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ORIGINAL RESEARCH

# Inflammatory indices—Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI)—during Pregnancy and Associations with Gestational Diabetes Mellitus

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**Purpose:** Gestational diabetes mellitus (GDM) is a prevalent complication during pregnancy. This study aimed to explore the associations between inflammatory indices during pregnancy and the development of GDM.

**Methods:** Data from the Fujian Birth Cohort Study between March 2019 and December 2022 were used. Participants who delivered a live-born singleton were included and categorized into GDM and non-GDM groups. Two inflammatory indices, the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI), were calculated for each trimester of pregnancy via hematological parameters from complete blood count tests. The distributions of inflammatory indicators across trimesters were compared between the GDM and non-GDM groups. Additionally, multivariable logistic regression models were employed to investigate the associations between inflammatory indices and the incidence of GDM.

**Results:** A total of 17297 participants were included, 21.2% of whom were diagnosed with GDM. In the first trimester, the median SIIs for the GDM and non-GDM groups were $817.7\times10^9$/L and $756.9\times10^9$/L, respectively, whereas the median SIRIs were $1.6\times10^9$/L and $1.5\times10^9$/L, respectively. In both groups, the SII increased to its peak in the second trimester before declining, whereas the SIRI progressively increased throughout pregnancy. The SII and SIRI were greater in the GDM group than in the non-GDM group during the first two trimesters but lower in the third trimester. Nonlinear positive associations between first-trimester SII and SIRI levels and GDM were observed, with extreme quartile odds ratios of 1.32 (95% CI: 1.19, 1.48) and 1.39 (95% CI: 1.24, 1.55), respectively.

**Conclusion:** The SII and SIRI increased and reached their peak values in the second and third trimesters of pregnancy, respectively. Elevated levels of the SII and SIRI in early pregnancy were linked to an increased risk of GDM, suggesting their potential utility as screening tools for GDM.

**Keywords:** gestational diabetes mellitus, GDM, systemic immune-inflammation index, SII, systemic inflammatory response index, SIRI

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# Introduction

Gestational diabetes mellitus (GDM), defined as hyperglycemia first detected during pregnancy, is the most common pregnancy complication.[1,2] GDM increases the risk of adverse pregnancy outcomes,[3] as well as the long-term risk of cardiometabolic disorders in both mothers and offspring.[2,4,5] Taking proactive measures to prevent and monitor GDM is essential for successful GDM management.

Pregnancy is characterized by an altered inflammatory profile compared with the nonpregnant state, and an imbalance between pro- and anti-inflammatory cytokines may cause several pregnancy complications.[6] Emerging evidence suggests that GDM is associated with a chronic inflammatory state.[7,8] Recent advances have introduced two novel systemic inflammatory indices[9,10] — the systemic immune-inflammation index (SII) and the system inflammation response index (SIRI)—derived from complete blood cell counts. These indices are increasingly utilized in disease diagnosis and outcome prediction.[11,12] For instance, studies have shown that elevated SII values are correlated with an increased risk of diabetes and are associated with increased mortality in diabetic patients.[13,14] In the pregnant population, the SIRI and SII have been proposed as inflammatory markers to predict some gestational complications and adverse outcomes,[15–17] but research on their relationships with GDM is rare.[18,19]

Consequently, we hypothesized that the SII and SIRI could be linked to GDM and used for early screening. Our objectives were to describe the SII and SIRI distribution patterns throughout the pregnancy trimesters, separated by GDM status, and uncover their relationships with GDM using the data from a large cohort.

# Materials and Methods

## Study Design

We utilized data from the Fujian Birth Cohort Study, which is a large-scale, ongoing, prospective cohort study. The study enrolled pregnant women who were within 14 gestational weeks, underwent prenatal examinations and gave birth at the study site. All participants provided written informed consent upon enrollment. They were interviewed through questionnaires at baseline, during each trimester of pregnancy and postdelivery. Clinical information and biological samples were collected during pregnancy, along with data on pregnancy outcomes. The study complies with the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee of the Fujian Maternity and Child Health Hospital (approval number: 2017KR030).

## Study Population and Study Group

This study included participants who delivered live-born singletons (n=21785) between March 2019 and December 2022. The exclusion criteria included pregnancies conceived via assisted reproductive technology (n=1619), those with a self-reported history of diabetes or GDM from previous pregnancies or those taking hypoglycemic drugs (n=913). Participants with hyperglycemia (fasting plasma glucose [FPG] $\geq$ 7.0 mmol/L) (n=28) were also excluded. Moreover, those who lacked FPG data (n=1678) or complete blood count (CBC) data (n=250) at enrollment were excluded. Finally, data from 17297 participants were analyzed (Figure S1), 14901 of whom had complete CBC data for all trimesters.

The participants were categorized on the basis of hospital records from prenatal examinations. Those diagnosed with GDM were classified into the GDM group, while all others were classified into the non-GDM group. The diagnosis of GDM adhered to the Chinese guidelines,[20,21] primarily employing a 75g-2-hour oral glucose tolerance test (OGTT) conducted from 24–28 weeks of pregnancy (where the fasting glucose level was > 5.1 mmol/L; the 1-h glucose level was > 10.0 mmol/L; and the 2-h glucose level was > 8.5 mmol/L, indicating GDM).

