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ORIGINAL RESEARCH

Association Between Systemic Immune-Inflammation Index and Stress Urinary Incontinence in Adult Women: A Population-Based Study

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Background: Systemic immune-inflammation index (SII) is a novel inflammatory marker, and inflammation may contribute significantly to the aetiology of stress urinary incontinence (SUI), in addition to recognized factors. This study aims to explore the association between SII and SUI in women.

Methods: Adult participants from the 2007–2018 NHANES were included. Weighted multivariate logistic regression and subgroup analysis were conducted to determine the relationship between SII and SUI. The non-linear relationship between SII and SUI risk was evaluated using restricted cubic splines (RCS), and the inflection point was determined by two-piecewise logistic regression.

Results: A total of 10,776 women were included, of whom 4407 (40.9%) had SUI. After adjusting for all confounders, a significant positive association between SII and SUI risk was observed (OR: 1.09; 95% CI: 1.01–1.19, $P = 0.021$); Moreover, when compared with the women in the lowest SII tertile, those in the highest SII tertile had a 15% increased risk of SUI (OR: 1.15; 95% CI: 1.00–1.31, $P = 0.049$). Subgroup analysis showed that there were consistent relationships between SII and SUI across most subgroups. A non-linear relationship between log2SII and SUI was observed by RCS analysis. Furthermore, the two-piecewise logistic regression demonstrated that the odds of being SUI increased with the SII level, and this rising trend gradually slowed down after passing the inflection point of 8.64.

Conclusion: Our findings suggest an association between elevated SII levels and an increased likelihood of SUI in women. Further well-designed prospective studies are needed to substantiate our results.

Keywords: systemic immune-inflammation index, stress urinary incontinence, population-based study, NHANES, cross-sectional study

Introduction

Stress urinary incontinence (SUI), a prevalent pelvic floor dysfunction, is characterized by involuntary loss of urine with increases in abdominal pressure such as exercise or coughing.[1] The prevalence of SUI increases with age, with reported instances ranging from 18.9% to 26% in adult women.[2,3] Despite its high prevalence, SUI remains under-diagnosed and under-treated, leading to social isolation and psychological distress for patients and increasing the risk of falls, depression and sleep disturbances.[4–6] Besides age, established risk factors for SUI in women include pregnancy, childbirth, hormonal influences, obesity, and weight gain.[7] Additionally, some research indicates that conditions such as urinary tract infections and gynecological inflammation may further aggravate SUI symptoms.[8,9]

Inflammation, as an adaptive response triggered by harmful stimuli, which can affect the synthesis and metabolism of connective tissue, damage the pelvic floor ligament, and promote the occurrence of SUI.[8] Additionally, SUI has been linked to the reconstruction of the extra-cellular matrix (ECM), which is pivotal in the adhesion, proliferation, differentiation, and gene expression of pelvic floor supporting tissues and cells.[10] It is well known that the ECM and the innate immune response to

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infection are inextricably linked.[11] Tissue damage resulting from an infection or autoimmune disorder initiates the breakdown of collagen in the ECM, which subsequently intensifying inflammation.[12] Therefore, understanding the relationship between inflammation and SUI is imperative for developing preventative and therapeutic strategies for SUI.

The systemic immune-inflammation index (SII), initially proposed by Hu et al in 2014, is a novel biomarker calculated from platelet count x neutrophil count x lymphocyte count, which can reflect the local immune response and systemic inflammation throughout the body.[13] This index was widely used in clinical research to provide prognostic information for patients suffering from various malignant tumors.[14] In addition, some studies have also demonstrated the high predictive value of the SII in other diseases such as hyperlipidemia[15] and rheumatoid arthritis.[16] However, the relationship between SUI and SII remains poorly characterized. Therefore, we performed a population-based cross-sectional analysis to investigate the association between SII and SUI and provide new insights into the role of systemic immune-inflammatory responses in the pathophysiology of SUI in women using data from NHANES.

Methods

Study Population

Our study was designed using publicly available data from the NHANES 2007–2018. NHANES is a series of complex, multistage, probability sample surveys of the US population conducted by the Centers for Disease Control and Prevention (CDC) to collect nationally representative health-related data.

In this study, we analyzed NHANES data including women aged ≥ 20 years with complete self-reported SUI information (n = 12,783) collected during 2007–2018. Individuals with missing SII (n = 507) and other variables data (n = 1500) were excluded from 12,783 women. Ultimately, our analysis included 10,776 participants. Details of the selection process are shown in Figure 1. Each participant provided a written consent, and NHANES was approved by the National Center for Health Statistics Ethics Review Board.

