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# Association of the inflammatory burden index with the risk of pre-diabetes and diabetes mellitus: a cross-sectional study

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## Abstract

**Objective** This study aims to investigate the association between the Inflammatory Burden Index (IBI) and the prevalence of pre-diabetes (pre-DM) and diabetes mellitus (DM) in the U.S. population from 1999 to 2010. By analyzing relevant data collected during this period, the study seeks to understand IBI's role in the onset of pre-DM and DM and its potential implications for public health.

**Methods** A cross-sectional analysis was conducted using data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010. A total of 29,554 participants were included, with diabetes status determined by self-reported diagnoses and clinical indicators (such as glycosylated hemoglobin and fasting blood glucose). The Inflammatory Burden Index (IBI) was calculated using C-reactive protein (CRP) multiplied by the neutrophil-to-lymphocyte ratio. The generalized additive model (GAM) was employed to examine the relationship between increasing IBI and the incidence of pre-DM and DM.

**Result** The study included 29,554 participants, with 14,290 (48.4%) men and 15,264 (51.6%) women, and a mean age of 48.3 years (SD = 19.1). The findings revealed a significant association between IBI and the risk of pre-DM and DM. In the fully adjusted model, a stronger relationship was observed between pre-DM, DM, and IBI. The prevalence of pre-DM and DM was significantly higher in the fourth quartile (Q4) compared to the first quartile (Q1), with a 26% prevalence of pre-DM and an 18% prevalence of DM when IBI was greater than 1.04.

**Conclusion** Our study demonstrates a significant correlation between IBI and the risk of pre-DM and DM in the U.S. population. Given these findings, we recommend that IBI be considered as a key indicator for the management and treatment of pre-DM and DM in clinical settings.

**Keywords** IBI, Diabetes mellitus, Pre-diabetes, NHANES, Cross-sectional study, Relevance analysis

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## Introduction

Pre-diabetes (Pre-DM) is a transitional stage preceding the onset of diabetes mellitus (DM), characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or a combination of both. It represents a hyperglycemic state lying between normoglycemia and DM, often referred to as the "undiseased" stage that is common to a variety of major diseases [1–2]. Effectively managing the Pre-DM population is critical for controlling or even reversing the progression to DM. Therefore, timely prediction and intervention are pivotal for Pre-DM control and the tertiary prevention of DM. Diabetes mellitus (DM) is associated with increased incidence and mortality, reflecting an accelerated aging process. It is primarily characterized by elevated fasting blood glucose (FPG) levels or increased glycated hemoglobin (HbA1C) [3]. As a chronic condition, DM is now the eighth leading cause of permanent disabilities globally and has become a pressing public health issue [4]. In 2021, 529 million people worldwide were living with DM, and by 2050, this number is projected to rise to 1.31 billion [5]. Although the pathogenesis of DM is complex, insulin resistance (IR) is widely recognized as a primary contributor [6], though the precise mechanisms remain unclear.

Chronic low-grade inflammation in the body is closely linked to both Pre-DM and DM and is one of the key factors in the development of insulin resistance [7]. Chronic hyperglycemia damages various tissues, triggering the immune system and leading to persistent inflammation. This inflammation exacerbates insulin resistance, making blood glucose control more difficult and creating a vicious cycle that can manifest as pre-diabetic symptoms. In individuals with DM, insulin action is impaired, preventing cells from properly absorbing glucose and resulting in elevated blood sugar levels. This metabolic imbalance activates the immune system, further driving chronic inflammation, which in turn impairs insulin function and increases insulin resistance [8]. Several studies have indicated that DM is influenced by multiple factors, including genetics and lifestyle. Managing these risk factors is crucial for early prevention and risk control. With a better understanding of the differences in Pre-DM and DM burdens across populations and the common risk factors involved, more targeted and effective strategies can be developed to manage and reduce DM risk amidst complex contributing factors.

Hematological parameters are valuable indicators for assessing the severity and prognosis of various diseases. Inflammatory markers and hematological indicators can serve as direct or indirect measures of the body's inflammatory status. One such marker is C-reactive protein (CRP), which is closely correlated with insulin resistance [9]. CRP inhibits insulin receptor tyrosine kinase activity and promotes the phosphorylation of insulin receptor substrates, thereby affecting insulin synthesis and secretion in pancreatic islet cells, contributing to the development of insulin resistance [10]. Elevated levels of TNF-α in DM patients also activate neutrophils, inducing the overexpression of nicotinamide adenine dinucleotide phosphate oxidase, leading to the generation of reactive oxygen species. These species, in turn, promote the formation of neutrophil extracellular traps (NETs) [11]. The formation of NETs releases neutrophil elastase, which degrades the insulin receptor substrate 1, further exacerbating insulin resistance. Regarding lymphocytes, regulatory T cells (Tregs) play a significant role by inhibiting the production of gamma interferon and TNF-α by effector T cells through an IL-10-mediated pathway. Tregs can help prevent the onset of pre-diabetes and DM by inhibiting the pro-inflammatory response. T-lymphocyte subpopulations are critical in defending against viral infections and modulating immune responses.

