Research Square

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Nonlinear association of NPAR with diabetic nephropathy: evidence from a cross-sectional study

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Abstract

Background

Diabetic nephropathy (DN) is a major microvascular complication among diabetic patients, with its high prevalence and poor prognosis presenting significant challenges to global public health. The neutrophil percentage-to-albumin ratio (NPAR), a novel biomarker that integrates inflammatory status and nutritional metabolism, has not been clearly linked to DN risk. This study aims to systematically examine the association between NPAR and DN using a cross-sectional design, with a focus on identifying potential nonlinear relationships, thereby providing evidence for DN risk assessment and clinical decision-making.

Methods

A total of 8,336 diabetic patients from the National Health and Nutrition Examination Survey (NHANES,1999–2018) were included in the analysis. Weighted logistic regression models were used to evaluate the association between NPAR and the risk of DN. Restricted cubic spline (RCS) modeling was employed to assess dose-response relationships and detect potential nonlinear patterns, with the inflection point identified using a stepwise recursive method. A two-stage regression model was applied to evaluate the differential effects on either side of the inflection point. Subgroup analyses were conducted to explore potential effect modifications, while multiple imputation was performed to address missing data and confirm the robustness of the findings.

Results

Among the 8,336 participants, 1,927 (20.14%) were diagnosed with DN. After adjusting for confounding variables, weighted logistic regression revealed a significant positive association between NPAR and DN risk (OR = 1.39, 95% CI: 1.24–1.55). Quartile analysis indicated that individuals in the highest quartile (Q4) had significantly higher odds of DN compared to the reference group (OR = 2.24, 95% CI: 1.85–2.70). RCS analysis confirmed a significant nonlinear association (overall $P < 0.001$, nonlinear $P < 0.001$), characterized by a J-shaped curve, with the inflection point identified at 14.48. The two-stage regression model showed that when NPAR was below 14.48, no significant association was observed (OR = 1.04, 95% CI: 0.99–1.09). However, when NPAR was equal to or greater than 14.48, each unit increase in NPAR was significantly associated with a higher risk of DN (OR = 1.21, 95% CI: 1.17–1.26). Subgroup analysis revealed a significant interaction between education level and NPAR's effect on DN risk (P interaction < 0.05), and sensitivity analysis confirmed the stability of the results.

Conclusion

This study provides the first systematic evidence of a nonlinear association between NPAR and DN risk, characterized by a J-shaped curve with an inflection point at 14.48. When NPAR is equal to or exceeds this threshold, an increase in NPAR is significantly associated with higher DN risk, whereas no significant association is observed below this level. These findings offer a quantitative basis for early DN risk stratification—suggesting that maintaining NPAR below 14.48 may help reduce risk, while individuals with NPAR above this threshold should undergo enhanced screening and evaluation. These results support the clinical application of NPAR as a biomarker for individualized intervention strategies.

Introduction

The global prevalence of diabetes has been on a steady upward trend in recent years. Projections indicate that by 2050, the number of individuals living with diabetes is expected to reach 1.31 billion [1]. Diabetic nephropathy (DN), a common and severe complication of diabetes, affects a significant proportion of patients. Approximately 50% of type 2 diabetes mellitus (T2DM) patients and one-third of type 1 diabetes patients are at risk of developing kidney disease [2].In its early stages, DN typically manifests as albuminuria and renal insufficiency. As the disease progresses, patients often progress to chronic kidney disease (CKD) and eventually end - stage renal disease (ESKD), which necessitates dialysis or kidney transplantation [3].Notwithstanding the significant progress made in blood glucose management and kidney-protective therapies, the incidence of DN continues to increase. This situation underscores the urgent need to identify novel biomarkers to enhance risk stratification and enable timely early intervention strategies.