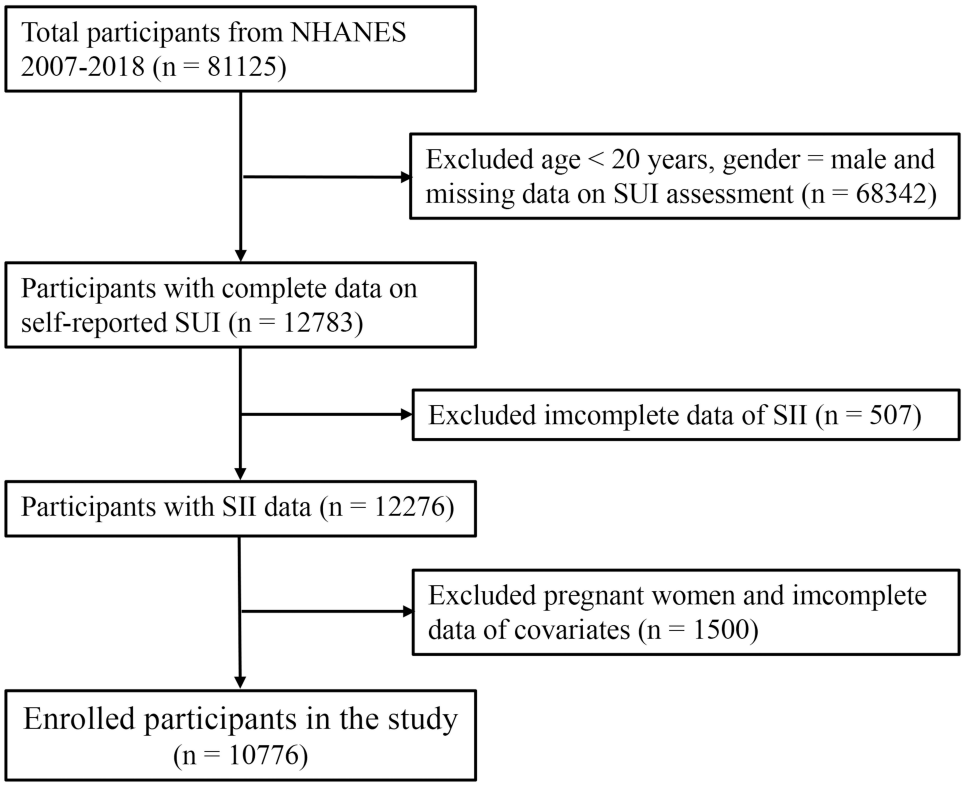

Figure 1 Flowchart of participants selection.

Assessment of SUI

Evaluation of the SUI was conducted through the administration of a self-reported questionnaire, and face-to-face interviews with all participants aged 20 and over were conducted by trained interviewers. To determine whether participants had experienced SUI in the previous 12 months, they were queried: "Have you leaked or lost control of even a small amount of urine with an activity like coughing, lifting, or exercise?" SUI was determined if the participant answered "Yes". To assess the severity of SUI, participants were further asked: "How frequently does this occur?" The severity of SUI was categorized into two groups: monthly SUI and weekly SUI. The classification criteria were as follows: Responses of "less than once a month" or "a few times a month" were categorized as "monthly SUI". Responses of "a few times a week" or "every day and/or night" were categorized as "weekly SUI".

Assessment of SII

SII was used as the designated exposure variable in our study. Using automated hematology-analyzing devices (Coulter®DxH 800 analyzer), the lymphocyte count (LC), neutrophil count (NC), and platelet count (PC) were measured by complete blood counts and expressed as $\times 10^3$ cells/μL. The SII was determined by the formula PC × NC/LC in accordance with methods reported in previous studies.[13]

Covariates Definition

Information on covariates was collected by using standardized questionnaires, including age, race, education, marital status, ratio of family income to poverty (PIR), body mass index (BMI), waist circumference (WC), smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes. Vigorous or moderate physical activity was defined as activities inducing a substantial or modest increase in breathing or heart rate. Never smokers were defined as those who had smoked fewer than 100 cigarettes in their lifetime, former smokers as those who had quit smoking but had a history of more than 100 cigarettes, and current smokers as those who were currently smoking and had consumed at least 100 cigarettes. Drinking status was defined as having consumed at least 12 alcoholic beverages within one year. Hypertension was defined as being told by a doctor or other health professional that you have high blood pressure. Diabetes was defined as a reported diagnosis of diabetes and the use of diabetes medications or insulin.

