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ORIGINAL ARTICLE

Inflammation Mediates the Association between ABSI and Prostate-Specific Antigen: Results from the National Health and Nutrition Examination Survey 2001-2010

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Abstract

Background: Abdominal obesity, quantified by the body shape index (ABSI), has been implicated in prostate carcinogenesis, yet the mediating role of systemic inflammation remains underexplored. This study aimed to investigate the potential mediating effects of systemic immune-inflammatory biomarkers—the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI)—on the association between ABSI and total prostate-specific antigen (PSA) levels.

Methods: We used data from the National Health and Nutrition Examination Survey (NHANES) 2001--2010 and conducted a cross-sectional analysis of 6,956 male participants aged ≥ 40 years. The ABSI was calculated to assess abdominal obesity, whereas the SII and SIRI were derived from blood cell counts. Weighted linear regression and restricted cubic spline models were used to evaluate the associations between ABSI, inflammatory indices, and PSA. Mediation analysis quantified the indirect effects of the SII/SIRI on the ABSI-PSA relationship.

Results: A greater ABSI was associated with elevated total PSA concentrations (β = 0.34, 95% CI: 0.15–0.54, $P < 0.001$). The SII and SIRI were significantly positively correlated with the total PSA concentration (β = 0.28, 95% CI: 0.19, 0.36, $P < 0.001$; β = 0.25, 95% CI: 0.16, 0.34, $P < 0.001$). Mediation analysis revealed that the SII and SIRI accounted for 7.4% and 8.9% of the total effect between ABSI and total PSA concentration ($P < 0.001$). Subgroup analysis confirmed that covariates did not affect the association between ABSI and total PSA concentration (P interaction > 0.05).

Conclusion: Systemic inflammation, captured by the SII and SIRI, partially mediated the link between abdominal obesity (assessed via the ABSI) and elevated PSA levels. These findings highlight obesity-driven inflammation as a key mechanistic pathway underlying prostate-specific biomarker dysregulation, emphasizing the clinical utility of integrating ABSI with inflammatory indices for risk stratification. Targeted public health strategies focusing on reducing abdominal obesity and anti-inflammatory interventions could mitigate prostate cancer risk.

Keywords: Body shape index; Prostate-specific antigen; Systemic immune-inflammation index; Systemic inflammatory response index; NHANES

Introduction

The ABSI is a novel anthropometric parameter that has significant advantages in obesity-related risk stratification through its unique ability to quantify central adiposity independently of body mass index (BMI) [1]. In the cardiovascular domain, ABSI has a dose–response relationship with all-cause and cardiovascular mortality in diabetic patients [2]and is independently associated with coronary heart disease incidence in obese individuals[3] . Furthermore, the ABSI has been shown to effectively predict major cardiovascular events, including nonfatal stroke and acute coronary syndrome, in both general and high-risk populations[3,4] . In terms of metabolic and reproductive health, an elevated ABSI is correlated with metabolic syndrome[5] and target organ injury in hypertensive patients[6]. Longitudinal studies highlight its superior prognostic utility for all-cause mortality in elderly populations, particularly those with osteoporosis or diabetes[2,7]. Additionally, ABSI has translational value in surgical contexts, effectively predicting postoperative complications in gastric cancer patients[8] and correlating with autonomic nervous system dysfunction through reduced cardiac activity[9]. Collectively, ABSI serves as a superior indicator for quantifying abdominal obesity and its systemic inflammatory consequences by enhancing the specificity of body fat distribution analysis.

Prostate cancer (PCa) has emerged as the second most common malignancy in males globally, with epidemiological projections estimating a doubling of annual new cases from 1.4 million (2020) to 2.9 million by 2040[10]. This escalating burden arises from a multifactorial etiology encompassing genetic predispositions, environmental exposures, and lifestyle factors that collectively contribute to PCa pathogenesis[11,12]. The asymptomatic progression of prostate cancer necessitates early detection strategies, with PSA—a glycoprotein derived from the prostatic epithelium—serving as a pivotal screening tool for decades[13].

Recent advances in molecular pathology have identified inflammatory cascades induced by adipose tissue dysfunction as critical mediators linking obesity to PSA dysregulation and carcinogenic progression[14]. Obesity, defined by the World Health Organization (WHO) as a body mass index (BMI) ≥30 kg/m², has been increasingly recognized as a modifiable risk factor[15]. Adipose tissue dysfunction induced by obesity is recognized as a key driver of systemic chronic low-grade inflammation, which is pathologically characterized by elevated circulating levels of proinflammatory cytokines (e.g., TNF-α and IL-6) alongside dysregulated secretion of adipokines such as leptin and adiponectin[14–16]. The synergy between chronic inflammatory processes (mediated by proinflammatory cytokines) and metabolic disturbances (characterized by hyperinsulinemia and androgen dysregulation) drives prostate microenvironment remodeling through oxidative damage, insulin/insulin-like growth factor (IGF)-1 axis activation, and sex hormone-binding globulin (SHBG)-mediated increases in androgen bioavailability [15,17,18].

