62)	926(19.40)	537(10.11)	422(7.61)	423(7.79)	
Non-Hispanic White	3830(34.22)	693(52.77)	963(61.30)	1064(64.48)	1110(64.89)	
Other Hispanic	1185(10.59)	237(6.70)	296(7.58)	336(8.00)	316(7.71)	
Other Race	2134(19.07)	570(11.04)	548(9.89)	537(9.56)	479(8.45)	
Education level						**0.004**
Under high school	657(5.87)	164(4.16)	193(4.24)	164(3.83)	136(3.13)	
High school or equivalent	4096(36.6)	1043(33.17)	970(29.08)	1009(32.69)	1074(34.94)	
Above high school	6437(57.52)	1590(62.67)	1635(66.68)	1629(63.48)	1583(61.93)	
PIR						0.27
< 1.30	3815(34.11)	888(22.86)	980(25.35)	938(23.29)	1009(26.88)	
1.30–3.49	3992(35.69)	1014(35.33)	1019(34.26)	999(34.47)	960(33.39)	
> = 3.50	3377(30.19)	892(41.81)	798(40.39)	865(42.24)	822(39.74)	
Smoke status						**0.01**
Never smoker	6850(62.55)	1740(61.19)	1756(61.48)	1736(60.24)	1618(57.21)	
Former smoker	1747(15.95)	416(18.80)	462(20.28)	415(17.96)	454(18.92)	
Now smoker	2354(21.5)	563(20.01)	517(18.24)	606(21.80)	668(23.88)	
Alcohol status						**0.03**
Never alcohol user	1592(15.53)	433(12.01)	396(10.68)	375(10.12)	388(11.18)	
Former alcohol user	896(8.74)	208(7.34)	215(6.93)	229(8.86)	244(9.25)	
Mild alcohol user	3263(31.83)	875(35.09)	836(35.35)	793(32.09)	759(31.27)	
Moderate alcohol user	1855(18.09)	418(18.67)	469(21.02)	489(21.66)	479(19.39)	
Heavy alcohol user	2646(25.81)	640(26.90)	643(26.03)	666(27.28)	697(28.91)	
Physical activity level						**< 0.0001**
NMVPA (0 MET-mins/week)	2069(18.49)	640(26.90)	643(26.03)	666(27.28)	697(28.91)	
LMVPA (1–599 MET-mins/week)	1375(12.29)	303(10.06)	347(11.00)	348(11.74)	377(13.89)	
MMVPA (600–1199 MET-mins/week)	1168(10.44)	276(9.15)	286(9.29)	297(10.22)	309(11.80)	
HMVPA (≥ 1200 MET-mins/week)	6580(58.79)	1750(66.75)	1669(64.57)	1637(61.29)	1524(54.44)	
BMI						**< 0.0001**
Normal	3743(33.44)	1091(38.31)	975(34.59)	842(28.22)	835(29.35)	
Overweight	3504(31.31)	905(33.29)	916(34.82)	898(32.78)	785(29.16)	
Obese	3945(35.25)	802(28.40)	907(30.60)	1062(39.00)	1174(41.49)	
WC	96.88(0.32)	93.87(0.47)	95.38(0.47)	98.52(0.47)	99.31(0.44)	**< 0.0001**
Muscle Quality						**< 0.001**
Extremely low	1319(12.81)	285(22.47)	299(22.24)	320(25.19)	415(30.50)	
Low	1187(9.62)	272(18.16)	275(17.85)	316(20.26)	324(19.48)	
Normal	3246(28.22)	831(59.37)	872(59.91)	783(54.55)	760(50.02)	
Insulin resistance						**< 0.0001**
Yes	5512(47.33)	1172(39.83)	1354(45.64)	1457(50.54)	1529(52.23)	
No	5680(52.67)	1626(60.17)	1444(54.36)	1345(49.46)	1265(47.77)	
DM						**0.001**
Yes	1059(9.46)	231(6.43)	247(6.30)	268(7.90)	313(9.02)	
No	10,133(90.54)	2567(93.57)	2551(93.70)	2534(92.10)	2481(90.98)	
Hypertension						**0.001**

Table 1 (continued)