## Inflammatory Indicators

To measure inflammation during pregnancy, we used two composite indices, the SII and the SIRI, by integrating counts from three subsets of white blood cells, monocytes (M), neutrophils (N), and lymphocytes (L), along with platelets (P).[9,10] Specifically, the SII is calculated as P×N/L, and the SIRI is calculated as N×M/L. The hematological parameters were derived from CBC tests conducted in each trimester. In addition to the SII and SIRI, we explored three traditional

inflammatory indicators: the neutrophil-to-lymphocyte ratio (NLR=N/L), the platelet-to-lymphocyte ratio (PLR=P/L), and the lymphocyte-to-monocyte ratio (LMR=L/M).

## Data Collection and Variables

Participant characteristics and pregnancy-related risk factors were obtained via self-report questionnaires at enrollment. The questionnaires included the following information: maternal demographics, such as age, education level, and monthly income; health information, including height, weight, smoking and drinking habits; medication taken around this pregnancy; disease history (such as diabetes and hypertension); and information on previous pregnancies, including any complications or outcomes.

Data concerning this pregnancy were sourced mainly from the hospital electronic medical records system. Gestational age was determined by the initial day of the last menstrual period and confirmed via ultrasound examination during the first trimester. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of the height in meters. Blood pressure (BP) was measured on the right upper arm via an oscillometric device. Venous blood samples were collected every trimester and sent to the hospital laboratory for CBC and biochemical tests.

## Statistical Analysis

Continuous variables are presented as the means and standard deviations (SDs) or medians and interquartile ranges (IQRs), as appropriate, while frequencies and percentages are used for categorical variables. The standardized mean difference (SMD) was computed to assess the disparities in characteristics between the GDM and non-GDM groups, with an absolute value of SMD smaller than 0.2 indicating a small difference.

The levels of inflammatory indices (SII and SIRI) in different trimesters were compared between the GDM and non-GDM groups, and a mixed model for repeated measures was used to identify temporal changes between groups across trimesters. To investigate the relationships between inflammatory indices and GDM, multivariable logistic regression models were constructed, incorporating covariates, including prepregnancy factors (age, education, monthly income, smoking, alcohol consumption, previous pregnancies, previous pregnancy complications, BMI before pregnancy), and key clinical measures at the baseline examination (BP, FPG, triglyceride [TG]). The inflammatory indices in the models were analyzed as continuous variables and then categorized into four groups by quartiles. Restricted cubic spline (RCS) analysis was used to assess the nonlinear associations. Additionally, a sensitivity analysis was conducted through a 1:1 matched case-control design, and the matching factors included age (±3 years old), gestational week at delivery (<37 weeks or ≥37 weeks), BMI before pregnancy (<18.5 kg/$m^2$, 18.5--24 kg/$m^2$, or >24 kg/$m^2$), BP (≤120/80 mmHg or >120/80 mmHg), FPG (<5.1 mmol/L or ≥5.1 mmol/L) and TG (<1.7 mmol/L or ≥1.7 mmol/L). The analyses were then repeated in this matched cohort.

All the statistical tests were two sided, with a significance level of 0.05. The analyses were performed via R software, version 4.3.2.

# Results

## Participant Characteristics

The study included 17297 participants, with an average gestational age at delivery of 39.2 (SD: 1.4) weeks. Among them, 21.2% were diagnosed with GDM. The mean age of the participants was 29.6 (SD: 3.9) years, with those in the GDM group being slightly older than those in the non-GDM group were (Table 1). Participants with GDM had a higher BMI both before pregnancy (GDM vs non-GDM: 21.8 vs 20.8 kg/$m^2$) and in the first trimester of pregnancy (22.1 vs 21.1 kg/$m^2$). Clinical measures revealed elevated levels of FPG and TG among GDM participants relative to non-GDM participants. The median SIIs of the GDM and non-GDM groups in the first trimester were $817.7\times10^9$/L and $756.9\times10^9$/L (SMD: 0.16), respectively, and the SIRI was $1.6\times10^9$/L for the GDM group compared with $1.5\times10^9$/L for the non-GDM group (SMD: 0.16). Detailed comparisons of specific blood cell counts and other baseline characteristics are shown in Table 1.