Systemic inflammation constitutes a central pathophysiological mechanism linking obesity to prostate-related disorders, positioning it as a critical mediator of disease progression. As composite metrics incorporating peripheral blood cell counts (including neutrophils, lymphocytes, and platelets), SII and SIRI have been validated as reliable biomarkers of systemic inflammatory status[19]. In contrast to conventional single-marker methods, these indices quantify the dynamic interaction between immune activation and chronic inflammation, demonstrating enhanced prognostic capabilities in both metabolic disorders and oncological conditions[20,21]. Importantly, these biomarkers exhibit specific pathophysiological relevance, with extensive clinical investigations consistently demonstrating significant correlations with obesity-related phenotypes. For example, elevated SII and SIRI values are correlated with abdominal obesity, insulin resistance, and metabolic syndrome, reflecting the systemic inflammatory burden driven by dysfunctional adipose tissue[22–24]. Collectively, these findings substantiate the mediating role of the SII and SIRI in the pathway connecting adiposity to prostate-specific biomarker dysregulation.

Despite these advances, critical knowledge gaps remain unaddressed. First, although the obesity–inflammation–PSA axis is mechanistically plausible, no explicit testing has been conducted

to determine whether systemic inflammation mediates the relationship between abdominal obesity (as quantified by the ABSI) and PSA levels. Second, current research predominantly examines individual inflammatory markers (e.g., C-reactive protein, (IL-6)), neglecting the potential utility of composite indices such as the SII and SIRI for comprehensive risk stratification. Third, the clinical utility of integrating metabolic–inflammatory biomarkers into PSA-based screening algorithms remains unexplored, limiting their translational potential.

This study bridges these gaps by employing data-driven mediation analysis to test the hypothesis that the SII and SIRI mediate the ABSI-PSA association, with rigorous statistical evaluation of the mediating effects of systemic inflammation within a population-based epidemiological framework. By leveraging large-scale clinical datasets, we present empirical evidence demonstrating that obesity-associated inflammatory pathways contribute to PSA elevation, thereby informing biomarker-driven screening strategies.

2 Methods

2.1 Study Design and Population

The National Health and Nutrition Examination Survey (NHANES) constitutes a nationally representative cross-sectional surveillance program employing a complex, stratified multistage probability sampling design, that is administered continuously by the National Center for Health Statistics (NCHS). The study protocol obtained ethical approval from the NCHS Institutional Review Board (IRB), with written informed consent secured from all participants prior to data collection. Comprehensive documentation regarding the survey's methodological framework and standardized data collection procedures are accessible through the official NHANES portal (https://www.cdc.gov/nchs/nhanes). For this study, we utilized NHANES data from 2001–2010, which were harmonized across cycles to ensure consistency in variable definitions .The study included males aged ≥40 years with complete data on the ABSI, SII, SIRI, and PSA. The exclusion criteria included individuals aged <40 years, those with missing survey weights (N=17,245), incomplete PSA measurements (N=1,059), or insufficient data for ABSI/SII/SIRI calculations (N=442). The final sample size was 6,956 participants(Figure 1).

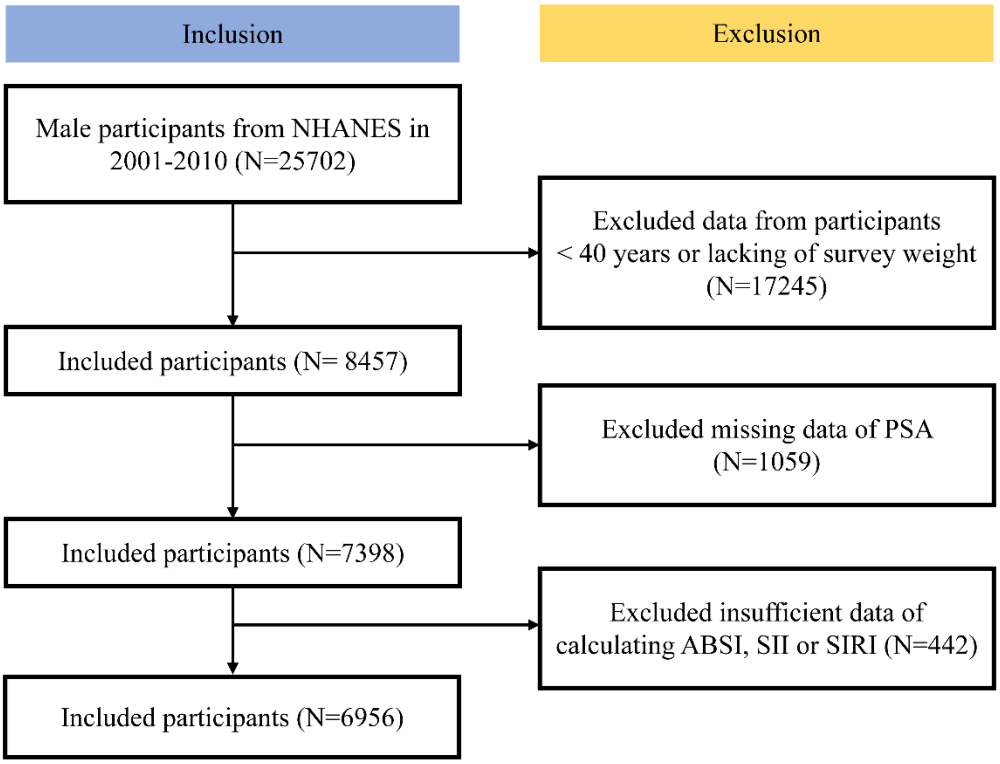

Figure 1 Flow chart of the study

2.2 ABSI Calculation

The ABSI was calculated as $\frac{WC}{\left(BMI^{\frac{2}{3}} \times height^{\frac{1}{2}}\right)}$, described by Krakauer et al[25]. to normalize waist circumference (WC) by BMI and height to assess central adiposity independent of BMI categories.