IBI is an emerging indicator that indirectly reflects the inflammatory imbalance in the body. It has been shown to predict conditions such as rheumatoid arthritis, all-cause mortality [12], and aneurysmal subarachnoid hemorrhage [13]. IBI is calculated as CRP multiplied by the neutrophil-to-lymphocyte ratio. Previous studies have demonstrated that severe inflammatory imbalances may exist in individuals with abnormal glucose metabolism, including those with pre-diabetes (pre-DM) and diabetes mellitus (DM) [14]. Additionally, composite inflammatory indices based on leukocyte subtypes, such as the systemic immune-inflammatory index (SII, calculated as neutrophils × platelets/lymphocytes) and the systemic inflammatory response index (SIRI, calculated as neutrophils × monocytes/lymphocytes), have shown value in predicting diabetes and its complications [15–16]. While these indices can predict the onset of diabetes to some extent, they still have limitations. Most notably, these composite inflammation indices typically exclude CRP, which is a crucial marker for assessing overall inflammation in the body [17]. In contrast, IBI, as a composite inflammation index, offers a more stable and accurate assessment of inflammation. It provides a more comprehensive reflection of the body's inflammatory burden and quantifies the current level of inflammation more precisely. Therefore, IBI may serve as a better indicator of the inflammatory state in a population than CRP, neutrophils, or lymphocytes alone. A study involving 6,369 cancer patients demonstrated that IBI assessed high and medium-low inflammatory loads with the highest accuracy compared to other systemic inflammation biomarkers, positioning IBI as a potential predictive biomarker of inflammatory burden in cancer patients [18]. Further, a multicenter prospective cohort study in China confirmed that IBI was independently associated with overall survival and 90-day outcomes in patients with non-small

cell lung cancer, suggesting its role as an optimal systemic inflammation biomarker [19]. Additionally, a study by Xiong et al., which included 22,343 participants, showed that IBI, as a quantifier of inflammation, was positively associated with osteoarthritis and all-cause mortality [20].

Currently, no scholars have studied the relationship between IBI and pre-DM and DM. therefore, this study aimed to investigate the association between IBI and pre-DM and DM, and we utilized data from the National Health and Nutrition Examination Survey (NHANES), hypothesizing that there is a positive correlation between IBI and the risk of pre-DM and DM prevalence in the U.S. population in an effort to inform the diagnosis and treatment of pre-DM and DM or the prevention.

## Materials and methods

### Study population

The National Center for Health Statistics (NCHS) administers the National Health and Nutrition Examination Survey (NHANES), a nationwide program designed to assess the health and nutritional status of Americans. For this study, we utilized NHANES data from 1999 to 2010. The survey methodology was approved by the NCHS Research Ethics Review Board, and all participants provided signed, informed consent. From the total of 62,160 participants from 1999 to 2010, we excluded individuals who lacked C-reactive protein (CRP) data ($n = 14{,}723$), individuals without neutrophil and lymphocyte count data ($n = 211$).

### Diagnosis of DM and pre-DM

According to the 2021 Diabetes Healthcare Standards [21], the definition of DM can be confirmed based on any of the following criteria: 1) patient self-reported that he/she was diagnosed with DM by his/her physician; 2) currently taking glucose-lowering medications or receiving insulin injections; 3) random blood glucose level equal or higher than 11.1 mmol/L; 4) glycated hemoglobin level equal or higher than 6.5%; 5) fasting blood glucose (FPG)) level equal or higher than 7.0 mmol/L; 6) a 2-hour blood glucose level equal or higher than 11.1 mmol/L on an oral glucose tolerance test (OGTT). The definition of pre-DM can be confirmed based on any of the following criteria [21]: 1) patient self-reported that he/she was diagnosed with pre-DM by his/her physician; 2) glycated hemoglobin level equal or higher than 5.7% and lower than 6.5%; 3) fasting blood glucose (FPG) level equal or higher than 5.6 mmol/L and lower than 7.0 mmol/L; 4) a 2-hour blood glucose level equal or higher than 7.8 mmol/L and lower than 11.1 mmol/L on an oral glucose tolerance test (OGTT)".

### Calculation of IBI

We calculated IBI by C-reactive protein times neutrophil count divided by lymphocyte count [12].

Venous blood samples were collected in the early morning during fasting for routine clinical chemistry testing. Neutrophils and lymphocytes in whole blood were analysed by the Coulter counter method and CRP was quantified by latex enhanced immunoturbidimetric assay.

$$IBI = CRP * neutrophils/lymphocyte\,s\,(mg/L)$$

### Covariate

We included a comprehensive set of covariates that have been identified as strong predictors of pre-diabetes (pre-DM) and diabetes mellitus (DM) risk in the literature [21–27]. These covariates include social and economic factors such as age, educational level, and marital status; health-related behaviors such as smoking and alcohol consumption; and personal health conditions including heart disease, stroke, hyperlipidemia (cholesterol level > 240 mg/dL or triglycerides > 200 mg/dL) [28] and hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) [29]. Race/ethnicity was categorized into Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Non-Hispanic Asian. Educational level was categorized as below high school, high school or GED, and above high school. Marital status categories included Refused, Married, Widowed, Divorced, Separated, Never Married, and Living with Partner. The Poverty-Income Ratio (PIR), which reflects household income status, was calculated by dividing household (or individual) income by the applicable poverty threshold for the study year and was categorized as ≥ 1, ≤0.99, or Refused. For physical measurements, height and weight were recorded, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, with BMI categorized as < 25 kg/m², 25–29.9 kg/m², and ≥ 30 kg/m². Smoking status was classified as never smoker (fewer than 100 cigarettes lifetime), ex-smoker (smoked > 100 cigarettes but not currently smoking), or current smoker (smoked > 100 cigarettes and smoking at the time of the survey). Drinking habits were categorized as < 12 drinks per year or ≥ 12 drinks per year (Table 1). Comprehensive measurement protocols for these variables are publicly available at https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx.