Total	Total	Q1	Q2	Q3	Q4	*P* value
Yes	2927(26.15)	681(23.12)	682(23.39)	759(26.28)	805(29.36)	
No	8265(73.85)	2117(76.88)	2116(76.61)	2043(73.72)	1989(70.64)	
Hyperlipidemia						**< 0.0001**
Yes	6756(60.36)	1540(55.81)	1683(59.55)	1750(63.47)	1783(63.82)	
No	4436(39.64)	1258(44.19)	1115(40.45)	1052(36.53)	1011(36.18)	
NAFLD						**< 0.0001**
Yes	3746(33.47)	792(27.12)	895(29.29)	1034(33.89)	1025(35.63)	
No	7446(66.53)	2006(72.88)	1903(70.71)	1768(66.11)	1769(64.37)	
ALT [U/L]	25.76(0.24)	26.21(0.59)	26.25(0.44)	26.03(0.51)	24.65(0.40)	**0.02**
AST [U/L]	25.05(0.19)	25.97(0.47)	25.15(0.40)	24.74(0.34)	24.48(0.46)	0.20
Creatinine [mg/dl]	0.86(0.00)	0.87(0.01)	0.86(0.01)	0.85(0.01)	0.84(0.01)	**< 0.001**
Uric acid [umol/L]	316.31(1.25)	316.95(2.58)	317.07(1.96)	317.96(2.26)	313.38(1.74)	0.21
Total percentage fat [%]	32.70(0.15)	30.20(0.24)	31.80(0.23)	33.58(0.23)	34.83(0.21)	**< 0.0001**
Android percentage fat [%]	34.71(0.18)	32.11(0.26)	33.82(0.26)	35.80(0.26)	36.72(0.25)	**< 0.0001**
Gynoid percentage fat [%]	35.30(0.13)	33.07(0.25)	34.51(0.21)	36.01(0.24)	37.27(0.20)	**< 0.0001**
Total abdominal fat area [cm^2]	432.44(4.14)	377.17(5.58)	408.14(5.71)	455.29(6.17)	480.84(5.71)	**< 0.0001**
Subcutaneous fat area [cm^2]	331.31(3.26)	287.88(4.52)	312.77(4.45)	348.42(5.11)	369.64(4.45)	**< 0.0001**
Visceral adipose tissue area [cm^2]	101.13(1.14)	89.29(1.52)	95.37(1.54)	106.87(1.68)	111.20(1.89)	**< 0.0001**
V/S ratio	0.34 (0.00)	0.36(0.00)	0.34(0.00)	0.34(0.00)	0.33(0.00)	**< 0.001**

V/S ratio visceral to subcutaneous adipose area ratio, *DM* Diabetes mellitus, *WC* Waist circumference, *PIR* Income level, *NAFLD*, Nonalcoholic fatty liver disease
(Mean or proportion)

adipose tissue area (β, 95%CI: 1.91, 0.24–3.58) and V/S ratio (β,95%CI: 0.005, 0.00–0.02), and no significant association was observed between log2-SII and gynoid percentage fat. To assess the robustness of our findings, we conducted a sensitivity analysis by categorizing the SII into quartiles (Q1-Q4) instead of using it as a continuous variable. The results of the sensitivity analysis were largely consistent with the main analysis. Specifically, when SII was treated as a continuous variable, there was no significant association found between SII and gynoid percentage fat. However, when SII was analyzed as a categorical variable, the results indicated that individuals in the higher SII quartile groups (third and fourth quartiles) had higher gynoid percentage fat compared to those in the lowest SII quartile group. Additionly, we also conducted a further analysis of the different sub-types of adipose tissue depots and their associations with specific components of the SII. The results showed that PC was significantly related to total percentage fat, android percentage fat, gynoid percentage fat, total abdominal fat area, and subcutaneous fat area. Additionally, we found that neutrophil count (NC) had a close correlation with total abdominal fat area, visceral adipose tissue area, and the visceral-to-subcutaneous fat (V/S) ratio. In contrast, lymphocyte count (LC) showed no significant relationship with any of the adipose tissue subtypes (see uploaded Supplementary Table 3–5).