Statistical Analysis

According to the guidelines for using NHANES data, we considered the complex survey design elements of NHANES wherever feasible, including sample weights, clustering, and stratification.[17] Continuous variables were expressed as the mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Participants were separated into two groups based on whether they had SUI. Baseline variables differences were tested by weighted *t*-test (continuous data) or weighted chi-square test (categorical variables). Given the skewed distribution of SII, we computed $\log_2$-transformed values for statistical analysis. The association between SII and SUI was explored using a survey-weighted multivariate logistic regression model. We also compared the relationship between the SII and the severity of SUI by dividing SUI into a monthly SUI and a weekly SUI. The level of SII was $\log_2$-transformed as continuous variables and grouped into tertiles as categorical variables to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Model 1 is a crude model with no covariates adjusted. Model 2 is a minimally adjusted model adjusted for age, race, education level, PIR and marital status. Model 3 is a fully-adjusted model with BMI, WC, smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension and diabetes added as covariates to model 2. Subgroup analysis and interaction term were used to explore differences among different populations. The nonlinear relationship between SII levels and SUI was evaluated using restricted cubic splines (RCS), with adjustments made for all covariates. Furthermore, due to nonlinearity was detected, we applied a two-piecewise logistic regression model to explore the threshold effect of SII on SUI and determine the inflection point. All statistical analyses were conducted in R software (version 4.1.3; https://cran.r-project.org) and $P < 0.05$ was considered statistically significant (two-tailed).

Results

Population Characteristics

Table 1 presents the participants' general characteristics (n = 10,776). Among the participants, the average age was 49.11 ± 17.48 years, with 4407 (40.9%) women suffering from SUI. There were significant differences between the two groups in terms of age, race, education, marital status, PIR, BMI, WC, smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension, diabetes, NC and SII Compared with non-SUI women, those with SUI were more likely to be older, Mexican-American or non-Hispanic white, married and less educated, have a higher BMI, WC, gravidity and number of vaginal deliveries, and have higher rates of diabetes and hypertension. Additionally, they also exhibited higher levels of NC and SII.

Table 1 Basic Characteristics of the Study Population in NHANES 2007–2018 (n = 10,776)

Items	Overall	Non-SUI	SUI	*P*
N (%)	10,776 (100.0)	6369 (59.1)	4407 (40.9)	
Age (y)				
Mean ± SD	49.11 ± 17.48	46.81 ± 18.24	52.42 ± 15.76	**< 0.001**
Race				
Mexican American	1624 (15.1)	871 (13.7)	753 (17.1)	**< 0.001**
Other Hispanic	1202 (11.2)	698 (11.0)	504 (11.4)	
Non-Hispanic White	4741 (40.0)	2581 (40.5)	2160 (49.0)	
Non-Hispanic Black	2168 (20.1)	1524 (23.9)	644 (14.6)	
Other races	1041 (9.7)	695 (10.9)	346 (7.9)	
Education				
Under high school	2457 (22.8)	1340 (21.0)	1117 (25.3)	**0.005**
High school or equivalent	2308 (21.4)	1366 (21.4)	942 (21.4)	
College graduate or above	6011 (55.8)	3663 (57.5)	2348 (53.3)	
Marital status				
Married/cohabiting	5882 (54.6)	3284 (51.6)	2598 (59.0)	**< 0.001**
Widowed/divorced/separated	2998 (27.8)	1671 (26.2)	1327 (30.1)	
Never married	1896 (17.6)	1414 (22.2)	482 (10.9)	
PIR				
≤ 1.3	3653 (33.9)	2156 (33.9)	1497 (34.0)	**< 0.001**
1.3–3.5	3990 (37.0)	2384 (37.4)	1606 (36.4)	
> 3.5	3133 (29.1)	1829 (28.7)	1304 (29.6)	
BMI (kg/m^2)				
< 24.9	3226 (29.9)	2219 (34.8)	1007 (22.9)	**< 0.001**
25–29.9	3091 (28.7)	1817 (28.5)	1274 (28.9)	
≥ 30	4459 (41.4)	2333 (36.6)	2126 (48.2)	
Waist circumference (cm)				
< 88	3272 (30.4)	2276 (35.7)	996 (22.6)	**< 0.001**
≥ 88	7504 (69.6)	4093 (64.3)	3411 (77.4)	
Smoking status				
Never	6819 (63.3)	4196 (65.9)	2623 (59.5)	**< 0.001**
Former	2024 (18.8)	1090 (17.1)	934 (21.2)	
Current	1933 (17.9)	1083 (17.0)	850 (19.3)	
Drinking status				
No	4127 (38.3)	2507 (39.4)	1620 (36.8)	**0.010**
Yes	6649 (61.7)	3862 (60.6)	2787 (63.2)	
Physical activity				
None	5784 (53.7)	3310 (52.0)	2474 (56.1)	**< 0.001**
Moderate	3107 (28.8)	1827 (28.7)	1280 (29.0)	
Vigorous	1885 (17.5)	1232 (19.3)	653 (14.8)	