2.3 SII and SIRI Calculations

Venous blood samples were analyzed via the Beckman Coulter DxH 800 automated hematology analyzer at the NHANES Mobile Examination Center (MEC) to obtain complete blood count (CBC) results for all participants. Lymphocyte, neutrophil, monocyte, and platelet counts were measured at 10^3 cells/μL. The systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI) were calculated according to published formulas[26,27].

SII = (platelet count × neutrophil count)/ lymphocyte count

SIRI = (neutrophil count × monocyte count)/ lymphocyte count

2.4 PSA Measurement

Total prostate-specific antigen (PSA) levels in the serum were measured via the Hybritech chemiluminescent immunoassay (Beckman Coulter Access 2).

2.5 Covariates

Covariates consisted of sociodemographic and life behavior variables. Sociodemographic variables included sex (male, female), age (40–59 years, and ≥ 60 years), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race, including multiracial), educational level (less than high school, high school graduate/GED or equivalent, and higher than high school), household poverty-to-income ratio (PIR) (≤ 1.3, 1.3–3.5, and > 3.5) and marital status (married/living with a partner, widowed/divorced/separated, and never married). The life behavior variables contained included smoking status and drinking status. Smokers were defined as those who smoked more than 100 cigarettes in their lifetime[28].Drinkers were defined as those who consumed more than 12 drinks in a year[29]. Medical history, including diagnoses of diabetes and hypertension, was collected through structured interviews. These variables were selected on the basis of their potential influence on PSA levels and systemic inflammation.

2.6 Statistical Analysis

In this study, we utilized MEC examination weights to represent the U.S. population given the complex multistage sampling design of the NHANES database[30].We divided the research subjects into four groups on the basis of the quartiles of ABSI (Q1-Q4) and compared the differences in the distributions of different variables across the four groups. Continuous variables are presented as the weighted mean ± standard deviation (SD) and were analyzed via weighted t-tests. Categorical variables are expressed as weighted proportions and were analyzed via weighted chi-square tests. To address the skewness of the SII and the SIRI, we applied a natural logarithm transformation (Ln-transformation). Missing covariates were handled via the "MICE" package for multiple imputation (MI)[31].

First, we examined the relationships between ABSI, SII, SIRI, and total PSA levels via a weighted linear regression model. The ABSI, SII, and SIRI were included in both the continuous and categorical analyses. Three models were constructed in this section. In Model 1, no potential confounding factors were adjusted. In contrast, Model 2 incorporated adjustments for several demographic characteristics, including sex, age, race, education level, PIR, and marital status. In Model 3, we adjusted for all covariates[32]. To explore the potential nonlinear associations among the ABSI, SII, SIRI, and total PSA concentration, we developed restricted cubic spline (RCS) regression models with knots at the 10th, 50th, and 90th percentiles[33]. Subgroup analyses were subsequently performed to assess potential interaction effects between ABSI and covariates on total PSA concentrations. Likelihood ratio tests were employed to evaluate interaction effects[34].Finally, we investigated the mediating role of the inflammation index in the association between ABSI and total PSA concentration. Mediation analysis tests the three effects generated by independent variables, mediator variables, and dependent variables, including total effect (TE), indirect effect (IE) and direct effect (DE)[35].We conducted 1000 repeated samplings to increase the accuracy of the results.

All analyses were carried out via R (version 4.4.1). Two-tailed P values < 0.05 were considered statistically significant.

3. Results

3.1 Characteristics of the Study Participants

This study included a total of 6,956 male participants. The participants were divided into four groups on the basis of ABSI level: the Q1 group (ABSI ≤ 0.081), the Q2 group (ABSI 0.081-0.084), the Q3 group (ABSI 0.084-0.087), and the Q4 group (ABSI > 0.087). The clinical characteristics of the participants stratified by ABSI are shown in **Table 1**. Significant differences were observed for all variables (P < 0.05). The participants with higher ABSIs tended to be older, non-Hispanic White, with lower education levels, lower income, widowed/divorced/separated, be more likely to smoke and drink, and have a higher prevalence of diabetes and hypertension. Additionally, participants with higher ABSI values had significantly higher SII, SIRI, and total PSA concentrations.

Table 1 Characteristics of male participants grouped by ABSI quartile from NHANES 2001-2010.

