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The mediating role of chronic low-grade inflammation participation in the relationship between obesity and type 2 diabetes: findings from the NHANES

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Abstract

Background Chronic low-grade inflammation may mediate the relationship between obesity and diabetes, yet clinical research in this area remains scarce. Thus, this study aimed to explore the mediating role of chronic low-grade inflammation in this relationship using the National Health and Nutrition Examination Survey (NHANES).

Methods This study involved 2,482 participants enrolled in the NHANES between 2005 and 2016. Based on the complex sampling survey weights of NHANES, logistic regression models were fitted, adjusting for various covariates to investigate the relationship between BMI, INFLA score, and diabetes. Moreover, weighted quantile sum (WQS) regression models were fitted to analyze the proportional contribution of individual components within the INFLA score. Finally, mediation analysis was conducted to quantitatively assess the magnitude of the mediating effect of the INFLA score on the relationship between BMI and diabetes.

Results After adjusting for all potential confounding factors, a significant positive correlation was noted between INFLA score and diabetes [OR (95% CI), 1.038(1.003–1.075), $p = 0.035$]. Additionally, a significant positive correlation was observed between the high INFLA group and diabetes compared to the low INFLA group [OR (95% CI), 1.599(1.031–2.481), $p = 0.037$]. WQS regression models revealed that the proportional contributions of C-reactive protein, white blood cell count, platelet count, and neutrophil-to-lymphocyte ratio (NLR) were 55.5%, 34.8%, 8.46%, and 1.19%, respectively. Finally, the results of the mediation analysis indicated that the indirect effect of the INFLA score accounted for 10.20%.

Conclusions Chronic low-grade inflammation was associated with diabetes and partially mediates the relationship between obesity and diabetes.

Keywords Chronic low-grade inflammation, INFLA score, Obesity, Type 2 diabetes

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Introduction

In recent years, the global prevalence of diabetes has been progressively increasing, emerging as a major public health concern [1, 2]. As of 2022, approximately 537 million people worldwide have been reported to be diagnosed with T2DM, with this number projected to increase by 46% by 2045 [3]. Consequently, diabetes and its related complications impose a significant economic burden on society and significantly affect the quality of life of patients [4, 5].

Obesity stands out as a primary risk factor for diabetes, with elevated BMI being associated with an increased risk of developing diabetes [6]. The potential mechanisms by which obesity leads to diabetes onset are diverse. Earlier research reported that obesity contributes to diabetes by disrupting the secretion of adipokines from adipose tissues [7]. Additionally, they documented that gut microbiota or virome may mediate the relationship between obesity and diabetes [8, 9].