(*Continued*)

Table 1 (Continued).

Items	Overall	Non-SUI	SUI	*P*
Gravidity				
< 2	5146 (47.8)	3371 (52.9)	1775 (40.3)	**< 0.001**
3–4	3585 (33.3)	1900 (29.8)	1685 (38.2)	
≥ 5	2045 (19.0)	1098 (17.2)	947 (21.5)	
Vaginal delivery				
< 2	7339 (68.1)	4571 (71.8)	2768 (62.8)	**< 0.001**
3–4	2529 (23.5)	1323 (20.8)	1206 (27.4)	
≥ 5	908 (8.4)	475 (7.5)	433 (9.8)	
Hypertension				
No	6859 (63.7)	4308 (67.6)	2551 (57.9)	**< 0.001**
Yes	3917 (36.3)	2061 (32.4)	1856 (42.1)	
Diabetes				
No	9250 (85.8)	5612 (88.1)	3638 (82.6)	**< 0.001**
Yes	1526 (14.2)	757 (11.9)	769 (17.4)	
Laboratory features				
LC ($\times 10^3$ cells/μL)	2.22 ± 0.94	2.21 ± 0.95	2.24 ± 0.92	0.899
NC ($\times 10^3$ cells/μL)	4.32 ± 1.77	4.24 ± 1.75	4.44 ± 1.79	**< 0.001**
PC ($\times 10^3$ cells/μL)	258.31 ± 66.93	257.39 ± 66.63	259.65 ± 67.34	0.277
SII ($\times 10^3$ cells/μL)	549.75 ± 339.69	539.41 ± 322.63	564.70 ± 362.46	**0.002**

Notes: Categorical variables were presented as n (%); Continuous variables were presented as mean ± SD. The use of bold font is to show that the *p*-value of the statistic is less than 0.05, making it more prominent.

Abbreviations: SUI, stress urinary incontinence; PIR, Ratio of family income to poverty; BMI, body mass index; LC, lymphocyte; NC, neutrophil, PC, platelet; PLR, platelet-lymphocyte ratio; NLR, neutrophil-lymphocyte ratio; PPN, product of platelet count and neutrophil count; SII, systemic immune-inflammation index.

Association Between SII and SUI

The relationship between SII and SUI was displayed in Table 2. A notable link was found in both the crude model (OR: 1.15; 95% CI: 1.08–1.23, $P < 0.001$) and the minimally adjusted model (OR: 1.16; 95% CI: 1.08–1.24, $P < 0.001$). In the fully adjusted model, the positive association between SII remained consistent (OR: 1.09; 95% CI: 1.01–1.19, $P = 0.021$), suggesting a 9% increased risk of SUI for each unit increase in log2SII. In addition, we further used the SII as a categorical variable (tertiles) for further analysis. Compared with the lowest SII tertile, the odds of SUI in the highest

Table 2 Association Between Systemic Immune-Inflammation Index (SII) and SUI in Women

Items	Crude model (Model 1)		Minimally-adjusted model (Model 2)		Fully-adjusted model (Model 3)	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Log_2SII	**1.15 (1.08, 1.23)**	**< 0.001**	**1.16 (1.08, 1.24)**	**< 0.001**	**1.09 (1.01, 1.18)**	**0.021**
Stratified by log_2SII tertiles						
Tertile 1	Reference		Reference		Reference	
Tertile 2	**1.34 (1.18, 1.52)**	**< 0.001**	**1.32 (1.16, 1.51)**	**< 0.001**	**1.24 (1.08, 1.42)**	**0.002**
Tertile 3	**1.25 (1.11, 1.41)**	**< 0.001**	**1.27 (1.11, 1.45)**	**< 0.001**	**1.15 (1.00, 1.31)**	**0.049**
P for trend*	**< 0.001**		**< 0.001**		0.057	

Notes: SII was converted from a continuous variable to a categorical variable (tertiles). Model 1 was adjusted for no covariates; Model 2 was adjusted for age, race, education level, PIR, and marital status; Model 3 was adjusted for age, race, marital status, education level, PIR, BMI, waist circumference, smoking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes. Log_2SII, log_2-transformed concentration of SII. *Test for trend (*p* for trend) based on variable containing median value for each tertile. The use of bold font is to show that the *p*-value of the statistic is less than 0.05, making it more prominent.