The pathogenesis of DN is intricate, entailing the intricate interplay of multiple factors, including metabolic disorders, hemodynamic aberrations, oxidative stress, and inflammatory responses. In recent years, a growing body of research has illuminated that the activation of inflammatory signaling pathways, which can precipitate kidney injury, represents a pivotal pathological mechanism underlying the onset and progression of DN [4].The transcriptional levels of pro - inflammatory factors and chemokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL- 1β), and interleukin-6 (IL-6), are upregulated. This upregulation further exacerbates renal damage in patients with DN [5]. Furthermore, certain basic inflammatory markers, such as neutrophils, lymphocytes, and platelets, have been demonstrated to be associated with the progression of DN [6, 7].Inflammation is intricately linked to DN. Harnessing the predictive value of inflammatory markers holds great potential for facilitating early screening and intervention in DN. Conventional biomarkers, such as the urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), are beset with certain limitations regarding sensitivity and specificity, particularly in the early phases of the disease [8].Consequently, the identification of comprehensive indicators capable of reflecting multifaceted pathological processes, including chronic inflammation and metabolic disorders, can provide a more thorough indication of the body's metabolic imbalance and inflammatory response status. This approach may also offer novel warnings for the early screening of DN.The neutrophil-to-albumin ratio (NPAR) represents an emerging inflammatory biomarker that has garnered substantial research interest, as it integrates both inflammatory and nutritional-metabolic parameters. Mechanistically, neutrophil activation under

inflammatory pathologies drives the elaboration of neutrophil extracellular traps (NETs), which have been implicated in inducing tissue injury. Concurrently, excessive NETs can disrupt the architectural integrity and functional homeostasis of renal glomeruli, thereby promoting renal fibrogenesis and exacerbating the progression of diabetic nephropathy[9]. While serum albumin level represents a pivotal biomarker for renal function assessment and DN progression. Hypoalbuminemia has been well-documented to correlate with adverse renal outcomes in DN patients [10].As a composite index integrating two established laboratory parameters, NPAR may more comprehensively reflect the imbalance of nutritional-metabolic disorders and the dynamic interplay between pro- and anti-inflammatory pathways. Prior studies have validated NPAR as a prognostic indicator in acute kidney injury [11], cardiogenic shock [12], severe sepsis [13], and oncological diseases [14]. Specifically, Li X, Gu Z, et al. [15] demonstrated that NPAR was independently associated with all-cause and cardiovascular mortality in diabetic populations. Concurrently, a cross-sectional analysis by He X, Dai F, et al. [16] revealed significantly elevated NPAR levels in T2DM patients with retinopathy. Additionally, Li H et al. [17] reported a positive correlation between NPAR and DN prevalence.Notably, Li X [15], Ji H [18], Jing Y [19], and Chen J [20] further uncovered a J-shaped association between NPAR and diabetes-related mortality risk. Nevertheless, no prior research has clearly investigated whether there exists an inflection point between NPAR and DN. Given that the condition of DN patients typically deteriorates over time, the relationship between NPAR and DN warrants further in-depth exploration.This study aims to conduct a comprehensive analysis of the association between NPAR and DN, with the goal of clarifying the screening utility of this accessible and practical biomarker. Such insights can provide valuable references for clinicians in the diagnosis of DN patients and serve as an early warning for the intervention and treatment of DN. Therefore, this study aims to undertake a comprehensive evaluation of the NPAR-DN association using nationally representative data from the National Health and Nutrition Examination Survey (NHANES), thereby providing enhanced guidance for the management of DN.

Methods

Data sources and study population

The data for this research were sourced from the NHANES, a cross-sectional survey representative of the national US population. The survey was designed by the National Center for Health Statistics (NCHS) and employed a continuous, stratified, multi-stage random sampling approach. NHANES offers health and nutrition statistics regarding the non-institutionalized civilian population in the United States. This study received approval from the NCHS Research Ethics Committee and was carried out in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent. Detailed data are available at https://www.cdc.gov/nchs/nhanes/.

The present study encompassed 101,316 participants from 10 cycles spanning from 1999 to 2018. In line with the study design, the participants were restricted to those with diabetes. Consequently, 9,568 participants who met the diabetes criteria were selected. We then excluded 1,182 participants with

missing UACR and eGFR data, as well as 50 participants lacking NPAR data. Finally, 8,336 participants were included in this study (Fig. 1).

Definition of DM

In accordance with the diagnostic criteria of the American Diabetes Association (ADA) [21] and self-report questionnaire, DM was diagnosed under the following conditions: self-reported; using insulin or oral medications; fasting blood glucose (FBG) of 7.0 mmol/L or higher; random blood glucose or 2-hour blood glucose during an oral glucose tolerance test of 11.1 mmol/L or higher; or a glycated hemoglobin A1c (HbA1c) level of 6.5% or higher.

Definition of DN

The diagnosis of DN was based on ACR of 30 mg/g or higher and/or eGFR of less than 60 mL/min/1.73m²[22]. The eGFR was calculated using the formula recommended by the National Kidney Foundation [23].