As is well documented, obesity is often accompanied by increased oxidative stress, leading to elevated levels of inflammation [10]. An earlier study identified a close correlation between obesity and chronic low-grade inflammation [11]. The latter similarly affects the endocrine system, immune system, and metabolic processes, thereby predisposing individuals to various diseases such as diabetes and cardiovascular diseases [12, 13]. Basic research suggests that chronic low-grade inflammation mediates the effect of obesity on diabetes [14, 15]. However, clinical studies on this topic remain limited.
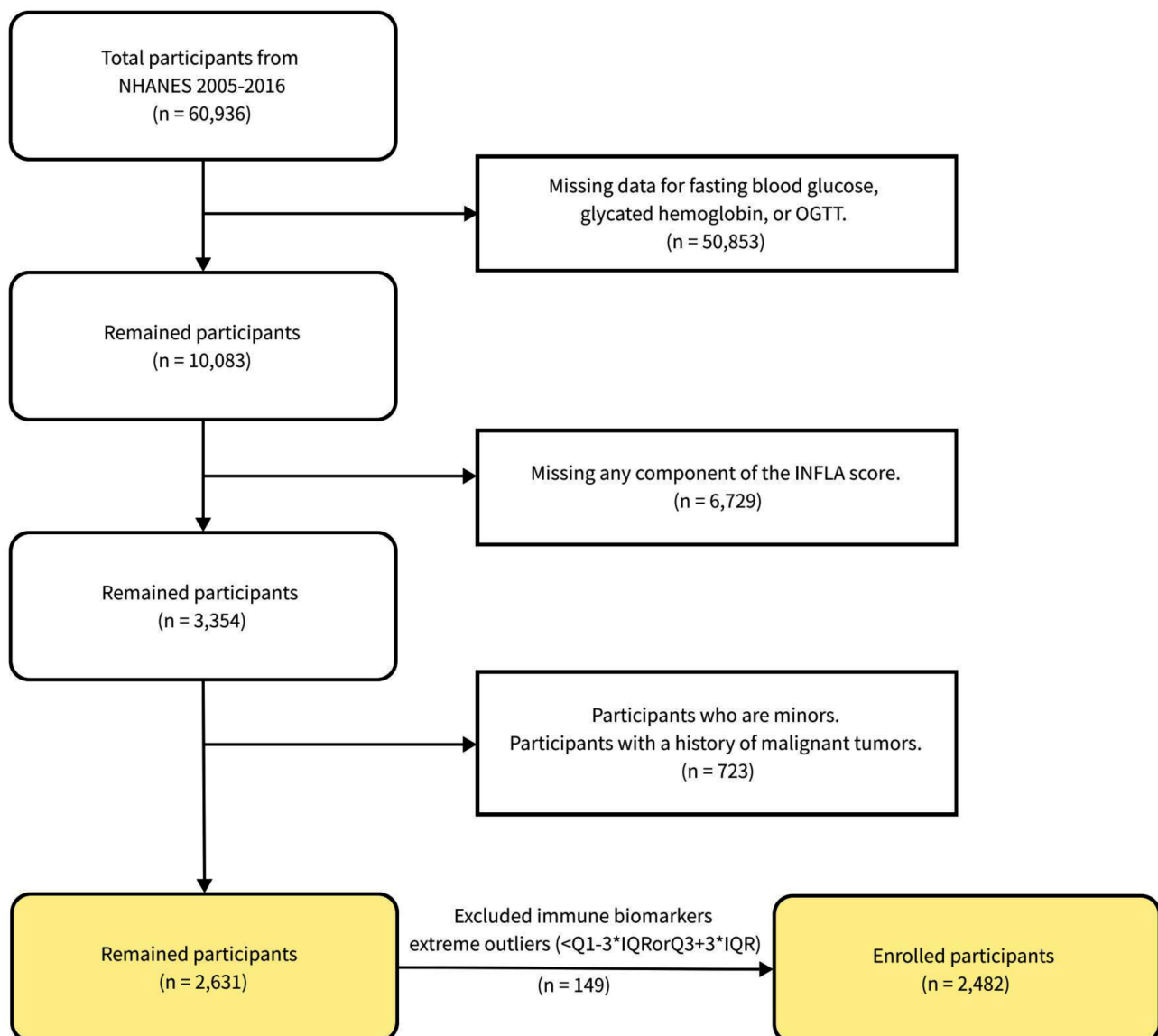