Variables	**Total**	**ABSI**				***P***
		Q1(≤ 0.081)	**Q2 (0.081-0.084)**	**Q3 (0.084-0.087)**	**Q4 (> 0.087)**	
n	6956	1739	1739	1739	1739	
Age, n (%)						< 0.001
40-59	3621 (67.8)	1399 (88.6)	1094 (77)	764 (61.2)	364 (35.8)	
≥60	3335 (32.2)	340 (11.4)	645 (23)	975 (38.8)	1375 (64.2)	
Race, n (%)						< 0.001
Mexican American	1245 (6.1)	291 (6.7)	350 (6.4)	343 (6.4)	261 (4.4)	
Other Hispanic	420 (3.4)	113 (4)	116 (3.3)	104 (3.3)	87 (2.7)	
Non-Hispanic White	3780 (76.9)	674 (66.2)	896 (77.9)	1005 (80)	1205 (86)	
Non-Hispanic Black	1265 (8.9)	582 (17)	318 (7.9)	224 (5.6)	141 (3.5)	
Other Race - Including Multi-Racial	246 (4.8)	79 (6.2)	59 (4.5)	63 (4.6)	45 (3.4)	
Education, n (%)						< 0.001
Less than high school	2157 (18.3)	418 (13.9)	499 (16.1)	579 (20.5)	661 (24.6)	
High school grad/GED or equivalent	1622 (25.4)	396 (23.3)	388 (24.2)	444 (27.8)	394 (26.8)	
Higher than high school	3177 (56.3)	925 (62.9)	852 (59.7)	716 (51.8)	684 (48.5)	
PIR, n (%)						< 0.001
≤1.3	1720 (14.8)	391 (13.5)	389 (13.1)	434 (15.3)	506 (18.4)	
1.3-3.5	2613 (33)	573 (28.6)	632 (30.8)	674 (34.3)	734 (40.3)	
>3.5	2623 (52.1)	775 (58)	718 (56)	631 (50.4)	499 (41.3)	
Marital status, n (%)						< 0.001
Married/living with	5106	1279 (77.3)	1315 (78.1)	1311 (77.2)	1201 (73)	

partner	(76.6)					
Widowed/divorced/ separated	1377 (17)	284 (13.8)	309 (16.3)	341 (17.7)	443 (21.4)	
Never married	473 (6.4)	176 (9)	115 (5.6)	87 (5.2)	95 (5.5)	
Smoking status, n (%)						< 0.001
Yes	4339 (58.8)	901 (46.4)	1054 (57.4)	1124 (63.4)	1260 (71.4)	
No	2617 (41.2)	838 (53.6)	685 (42.6)	615 (36.6)	479 (28.6)	
Drinking status, n (%)						0.011
Yes	5725 (83.7)	1424 (84.7)	1464 (86)	1429 (82.3)	1408 (81.1)	
No	1231 (16.3)	315 (15.3)	275 (14)	310 (17.7)	331 (18.9)	
Diabetes, n (%)						< 0.001
Yes	1056 (11.3)	168 (7)	208 (8.3)	294 (12.3)	386 (19.9)	
No	5900 (88.7)	1571 (93)	1531 (91.7)	1445 (87.7)	1353 (80.1)	
Hypertension, n (%)						< 0.001
Yes	2943 (38.7)	533 (28.9)	672 (34.2)	800 (44.1)	938 (51.3)	
No	4013 (61.3)	1206 (71.1)	1067 (65.8)	939 (55.9)	801 (48.7)	
SII, mean (SD)	569.7 (386.2)	511.65 (431.98)	561.55 (317.23)	577.2 (341.59)	648.07 (441.19)	< 0.001
SIRI, mean (SD)	1.36 (0.92)	1.14 (0.72)	1.31 (0.80)	1.39 (0.90)	1.68 (1.17)	< 0.001
PSA, mean (SD)	1.48 (2.34)	1.20 (2.02)	1.30 (1.60)	1.55 (2.47)	2.02 (3.19)	< 0.001

3.2 Associations between ABSI, SII, SIRI, and PSA

Table 2 presents the results of the weighted linear regression models examining the associations between ABSI, SII, SIRI, and total PSA concentrations. In the unadjusted model (Model 1), each 0.01-unit increase in ABSI was associated with a 0.81 increase in total PSA concentration (β: 0.81, 95% CI: 0.63, 0.99, P < 0.001). After adjusting for age, race, education level, PIR, and marital status (Model 2), each 0.01-unit increase in ABSI was associated with a 0.29 increase in total PSA concentration (β: 0.29, 95% CI: 0.10, 0.48, P = 0.003). Further adjustment for smoking, drinking, diabetes, and hypertension (Model 3) revealed that each 0.01-unit increase in ABSI was still associated with a 0.34 increase in total PSA concentration (β: 0.34, 95% CI: 0.15, 0.54, P < 0.001). Compared with the lowest ABSI (Q1) group, the highest ABSI (Q4) group presented a 0.82 increase in total PSA concentration in the unadjusted model (β: 0.82, 95% CI: 0.64, 1.0, P < 0.001) and a 0.26 increase in the fully adjusted model (β: 0.26, 95% CI: 0.07, 0.46, P = 0.010), with a significant positive trend (P for trend < 0.05).