Definition of NPAR

All study specimens were analyzed at a central NHANES laboratory. Automated hematologic analysis equipment was employed to measure the percentage of neutrophils and serum albumin levels.

The NPAR was calculated using the following formula: NPAR = (percentage of neutrophils (in total white blood cells) (%)) × 100 / albumin (g/dL) [24].

Covariates

Based on prior research, the following potential covariates were incorporated: age, sex, height, weight, body mass index (BMI), race, educational attainment, marital status, poverty-income ratio (PIR), coronary heart disease (CHD), hypertension, smoking status, and alcohol consumption status.

Regarding race, it was classified into five groups: Mexican American, non - Hispanic white, non - Hispanic black, and other races (including multiracial). Educational attainment was categorized as less than high school, high school graduate or equivalent, and more than high school. Marital status was classified as married/living with a partner, unmarried, and separated from a partner (including widowed/divorced/separated). PIR was grouped as < 1.35 (low income), 1.35–2.99 (middle income), and ≥ 3.00 (high income). The diagnosis of CHD was obtained either through self - report questionnaire or based on a physician's diagnosis. Hypertension was determined by a physician's diagnosis, use of oral antihypertensive medications, and blood pressure readings of 140/90 mmHg or higher on two separate occasions [25].

Statistical analysis

Given the complexity of sampling surveys, all data were weighted for analysis, as per the recommendations of NHANES. Weighted linear regression (for continuous variables) or weighted chi - square tests (for categorical variables) were utilized to compare the baseline characteristics between the non - DN and DN groups. Weighted univariate and multivariate logistic regression analyses were conducted to investigate the association between NPAR quartiles and DN in different models. In the crude models, no adjustment for confounding variables was made. In Model 1, age and gender were adjusted. In Model 2, additional adjustments were made for height, weight, race, educational attainment, marital status, PIR, alcohol consumption status, smoking status, and history of CHD and hypertension. To assess potential multicollinearity among variables, a collinearity diagnosis was performed on the data (see Supplementary table). No covariates were found to have a significant impact on the collinearity diagnosis. Furthermore, weighted data were used to compare different subgroups and weighted interactions between variables. To explore the relationship between NPAR and DN, restricted cubic splines (RCS) were applied to fit the nonlinear relationship, and a two - stage linear regression model was used to calculate the turning point of NPAR. The optimal model was determined by the log - likelihood ratio (LR) test. For missing variables, multiple imputation followed by sensitivity analyses was carried out to determine the reliability of the results.

Statistical analysis of the data was performed using R software. A P - value of less than 0.05 was regarded as statistically significant.

Results

Baseline characteristics of the study participants

A total of 9,568 individuals with T2DM were included in the analysis, among whom 1927 (20.14%) were diagnosed with DN. As anticipated, the NPAR was significantly elevated in the DN group compared to the non-DN group (DN group: 15.31; non-DN group: 14.31, $P < 0.001$). Statistically significant differences between the two groups were observed across multiple demographic and clinical variables, including age, race, education level, marital status, PIR, smoking status, alcohol consumption status, prevalence of CHD, and hypertension ($P < 0.001$). Compared to the non-DN group, the DN group was characterized by an older age, a higher proportion of non-Hispanic black individuals, lower educational levels, a higher prevalence of widowed/divorced/separated status, a greater proportion of former drinkers, and a higher incidence of hypertension history. Conversely, the non-DN group was more likely to have a higher PIR, a history of never smoking, and an absence of coronary heart disease. There was no significant statistical difference in the gender distribution between the two groups, with a predominance of male patients in both groups ($P > 0.05$). (Table 1.)

Table 1
Baseline Characteristics of Participants Stratified by Presence of Diabetic Nephropathy.