### Statistical analysis

The mean, along with its minimum and maximum values, was used to represent continuous variables that followed a normal distribution. For variables with a skewed distribution, the median and interquartile range (IQR) were

**Table 1** The classifications of covariates

| Covariates | Classification |
|---|---|
| Gender | Male; female |
| Age(year) | ≥ 18 |
| Race | Mexican American; Other Hispanic; Non-Hispanic White; Non-Hispanic Black; Non-Hispanic Asian |
| Educational Level | Less than high school; High school or GED; Above high school |
| Marital status | Refused; Married; Widowed; Divorced; Separated; Never married; Living with partner |
| Poverty income ratio | ≥ 1; ≤0.99; Refused |
| Drinking Status | < 12 drinks/year; ≥12 drinks/year |
| Smoking Status | Never; Now; Former |
| Body mass index | < 25 kg/m$^2$; 25–29.9 kg/m$^2$; ≥30 kg/m$^2$ |
| Hyperlipidemic | No; yes |
| Hypertension | No; yes |
| Heart disease | No; yes |
| Stroke | No; yes |

used. Categorical variables were presented as frequencies and percentages. Differences in the Inflammatory Burden Index (IBI) between groups were compared using one-way analysis of variance (ANOVA), Kruskal-Wallis H test, chi-square test, or Fisher's exact test. To assess the effect of IBI on the risk of pre-diabetes and diabetes onset, a binary logistic regression model was employed, and odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated. Demographic characteristics such as age, gender, and ethnicity, as well as adverse lifestyle factors (e.g., smoking, alcohol consumption) and past medical history (e.g., hypertension, hyperlipidemia, stroke), were included as covariates to adjust for in the model. The relationship between IBI and pre-DM and DM was analyzed both as a continuous variable and as a quartile categorical variable. A generalized additive model (GAM) with natural splines was used to explore the non-linear relationship between IBI and pre-DM and DM. For non-linear relationships identified, a two-piecewise regression model based on smooth plot visualization was applied to determine the threshold effect of IBI on pre-DM and DM. Additionally, stratified analyses were performed based on gender, ethnicity, education level, marital status, poverty-to-income ratio, BMI, smoking status, drinking status, hypertension, hyperlipidemia, heart disease, and stroke. Multivariate logistic regression models were used to assess stratified heterogeneity and test for interactions.

All data analyses were conducted using the Free Statistics analysis platform (version 1.9) and R Statistical Software (version 4.2.2, available at http://www.R-project.org, R Foundation) in Beijing, China. A two-sided $p$-value of less than 0.05 was considered statistically significant in the analysis.

## Result

### Baseline characteristics

Applying the inclusion and exclusion criteria resulted in a total of 29,554 participants, with a mean age of 48.3 years (SD = 19.1). Among the participants, 14,290 (48.4%) were male and 15,264 (51.6%) were female. Diabetes mellitus (DM) affected 14.2% of the participants, while 26.6% were diagnosed with pre-diabetes (pre-DM). Table 2 provides a detailed overview of the clinical characteristics of the participants, categorized by DM status.

The number of male patients was higher than that of females. Body mass index (BMI) was generally higher in patients with DM and pre-DM compared to those without, suggesting that obesity may influence the onset of DM. The mean Inflammatory Burden Index (IBI) was 0.9 ± 1.3 mg/L, with the highest mean IBI found in patients with DM (IBI: 1.3 ± 1.6 mg/L). Additionally, the incidence of hyperlipidemia, hypertension, stroke, and coronary heart disease was significantly higher in this population.

And those missing information on pre-diabetes (pre-DM) or diabetes mellitus (DM) status ($n$ = 7,895). We excluded all participant in the NHANES who was aged 18 years or younger ($n$ = 9,777). After these exclusions, 29,554 participants remained in the study (Fig. 1). Of the 32,606 subjects excluded, 16,295 (50%) were male and 16,311 (50%) were female. In terms of age distribution, 26,781 were younger than 18 years, 4,123 were between 18 and 60 years, and 1,779 were older than 60 years. Ethnically, 30.2% were Mexican American, 6.6% were of Other Hispanic origin, 31.2% were Non-Hispanic White, 26.7% were Non-Hispanic Black, and 5.2% were Non-Hispanic Asian.

### Association between IBI and the prevalence of pre-DM

In the univariate logistic regression analysis, IBI, as a continuous variable, was significantly associated with the risk of pre-diabetes (pre-DM) (OR = 1.25, 95% CI = 1.22 to

**Table 2** Characteristics of the study population, National health and nutrition examination survey (NHANES) 1999–2010 (*N* = 29,554)