**Table 1** Baseline Characteristics of Pregnant Women, Grouped by Gestational Diabetes Mellitus Status

| | Overall | GDM | Non-GDM | SMD[a] |
|---|---|---|---|---|
| Number of participants | 17297 | 3673 | 13,624 | |
| Age, years, mean (SD) | 29.6 (3.9) | 30.5 (4) | 29.3 (3.9) | **0.3061** |
| College and above, n (%) | 12,946 (74.8) | 2733 (74.4) | 10,213 (75.0) | −0.0128 |
| Monthly income ≥ 9000 yuan, n (%) | 8415 (48.7) | 1745 (47.5) | 6670 (49.0) | −0.0290 |
| Smoking, n (%) | 364 (2.1) | 84 (2.3) | 280 (2.1) | 0.0159 |
| Drinking, n (%) | 2385 (13.8) | 535 (14.6) | 1850 (13.6) | 0.0284 |
| Prepregnancy BMI[b], $kg/m^2$, mean (SD) | 21 (2.8) | 21.8 (3) | 20.8 (2.7) | **0.3349** |
| BMI at baseline[b], $kg/m^2$, mean (SD) | 21.3 (2.9) | 22.1 (3.1) | 21.1 (2.8) | **0.3641** |
| Information of previous pregnancies | | | | |
| Previous pregnancies, n (%) | 9416 (54.4) | 2097 (57.1) | 7319 (53.7) | 0.0679 |
| Previous births, n (%) | 6738 (39.0) | 1488 (40.5) | 5250 (38.5) | 0.040 |
| Previous gestational complications, n (%) | 862 (5.0) | 211 (5.7) | 651 (4.8) | 0.0433 |
| Clinical measures | | | | |
| Gestational age at baseline, week, mean (SD) | 11.1 (1.2) | 11.1 (1.1) | 11.1 (1.2) | −0.0105 |
| SBP, mmHg, mean (SD) | 114.2 (11) | 115.5 (11.3) | 113.8 (10.9) | 0.1496 |
| DBP, mmHg, mean (SD) | 68.9 (9.8) | 70 (13.6) | 68.6 (8.5) | 0.1272 |
| FPG, mg/dL, mean (SD) | 4.7 (0.3) | 4.8 (0.4) | 4.7 (0.3) | **0.3917** |
| TG, mmol/L, mean (SD) | 1.3 (0.5) | 1.5 (0.6) | 1.3 (0.5) | **0.3485** |
| TC, mmol/L, mean (SD) | 4.6 (0.7) | 4.7 (0.8) | 4.6 (0.7) | 0.1537 |
| LDL-C, mmol/L, mean (SD) | 2.4 (0.6) | 2.5 (0.6) | 2.4 (0.6) | 0.1832 |
| HDL-C, mmol/L, mean (SD) | 1.7 (0.3) | 1.7 (0.3) | 1.7 (0.3) | −0.0903 |
| Complete blood count | | | | |
| Platelet, $10^9$/L, mean (SD) | 243.4 (50.8) | 249.1 (51.5) | 241.9 (50.5) | 0.1422 |
| Neutrophil, $10^9$/L, mean (SD) | 6.1 (1.6) | 6.4 (1.7) | 6 (1.6) | **0.2390** |
| Lymphocyte, $10^9$/L, mean (SD) | 1.9 (0.5) | 1.9 (0.5) | 1.9 (0.5) | 0.1024 |
| Monocyte, $10^9$/L, mean (SD) | 0.5 (0.1) | 0.5 (0.2) | 0.5 (0.1) | 0.1404 |
| Inflammatory indicators | | | | |
| SII[c], $10^9$/L, median (IQR) | 769.9 (594.1, 993.6) | 817.7 (628.6, 1038.4) | 756.9 (585.8, 979.3) | 0.1589 |
| SIRI[d], $10^9$/L, median (IQR) | 1.5 (1.1, 2.0) | 1.6 (1.2, 2.2) | 1.5 (1.1, 2.0) | 0.1576 |

**Notes**: [a]Standardized mean difference (SMD) is computed to compare characteristics between participants with GDM and without GDM. Absolute SMDs of 0.2, 0.5, and 0.8 represent small, medium, and large differences, respectively. Absolute SMD values greater than or equal to 0.2 are highlighted in bold. [b]BMI=weight (kg)/(height [m])$^2$. [c]SII=P×N/L, where P indicates platelets, N indicates neutrophils, and L indicates lymphocytes. [d]SIRI=N×M/L, where N indicates neutrophils, M indicates monocytes, and L indicates lymphocytes.

**Abbreviations**: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standardized deviation; SII, systemic immune-inflammation index; SIRI, system inflammation response index; SMD, standardized mean difference; TC, total cholesterol; TG, triglyceride.

## Inflammatory Indicators During Pregnancy

Among the 14901 participants (GDM: 3094 [20.8%]) who had CBC results in all trimesters, the SII increased from an initial value of 768.9 (IQR: 592.7--992.5) $\times 10^9$/L in the first trimester to a peak value of 840.1 (IQR: 664.4--1056.9) $\times 10^9$/L in the second trimester before diminishing to 797.3 (IQR: 625.0--1019.8) $\times 10^9$/L in the third trimester; meanwhile, the SIRI consistently increased (first trimester: 1.5 [IQR: 1.1--2.0] $\times 10^9$/L, second trimester: 2.2 [IQR: 1.6--3.0] $\times 10^9$/L, third trimester: 2.6 [IQR: 1.9--3.5] $\times 10^9$/L) throughout pregnancy. In the GDM group, the SII and SIRI were greater than those in the non-GDM group during the first two trimesters but lower in the third trimester (Figure 1, Table 2), with significant differences in trends across trimesters (both $P_{group*trimester}<0.001$).

With respect to other indicators of inflammation, such as the NLR, PLR, and LMR, the disparities between the GDM and non-GDM groups, as represented by the SMD, were less pronounced than those observed for the SII and SIRI (Table 2), except that the LMR of the GDM group in the third trimester was significantly greater than that of the non-GDM group. More details of the inflammatory indicators and blood cell counts across trimesters are listed in Table 2.