Abbreviation: SUI, stress urinary incontinence.

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SII tertile were 25% higher in the crude model (OR: 1.25; 95% CI: 1.11–1.41, $P < 0.001$), 27% higher in the minimally adjusted model (OR: 1.27; 95% CI: 1.11–1.45, $P < 0.001$), and 15% higher in the fully adjusted model (OR: 1.15; 95% CI: 1.00–1.31, P = 0.049). In addition, analyses focusing on SUI severity (Table S1) yielded similar findings. Higher SII levels were significantly associated with increased severity of SUI, particularly for monthly SUI. *P* values for trend also indicated a significant linear association between SII and SUI risk, although the significance was attenuated in the fully adjusted model (*P* for trend = 0.057).

Subgroup Analysis

Further subgroup analysis showed that there were consistent relationships between SII level and SUI across most subgroups (Figure 2). The results revealed that there was a positive correlation between SII and SUI in participants who were non-Hispanic white, with PIR > 3.5, the number of vaginal deliveries > 2, moderate physical activity, no diabetes and no hypertension. In addition, we also noted a positive association between SII and SUI in participants with WC < 88 cm, and those who were widowed/divorced/separated, although this correlation was borderline significant. The interaction tests revealed that there were no significant differences in the relationships between SII and SUI for age, race, marital status, PIR, BMI, WC, physical activity, hypertension and diabetes (all *P* for interaction > 0.05), except for vaginal deliveries (*P* for interaction = 0.040).

The Non-Linear Association Between SII and SUI

Using RCS, a non-linear relationship between $\log_2$SII and SUI was discovered after adjusting for all covariates (*P* for non-linearity = 0.020; Figure 3). A threshold effect analysis of SII on SUI was further conducted by the two-piecewise logistic regression. As shown in Figure 4, the inflection point of $\log_2$SII was 8.64. The odds of being SUI increased with the SII level, and this rising trend gradually slowed down after exceeding 8.64. Each unit increase of SII was associated with a 26% increase of the risk of SUI below 8.64 (OR: 1.26; 95% CI: 1.02–1.54, $P < 0.05$), and the relationship was not statistically significant above 8.64 (OR: 0.98; 95% CI: 0.85–1.12, $P = 0.721$) (Table 3).

Discussion

In our study, we found a significant correlation between SII and SUI. This association remained even after adjusting for multiple confounding variables in both continuous and categorical analyses of SII. Notably, we also identified a non-linear relationship and observed a threshold effect between SII and SUI, with an inflection point of 8.64. These findings suggest that an elevated SII is an independent risk factor for SUI when $\log_2$SII were below 8.64.

Currently, some studies have investigated the role of inflammation in lower urinary tract Symptoms. An epidemiological study reported that vaginitis and cervicitis were risk factors for urinary incontinence.[18] Li et al[8] reported that urinary tract infection and gynaecological inflammation can worsen the symptoms of SUI. Furthermore, Aldridge et al[19] found that 62% of patients with SUI had chronic urethritis and prolonged inflammatory stimulation led to fibrosis of the urethral mucosa, diminished mucus secretion, and decreased submucosal vascularity. Such changes compromised the urethral mucosa's sealing effect, thereby increasing the likelihood of SUI. Wei et al[20] reported a link between elevated SII and overactive bladder (OAB). Both OAB and SUI are manifestations of pelvic floor dysfunction, involving shared inflammatory pathways. Neuroinflammation and inflammatory factors play critical roles in tissue damage and pelvic floor degeneration, thereby worsening the symptoms of both conditions. Given its simplicity and accessibility, SII holds promise as a valuable biomarker for the clinical evaluation and treatment monitoring of OAB and SUI.