Similarly, the SII and SIRI were significantly positively associated with total PSA concentrations. In the fully adjusted model, each 1-unit increase in Ln-SII was associated with a 0.28 increase in total PSA concentration (β: 0.28, 95% CI: 0.19, 0.36, P < 0.001), and each 1-unit increase in Ln-SIRI was associated with a 0.25 increase in total PSA concentration (β: 0.25, 95% CI: 0.16, 0.34, P < 0.001). According to the

categorical analyses, compared with the lowest SII and SIRI (Q1) groups, the Q2, Q3, and Q4 groups presented higher total PSA concentrations (all $\beta > 0$, $P < 0.05$). Furthermore, the significant positive trends were obvious (both P for trend < 0.001).

Table 2 Associations of the ABSI, SII and SIRI with total PSA concentrations according to weighted linear regression models.

	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
ABSI						
Per 0.01-unit increment in ABSI	0.81 (0.63, 0.99)	< 0.001	0.29 (0.10, 0.48)	0.003	0.34 (0.15, 0.54)	<0.001
Q1	Reference		Reference		Reference	
Q2	0.10 (-0.02, 0.21)	0.099	-0.01(-0.13, 0.10)	0.802	0.00 (-0.11, 0.12)	0.939
Q3	0.35 (0.21, 0.49)	< 0.001	0.05 (-0.09, 0.19)	0.505	0.08 (-0.06, 0.22)	0.267
Q4	0.82 (0.64, 1.0)	< 0.001	0.20 (0.01, 0.40)	0.036	0.26 (0.07, 0.46)	0.010
P for trend	< 0.001		0.029		0.007	
Ln-SII						
Per 1 unit increment in ln-SII	0.29 (0.20, 0.38)	< 0.001	0.27 (0.18, 0.36)	< 0.001	0.28 (0.19, 0.36)	< 0.001
Q1	Reference		Reference		Reference	
Q2	0.24 (0.10, 0.37)	< 0.001	0.25 (0.12, 0.38)	< 0.001	0.25 (0.12, 0.38)	< 0.001
Q3	0.24 (0.11, 0.37)	< 0.001	0.28 (0.14, 0.42)	< 0.001	0.27 (0.13, 0.41)	< 0.001
Q4	0.47 (0.32, 0.63)	< 0.001	0.41 (0.27, 0.56)	< 0.001	0.43 (0.28, 0.57)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
Ln-SIRI						
Per 1 unit increment in ln-SIRI	0.38 (0.28, 0.47)	< 0.001	0.24 (0.15, 0.33)	< 0.001	0.25 (0.16, 0.34)	< 0.001
Q1	Reference		Reference		Reference	
Q2	0.12 (0.00, 0.25)	0.053	0.14 (0.02, 0.26)	0.019	0.15 (0.03, 0.27)	0.014
Q3	0.26 (0.16, 0.37)	< 0.001	0.14 (0.04, 0.25)	0.007	0.16 (0.05, 0.26)	0.004
Q4	0.57 (0.43, 0.72)	< 0.001	0.37 (0.23, 0.50)	< 0.001	0.39 (0.25, 0.53)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

Model 1 was not adjusted for any covariate.
Model 2 was adjusted for age, race, education, PIR, marital status.
Model 3 was adjusted for age, race, education, PIR, marital status, smoking status, drinking status, diabetes and hypertension.

We subsequently constructed an RCS regression model to explore the nonlinear relationships between ABSI, SII, SIRI, and PSA levels (**Figure 2**). The model demonstrated a nonlinear positive correlation between ABSI and PSA levels after all covariates were considered (P for nonlinearity < 0.05). In addition, we found that nonlinear positive correlations between the SII, and the SIRI

and PSA levels were displayed in the RCS regression model (P for nonlinearity > 0.05).

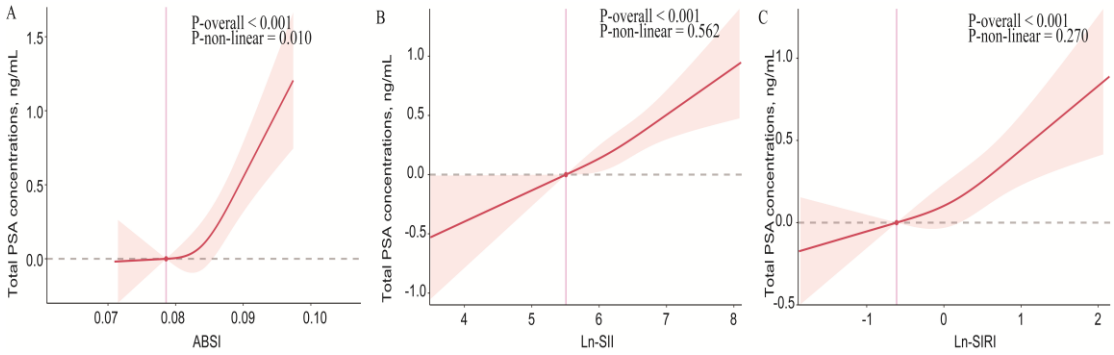

Figure 2 Associations of the ABSI, SII and SIRI with total PSA concentration in the RCS regression model. The models were adjusted for age, race, education, PIR, marital status, smoking status, drinking status, diabetes and hypertension.

3.4 Subgroup Analyses

Then, we explored the associations of ABSI with total PSA concentrations according to different groups of age, race, education, PIR, marital status, drinking status, smoking status, diabetes and hypertension (**Figure 3**). In the vast majority of the groups, the ABSI was positively correlated with the total PSA concentration, which is consistent with the above analysis results. We did not find that the ABSI and any covariate had an obvious interaction effect on the total PSA concentration (P for interaction > 0.05).