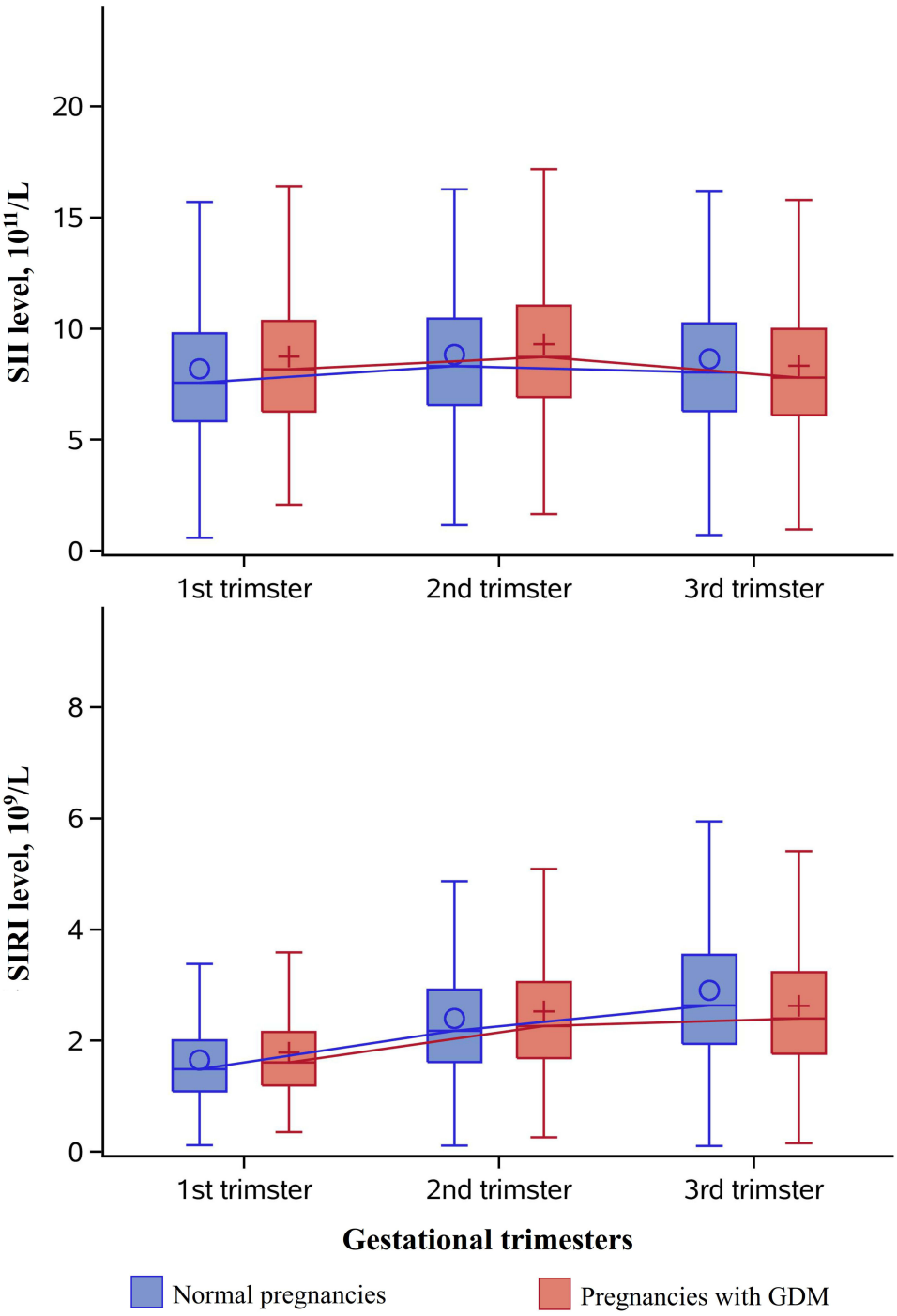


**Figure 1** Differences in inflammatory indicators across trimesters of pregnancy between the GDM and non-GDM groups. The box plot compares the distributions of the SII (top) and SIRI (bottom) between normal pregnancies (non-GDM group, shown in blue) and pregnancies with GDM (GDM group, shown in red) across different gestational trimesters. The horizontal line in the box represents the median value, and a straight line connects the median of each trimester to show the trend. The circles and plus signs in the boxes represent the mean values for the GDM and non-GDM groups in each trimester, respectively. GDM, gestational diabetes mellitus; SII, systemic immune-inflammation index; SIRI, system inflammation response index.