Fig. 1 Pattern diagram of the screening process for all participants

Table 1 Baseline characteristics of participants stratified by diabetes status

	All	Non-Diabetes group	Diabetes group	*P* value
N(%)	2482	2241(90.29)	241(9.71)	
Age, years, mean ± SD	48.24 ± 17.45	47.05 ± 17.26	59.34 ± 15.20	< 0.001
Gender, n(%)				0.047
Male	1193(48.07)	1062(47.39)	131(54.36)	
Female	1289(51.93)	1179(52.61)	110(45.64)	
Race, n(%)				0.059
Other races	535(21.55)	495(22.09)	40(16.60)	
White races	1947(78.44)	1746(77.91)	201(83.40)	
Poverty-income ratio, n(%)				0.309
<3.0	1589(64.02)	1427(63.68)	162(67.22)	
≥3.0	893(35.98)	814(36.32)	79(32.78)	
Educational level, n(%)				< 0.001
High school education and below	1252(50.44)	1099(49.04)	153(63.48)	
Above high school education	1230(49.56)	1142(50.96)	88(36.52)	
BMI, kg/m^2, mean ± SD	28.45 ± 6.27	28.16 ± 6.17	31.15 ± 6.52	< 0.001
Cotinine, ng/mL, mean ± SD	52.72 ± 119.44	52.59 ± 118.02	53.95 ± 132.21	0.867
Alcohol intake, n(%)				1.000
No	644(25.95)	581(25.93)	63(26.14)	
Yes	1838(74.05)	1660(74.07)	178(73.86)	
Systolic blood pressure, mmHg, mean ± SD	120.81 ± 16.65	119.91 ± 16.15	129.16 ± 18.79	< 0.001
Diastolic blood pressure, mmHg, mean ± SD	68.13 ± 11.94	68.01 ± 11.63	69.25 ± 14.46	0.124
Serum HDL cholesterol, mg/dL, mean ± SD	54.74 ± 16.30	55.18 ± 16.07	50.63 ± 17.79	< 0.001
Serum LDL cholesterol, mg/dL, mean ± SD	118.45 ± 34.42	118.53 ± 34.38	117.77 ± 34.88	0.746
Serum triglycerides, mg/dL, mean ± SD	123.41 ± 98.89	116.77 ± 82.07	185.18 ± 184.34	< 0.001
Aspartate Aminotransferase (AST), U/L, mean ± SD	26.73 ± 28.63	26.51 ± 29.72	28.78 ± 15.14	0.243
Alanine Aminotransferase (ALT), U/L, mean ± SD	26.42 ± 25.39	26.03 ± 26.08	30.04 ± 17.33	0.020
Gamma Glutamyl Transferase (GGT), IU/L mean ± SD	28.69 ± 51.89	27.31 ± 50.80	41.53 ± 59.77	< 0.001
Uric acid, mg/dL, mean ± SD	5.43 ± 1.36	5.39 ± 1.35	5.84 ± 1.39	< 0.001
Serum creatinine, mg/dL, mean ± SD	0.88 ± 0.42	0.87 ± 0.37	0.96 ± 0.74	0.001
Neutrophil-to-Lymphocyte Ratio (NLR), mean ± SD	2.03 ± 0.87	2.01 ± 0.86	2.20 ± 0.94	0.001
White blood cell count, 1000 cells/uL, mean ± SD	6.55 ± 1.81	6.49 ± 1.78	7.05 ± 2.00	< 0.001
Platelet count SI, 1000 cells/uL, mean ± SD	245.90 ± 63.91	246.18 ± 63.97	243.31 ± 63.52	0.508
C-reactive protein, mg/dL, mean ± SD	0.29 ± 0.32	0.28 ± 0.32	0.40 ± 0.35	< 0.001
INFLA score, mean ± SD	-0.18 ± 6.35	-0.40 ± 6.30	1.81 ± 6.47	< 0.001

The National Health and Nutrition Examination Survey (NHANES) is a significant population health and nutritional status survey conducted by the government of the United States [16]. It employs random sampling nationwide and invites participants to undergo medical examinations, surveys, and nutritional assessments for data collection. The NHANES database contains data from multiple cycles, with each cycle typically lasting two years. The current study aimed to explore the mediating role of low-grade inflammation in the relationship between obesity and diabetes using the NHANES database.

Materials and methods
Study population
NHANES conducted OGTT testing on a subset of participants between 2005 and 2016. Out of a total of six cycles of data, a preliminary cohort of 60,936 participants was initially included in the study. Next, participants with missing data on fasting blood glucose levels, glycated hemoglobin levels, or OGTT were excluded (*n*=50,853). Subsequently, individuals lacking any component data in the INFLA index were excluded (*n*=6,729). Additionally, minors or participants with a history of malignant tumors were excluded (*n*=723). Likewise, participants with extreme immunological values (< quartile Q1-3*interquartile (IQR) or >Q3+3*IQR) were excluded (*n*=149). Ultimately, 2,482 participants were included in this study for further analysis (Fig. 1).

All participants had provided written informed consent. The NHANES project was approved by the Ethics Review Committee of the Centers for Disease Control and Prevention (CDC) in the United States.

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Table 2 Results of univariate regression analysis for BMI, INFLA score, and diabetes

Exposure	Statistics	Outcome	
		INFLA score[Beta(95% CI), *P*-value]	Diabetes[OR(95% CI), *P*-value]
BMI, kg/m^2	28.45(6.27)	0.327(0.279–0.374), <0.001	1.090(1.071–1.109), <0.001
BMI Groups			
≤25	877(35.33%)	Ref	Ref
(25, 30]	831(33.48%)	1.697(0.903–2.492), <0.001	2.435(1.459–4.064), 0.001
>30	774(31.18%)	4.228(3.535–4.921), <0.001	4.788(3.171–7.231), <0.001
INFLA	-0.18(6.35)	-	1.072(1.041–1.104), <0.001
INFLA Quantile			
≤-3	911(36.70%)	-	Ref
(-3, 3]	859(34.61%)	-	1.205(0.774–1.878), 0.401
>3	712(28.69%)	-	2.485(1.662–3.716), <0.001

Definition of BMI and obesity

BMI is defined as height (cm) divided by the square of weight (kg). In the regression analysis, using BMI as the exposure factor, patients were categorized into three groups stratified by BMI, namely the low BMI (≤25), medium BMI (25~30), and high BMI (>30) groups. Obesity is measured by BMI and BMI over 30 is defined as obesity.