Characteristic	ß (95%CI)	P value	P for interaction
Age			0.127
40-59	0.15 (0.03, 0.27)	0.016	
≥60	0.71 (0.26, 1.16)	0.003	
Race			0.113
Mexican American	0.29 (−0.02, 0.60)	0.071	
Other Hispanic	2.03 (0.09, 3.97)	0.043	
Non-Hispanic White	0.33 (0.14, 0.53)	0.001	
Non-Hispanic Black	0.32 (−0.10, 0.74)	0.141	
Other Race - Including Multi-Racial	−0.59 (−1.41, 0.22)	0.156	
Education			0.101
Less than high school	0.74 (0.23, 1.26)	0.006	
High school grad/GED or equivalent	0.07 (−0.32, 0.46)	0.736	
Higher than high school	0.32 (0.15, 0.48)	<0.001	
PIR			0.304
≤1.3	0.36 (−0.08, 0.80)	0.112	
1.3-3.5	0.41 (0.07, 0.75)	0.020	
>3.5	0.28 (0.07, 0.49)	0.010	
Marital status			0.542
Married/living with partner	0.30 (0.09, 0.52)	0.007	
Widowed/divorced/separated	0.44 (0.11, 0.76)	0.010	
Never married	0.43 (−0.40, 1.27)	0.315	
Smoking status			0.127
Yes	0.29 (0.03, 0.55)	0.033	
No	0.44 (0.18, 0.70)	0.002	
Drinking status			0.331
Yes	0.39 (0.17, 0.61)	<0.001	
No	0.11 (−0.20, 0.42)	0.488	
Diabetes			0.350
Yes	0.72 (0.14, 1.30)	0.017	
No	0.29 (0.10, 0.49)	0.005	
Hypertention			0.624
Yes	0.35 (0.07, 0.63)	0.019	
No	0.34 (0.12, 0.57)	0.004	

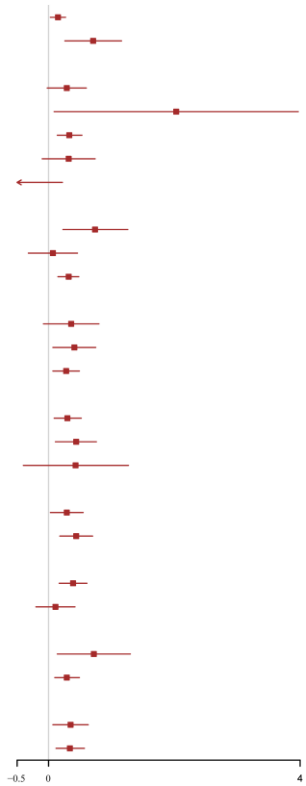

Figure 3 Subgroup analyses of ABSI, SII and SIRI with total PSA concentrations in the RCS regression model. The model was adjusted for age, race, education, PIR, marital status, smoking status, drinking status, diabetes and hypertension.

3.5 Mediating role of the inflammation index

Finally, mediation analyses were employed to

explore the mediating effect of the SII and the SIRI (**Figure 4**). In the two mediation models, TE, IE and DE were all obvious (P < 0.05). Specifically, ln-SII and ln-SIRI mediated the associations between ABSI and total PSA levels, explaining 7.4% and 8.9%, respectively, of the corresponding associations (P < 0.001). These findings demonstrated that inflammation may be a mechanism by which ABSI increases total PSA levels.