Characteristic	Non-DN	DN	P-value
Participants	6409	1927	
Age, years	57.00 (47.00 ,66.00)	71.00 (62.00 ,79.00)	< 0.001
Weight, kg	89.60 (75.80 ,106.00)	85.50 (72.60 ,103.50)	< 0.001
Height, m	167.80 (160.30 ,175.30)	166.10 (158.50 ,173.10)	< 0.001
NPAR	14.31 (12.65 ,15.94)	15.31 (13.43 ,17.17)	< 0.001
Sex			0.441
Female	3094 (48.28%)	911 (47.28%)	
Male	3315 (51.72%)	1016 (52.72%)	
Ethnicity			< 0.001
Non-Hispanic White	1429 (22.30%)	301 (15.62%)	
Non-Hispanic Black	2161 (33.72%)	875 (45.41%)	
Mexican American	1541 (24.04%)	462 (23.98%)	
Other races	1278 (19.94%)	289 (15.00%)	
Education			< 0.001
Below high school	1256 (19.62%)	443 (23.04%)	
High school or equivalent	2546 (39.77%)	795 (41.34%)	
Above high school	2600 (40.61%)	685 (35.62%)	
Marital status			< 0.001
Married/cohabiting	3894 (62.00%)	1012 (52.98%)	
Widowed/divorced/separated	1742 (27.73%)	783 (40.99%)	
Never married	645 (10.27%)	115 (6.02%)	
PIR			< 0.001
Low	2146 (37.09%)	681 (39.03%)	
Medium	1821 (31.47%)	635 (36.39%)	
High	1819 (31.44%)	429 (24.58%)	

Abbreviations: NPAR: Neutrophil-Percentage-to-Albumin Ratio; PIR: Poverty income ratio; CHD: Coronary Heart Disease.

Characteristic	Non-DN	DN	P-value
Smoking status			< 0.001
Never	3180 (50.62%)	911 (47.45%)	
Former	1985 (31.60%)	786 (40.94%)	
Now	1117 (17.78%)	223 (11.61%)	
Drinking status			< 0.001
Never	989 (17.51%)	387 (22.55%)	
Former	1437 (25.44%)	605 (35.26%)	
Mild	1790 (31.69%)	495 (28.85%)	
Moderate	615 (10.89%)	109 (6.35%)	
Heavy	818 (14.48%)	120 (6.99%)	
Hypertension history			< 0.001
No	2237 (34.95%)	284 (14.76%)	
Yes	4164 (65.05%)	1640 (85.24%)	
CHD history			< 0.001
No	5751 (92.31%)	1554 (82.48%)	
Yes	479 (7.69%)	330 (17.52%)	

Abbreviations: NPAR: Neutrophil-Percentage-to-Albumin Ratio; PIR: Poverty income ratio; CHD: Coronary Heart Disease.

Association between NPAR and DN prevalence

To mitigate the influence of confounding factors, multiple logistic regression models were employed for data analysis (Table 2). When NPAR was treated as a continuous variable, all three models (the crude model, Model 1, and Model 2) exhibited a strong positive correlation. In the crude model, for every one standard deviation (SD) increase in NPAR, the odds of developing DN increased by 50% (95% confidence interval [CI]: 1.37, 1.63). In Model 2, which was adjusted for all covariates, this correlation remained significant (odds ratio [OR] = 1.39, 95% CI: 1.24, 1.55). Subsequently, NPAR was categorized into quartiles, with the lowest quartile (Q1) serving as the reference. In the fully adjusted model, the adjusted OR for the highest quartile (Q4) was 2.24 (95% CI: 1.85, 2.70), indicating that the risk of DN in Q4 was 1.24 times higher than that in Q1. Notably, the risk of DN gradually increased from Q1 to Q4, and the differences were statistically significant ($P < 0.001$). These findings suggest that a higher NPAR is associated with a greater prevalence of DN. Interestingly, in Model 2, there was no significant

association between the Q2 group of NPAR and DN (OR = 1.13, 95% CI: 0.93, 1.37), further supporting the concept of a turning point for NPAR.

Table 2
Logistic regression analyses for the association between NPAR and the diabetic nephropathy in different models

Exposure	OR (95%CI)		
	Crude Model	**Adjust I**	**Adjust II**
NPAR (per SD)	1.50 (1.37, 1.63)	1.45 (1.32, 1.59)	1.39 (1.24, 1.55)
NPAR (quartiles)			
Q1	1.0(Ref)	1.0(Ref)	1.0(Ref)
Q2	1.26 (1.07, 1.47)	1.19 (1.00, 1.41)	1.13 (0.93, 1.37)
Q3	1.53 (1.30, 1.78)	1.34 (1.14, 1.59)	1.31 (1.08, 1.59)
Q4	2.82 (2.43, 3.27)	2.53 (2.16, 2.96)	2.24 (1.85, 2.70)
p-trend	< 0.0001	< 0.0001	< 0.0001
Abbreviations: OR: Odds ratios; SD: standard deviation.			
Crude Model adjust for: None.			
Model I model adjust for: Age and Sex.			
Model II model adjust for: Age; Sex; Height, weight, ethnicity, education, marital status, PIR, drinking status, smoking status, CHD history and hypertension history.			