Definition of INFLA score

In the current study, the aggregated inflammation score (INFLA-score) was regarded as a comprehensive indicator of low-grade inflammation in the body. The INFLA score is composed of four components (CRP, WBC count, platelet count, and neutrophil-to-lymphocyte ratio (NLR)), which are considered synergistic inflammatory markers. The specific method for calculating the INFLA score involves dividing the four components into deciles, with values ranging from +1 to +4 assigned to deciles 7 to 10 and values ranging from −4 to -1 assigned to deciles 1 to 4. All values are then summed, resulting in

an INFLA score ranging from −16 to +16, where higher scores reflect higher levels of low-grade inflammation [17].

The measurement methods and procedures for all biochemical indicators are detailed in the supplementary materials.

Definition of diabetes

According to the diagnostic criteria of the American Diabetes Association (ADA), diabetes is defined by self-reported diagnosis, fasting blood glucose level (FBG)≥126 mg/dL, hemoglobin A1c level (HbA1c) level≥6.5%, or a two-hour blood glucose level during an oral glucose tolerance test (OGTT)≥200 mg/dL [18]. Ultimately, based on these criteria, diabetes can be categorized as a binary variable.

Definition of covariates

Information on various demographic and health-related factors was collected from the NHANES Household Interview, including age, gender, race/ethnicity, educational level, household income, alcohol consumption status, and physical examination. Race was categorized as White and Other, whilst educational level was classified as college/university degree or below. Household income and poverty ratio were divided into 0–3.0 or >3.0. Drinkers were defined as individuals who consumed at least 12 alcoholic drinks within a year. Systolic and diastolic blood pressures were calculated by the average of three measurements. Hypertension was defined as a systolic blood pressure of ≥140mmHg, a diastolic blood pressure of ≥90mmHg, or a self-reported diagnosis of hypertension.

Clinical indicators such as serum cotinine, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl translerase (GGT), uric acid (UA), and creatinine (CR) were quantified in the NHANES laboratory. Serum cotinine is the primary metabolite formed after nicotine metabolism in the body, accurately reflecting an

Table 3 Results of multivariate logistic regression analysis for INFLA score and diabetes

Exposure	OR(95% CI), *P*-value		
	Model 1	Model 2	Model 3
INFLA score	1.074(1.040–1.108), <0.001	1.045(1.009–1.082), 0.014	1.038(1.003–1.075), 0.035
INFLA score Quantile			
Q1, ≤-3	Ref	Ref	Ref
Q2, (-3, 3]	1.136(0.750–1.721), 0.539	0.964(0.624–1.490), 0.866	0.856(0.560–1.307), 0.457
Q3, >3	2.505(1.647–3.812), <0.001	1.780(1.127–2.811), 0.015	1.599(1.031–2.481), 0.037

Model 1 adjusted for age, gender, race, poverty-income ratio and educational level

Model 2 adjusted for age, gender, race, poverty-income ratio, educational level, BMI, serum cotinine, alcohol intake and systolic blood pressure

Model 3 adjusted for age, gender, race, poverty-income ratio, educational level, BMI, serum cotinine, alcohol intake, systolic blood pressure, HDL, LDL, TG, ALT, GGT, uric acid and serum creatinine

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Table 4 Results of subgroup analysis based on age, gender, race, poverty-income ratio, and educational level

Subgroup	Quantity (percentage)	Non-adjusted model		Adjusted model	
		OR(95%CI), *P*-value	P-interacton	OR(95%CI), *P*-value	P-interacton
Age, years			0.4195		0.96941
20 ~ 40	931(37.51%)	1.135(1.041–1.237), 0.005		1.099(0.992–1.217), 0.070	
41 ~ 60	885(35.66%)	1.075(1.028–1.124), 0.002		1.037(0.986–1.090), 0.151	
>60	666(26.83%)	1.058(1.018–1.099), 0.005		1.034(0.990–1.079), 0.126	
Gender			0.5527		0.28956
Male	1193(48.07%)	1.066(1.020–1.114), 0.006		1.017(0.965–1.072), 0.519	
Female	1289(51.93%)	1.088(1.037–1.142), 0.001		1.069(1.008–1.134), 0.027	
Race			0.0166		0.01853
Other races	535(21.56%)	0.999(0.941–1.059), 0.960		0.985(0.918–1.057), 0.656	
White races	1947(78.44%)	1.082(1.048–1.118), <0.001		1.047(1.008–1.087), 0.019	
Poverty-income ratio			0.76085		0.42145
<3.0	1589(64.02%)	1.068(1.034–1.103), <0.001		1.041(1.001–1.083), 0.046	
≥3.0	893(35.98%)	1.077(1.027–1.130), 0.003		1.037(0.982–1.096), 0.184	
Educational level			0.1036		0.86381
High school education and below	1252(50.44%)	1.042(1.001–1.085), 0.044		1.034(0.985–1.086), 0.166	
Above high school education	1230(45.56%)	1.098(1.048–1.150), <0.001		1.045(0.995–1.097), 0.078	