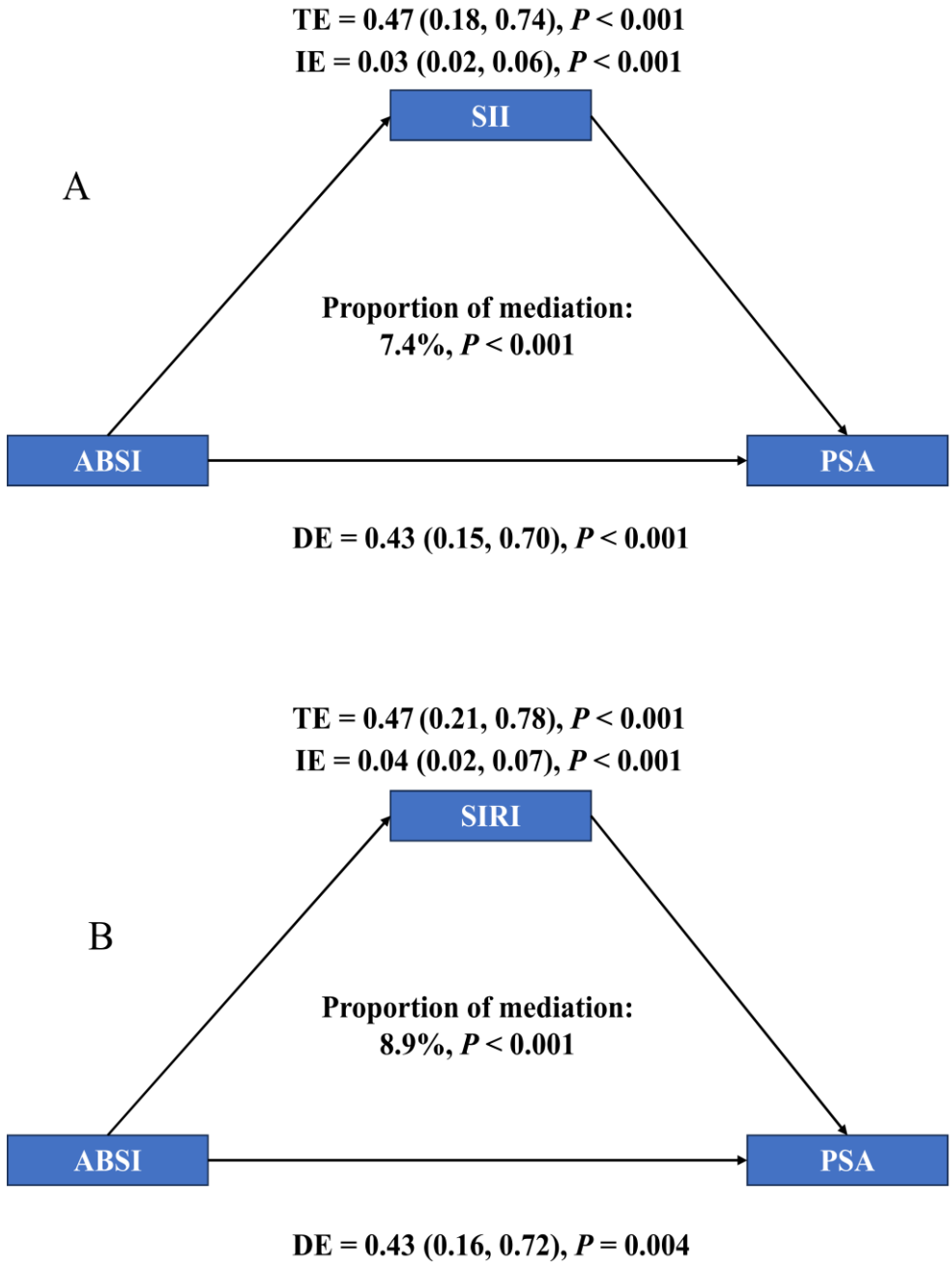

Figure 4 Mediation analysis of the mediating role of the inflammation index in the association between ABSI and total PSA concentration.

4 Discussion

This study elucidates a novel mechanistic pathway in which systemic inflammatory biomarkers (SII and SIRI) serve as partial mediators between central adiposity, quantified by ABSI, and elevated total PSA concentrations. Quantitative mediation analysis demonstrated that the SII and

SIRI accounted for 7.4% and 8.9%, respectively, of the total effect on this adiposity–PSA relationship. These findings indicate that systemic inflammatory pathways substantially contribute to the pathophysiological link connecting abdominal obesity to prostate-related biomarkers.

ABSI-quantified abdominal adiposity promotes prostate carcinogenesis through obesity-driven chronic inflammation, as reflected by elevated SII and SIRI values. Visceral fat accumulation, as measured by ABSI, induces metabolic inflammation through adipose tissue remodeling, characterized by M1 macrophage polarization and neutrophil infiltration, which amplify IL-6 and TNF-α production[36–38]. These cytokines propagate systemic inflammation (reflected by elevated SII/SIRI) while inducing localized prostatic oxidative stress and DNA damage through reactive oxygen species generation[39]. Concurrently, obesity-associated metabolic perturbations particularly hyperinsulinemia and associated insulin/IGF-1 axis activation[40] synergize with chronic inflammation to reshape the prostatic niche. Hyperinsulinemia suppresses hepatic SHBG synthesis, consequently increasing bioavailable testosterone while paradoxically creating a hypogonadal microenvironment through feedback inhibition of luteinizing hormone. This hormonal imbalance, compounded by elevated IGF-1 levels that promote angiogenesis and inhibit apoptosis, establishes a protumorigenic milieu conducive to prostate carcinogenesis [17,18]. Furthermore, increased SII/SIRI induced inflammation reprograms the prostate microenvironment through NF-κB-mediated epithelial–mesenchymal transition and redox-sensitive epigenetic modifications, potentially altering PSA secretion or clearance[39,41,42]. Collectively, ABSI-measured visceral fat accumulation predicts PSA fluctuations through the systemic inflammation biomarkers SII/SIRI, reflecting integrated metabolic–inflammatory pathways that drive prostatic microenvironmental reprogramming.