## Inflammatory Indices and GDM

In the first trimester, the SII and SIRI were significantly associated with GDM (Table 3). A 100-unit increase in the SII was related to a greater prevalence of GDM (odds ratio [OR]: 1.03, 95% confidence interval [CI]: 1.02–1.04) after adjustment; through RCS, a nonlinear relationship was found (P for nonlinear: 0.013, Figure 2); notably, higher quartiles of the SII had increased ORs of GDM (Q2: 1.11 [95% CI: 0.99–1.24], Q3: 1.26 [95% CI: 1.13–1.40], and Q4: 1.32 [95%

**Table 2** Blood Cell Counts and Inflammatory Indicators Across Trimesters of Pregnancy, Grouped by Gestational Diabetes Mellitus

| | First Trimester | | | Second Trimester | | | Third Trimester | | |
|---|---|---|---|---|---|---|---|---|---|
| | **GDM** | **Non-GDM** | **SMD[a]** | **GDM** | **Non-GDM** | **SMD[a]** | **GDM** | **Non-GDM** | **SMD[a]** |
| Complete blood count, $10^9$/L, mean (SD) | | | | | | | | | |
| Platelet | 249 (51.6) | 241.8 (50.4) | 0.1408 | 230.2 (50) | 225.1 (48.4) | 0.1042 | 211.9 (50.1) | 212.9 (49.9) | −0.0208 |
| Neutrophil | 6.4 (1.7) | 6 (1.6) | **0.2401** | 7.5 (1.9) | 7.3 (1.9) | 0.1339 | 6.8 (1.8) | 7.2 (1.9) | −0.1935 |
| Lymphocyte | 1.9 (0.5) | 1.9 (0.5) | 0.1057 | 1.9 (0.5) | 1.9 (0.5) | 0.0122 | 1.8 (0.5) | 1.9 (0.5) | −0.0801 |
| Monocyte | 0.5 (0.2) | 0.5 (0.1) | 0.1439 | 0.6 (0.2) | 0.6 (0.2) | 0.0651 | 0.7 (0.2) | 0.7 (0.2) | **−0.2291** |
| Inflammatory indicators, median (IQR) | | | | | | | | | |
| SII[b], $10^9$/L | 817.3 (627.2, 1035.5) | 756.6 (584.5, 979.3) | 0.1567 | 872.6 (692.3, 1103.7) | 831 (656.1, 1044.7) | 0.1318 | 779.4 (610.8, 998.7) | 803.2 (628.4, 1024.5) | −0.0858 |
| SIRI[c], $10^9$/L | 1.6 (1.2, 2.2) | 1.5 (1.1, 2) | 0.1579 | 2.3 (1.7, 3.1) | 2.2 (1.6, 2.9) | 0.1054 | 2.4 (1.8, 3.2) | 2.6 (1.9, 3.5) | **−0.2046** |
| NLR | 3.3 (2.7, 4.1) | 3.2 (2.6, 4) | 0.1071 | 3.9 (3.2, 4.7) | 3.8 (3.1, 4.6) | 0.0913 | 3.8 (3.1, 4.6) | 3.9 (3.2, 4.7) | −0.0855 |
| PLR | 130.8 (109.5, 156) | 129.8 (108.7, 156.2) | 0.0056 | 119.2 (100, 141.9) | 117 (97.6, 140.3) | 0.0528 | 117.3 (96.9, 140.5) | 114.9 (95.5, 138.7) | 0.0490 |
| LMR | 3.9 (3.2, 4.7) | 3.9 (3.2, 4.8) | −0.0544 | 3.2 (2.6, 3.9) | 3.2 (2.7, 3.9) | −0.0432 | 2.8 (2.3, 3.4) | 2.6 (2.2, 3.2) | 0.1416 |

**Notes**: The analyses were performed on 14901 participants who had CBC tests in all three trimesters. [a]Standardized mean difference (SMD) is computed to compare blood cell counts and inflammatory indicators between participants with GDM and without GDM. Absolute SMDs of 0.2, 0.5, and 0.8 represent small, medium, and large differences, respectively. Absolute SMD values greater than or equal to 0.2 are highlighted in bold. [b]SII=P×N/L, where P indicates platelets, N indicates neutrophils, and L indicates lymphocytes. [c]SIRI=N×M/L, where N indicates neutrophils, M indicates monocytes, and L indicates lymphocytes.

**Abbreviations**: GDM, gestational diabetes mellitus; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standardized deviation; SII, systemic immune-inflammation index; SIRI, system inflammation response index; SMD, standardized mean difference.