Model adjusted for age, gender, race, poverty-income ratio, educational level, serum cotinine, alcohol intake, systolic blood pressure, HDL, LDL, TG, ALT, GGT, uric acid and serum creatinine. Variable that are grouped are excluded

individual's tobacco exposure level, including both active and passive smoking, and thus providing a reliable and objective measure of smoking levels [19].

Statistical analysis

All statistical analyses were conducted using Python 3.10.13 and R 4.2.1. A two-tailed $P<0.05$ was considered statistically significant. Based on the description of baseline variables, the entire population was grouped and pooled, including the non-diabetic population and the diabetic population. Continuous variables following a normal distribution were presented as mean±standard deviation, while categorical variables were expressed as numbers (proportions). One-way analysis of variance was employed to compare continuous variables in order to assess baseline characteristic differences between the diabetic and non-diabetic populations, whereas Pearson's chi-square test was used to compare categorical variables.
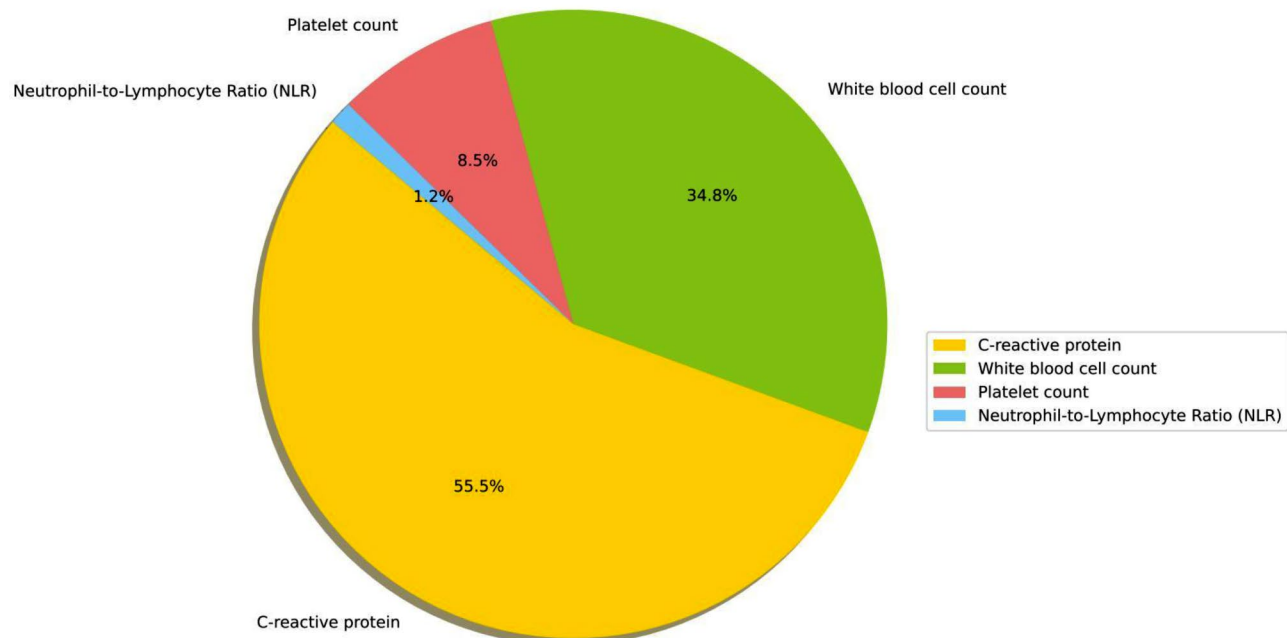

Fig. 2 Pie chart representing the weight of each component of INFLA score

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Table 5 Results of weighted quantile sum regression on INFLA score