Subgroup analysis

The results of the subgroup analysis for the association of SII and body fat distribution were listed in Fig. 4. The results suggested that the positive association between SII and android percentage fat was mainly among obese individuals (BMI > 30 kg/m^2) and non-obese individuals without DM or hypertension. Meanwhile, the positive association between SII and V/S ratio was mainly among in the female subgroup, the obese subgroup, individuals with non-alcoholic fatty liver disease (NAFLD), and those without diabetes mellitus. However, the positive association between SII and gynoid percentage fat was only among male subgroup, normal and obese subgroups (BMI < 25 or > 30 kg/m^2), insulin resistance (HOMA-IR > 2.6) subgroups and NAFLD subgroups.

Non-linear relationship and threshold effect analysis between SII with body fat distribution

After adjusting for all covariates, we conducted an analysis to explore the potential non-linear relationships between the SII and various measures of body fat distribution. Interestingly, we found that the relationship between SII and variables such as total percentage fat, android percentage fat, total abdominal fat area, and subcutaneous fat area followed an inverted U-shaped pattern. The specific results were shown in Fig. 5. The log-likelihood ratio test resulted in a highly significant

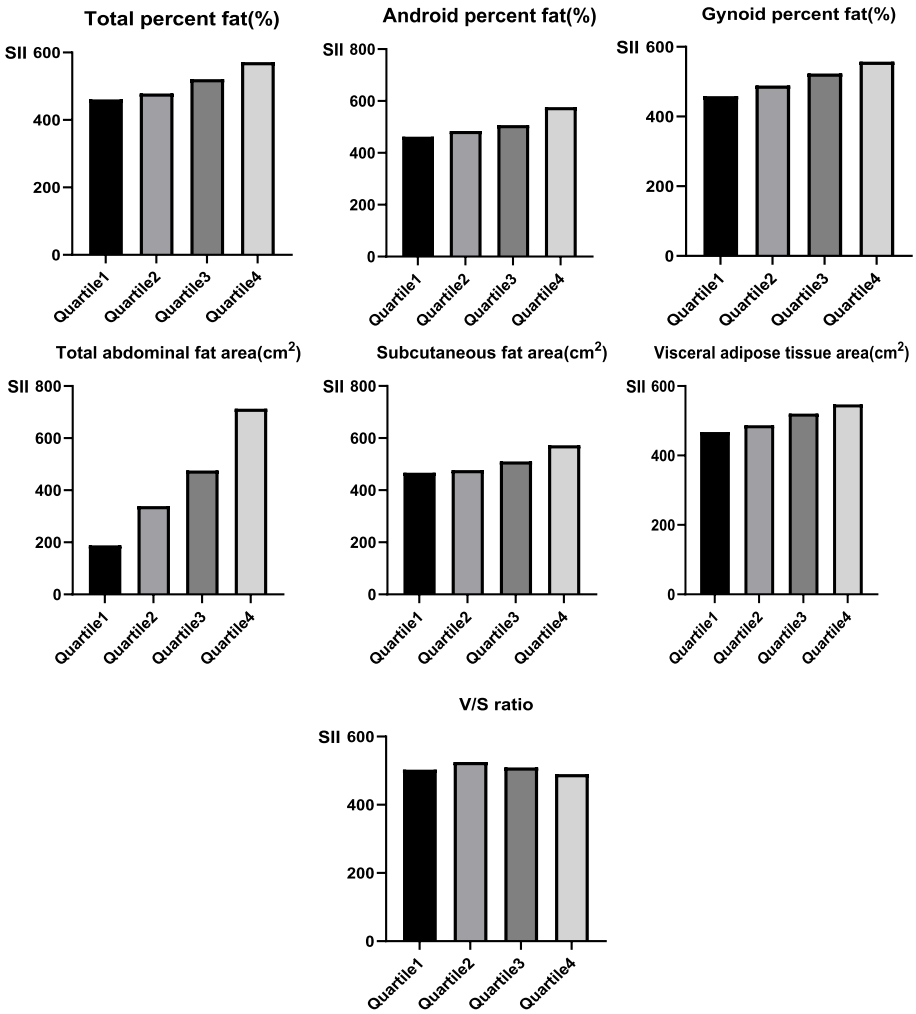

Fig. 3 The box graph shows the mean total percentage fat(%), android percentage fat(%), gynoid percentage fat(%), total abdominal fat area(cm^2), subcutaneous fat area(cm^2), visceral adipose tissue area(cm^2) and V/S ration in the quartiles of SII group

p-value (< 0.0001) when comparing the linear regression model to the two-piecewise linear regression model. This indicates that the two-piecewise linear regression model provided a significantly better fit for the data compared to the linear regression model. Table 3 displays the results obtained through the utilization of the recursive algorithm with the two-piecewise linear regression model.