Another study revealed a positive correlation between higher dietary inflammatory index levels, indicative of a pro-inflammatory diet, and the increased likelihood of SUI.[21] These indicate that inflammation may be a underlying mechanism in the development of SUI. Increasing evidence implies a role of chronic inflammation in the pathogenesis and progression of SUI, however, the exact molecular mechanisms remain unclear. Proinflammatory cytokines, in particular, tumour necrosis factor (TNF), interleukin-6 (IL-6) and transforming growth factor-β, (TGF-β), modulate the expression of a wide range of ECM molecules and are pivotal in tissue remodeling during inflammation.[22] In a study of the effects of simulated birth traumas on urethral continence function in rats,[23] TNFR1 and IL- 6 were found to be significantly increased after multiple vaginal dilations, whereas TGF-β1 was increased after both single and multiple

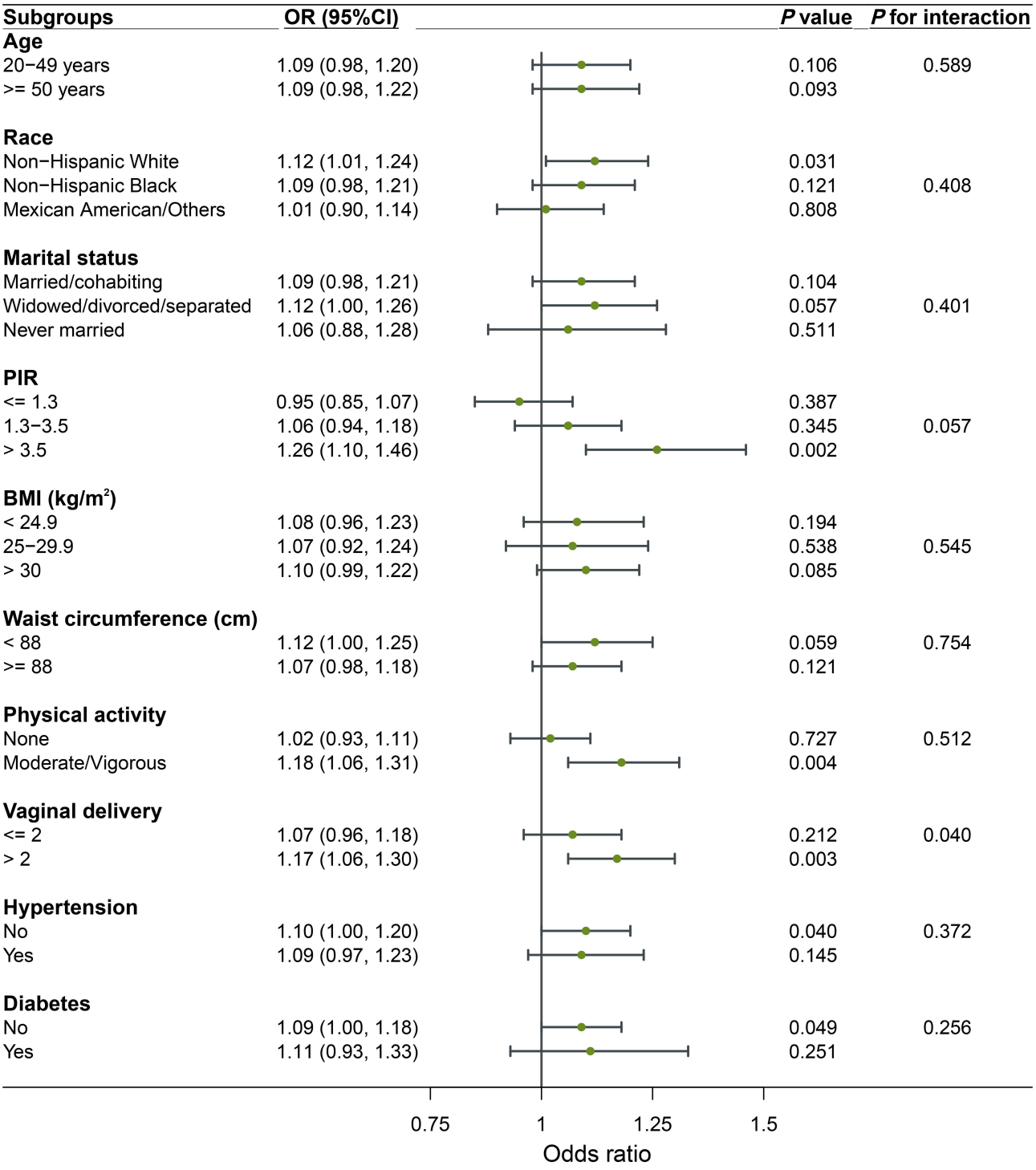

Figure 2 Subgroup analysis for the association between systemic immune-inflammation index (SII) and SUI in women. Models were adjusted for age, race, marital status, education level, PIR, BMI, waist circumference, smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes.
Abbreviation: SUI, stress urinary incontinence.