| Characteristic | Symptom of diabetes | | | | |
|---|---|---|---|---|---|
| **Variables** | **Total** | **Without pre-DM/DM** | **Pre-DM** | **DM** | ***p*-Value** |
| NO. | 29,554 | 17,473 | 7872 | 4209 | |
| Age(year), Mean ± SD | 48.3 ± 19.1 | 42.0 ± 18.2 | 55.1 ± 17.5 | 61.9 ± 13.9 | < 0.001 |
| Gender, n (%) | | | | | < 0.001 |
| Male | 14,290 (48.4) | 7889 (45.1) | 4233 (53.8) | 2168 (51.5) | |
| Female | 15,264 (51.6) | 9584 (54.9) | 3639 (46.2) | 2041 (48.5) | |
| Race, n (%) | | | | | < 0.001 |
| Mexican American | 6235 (21.1) | 3663 (21) | 1559 (19.8) | 1013 (24.1) | |
| Other Hispanic | 1963 (6.6) | 1080 (6.2) | 577 (7.3) | 306 (7.3) | |
| Non-Hispanic White | 14,393 (48.7) | 8918 (51) | 3774 (47.9) | 1701 (40.4) | |
| Non-Hispanic Black | 5735 (19.4) | 3097 (17.7) | 1627 (20.7) | 1011 (24) | |
| Non-Hispanic Asian | 1228 (4.2) | 715 (4.1) | 335 (4.3) | 178 (4.2) | |
| Marital status, n (%) | | | | | < 0.001 |
| Refused | 725 (2.5) | 540 (3.1) | 129 (1.6) | 56 (1.3) | |
| Married | 15,356 (52.0) | 8659 (49.6) | 4359 (55.4) | 2338 (55.5) | |
| Widowed | 2564 (8.7) | 937 (5.4) | 910 (11.6) | 717 (17) | |
| Divorced | 2702 (9.1) | 1427 (8.2) | 788 (10) | 487 (11.6) | |
| Separated | 912 (3.1) | 504 (2.9) | 263 (3.3) | 145 (3.4) | |
| Never married | 5327 (18.0) | 4058 (23.2) | 943 (12) | 326 (7.7) | |
| Living with partner | 1968 (6.7) | 1348 (7.7) | 480 (6.1) | 140 (3.3) | |
| Poverty income ratio, n (%) | | | | | < 0.001 |
| ≤0.99 | 5474 (18.5) | 3264 (18.7) | 1370 (17.4) | 840 (20) | |
| ≥1 | 21,694 (73.4) | 12,877 (73.7) | 5841 (74.2) | 2976 (70.7) | |
| Refused | 2386 (8.1) | 1332 (7.6) | 661 (8.4) | 393 (9.3) | |
| Drinking Status, n (%) | | | | | < 0.001 |
| <12drinks/year | 16,810 (56.9) | 10,265 (58.7) | 4110 (52.2) | 2435 (57.9) | |
| ≥12drinks/year | 12,744 (43.1) | 7208 (41.3) | 3762 (47.8) | 1774 (42.1) | |
| Smoking Status | | | | | < 0.001 |
| Never | 16,079 (54.4) | 10,083 (57.7) | 3974 (50.5) | 2022 (48) | |
| Current | 6194 (21.0) | 3808 (21.8) | 1671 (21.2) | 715 (17) | |
| Former | 7281 (24.6) | 3582 (20.5) | 2227 (28.3) | 1472 (35) | |
| Body mass index, n (%) | | | | | < 0.001 |
| <25 kg/m$^2$ | 9129 (31.5) | 6821 (39.7) | 1741 (22.5) | 567 (13.9) | |
| 25–29.9 kg/m$^2$ | 10,037 (34.6) | 5939 (34.6) | 2821 (36.5) | 1277 (31.4) | |
| ≥30 kg/m$^2$ | 9812 (33.9) | 4429 (25.8) | 3162 (40.9) | 2221 (54.6) | |
| Educational level, n (%) | | | | | < 0.001 |
| Refused | 1297 (4.4) | 1125 (6.4) | 155 (2) | 17 (0.4) | |
| Less than high school | 8623 (29.2) | 4231 (24.2) | 2579 (32.8) | 1813 (43.1) | |
| High school or GED | 6710 (22.7) | 3879 (22.2) | 1895 (24.1) | 936 (22.2) | |
| Above high school | 12,924 (43.7) | 8238 (47.1) | 3243 (41.2) | 1443 (34.3) | |
| Hyperlipidemic, n (%) | | | | | < 0.001 |
| Yes | 8154 (27.6) | 3348 (19.2) | 2726 (34.6) | 2080 (49.4) | |
| No | 21,400 (72.4) | 14,125 (80.8) | 5146 (65.4) | 2129 (50.6) | |
| Hypertension, n (%) | | | | | < 0.001 |
| Yes | 9350 (31.6) | 3551 (20.3) | 3115 (39.6) | 2684 (63.8) | |
| No | 20,204 (68.4) | 13,922 (79.7) | 4757 (60.4) | 1525 (36.2) | |
| Stroke, n (%) | | | | | < 0.001 |
| Yes | 1010 (3.4) | 329 (1.9) | 319 (4.1) | 362 (8.6) | |
| No | 28,544 (96.6) | 17,144 (98.1) | 7553 (95.9) | 3847 (91.4) | |
| Heart Disease, n (%) | | | | | < 0.001 |
| Yes | 1192 (4.0) | 382 (2.2) | 360 (4.6) | 450 (10.7) | |
| No | 28,362 (96.0) | 17,091 (97.8) | 7512 (95.4) | 3759 (89.3) | |
| IBI, Mean ± SD | 0.9 ± 1.4 | 0.9 ± 1.3 | 1.0 ± 1.4 | 1.3 ± 1.6 | < 0.001 |