The point of inflection in the U-shaped association between SII and total percentage fat, android percentage fat and total abdominal fat area were 824.93, 749.22 and 855.2, respectively. Regarding the percentage of total body fat, our findings indicate that there is no significant association to the right of the inflection point. The effect size (log2 transformed) was -0.13 (95% CI: -0.71, 0.44) with a *p*-value of 0.64, suggesting a lack of statistical significance. However, on the left side of the inflection point, we observed a significant positive correlation between SII and total percentage fat. The effect size (log2 transformed) was 0.33 (95% CI: 0.13, 0.54) with a *p*-value of 0.003, indicating a strong and significant association. This means that lower SII levels were strongly associated with higher total percentage fat. Accordingly, the results indicated a positive association between lower SII levels and android percentage fat and total abdominal fat area.

Discussion

This study found that SII was positively associated with total percentage fat, android percentage fat, total abdominal fat area, subcutaneous fat area, visceral adipose tissue area and V/S ratio. Furthermore, SII exhibited an inverted U-shaped relationship with total percentage fat, android percentage fat, total abdominal fat area and subcutaneous fat area. Threshold effect analysis indicated a positive association between lower SII levels and total percentage fat, android percentage fat and total abdominal fat area.

Table 2 The Logistic Regression results for Log2SII and total percentage fat, android percentage fat, gynoid percentage fat, total abdominal fat area, subcutaneous fat area, visceral adipose tissue area and V/S ratio