	Non-adjusted model	Ad-justed model
Component mean weight		
C-reactive protein	0.633	0.555
White blood cell count	0.243	0.348
Platelet count	<0.001	0.0846
Neutrophil-to-Lymphocyte Ratio (NLR)	0.124	0.0119
WQS P-value		
Positive	**<0.001**	**0.0144**
Negative	0.884	0.13226

Model adjusted for age, gender, race, poverty-income ratio, educational level, BMI, serum cotinine, alcohol intake, systolic blood pressure, HDL, LDL, TG, ALT, GGT, uric acid and serum creatinine

To examine the association between BMI, INFLA score, and diabetes, univariate regression analysis was first performed to preliminarily examine the relationships among the three variables. Furthermore, three multivariable regression models adjusted for different covariates were generated. Model 1 was exclusively adjusted for demographic factors (age, gender, race, educational level, and poverty income ratio). Meanwhile, model 2 included adjustments from Model 1 plus alcohol consumption, serum cotinine levels, systolic blood pressure, diastolic blood pressure, and BMI. Finally, model 3 was further adjusted for laboratory biochemical indicators, including TG, LDL, HDL, ALT, AST, GGT, UA, and CR. To mitigate the impact of multicollinearity, the variance inflation factor (VIF) was determined, with variables having a VIF over 5 considered to exhibit multicollinearity and thus excluded. Considering the complex sampling design of NHANES, sample weights, clustering, and stratification were incorporated, which are necessary for analyzing NHANES data.

Stratified analyses were also carried out based on age, gender, race, educational level, and poverty-income ratio. Moreover, interaction tests were performed to identify significant interactions between the different subgroups.

Weighted quantile sum (WQS) regression analysis was employed to assess the contribution of each component in the composite index to its effect. Its advantage lies in its ability to account for potential interactions between components in the mixture and provide insights into components contributing more significantly to health effects. 50% of the data was assigned to the training set, and the remaining 50% of the data was assigned to the validation set. Then, both positive and negative WQS regression analyses were conducted, and component weights and the overall significance P-values were determined using bootstrap resampling.

Finally, a mediation effect analysis was conducted, with BMI as the exposure factor, diabetes as the outcome factor, and INFLA as the mediator factor. The proportions of total, direct, and indirect effects were calculated. Bootstrap resampling was used to examine the significance of the mediation effects.

Results

Participant characteristics

Among all 2,482 participants with an average age of 48.24 years, 51.93% of whom were females, 241 were diabetics, yielding a prevalence rate of approximately 9.71%... The majority of participants were Caucasian (78.44%), and the distribution of educational levels between those with a college degree or higher and those below was roughly comparable.

The age of participants in the diabetes group was higher, and these patients were more likely to be male. Additionally, diabetes patients had lower educational levels, higher BMI, and higher systolic blood pressure. Similarly, the levels of TG, ALT, GGT, UC, and CR were higher in the diabetes group, whereas the level of HDL was lower. Lastly, the INFLA score was significantly higher in the diabetes group compared to the non-diabetes group. All these differences were statistically significant. In contrast, race and poverty ratio were similar between the two groups (Table 1).

Association between BMI, INFLA, and diabetes

In the regression analysis, using BMI as the exposure factor, patients were categorized into three groups stratified by BMI, namely the low BMI (≤ 25), medium BMI ($25 \sim 30$), and high BMI (>30) groups. Continuous variables and categorical variables of BMI were individually
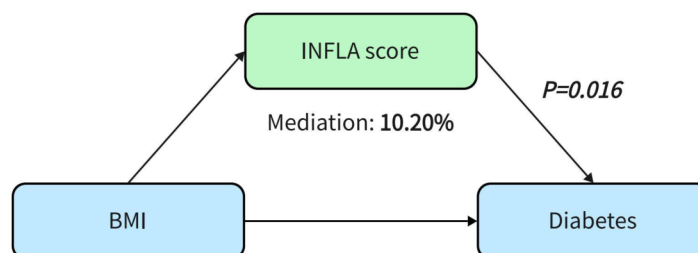

Fig. 3 Pattern diagram illustrating the proportion of mediation effect in INFLA score

regressed against the outcome of INFLA using single-factor linear regression and against the binary outcome of diabetes using logistic regression. Interestingly, the results indicated a significant positive correlation between BMI and both INFLA [Beta (95% CI), 0.327(0.279–0.374), $p<0.001$] and diabetes [OR (95% CI), 1.090(1.071–1.109),$p<0.001$]. As anticipated, significant positive correlations were also observed in the medium and high BMI groups relative to the low BMI group.