**Table 3** Associations Between Inflammatory Indicators in the First Trimester and Gestational Diabetes Mellitus

| | Unadjusted | | | Adjusted for Prepregnancy Factors | | | Full-adjusted | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | AUC | OR (95% CI) | P value | AUC | OR (95% CI) | P value | AUC |
| **SII in the first trimester**[a] | | | | | | | | | |
| Continuous value, per $10^{11}$/L increase | 1.044 (1.034, 1.055) | <0.001 | 0.551 | 1.037 (1.027, 1.048) | <0.001 | 0.628 | 1.028 (1.017, 1.039) | <0.001 | 0.672 |
| Quartiles (ref: Q1) | | | 0.546 | | | 0.629 | | | 0.672 |
| Q2 | 1.180 (1.059, 1.315) | 0.003 | | 1.131 (1.013, 1.263) | 0.028 | | 1.108 (0.991, 1.240) | 0.072 | |
| Q3 | 1.422 (1.279, 1.581) | <0.001 | | 1.318 (1.183, 1.467) | <0.001 | | 1.257 (1.126, 1.404) | <0.001 | |
| Q4 | 1.552 (1.398, 1.723) | <0.001 | | 1.430 (1.285, 1.591) | <0.001 | | 1.323 (1.185, 1.478) | <0.001 | |
| **SIRI in the first trimester**[b] | | | | | | | | | |
| Continuous value, per $10^{9}$/L increase | 1.196 (1.148, 1.247) | <0.001 | 0.549 | 1.167 (1.118, 1.217) | <0.001 | 0.628 | 1.145 (1.096, 1.196) | <0.001 | 0.672 |
| Quartiles (ref: Q1) | | | 0.545 | | | 0.629 | | | 0.673 |
| Q2 | 1.240 (1.113, 1.382) | <0.001 | | 1.204 (1.079, 1.344) | <0.001 | | 1.175 (1.050, 1.314) | 0.005 | |
| Q3 | 1.437 (1.292, 1.598) | <0.001 | | 1.369 (1.229, 1.525) | <0.001 | | 1.350 (1.209, 1.508) | <0.001 | |
| Q4 | 1.550 (1.395, 1.722) | <0.001 | | 1.449 (1.301, 1.613) | <0.001 | | 1.389 (1.243, 1.553) | <0.001 | |

**Notes**: Logistic models were constructed, including the unadjusted model, the model adjusted for prepregnancy factors (including age, education, monthly income, smoking, alcohol consumption, previous pregnancies, previous pregnancy complications, and BMI before pregnancy), and the fully adjusted model (including the prepregnancy factors mentioned above and blood pressure, fasting plasma glucose, and triglyceride in the first trimester). [a]SII=P×N/L, where P indicates platelets, N indicates neutrophils, and L indicates lymphocytes. [b]SIRI=N×M/L, where N indicates neutrophils, M indicates monocytes, and L indicates lymphocytes.

**Abbreviations**: AUC, area under the curve; CI, confidence interval; OR, odds ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

CI: 1.19–1.48]). Similarly, every unit increase in the SIRI was associated with an OR of 1.15 (95% CI: 1.10–1.20) for GDM; there was also a nonlinear relationship between the SIRI and GDM (P for nonlinearity: 0.006, Figure 2); the higher quartiles of the SIRI were linked to increased GDM risk (OR for Q2: 1.18 [95% CI: 1.05–1.31], Q3: 1.35 [95% CI: 1.21–1.51], and Q4: 1.39 [95% CI: 1.24–1.55]).

Additionally, there were significant associations between the inflammatory indices in the second and third trimesters and the occurrence of GDM (Table S1). Elevated SII and SIRI values in the second trimester were associated with greater odds of GDM, whereas the opposite trend was observed in the third trimester.

For the sensitivity analysis, 7124 matched participants were included, and the baseline characteristics and values of the inflammatory indicators are listed in Tables S2 and S3, respectively. An increase in the SII and SIRI in the first trimester was correlated with a greater incidence of GDM, with ORs of 1.03 (95% CI: 1.01–1.04, per 100 units) and 1.17 (95% CI: 1.10–1.24, per unit), respectively (Table S4). The SII and SIRI in the third and fourth quartiles were found to be significantly associated with increased GDM (ORs for the SII, Q3: 1.25 [95% CI: 1.09–1.44], Q4: 1.26 [1.09–1.46]; ORs for the SIRI, Q3: 1.36 [1.18–1.57], Q4:1.38 [1.19–1.59]).

## Discussion

This study demonstrated that two inflammatory indices, the SII and SIRI, fluctuated throughout the trimester of pregnancy. The SII initially increased before it decreased in the third trimester, whereas the SIRI consistently increased during pregnancy. Higher levels of the SII and SIRI in the early stage were associated with an increased incidence of GDM, suggesting the potential of these indices as early warning markers for GDM.

GDM is a prevalent complication of pregnancy that has been on the rise over the past few decades.[22] The enhanced inflammatory response in the GDM population indicates potential fluctuations in inflammatory indicators during GDM development.[7,23] Investigating the role of chronic low-grade inflammation in GDM may improve early prediction and targeted prevention. We utilized the SII and SIRI, which are derived from routine CBC test results, to evaluate the inflammatory status of pregnant women. Furthermore, we identified the variation in these indices between those with and without GDM across pregnancy trimesters using the data of a large cohort study. Our findings revealed a peak in the SII during the second trimester and in the SIRI by the third trimester for pregnant women. However, the trajectories of these indices differed between the GDM and non-GDM groups, with the GDM group showing higher levels in the first two trimesters but lower levels in the third trimester than the non-GDM group did. This contrasts with a prior case-control