Exposure		Outcome	Model 1		Model 2		Model 3	
			β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value
Log2-SII		Total percentage fat	2.40(2.11,2.70)	**< 0.0001**	0.18(-0.05, 0.41)	0.11	0.23(0.03, 0.43)	**0.03**
	Q1		Ref		Ref		Ref	
	Q2		1.60(1.06,2.13)	**< 0.0001**	0.31(-0.11, 0.73)	0.12	0.30(-0.02, 0.63)	0.06
	Q3		3.37(2.78,3.97)	**< 0.0001**	0.53(0.00, 1.05)	0.05	0.57(0.17, 0.97)	**0.01**
	Q4		4.63(4.03,5.22)	**< 0.0001**	0.54(0.04, 1.04)	**0.04**	0.60(0.19, 1.01)	**0.01**
	P for trend			**< 0.0001**		**0.031**		**0.005**
		Android percentage fat	2.47(2.16,2.78)	**< 0.0001**	0.18(-0.05, 0.41)	0.11	0.26(0.06, 0.47)	**0.001**
	Q1		Ref		Ref		Ref	
	Q2		1.70(1.10,2.30)	**< 0.0001**	0.24(-0.29, 0.77)	0.29	0.20(-0.19, 0.59)	0.31
	Q3		3.68(3.05,4.32)	**< 0.0001**	0.54(-0.21, 1.29)	0.13	0.61(0.05, 1.16)	**0.03**
	Q4		4.61(3.99,5.22)	**< 0.0001**	0.45(-0.09, 0.98)	0.09	0.53(0.11,0.94)	**0.01**
	P for trend			**< 0.001**		0.072		**0.01**
		Gynoid percentage fat	2.14(1.86,2.42)	**< 0.0001**	0.07(-0.16, 0.30)	0.49	0.13(-0.08, 0.33)	0.21
	Q1		Ref		Ref		Ref	
	Q2		1.43(0.87,1.99)	**< 0.0001**	0.36(-0.18, 0.89)	0.19	0.39(-0.02, 0.79)	0.06
	Q3		2.94(2.29,3.58)	**< 0.0001**	0.42(-0.19, 1.02)	0.14	0.48(0.01, 0.95)	**0.04**
	Q4		4.19(3.60,4.79)	**< 0.0001**	0.39(-0.16, 0.93)	0.13	0.48(0.03, 0.92)	**0.04**
	P for trend			**0.029**		0.146		0.055
		Total abdominal fat area	56.59(49.22,63.96)	**< 0.0001**	3.74(0.67, 6.82)	**0.02**	4.38(1.65, 7.11)	**0.003**
	Q1		Ref		Ref		Ref	
	Q2		30.97(17.85, 44.09)	**< 0.0001**	1.26(-5.66, 8.18)	0.66	0.77(-4.73, 6.27)	0.78
	Q3		78.12(64.08, 92.17)	**< 0.0001**	5.29(-3.84,14.42)	0.20	5.74(-1.26,12.73)	0.10
	Q4		103.67(89.78,117.56)	**< 0.0001**	7.93(1.30,14.56)	**0.03**	8.37(3.04,13.70)	**0.003**
	P for trend			**< 0.0001**		**0.016**		**0.001**
		Subcutaneous fat area	44.09(38.26,49.91)	**< 0.0001**	1.78(-1.04, 4.59)	0.18	2.47(0.07, 4.86)	**0.04**
	Q1		Ref		Ref		Ref	
	Q2		24.89(14.35,35.44)	**< 0.0001**	1.40(-4.27, 7.08)	0.55	1.28(-3.05, 5.61)	0.55
	Q3		60.54(49.19,71.89)	**< 0.0001**	2.28(-5.09, 9.64)	0.46	3.05(-2.39, 8.49)	0.26
	Q4		81.76(70.59,92.93)	**< 0.0001**	4.66(-1.13, 10.45)	0.09	5.45(0.78, 10.11)	**0.02**
	P for trend			**< 0.001**		0.095		**0.023**
		Visceral adipose tissue area	12.50(10.21,14.79)	**< 0.0001**	1.97(0.01, 3.92)	0.05	1.91(0.24, 3.58)	**0.03**
	Q1		Ref		Ref		Ref	
	Q2		6.08(2.39, 9.77)	**0.002**	-0.15(-3.97, 3.68)	0.93	-0.51(-3.51, 2.49)	0.73
	Q3		17.58(13.52,21.64)	**< 0.0001**	3.01(-0.83, 6.85)	0.10	2.69(-0.18, 5.56)	0.07
	Q4		21.91(17.52,26.29)	**< 0.0001**	3.27(-0.74, 7.28)	0.09	2.92(-0.30, 6.14)	0.07
	P for trend			**< 0.001**		**0.038**		**0.021**
		V/S ratio	-0.01(-0.02,-0.01)	**< 0.001**	0.01(0.00,0.01)	**0.01**	0.01(0.00, 0.02)	**0.005**
	Q1		Ref		Ref		Ref	
	Q2		-0.02(-0.03,-0.01)	**0.003**	0.00(-0.02, 0.01)	0.44	0.00(-0.01, 0.00)	0.30
	Q3		-0.02(-0.03,-0.01)	**0.002**	0.01(-0.01, 0.02)	0.31	0.01(-0.01, 0.02)	0.36
	Q4		-0.03(-0.04,-0.02)	**< 0.0001**	0.01(0.00, 0.03)	0.07	0.01(0.00, 0.02)	0.07
	P for trend			0.885		**0.023**		**0.024**

The primary distribution of body fat occurs in two principal regions, leading to its common categorization into SAT and VAT [42]. Now, obesity is assessed through an augmentation in adipocyte count and surplus fat accumulation within adipocytes. Recent studies have opened up an intriguing avenue of exploration in the realm of