vaginal distensions. Elevation of these cytokines may contribute to ECM remodelling and deterioration of the urethral closure mechanism in multiple vaginal distensions, leading to the occurrence of SUI. Lin et al[24] found that the expression of TGF-β1 and Smad2 was significantly increased in the urethral tissue from rats with SUI, and that TGF-β1 could activate Smad2 in urethral smooth muscle cells in vitro. Smad2 is a major downstream regulator of TGF-β1, which plays a key role in inflammation and other diseases.[25] Previous studies have shown that TGF-β, the primary cytokine

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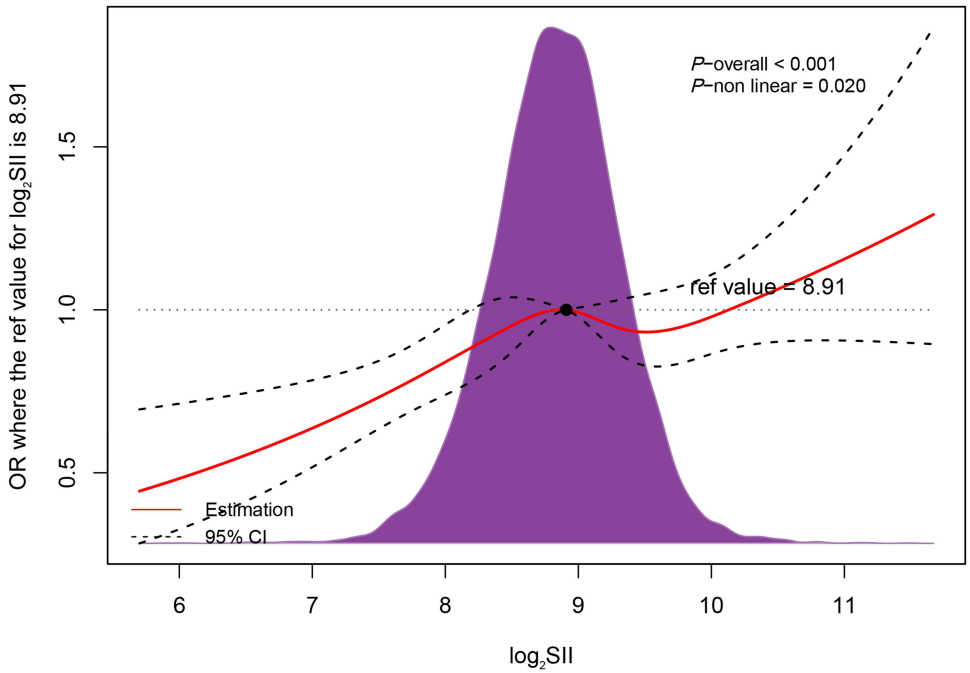

Figure 3 Restricted cubic spline (RCS) analysis of the association between log_2-SII and SUI. Model was adjusted for age, race, marital status, education level, PIR, BMI, waist circumference, smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes. The red line represents the best-fit line, and the black lines are 95% confidence intervals.
Abbreviations: SII, systemic immune-inflammation index; SUI, stress urinary incontinence.