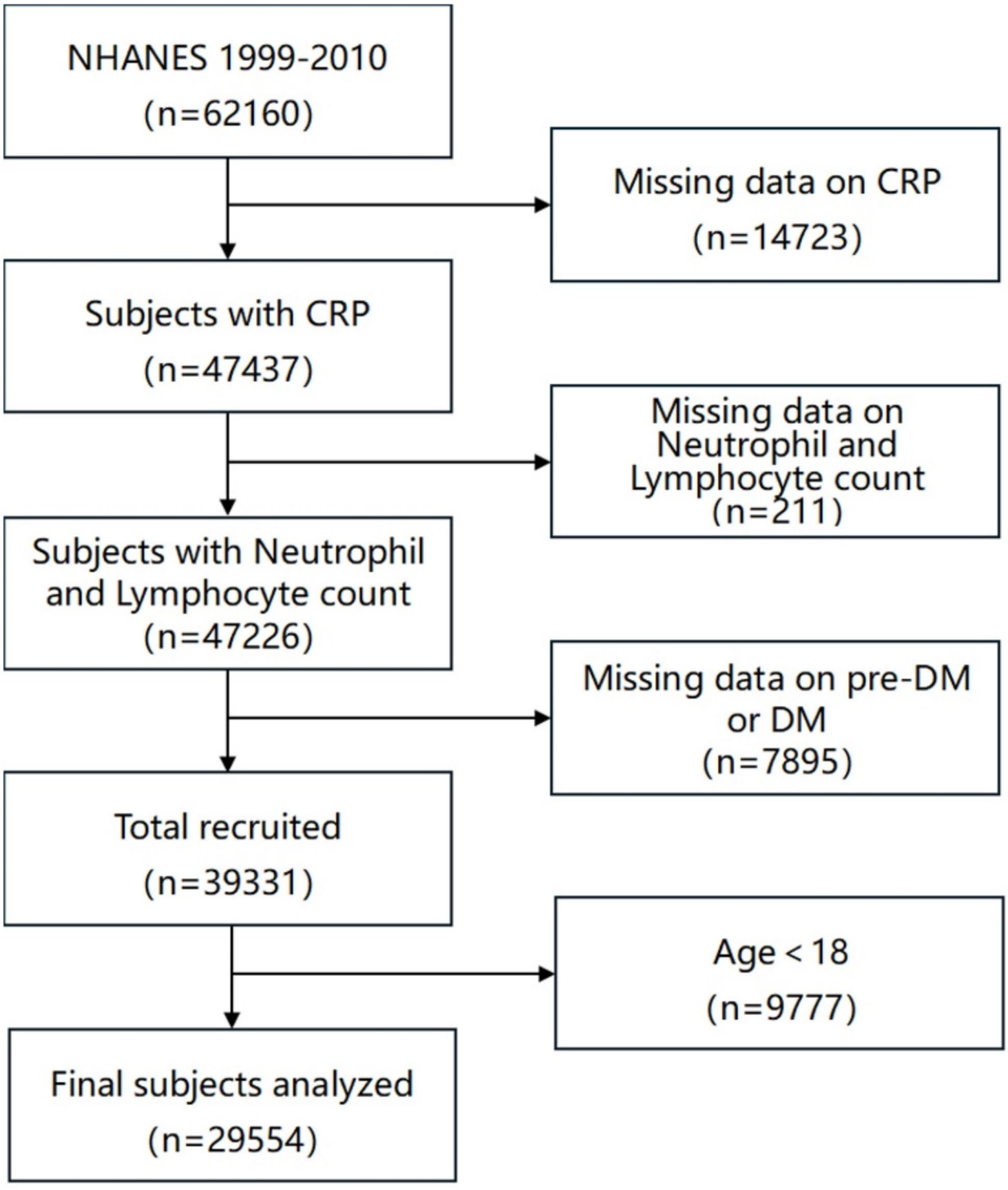


**Fig. 1** Flowchart illustrating the selection process for identifying qualified individuals

1.28, $p < 0.001$). After adjusting for potential confounders, including age, gender, race, marital status, education level, poverty-to-income ratio (PIR), and medical history, the association between IBI and pre-DM remained significant (OR = 1.08, 95% CI = 1.05 to 1.12, $p < 0.001$) (Supplementary Table S1, Model 4). When IBI was categorized into quartiles, the highest quartile (Q4) exhibited a significantly higher risk of pre-DM compared to the other groups (OR = 2.01, 95% CI = 1.86 to 2.18, $p < 0.001$), and this association persisted after adjusting

for other covariates (Supplementary Table S1). Figures 2 and 3 demonstrate the nonlinear relationship between IBI and the risk of pre-DM and diabetes mellitus (DM) ($p < 0.05$). Threshold analysis revealed that when IBI was below 1.376 mg/L, the odds ratio (OR) for pre-DM was 1.642 (95% CI = 1.498 to 1.8, $p < 0.001$). However, when IBI was ≥ 1.376 mg/L, the OR for pre-DM decreased to 1.022 (95% CI = 0.959 to 1.09, $p = 0.498$) (Supplementary Table S3).

**Association between IBI and the prevalence of DM**

In the univariate logistic regression analysis, IBI, as a continuous variable, was significantly associated with the risk of diabetes mellitus (DM) (OR = 1.05, 95% CI = 1.04 to 1.07, $p < 0.001$). After adjusting for age, gender, race, marital status, education level, poverty-to-income ratio (PIR), and medical history, the association between IBI and DM remained significant (OR = 1.06, 95% CI = 1.03 to 1.08, $p < 0.001$) (Supplementary Table S2, Model 4).