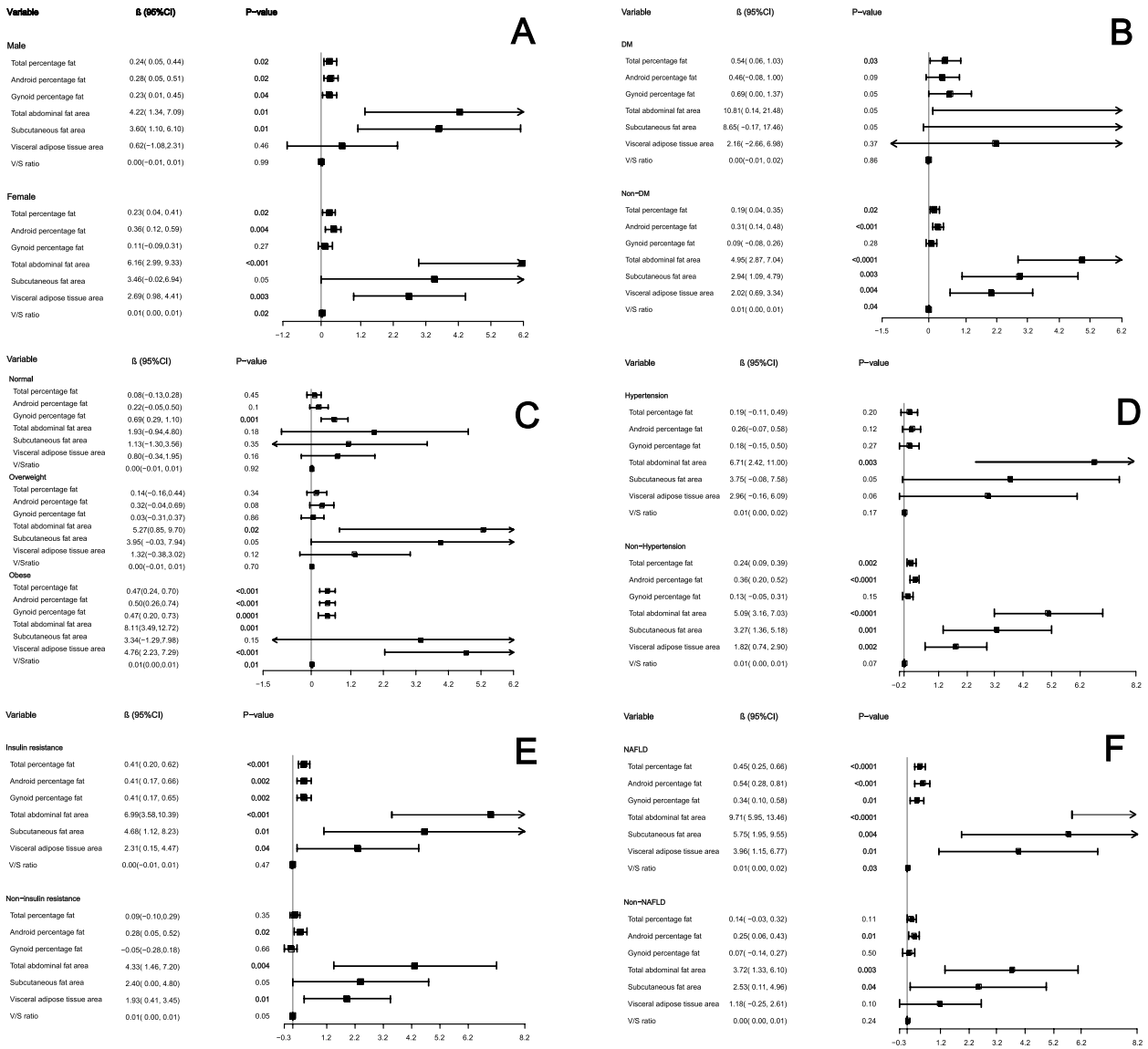

Fig. 4 The relationship between SII with body fat distribution in sex (A), diabetes (B), BMI (C), hypertension (D), insulin resistance (E), and NAFLD (F) subgroups

android and gynoid fat mass. These two types of fat mass exhibit distinct cellular characteristics. The android fat variant is characterized by larger adipose cells, known as hypertrophic cells, whereas the gynoid fat type showcases a higher number of adipocytes, indicating hyperplasia. Android fat distribution refers to the tendency for fat to accumulate in the abdominal region, chest, shoulders, and back of the neck. This pattern is commonly associated with central obesity and an "apple" body shape. It is often accompanied by a higher amount of visceral adipose tissue, which is fat stored around internal organs. Gynoid fat mass, on the other hand, refers to the accumulation of fat around the buttocks, thighs, and chest. This type of fat distribution is more common in women and is sometimes referred to as "reproductive fat." Gynoid fat serves as a nutrient source for offspring and contains essential long-chain polyunsaturated fatty acids (PUFA) that are important for fetal development [43].