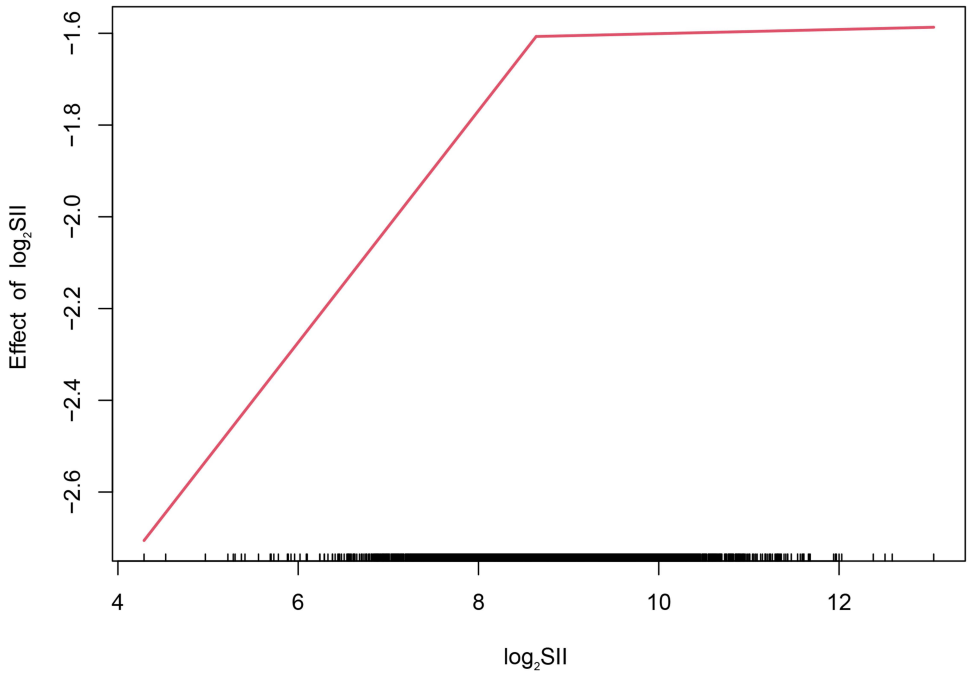

Figure 4 Association between log_2-SII and SUI by two-piecewise linear regression model. Model was adjusted for age, race, marital status, education level, PIR, BMI, waist circumference, smoking status, drinking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes.
Abbreviations: SII, systemic immune-inflammation index; SUI, stress urinary incontinence.

Table 3 Threshold Effect Analysis of SII on SUI by the Two-Piecewise Linear Regression

Log_2SII	Adjusted OR (95% CI)	P
Inflection point	8.64	
≤ 8.64	**1.26 (1.02, 1.54)**	**0.030**
> 8.64	0.98 (0.85, 1.12)	0.721
Log-likelihood ratio	**0.005**	

Notes: Model was adjusted for age, race, marital status, education level, PIR, BMI, waist circumference, smoking status, physical activity, gravidity, vaginal delivery, hypertension, and diabetes. The use of bold font is to show that the *p*-value of the statistic is less than 0.05, making it more prominent.

Abbreviations: SII, systemic immune-inflammation index; SUI, stress urinary incontinence; Log_2SII, log_2-transformed concentration of SII.

responsible for regulating ECM metabolism, enhances the expression of elastin, collagen, and fibronectin by phosphorylating Smad2 and Smad3, causing changes in the ECM composition of the urethral sphincter muscle.[10,26] These changes are closely related to the pathogenesis of urinary incontinence. Overall, inflammation seems to be a potential mechanism in the occurrence of SUI.

Subgroup analysis and interaction tests showed that the positive correlation between SII and SUI was consistent in most subgroups, but differed significantly for vaginal delivery. Existing research has demonstrated that childbirth is related to a pro-inflammatory cytokine response in the vagina.[27] In addition, childbirth, as an acutely stressful process, can cause dramatic changes in a woman's endocrine and immune systems with high levels of cytokines such as IL-1β, IL-6 and TNF-a.[28,29] Inflammation responses is especially remarkable during this period, which may account for the stronger correlation between SII and SUI in women with more than two vaginal deliveries compared to those with two or fewer deliveries.

Our study has some obvious advantages. Firstly, it is the first to examine the association between SII and SUI using the large sample size of the NHANES database. This sizable sample also enabled detailed subgroup analysis, enhancing the representativeness and validity of our findings and facilitating their generalization to the broader population. Secondly, we addressed the nonlinearity between SII and SUI and further explained this nonlinearity with a threshold effect analysis. However, due to the cross-sectional design of the study, we cannot conclude a causal relationship between SII and SUI. And platelet, neutrophil and lymphocyte counts were measured at a single time point at baseline, which may fail to capture subtle changes that may have occurred over time with follow-up. Further research is needed.

Conclusions

Our findings suggest that elevated SII levels are associated with an increased risk of SUI in women. A non-linear relationship and threshold effect between SII and SUI were observed, with an inflection point of 8.64. More well-designed prospective studies are necessary to substantiate our results.

Data Sharing Statement

Publicly available datasets were analyzed in this study. The data can be found here: https://www.cdc.gov/nchs/nhanes.

Ethics Statement

The survey was approved by the National Center for Health Statistics Ethics Review Board. The protocol was approved by the Ethics Committee of Women's Hospital of Nanjing Medical University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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