Furthermore, in the regression analysis using INFLA as the exposure factor, patients were stratified based on INFLA tertiles: low INFLA (≤-3), medium INFLA (-3 ~ 3), and high INFLA (>3). When diabetes was considered the binary outcome, a significant positive correlation was detected with INFLA [OR (95% CI), 1.072(1.041–1.104), $p<0.001$]. Additionally, a significant positive correlation was observed in the high INFLA group compared to the low INFLA group [OR (95% CI), 2.485(1.662–3.716), $p<0.001$]. (See Table 2).

To mitigate the potential confounding effects, a multivariable logistic regression model was constructed. Initially, variance inflation factors (VIFs) were computed, and variables with VIFs exceeding 5 were excluded. Consequently, in Model 2, the variable diastolic blood pressure was excluded, and the variable AST was excluded in Model 3. Ultimately, after adjusting for all covariates, a significant positive correlation was detected between INFLA score and diabetes [OR (95% CI), 1.038(1.003–1.075), $p=0.035$]. Lastly, a significant positive correlation was also noted in the high INFLA group relative to the low INFLA group [OR (95% CI), 1.599(1.031–2.481), $p=0.037$]. (See Table 3).

Results of subgroup analysis
To elucidate the disparities in the aforementioned findings across the population groups, subgroup analyses were conducted based on various demographic factors, comprising age, gender, race, educational level, and poverty-income ratio. In other words, regression analyses were re-performed by introducing interaction terms and adjusting for specific covariates. Age was stratified

Table 6 Results of mediation effect model on BMI, INFLA score and diabetes

	Non-adjusted model		Adjusted model	
	Estimate	*P*-value	Estimate	*p*-value
Total Effect	0.000947	<0.001	0.000949	<0.001
ACME	0.00571	<0.001	0.0000967	0.016
ADE	0.006657	<0.001	0.000852	<0.001
Prop. Mediated	14.22%	<0.001	10.20%	0.016

ACME (Averaged Causal Mediation Effects); ADE (Average Direct Effect); Prop. Mediated (Proportion Mediated)

Model adjusted for age, gender, race, poverty-income ratio, educational level, serum cotinine, alcohol intake, systolic blood pressure, HDL, LDL, TG, ALT, GGT, uric acid and serum creatinine

into three groups: 20–40 years, 41–60 years, and above 60 years. After adjusting for all covariates except for the stratification variable, the results revealed a consistent positive correlation between INFLA score and the outcome of diabetes across the age groups, genders, educational levels, and poverty income ratios in the overall population, with no significant interaction effects observed (P-interaction>0.05). Furthermore, there was an interaction effect between race and INFLA score (P-interaction<0.05). Specifically, a stronger positive correlation was found in the subgroup of individuals of White race compared to the overall population [OR (95% CI), 1.047(1.008–1.087), $p=0.019$], whereas this association was not significant in other racial subgroups (p-value>0.05). (See Table 4 for details).

Results of WQS model
Furthermore, the WQS model was established to analyze the weights of the four components in the INFLA score. After adjusting for all covariates, the results showed that C-reactive protein (55.5%) and white blood cell count (34.8%) accounted for the majority of the weight, whereas the contribution of platelet count (8.46%) and neutrophil-to-lymphocyte ratio (NLR) (1.19%) was comparatively lower. The positive WQS model was significant (P=0.014), whereas the negative WQS model was not significant (P>0.05). (See Fig. 2; Table 5).

Results of mediation analysis
The results of the mediation analysis signaled that the INFLA score partially mediated the relationship between BMI and diabetes. Specifically, after adjusting for all covariates, the total effect ($\beta_{total\ effect}$) was 9.49×10^{-4}, the direct effect (β_{ADE}) was 8.52×10^{-4}, the indirect effect (β_{ACME}) was 9.67×10^{-5}, and the proportion of the indirect effect was 10.20%. Noteworthily, both the direct and indirect effects were statistically significant (P<0.05). (Refer to Fig. 3; Table 6).

Sensitivity analysis
The binary classification of participants' hypertension status was incorporated as a covariate in the regression model to avoid bias in representing participants' blood pressure status solely by including systolic blood pressure. The results demonstrated that even after substituting systolic blood pressure with hypertension status, the statistical association between IFNLA and diabetes remained significant [OR (95% CI), 1.039(1.003–1.077), $p=0.034$] (see sTable S1).