The increase in SII mainly could affect the percentage and content of body fat for the following reasons: On the one hand, inflammation increases energy expenditure and decreases energy intake either directly or indirectly. Leptin expression is increased in adipose tissue by inflammation, which can expand adipose tissue (AT) [44]. Circulating concentrations of leptin rise and the cells it targets become resistant to its effects [45], which

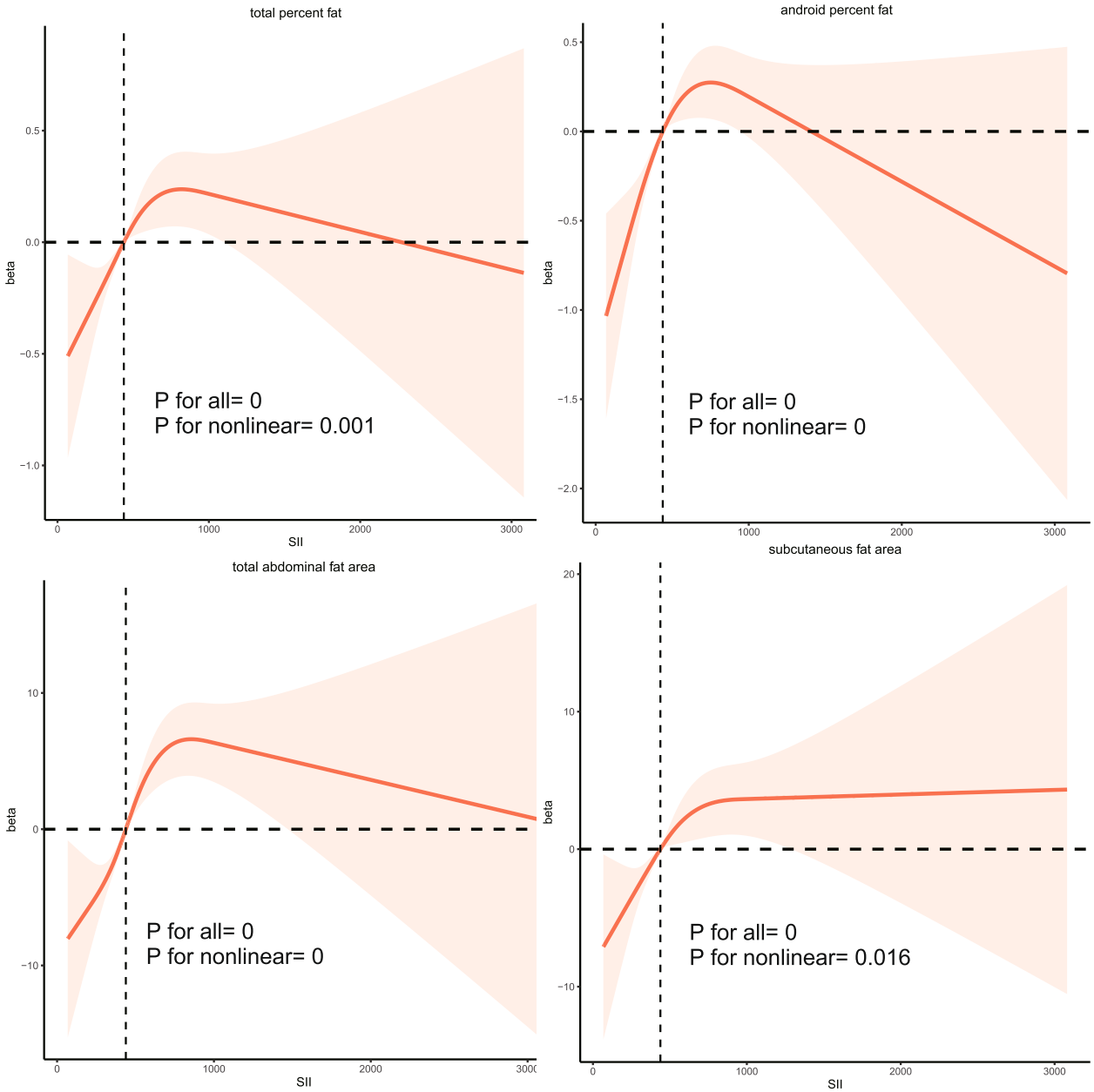

Fig. 5 The nonlinear relationship between SII and total percentage fat, android percent fat, total abdominal fat area and subcutaneous fat area