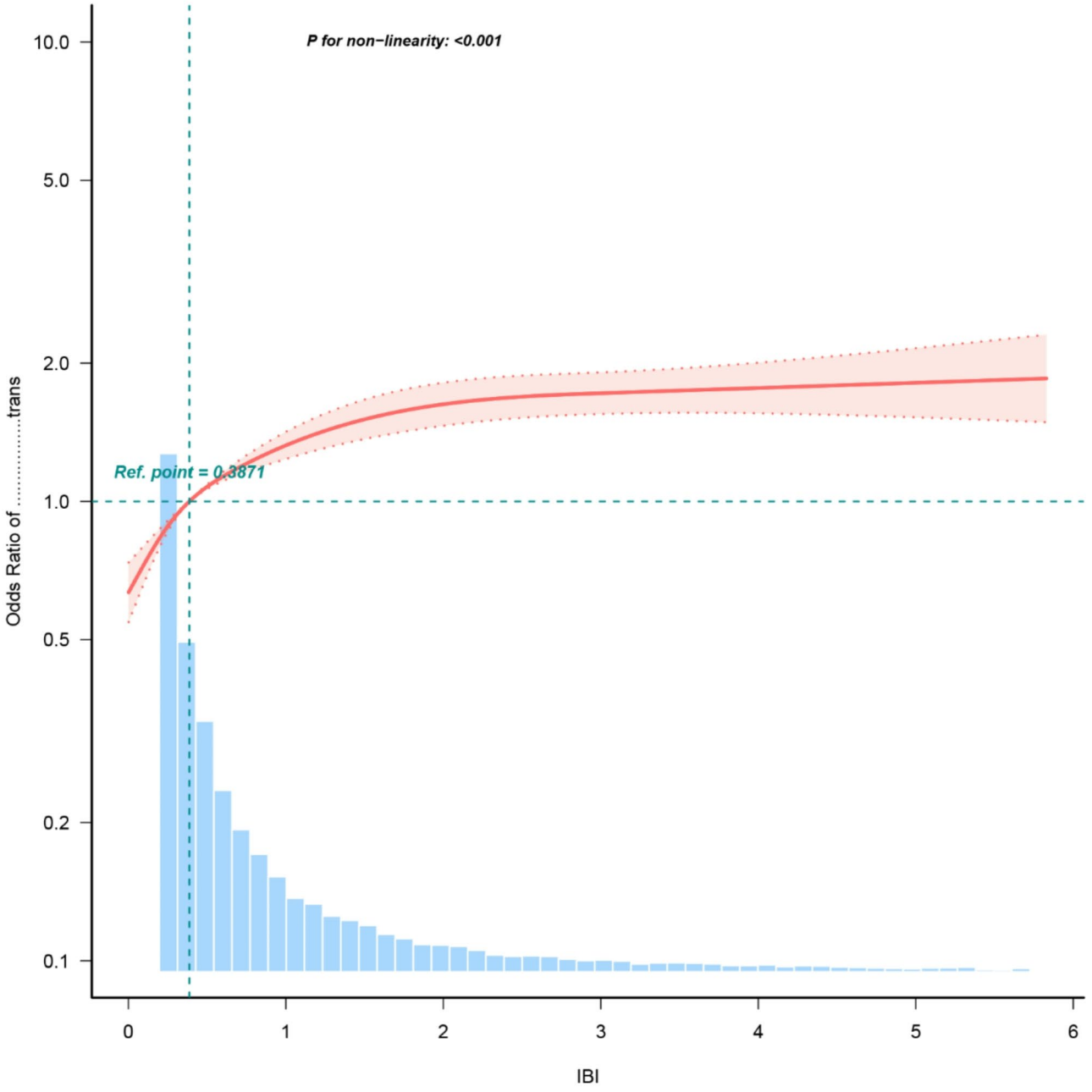


**Fig. 2** Limited cubic spline plots for the DM result by IBI levels after covariate adjustment. The light blue backdrop histograms display the proportion of the research population's IBI density distribution. Shaded ribbons represent the 95% confidence intervals and thick center lines, respectively, represent the computed adjusted odds ratios. The horizontal dotted lines (Reference point) display the odds ratio of 1.0