Discussion
This study utilized the NHANES database to explore the association between BMI, INFLA score, and diabetes. The results revealed that for each unit increase in the

INFLA score, there was a corresponding 3.8% increase in the prevalence of diabetes. Additionally, the prevalence of diabetes in the high INFLA group was 59.9% higher than in the low INFLA group. Furthermore, the mediation analysis determined that INFLA partially mediated the relationship between BMI and diabetes, with the indirect effect accounting for 10.2% of the association.

The association between chronic low-grade inflammation and diabetes noted in this study is consistent with the findings of previous studies. Past studies have indicated that elevated CRP levels are associated with an increased risk of type 2 diabetes, and thus, CRP can serve as a predictive factor for the development of diabetes [20, 21]. Ascribed to its relative stability and ease of measurement, CRP is commonly used as a marker for assessing systemic inflammation in humans [22]. However, a single marker may not fully reflect an individual's level of chronic low-grade inflammation [23]. In the present study, the WQS regression model demonstrated that CRP accounted for about half of the weight of the INFLA score, whilst the other half consisted of the other three components. Elevated Plt, WBC, and NLR are generally used as indicators of cellular inflammation in epidemiological studies [24, 25].

INFLA scores are frequently associated as intermediate factors with psychological disorders such as anxiety and depression [26, 27] and have been shown to mediate the association between acrylamide biomarkers and cancer mortality [28]. Additionally, it is well-established that obesity increases the level of chronic low-grade inflammation and can impair physiological function by mediating chronic low-grade inflammation [29, 30]. However, clinical studies on obesity mediating the occurrence of diabetes through chronic low-grade inflammation are currently lacking.

Multiple fundamental studies have evinced that obesity can drive chronic systemic inflammation, ultimately resulting in type 2 diabetes (T2D) [31]. The mechanisms by which inflammation mediates obesity-induced diabetes may be diverse. The enlarged adipose tissue leads to hypoxia due to inadequate perfusion and increased oxygen demand, which in turn induces inflammation. Substantial evidence suggests a direct correlation between inflammation and insulin resistance [32]. Additionally, obesity can promote the accumulation of immune cells, cytokines, and chemokines, eliciting pancreatic inflammation and impairing insulin secretion [31]. Obesity also leads to a significant increase in recruited hepatic macrophages, as well as local synthesis of inflammatory chemokines and cytokines, resulting in hepatic insulin resistance [14]. Prior research also suggested that obesity-induced dysbiosis of the gut microbiota triggers low-grade chronic inflammation, thereby exerting a cascade effect on insulin resistance [33]. In summary, the pathways through which obesity leads to diabetes are diverse, with chronic low-grade inflammation playing a prominent role.

To the best of our knowledge, this is the first study exploring the mediating effect of low-grade inflammation on the relationship between BMI and diabetes based on a large-scale database. Using the INFLA score enabled a more objective assessment of individuals' systemic chronic inflammation levels. We employed a curated dataset compiled from previous studies, which combined all files of NHANES III (1988–1994) and Continuous NHANES (1999–2018), taking into account variations in variable nomenclature and measurement units, thereby partially mitigating the effects of heterogeneity across different years. Furthermore, the complex weights of the stratified sampling of NHANES were incorporated and applied, thus providing a more accurate reflection of the overall population.

However, this study has several limitations that merit acknowledgment. Firstly, our research relied on cross-sectional data, which precludes establishing causal relationships between the investigated factors. Secondly, the NHANES database included only the U.S. population, thus the study findings may not be generalizable to other populations. Indeed, these results necessitate further validation among other racial groups. Lastly, despite our efforts to adjust for various confounding factors during the data analysis process, the inherent limitations of observational studies prevented the exclusion of other potential influences.

Conclusions

In summary, our study identified a relationship between INFLA score and diabetes, with the INFLA score partially mediating the relationship between BMI and diabetes. Despite numerous studies focusing on related mechanisms, further cohort studies are necessitated to validate our results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01671-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Declarations

Ethics approval and consent to participate
The National Health and Nutrition Examination Survey (NHANES) received approval from the Institutional Review Board of the National Center for Health Statistics. Written informed consent was obtained from all participants during the national survey conducted in the United States. All files are available in the supplementary materials.

Consent for publication
Not applicable.

Disclosure
All authors read and approved the final manuscript.

Competing interests
The authors declare no competing interests.

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