may play a part in the development and maintenance of obesity. On the other hand, as ectopic lipid accumulation impairs peripheral insulin signaling, and chronic low-grade systemic inflammation hinders insulin's effectiveness within the insulin signaling pathway, disturbing glucose balance and leading to systemic dysregulation [46], it is widely recognized that inflammation plays a significant role in metabolic disorders associated with obesity [47–49]. Studies have shown that SII is associated with obesity-related metabolic diseases such as hyperlipidemia [50], diabetic nephropathy [51] and NAFLD [23]. Whether body fat plays a part of the mediating role is still unclear, which is also one of our next research plans.

This study builds upon previous research by exploring the relationship between the SII and adiposity, considering both total body fat and regional fat distribution. It is well-established that body fat distribution, beyond simply body weight, plays a significant role in the development and clinical implications of conditions such

Table 3 Threshold effect analysis of SII on total percentage fat, android percentage fat and total abdominal fat area using two-piecewise linear regression model

	Adjusted β (95% CI)	*P* value
Total percentage fat		
Fitting by linear regression model	0.28(0.19, 0.38)	**< 0.0001**
Fitting by two-piecewise linear regression model		
Inflection point	824.93 (log2SII = 9.46)	
log2SII < 9.46	0.33(0.13, 0.54)	**0.003**
log2SII ≥ 9.46	-0.13(-0.71, 0.44)	0.64
Log likelihood ratio test	**< 0.0001**	
Android percentage fat		
Fitting by linear regression model	0.36(0.24, 0.49)	**< 0.0001**
Fitting by two-piecewise linear regression model		
Inflection point	749.22 (log2SII = 9.35)	
log2SII < 9.35	0.51(0.24, 0.77)	**< 0.001**
log2SII ≥ 9.35	-0.48(-1.11, 0.14)	0.12
Log likelihood ratio test	**< 0.0001**	
Total abdominal fat area		
Fitting by linear regression model	5.81(4.28, 7.35)	**< 0.0001**
Fitting by two-piecewise linear regression model		
Inflection point	855.21 (log2SII = 9.76)	
log2SII < 9.76	7.11(4.44, 9.78)	**< 0.0001**
log2SII ≥ 9.76	-0.38(-15.38, 14.61)	0.96
Log likelihood ratio test	**< 0.0001**	

as diabetes and cardiovascular diseases. The impact of body fat distribution on these conditions has been studied extensively since as early as 1947 and has been supported by a substantial body of subsequent research. Previous cross-sectional findings indicated that not only the degree of obesity but also the localization of fat was a risk factor for diabetes [29]. Android percentage fat, rather than the gynoid percentage fat, may be an important factor in determining the risk of cardiovascular disease [52]. Elevated levels of VAT and SAT are linked to the development of metabolic risk factors that cannot be explained solely by general adiposity.

There are several limitations to our study that should be acknowledged. Firstly, due to the cross-sectional design, we cannot establish causation or determine the temporal relationship between variables. Secondly, while we attempted to control for various confounding factors, there may still be residual confounding from unmeasured variables. Thirdly, certain covariate information was obtained through self-reported questionnaires, which may be subject to recall bias and may not fully represent the true situation [53]. Lastly, the potential limitations of the SII calculation—specifically the "ratio syndrome" where values become infinite in the absence of lymphocytes or zero in the absence of neutrophils. We will try to explore new indicators or mathematical methods to solve this problem.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01725-y.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.

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Authors' contributions
H-QZ conceived the presented idea. XL performed the analysis and manuscript writing. Y-CL, Y-DS and Y-HZ were involved in acquisition of data. JY, Y-WC and LZ were involved in interpretation of data. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials
The data used in this study are from a public database at https://www.cdc.gov/nchs/nhanes/index.htm, which can be accessed by everyone through the links provided in the paper.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by National Center for Health Statistics Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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