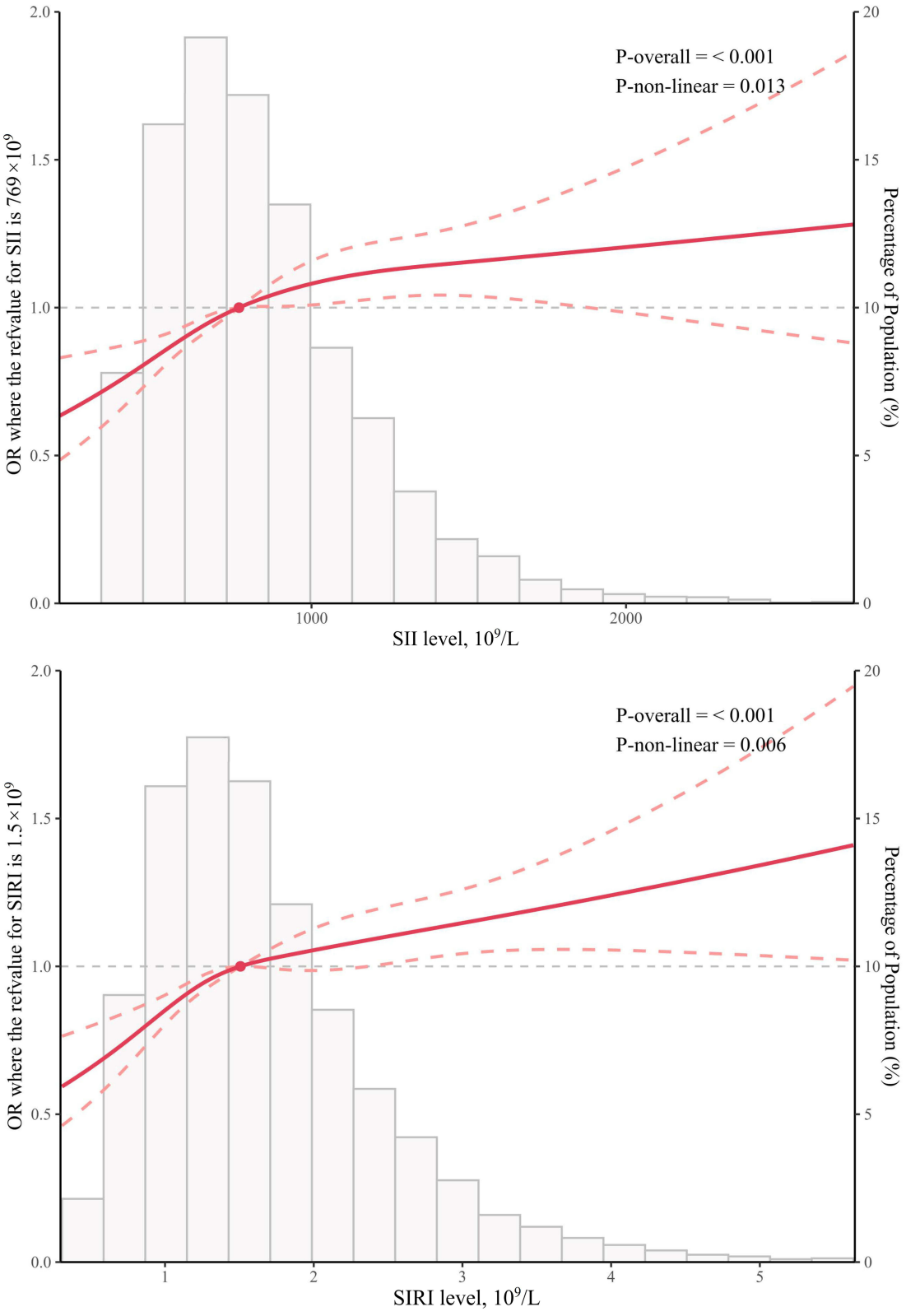


**Figure 2** Nonlinear relationships between inflammatory indicators in the first trimester of pregnancy and gestational diabetes mellitus. The plot of restricted cubic splines shows the relationships between the SII (top) and the SIRI (bottom) in the first trimester and GDM. The reference value is the median of the SII and SIRI. The bar chart shows the distribution of participants with different levels of inflammation indicators. The red solid lines represent OR values, and the dotted lines represent 95% confidence intervals. For better visualization, values beyond the 99th percentile are not displayed. GDM, gestational diabetes mellitus; OR, odds ratio; SII, systemic immune-inflammation index; SIRI, system inflammation response index.

study of 467 participants (GDM: 46.5%) that reported higher SII values in GDM subjects only in late pregnancy, with a continual increase in the SII.[18] In contrast, our study revealed a reduction in the SII during the third trimester, and the differences in SII levels between the GDM and non-GDM groups decreased. We considered that this discrepancy in results could stem from differences in participant characteristics and sample size. Unlike the study mentioned above, which randomly selected case and control subjects,[18] our research utilized data from a prospective real-world cohort and supplemented it by matched analyses, which yielded consistent results across the board. Currently, there are no recognized standard ranges for the SII and SIRI during pregnancy. We found only one published study that aimed to define the reference value of the SII and other inflammatory indicators during normal pregnancy in the Chinese population, and its results, including the value and trend of the SII across pregnancy trimesters (1st trimester: 754; 2nd trimester: 868, the highest value; 3rd trimester: 718), were similar to ours.[24] In addition, we further utilized the data of the National Health and Nutrition Examination Survey (NHANES) from 2003–2012, which includes pregnancy month records and corresponding CBC tests, to describe the inflammatory indices during pregnancy. The validation with the NHANES dataset echoed our observations on the distribution and shifts in the SII and SIRI levels (Table S5). Therefore, we assert the credibility of our research data and conclusions.