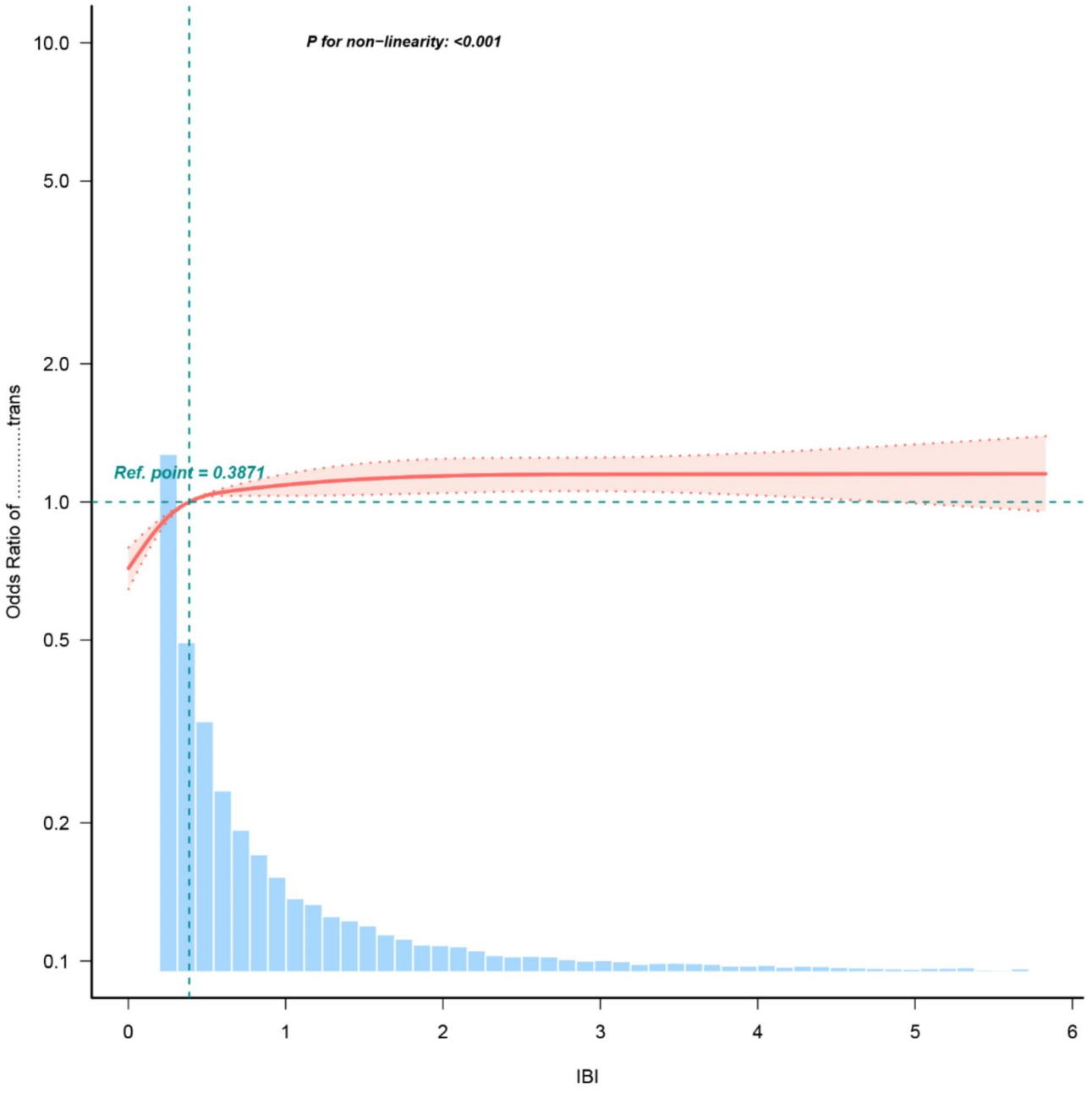


**Fig. 3** Limited cubic spline plots for the pre-DM result by IBI levels after covariate adjustment. The light blue backdrop histograms display the proportion of the research population's IBI density distribution. Shaded ribbons represent the 95% confidence intervals and thick center lines, respectively, represent the computed adjusted odds ratios. The horizontal dotted lines (Reference point) display the odds ratio of 1.0

When IBI was categorized into quartiles, the highest quartile (Q4) exhibited a significantly higher risk of developing DM compared to the other groups (OR = 1.59, 95% CI = 1.47 to 1.71, $p < 0.001$), and this association persisted after adjusting for other covariates (Supplementary Table S2). Figures 2 and 3 illustrate the nonlinear relationship between IBI and the risk of both pre-diabetes (pre-DM) and DM ($p < 0.05$). Threshold analysis revealed that when IBI was less than 1.295 mg/L, the odds ratio (OR) for DM was 1.8 (95% CI = 1.598 to 2.027, $p < 0.001$). However, when IBI was ≥ 1.295 mg/L, the OR for DM decreased to 1.036 (95% CI = 0.975 to 1.1, $p = 0.2512$) (Supplementary Table S4).

### Subgroup analyses and interactions to test the association between IBI and the risk of pre-DM

Subgroup analyses revealed that the positive association between IBI and pre-DM was statistically significant in most subgroups. However, this association was not statistically significant among Other Hispanic, Non-Hispanic

Asian, divorced individuals, those with unclear marital status, individuals with BMI ≥ 25, and those with a history of heart disease ($P > 0.05$). Interaction tests indicated that most covariates did not significantly interact with the relationship between IBI and pre-DM ($p > 0.05$). Only gender, marital status, BMI, and drinking status showed a significant effect on this relationship (Supplementary Table S5).

#### Subgroup analyses and interactions to test the association between IBI and the risk of DM

Subgroup analyses showed that the positive association between IBI and pre-DM was statistically significant in most subgroups. However, no statistically significant association was found among Non-Hispanic Asians, widowed individuals, or those with a history of heart disease or stroke ($P > 0.05$). Interaction tests revealed that most covariates did not significantly interact with the relationship between IBI and DM ($P > 0.05$). Only gender, race, marital status, BMI, drinking status, and certain past medical histories had a significant impact on this relationship (Supplementary Table S6).

## Discussion

The aim of our study was to explore the relationship between pre-DM, DM, and IBI. In our cross-sectional analysis of 29,554 participants, we found a significant association between higher IBI levels and the prevalence of pre-DM and DM. A nonlinear positive relationship was observed between IBI and the overall incidence of pre-DM and DM, which remained consistent after adjusting for factors such as gender, age, and health status. However, no significant correlation was found in participants with heart disease [30], likely due to the chronic low-grade inflammatory state inherent in these individuals, which may have influenced the predictive ability of IBI. Further analysis of the correlation between IBI quartiles and the prevalence of pre-DM and DM revealed that the association between the prevalence of pre-DM and DM and the fourth quartile (Q4) IBI was significantly stronger than the association with the first quartile (Q1) IBI. However, while individuals with higher IBI levels showed a slight increase in the risk of developing diabetes, this risk was relatively lower compared to those in the overweight and obese categories.

With the introduction of the concept of metabolic inflammation [31], the role of chronic inflammation in the pathogenesis of pre-DM and DM is gaining attention. IBI is a newly proposed indicator of inflammation with more comprehensive clinical significance and application prospects than traditional indicators. Some studies have found that IBI is an important biomarker for malignant tumors and can effectively predict the survival prognosis and quality of life of tumor patients. In previous studies, many inflammatory variables have been associated with diabetes risk, which is consistent with our findings. A cross-sectional study showed that NLR is a risk factor for all-cause and cardiovascular mortality in diabetic patients, and the study by Li et al. [12]. also suggests that NLR may be a potential inflammatory marker for diabetic nephropathy. CRP is a recognized marker capable of detecting validation in vivo while NLR is responsible for the immune response, and the IBI integrates the two to assess validation of the immune status from a holistic patient's point of view to better evaluate the patient's diabetic status prediction.