Subgroup analysis

To investigate whether the correlation between NPAR and the prevalence of DN varied across different populations, stratified analyses and interaction tests were conducted for each subgroup. After stratification by age, gender, BMI (with obesity defined as BMI ≥ 30 kg/m² based on standardized cut-off points [26]), race, educational attainment, marital status, PIR, alcohol consumption status, smoking status, history of hypertension, and history of CHD, the analysis results indicated that the positive correlation between NPAR and the prevalence of DN remained significant. Notably, a significant interaction was found between educational attainment and NPAR (P-interaction < 0.05). Specifically, individuals with an educational level below high school had a higher OR compared to those with higher educational level. In other subgroups, the interaction was not significant (Table 3).

Table 3
Stratified associations between NPAR and the diabetic nephropathy by age, sex, BMI, ethnicity, education, marital status, PIR, drinking status, smoking status, CHD history and hypertension history.

Subgroup	No. of participants	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	P-interaction
Age				0.05
< 60 years	3295	1.71 (1.52, 1.92)	1.70 (1.48, 1.96)	
≥ 60 years	5041	1.50 (1.41, 1.60)	1.43 (1.33, 1.54)	
Sex				0.53
Female	4005	1.45 (1.34, 1.56)	1.46 (1.33, 1.61)	
Male	4331	1.65 (1.53, 1.78)	1.41 (1.29, 1.55)	
BMI				0.15
< 30 kg/m2	3645	1.51 (1.39, 1.63)	1.35 (1.23, 1.50)	
≥ 30 kg/m2	4508	1.59 (1.47, 1.71)	1.49 (1.36, 1.63)	
Ethnicity				0.06
Non-Hispanic White	3036	1.40 (1.29, 1.52)	1.30 (1.17, 1.44)	
Non-Hispanic Black	2003	1.48 (1.34, 1.63)	1.51 (1.33, 1.70)	
Mexican American	1730	2.00 (1.74, 2.30)	1.67 (1.41, 1.99)	
Other races	1567	1.56 (1.36, 1.77)	1.43 (1.21, 1.68)	
Education				0.02
Below high school	1699	1.81 (1.61, 2.04)	1.75 (1.49, 2.05)	
High school or equivalent	3341	1.46 (1.35, 1.58)	1.32 (1.19, 1.46)	
Above high school	3285	1.52 (1.40, 1.66)	1.42 (1.27, 1.58)	

All abbreviations as in Table 1.

Subgroup	No. of participants	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	P-interaction
Marital status				0.33
Married/cohabiting	4906	1.64 (1.52, 1.76)	1.50 (1.37, 1.64)	
Widowed/divorced/separated	2525	1.42 (1.31, 1.55)	1.37 (1.23, 1.52)	
Never married	760	1.46 (1.20, 1.76)	1.36 (1.06, 1.76)	
PRI				0.25
Low	2827	1.42 (1.31, 1.55)	1.38 (1.24, 1.53)	
Medium	2456	1.69 (1.53, 1.86)	1.55 (1.38, 1.75)	
High	2248	1.54 (1.38, 1.72)	1.35 (1.19, 1.54)	
Drinking status				0.77
Current	3947	1.57 (1.44, 1.71)	1.40 (1.27, 1.55)	
Never/past	3418	1.50 (1.39, 1.62)	1.46 (1.33, 1.59)	
Smoking status				0.07
Current	1340	1.44 (1.25, 1.65)	1.24 (1.05, 1.47)	
Never/past	6862	1.58 (1.49, 1.67)	1.47 (1.37, 1.58)	
CHD history				0.88
No	7305	1.51 (1.43, 1.60)	1.43 (1.33, 1.54)	
Yes	809	1.50 (1.29, 1.74)	1.49 (1.23, 1.81)	
Hypertension history				0.78
No	2521	1.60 (1.41, 1.82)	1.38 (1.15, 1.65)	

All abbreviations as in Table 1.

Subgroup	No. of participants	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	P-interaction
Yes	5804	1.53 (1.44, 1.62)	1.44 (1.34, 1.55)	
All abbreviations as in Table 1.				