Our research revealed that higher inflammation indices in the first trimester of pregnancy were independently associated with an increased risk of GDM after adjusting for potential confounders, exhibiting a non-linear pattern; specifically, the odds of GDM are 1.32 times higher for pregnant women with SII in the highest quartile compared to those in the lowest quartile, and for SIRI, the odds are 1.39. Although these indices in the second and third trimesters were also associated with GDM, their clinical relevance appeared less pronounced than that in the first trimester. Previous research has highlighted the potential of the SII and SIRI in the early prediction of other pregnancy complications, such as preeclampsia and miscarriage,[15,16] whereas there are limited discussions regarding their associations with GDM.[19] Some studies have explored the predictive value of other inflammatory indicators composed of two blood cell types or single blood cell type for the occurrence of GDM.[25–27] A meta-analysis revealed that pregnancies diagnosed with GDM presented a greater NLR than those without GDM did, although the PLR was not significantly correlated with GDM.[28] In some studies, elevated levels of neutrophils, lymphocytes, monocytes, or platelets were reported to be associated with GDM or insulin resistance, but this remains controversial.[29] In addition, many studies have explored other serum inflammatory markers and GDM,[30] for example, a combination of low sex hormone-binding globulin (SHBG) and high-sensitivity C-reactive protein (hsCRP) has good predictive value for the detection of GDM;[31] TNF-α and IL-6 contribute to pregnancy-related insulin resistance and GDM, while GDM further increases their levels.[32] In general, our study underscored the relationships between SII, SIRI, and GDM, particularly highlighting the first trimester as a critical period for employing these indices in GDM risk assessment and monitoring.

The underlying mechanism between blood inflammatory indices and GDM is not fully understood, although how certain blood cells contribute to this condition has been explored.[29] For example, activated platelets can release platelet-derived extracellular vehicles and chemokines, affecting the function of immune cells and participating in intercellular communication and adhesion within the vasculature.[33,34] The activation of neutrophils generates a large amount of reactive oxygen species, which can provoke downstream inflammatory responses and contribute to insulin resistance.[35,36] As critical elements of the immune response, an imbalance between proinflammatory and anti-inflammatory T lymphocyte cells can increase the risk of GDM.[37] A reduction in monocytes may induce GDM development via the downregulation of anti-inflammatory factors, the upregulation of proinflammatory factors in peripheral blood, and alterations in the differentiation of placenta-derived macrophages.[38] The SII and SIRI, which are central to our investigation, include various hematological parameters, rendering them more comprehensive indicators of the inflammatory state, thereby potentially providing valuable insights into the relationship between inflammation and GDM.

The potential of certain blood cells or inflammatory indices to predict GDM in its early stages has been proposed.[19,29] However, the AUC results from our study suggested that the SII or SIRI may lack the specificity required to act as definitive predictive markers for GDM. Overall, adding inflammatory markers to clinical GDM risk prediction tools is currently debatable and challenging, as isolated makers may not provide adequate predictive ability.[30] Nonetheless, they could still function as clinically feasible, affordable and convenient tools for early monitoring of GDM, helping to identify the risk of developing GDM ahead of the routine examination for GDM, such as the OGTT during the second

trimester. Establishing GDM monitoring programs and reference standards for the SII and SIRI could complement blood glucose tests in the GDM prevention and management.

There are several limitations in this study. First, this birth cohort was not designed specifically for GDM; thus, the diagnosis of GDM was obtained primarily from medical records. Nevertheless, the diagnosis of GDM was in accordance with the Chinese guidelines, and the hospital electronic medical records system can ensure the prospective recording and accuracy of the data. Second, we did not have data on the SII and SIRI before pregnancy among the participants, which restricted our ability to compare the variations in inflammatory indicators before and during pregnancy. Moreover, detailed records of treatment approaches for pregnant women with GDM during pregnancy, such as drug use, were not meticulously documented. However, the data from self-report questionnaires in each trimester of pregnancy indicated minimal pharmacological intervention among the patients.

## Conclusion

The novel inflammatory indices, the SII and the SIRI, increased during pregnancy. The SII peaked in the second trimester, whereas the SIRI consistently increased across trimesters. Compared with those without GDM, participants with GDM had higher levels of both the SII and SIRI in the first two trimesters but lower levels in the third trimester. Notably, elevated SII and SIRI in early pregnancy were independently associated with a heightened risk of GDM, suggesting that these inflammatory indices could be used as clinically feasible supplements to blood glucose tests for the early detection of GDM.

## Abbreviations

CBC, complete blood count; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio;

SD, standardized deviation; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; SMD, standardized mean difference.

## Data Sharing Statement

The dataset used in the present study is not currently publicly available but is available from the corresponding author (Haibo-Li) upon reasonable request.

## Ethics Approval and Informed Consent

The study was approved by the ethics committee of Fujian Maternity and Child Health Hospital (approval number: 2017KR030). Informed consent was obtained from all participants before data collection.

## Author Contributions

All authors made a significant contribution to the work reported, whether 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; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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