Current studies on the associations between obesity indices (e.g., BMI) and PSA or PCa have reached inconsistent conclusions. A well-established negative correlation exists between elevated BMI and reduced PSA levels, which is primarily explained by hemodilution effects associated with obesity[43] . This phenomenon creates a diagnostic paradox: while younger obese individuals have higher PCa detection rates[44] , diluted PSA levels may reduce diagnostic sensitivity, potentially delaying cancer identification[45] . Conversely, population-based studies report no significant association between obesity and overall PCa incidence[46] , but several lines of evidence suggest that obesity is associated with a more aggressive tumor phenotype, including higher Gleason scores[47], more advanced pathological staging[48], and an increased risk of biochemical recurrence (BCR) after radical prostatectomy[48]. Notably, cross-sectional studies in the U.S. population revealed an independent inverse association between serum triglyceride levels and PSA concentrations among tumor-free adult males, and longitudinal analyses further revealed that elevated triglyceride concentrations were associated with an increased risk of subsequent clinically significant PCa[49].These contradictory results may reflect the dual effects of the interference of obesity with PSA testing and the procancer effects of metabolic abnormalities (e.g., hyperinsulinemia and chronic inflammation). Overall, the available data have not reached a consensus on whether the obesity index can reliably predict PSA changes or PCa outcomes, and there is a strong need for standardized testing methods and long-term longitudinal studies to clarify the clinical significance and causal associations.

The ability of the ABSI to quantify abdominal obesity, independent of BMI, demonstrates its unique value as a supplementary tool for prostate health risk stratification. Although BMI (calculated as weight divided by height squared, kg/m²) has been extensively employed in previous studies[50–53], ABSI fundamentally overcomes BMI's limitations in distinguishing fat distribution patterns via somatometric parameter-based normalization of waist circumference. This methodological advancement substantially improves the sensitivity of central adiposity quantification. This progress is particularly crucial given the well-established pathophysiological associations among visceral fat accumulation, metabolic dysregulation, and chronic inflammatory cascades , all of which are mechanistically linked to prostate carcinogenesis[54].

Our findings demonstrated that the association

between ABSI and PSA levels was mediated through chronic inflammatory pathways, highlighting the critical need to address obesity-related systemic inflammation for prostate cancer risk mitigation. Our study utilized the NHANES 2001–2010 dataset, which is widely recognized for its methodological rigor. Specifically, its multistage stratified sampling design ensured national representativeness of U.S. adults, whereas standardized protocols and comprehensive covariate data minimized measurement bias and facilitated confounder adjustment. To ensure analytical robustness, we employed advanced statistical methods, including weighted multivariable regression, restricted cubic spline analyses for nonlinear threshold detection, and multiple imputation techniques to handle missing data. The integration of NHANES's robust design with inflammation biomarker analysis advances the clinical utility of ABSI as a pragmatic tool for identifying occult visceral adiposity and refining prostate cancer risk stratification strategies.

The cross-sectional design of this study precludes causal inferences among ABSI, inflammation, and PSA. Residual confounding from unmeasured variables (e.g., genetic predisposition, dietary habits) may remain even after statistical adjustments. Furthermore, although the SII and SIRI are robust markers of systemic inflammation, they lack specificity for chronic low-grade inflammatory subtypes such as adipose tissue-specific inflammation. The lack of established thresholds for differentiating inflammatory severity further limits their clinical interpretability. Finally, the homogeneity of the study population limits generalizability to other ethnic groups, in which ABSI's predictive utility may vary owing to differences in body composition or fat distribution patterns.

Prospective cohort studies should be conducted to establish temporal associations among ABSI trajectories, inflammatory dynamics, and PSA changes. The incorporation of advanced biomarkers (e.g., adipokines and macrophage polarization markers) would elucidate tissue-specific inflammatory pathways that link visceral adiposity to prostate pathophysiology. Validation through multiethnic cohorts is needed to confirm the generalizability of ABSI, especially in populations exhibiting distinct adiposity phenotypes (e.g., South Asians characterized by elevated visceral adiposity at lower BMI thresholds). Intervention trials targeting abdominal obesity (e.g., lifestyle modifications, GLP-1 agonists) could assess whether reducing ABSI normalizes the SII/SIRI indices and PSA levels, providing mechanistic and therapeutic insights . Finally, the development of standardized ABSI-SII/SIRI risk stratification scores could facilitate personalized screening protocols for prostate disorders in individuals with metabolic dysfunction.

5. Conclusion

This study suggests that systemic inflammation may act as a pivotal mediator in the association between abdominal obesity (assessed via ABSI) and elevated PSA levels.This highlights obesity-driven inflammation as a potential key pathway in prostate biomarker dysregulation. The BMI-independent nature of the ABSI in quantifying central obesity enhances its utility for risk stratification, especially in elderly populations and metabolically compromised subgroups. While the cross-sectional design limits causal inference, these findings advocate integrating ABSI and inflammatory indices into screening protocols and prioritizing anti-inflammatory interventions for high-risk populations. Future studies should validate these mechanisms prospectively and explore tissue-specific inflammatory pathways.

Data Availability

The NHANES datasets are publicly accessible through the official platform: https://www.cdc.gov/nchs /nhanes/Index.htm.

Ethics Statement

The research protocol received ethical authorization from the National Center for Health Statistics Ethics Review Board. Written informed consent was obtained from all participants enrolled in the NHANES survey .

Author Contributions

KM: collected and cleaned the research data and wrote the paper. SH: performed the statistical analysis of the data and visualized the results. SL: reviewed the logical rigor of the experimental design and optimized the coherence of the argumentation process. ZM, ML: evaluated the innovative contribution of the research and identified the theoretical breakthroughs and

practical value. PZ: led the design of the research framework and proofread the full text.

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Conflict of Interest

The authors declare no competing interests

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