The mechanisms of altered IBI in pre-DM and DM patients are unclear, but there are numerous possible processes that could connect the onset of pre-DM and DM to IBI. Current research suggests that inflammation precedes the onset of diabetes and that elevated levels of inflammatory cytokines usually predict future weight gain. Studies have shown that injection of inflammatory cytokines into healthy, normal-weight rats triggers insulin resistance, which is consistent with the results of our subgroup analysis, which showed an increased risk of diabetes in individuals with a higher body mass index (BMI). Elevated BMI reflects excessive accumulation of abdominal fat, which leads to the production of cytokines and other metabolites, which in turn triggers insulin resistance and affects the insulin signaling pathways, including NF-κB, JNK, and TNF-α, while also impairing endothelial cell function. In addition, it contributes to the release of inflammatory substances, further exacerbating insulin resistance and leading to pancreatic β-cell dysfunction. Patients with chronic inflammation also have a significantly increased risk of diabetes [32]. Several studies have pointed out that activation of inflammatory pathways not only creates an inflammatory microenvironment within the pancreatic islets and impairs insulin secretion by β-cells, but also triggers insulin resistance in insulin target organs such as the liver and white adipose tissue. Under normal conditions, insulin target organs such as the brain, viscera, and pancreas maintain glycemic homeostasis by regulating the balance between immune responses and metabolism; whereas under metabolic disorders and inflammatory conditions, these organs form a local inflammatory microenvironment through the gut-hypothalamus-liver/adipose tissue/pancreas axis, which promotes systemic inflammation and thus accelerates the development of diabetes [33]. In addition, inflammation in the brain (especially in the hypothalamus) causes leptin resistance, which usually precedes and is closely associated with insulin resistance and diabetes. Leptin is a hormone that regulates appetite and metabolism, and its action is achieved mainly by affecting the hypothalamus. When the hypothalamus becomes resistant to leptin, glucose and fat metabolism

are disturbed, leading to weight gain and insulin resistance [34].

Although inflammation starts in adipocytes and the first cells that respond to obesity are these, as the storage of fat increases, so too do inflammation levels. One of the potential pathways involved is mitochondrial dysfunction, induced by enhanced cellular stress in addition to obesity. Oxidative stress is another possible mechanism [35]. Too much glucose is transported into adipocytes (which, as we recently learned, happens under conditions of high-fat diets and diabetes) [36], leading to an overproduction of reactive oxygen species (ROS). This, in turn, induces a cascade signaling inflammatory response within the cells. Neutrophils trigger the earliest innate immune responses of a host through various processes such as chemotaxis, phagocytosis, ROS release, and granular protein secretion, along with cytokine production/release. Furthermore, neutrophils serve as important regulators in shaping adaptive immunity and are major effector cells during systemic inflammatory responses [37].

In addition, inflammation in adipose tissue triggers insulin resistance, which is one of the main features of diabetes. Studies have shown that C-reactive protein (CRP) contributes to the development of insulin resistance. Complement, a group of biologically active proteins found on the surface of body fluids and cells in humans and animals, mediates immune and inflammatory responses. This system, often referred to as the complement system, plays an important role in the development and progression of diabetic macrovascular lesions. It has been found that CRP levels are significantly elevated in diabetic patients [38, 39], and CRP can activate the classical pathway of complement. These findings suggest that locally generated CRP in tissues may contribute to the progression of diabetic macrovascular lesions. In addition, our subgroup analyses revealed that men had a higher risk of DM and pre-DM than women. This may be attributed to factors such as aging [40], hormones [41], and higher levels of visceral fat in men [42].

A notable strength of our study lies in its utilization of the representative NHANES database, which bolsters the reliability of the findings through multi-stage stratified sampling. In addition, we carefully accounted for a range of factors, allowing for a more precise evaluation of the relationships under investigation. However, this study has several limitations. First, due to the cross-sectional design, we are unable to establish causal relationships between IBI and pre-DM or DM, meaning causality cannot be inferred from our findings. Second, although we controlled for several objective factors, the potential influence of confounding variables such as diet, physical activity, and family history could not be fully accounted for. Third, with regard to clinical implications, the diagnostic value of IBI may plateau at higher levels (IBI > 2), as illustrated in Fig. 2. This suggests that at elevated IBI levels, clinicians should consider additional biomarkers or clinical context when interpreting IBI values, particularly in patients with severe inflammation. A possible explanation for this plateau effect is that elevated IBI values might reflect acute conditions (e.g., infections or trauma) rather than chronic metabolic inflammation. This underscores the need for further investigation into the role of IBI across various clinical settings, which will be the focus of our ongoing research.

## Conclusion

Elevated IBI levels are strongly associated with an increased risk of diabetes mellitus (DM) in the US population, exhibiting a non-linear relationship. Moreover, the significant role of obesity in the development of pre-diabetes (pre-DM) cannot be overlooked. Further investigation is needed to elucidate the mechanisms linking IBI, obesity, and the progression to DM and pre-DM. This finding offers new insights and potential avenues for the future treatment and prevention of DM and pre-DM.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01911-6.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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**Author contributions**

SY, JL and HC wrote the report and made conceptualization, data management, and methodology suggestions. After revising the article and sharing the software application and data analysis, SY, FX, SW, HW, HH, MT and ML submitted the finished version. After reading the published version of the manuscript, all writers have given their approval.

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**Data availability**

Online repositories contain the datasets used in this investigation. The following contains the repository(s) names and accession number(s): https://www.n.cdc.gov/nchs/nhanes/analyticguidelines.aspx.

## Declarations

### Ethics approval and consent to participate

The National Health Statistics Research Ethics Review Board conducted an evaluation and granted approval for the NHANES study. Before the NHANES physical exam and data collection began, all eligible individuals provided their informed consent.
Not applicable.

### Consent for publication

Not applicable

### Competing interests

The authors declare no competing interests.

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