Nonlinear association between NPAR and DN

This study also utilized RCS to plot curves for exploring the nonlinear relationship between NPAR levels and the prevalence of DN. The RCS analysis (Fig. 2) revealed that NPAR and the prevalence of DN roughly exhibited a J-shaped relationship (P-overall < 0.001, P-non-linear < 0.001). Simultaneously, a visual inspection suggested the presence of a turning point in the risk change between NPAR and DN risk.Consequently, the stepwise recursive method was further employed to identify the turning point, and two-stage linear regression was conducted on both sides of the turning point (Table 4). Significantly, when NPAR < 14.48, there was no significant association between NPAR and DN risk (OR = 1.04, 95% CI: 0.99, 1.09), whereas when NPAR ≥ 14.48, the prevalence of DN increased with the increase in NPAR (OR = 1.21, 95% CI: 1.17, 1.26).

Table 4
The result of the two-piecewise linear regression model.

Outcome: diabetic nephropathy	OR (95%CI)	P-value
Fitting model by standard linear regression	1.14 (1.11, 1.16)	< 0.01
Inflection points of NPAR	14.48	
NPAR < 14.48	1.04 (0.99, 1.09)	0.15
NPAR ≥ 14.48	1.21 (1.17, 1.26)	< 0.01
P for log-likelihood ratio test	< 0.01	

Sensitivity analysis

Through sensitivity analysis using multiple imputation, the robustness of the association between NPAR and the risk of DN was verified (Table 5). From the four analyzed datasets, it was evident that for every one SD increase in NPAR, the risk of DN increased by 42% (95% CI: 1.29, 1.56). The quartile data of NPAR also demonstrated similar results. Compared to the lowest quartile of NPAR, the risk of DN in the highest quartile was 1.44 times higher (OR = 2.44, 95% CI: 2.07, 2.87). Consistent with the observed association between NPAR and the risk of DN, a significant statistical trend was evident in all four models (p-trend < 0.0001). These results collectively indicate that missing data did not exert a substantial impact on the association between NPAR and the prevalence of DN, thereby enhancing the reliability and validity of this study.

Table 5
Sensitivity analysis of the association between NPAR and diabetic nephropathy.

	OR (95% CI)			
	Sensitivity-1	**Sensitivity-2**	**Sensitivity-3**	**Sensitivity-4**
NPAR (per SD)	1.42 (1.29, 1.56)	1.42 (1.29, 1.56)	1.42 (1.29, 1.56)	1.42 (1.29, 1.56)
NPAR (quartiles)				
Q1	1.0(Ref)	1.0(Ref)	1.0(Ref)	1.0(Ref)
Q2	1.20 (1.01, 1.42)	1.20 (1.01, 1.43)	1.20 (1.01, 1.42)	1.20 (1.01, 1.42)
Q3	1.35 (1.14, 1.60)	1.35 (1.14, 1.60)	1.35 (1.14, 1.60)	1.35 (1.14, 1.60)
Q4	2.44 (2.07, 2.88)	2.44 (2.07, 2.88)	2.44 (2.07, 2.87)	2.44 (2.07, 2.87)
p-trend	< 0.01	< 0.01	< 0.01	< 0.01

Note: (1) Sensitivity-1 to Sensitivity-4 were repeated analyses using data after multiple imputations of missing covariates.

All abbreviations are listed in Table 1. Restricted cubic splines were adjusted for age, sex, height, weight, ethnicity, education, marital status, PIR, drinking status, smoking status, CHD history and hypertension history.

Discussion

In this cross-sectional study, data from 10 consecutive cycles of the NHANES database were analyzed to examine the potential link between the NPAR and the prevalence of DN among diabetic individuals in the United States. The results demonstrated a significant positive association between elevated NPAR levels and increased DN prevalence. Sensitivity analysis and subgroup analysis were conducted to further validate the reliability of the study results. A notable nonlinear relationship was observed between NPAR and DN risk, with a distinct threshold for risk alteration. Specifically, when NPAR values were below 14.48, no statistically significant correlation with DN was found. However, once NPAR reached or exceeded 14.48, an increase in NPAR was associated with a significant elevation in the incidence of DN. These observations suggest that NPAR could serve as a valuable early indicator for DN screening.

NPAR is an emerging, easily measurable inflammatory biomarker that has been shown to be associated with a variety of clinical diseases. Shen G et al. demonstrated a nonlinear relationship between NPAR and all-cause mortality in diabetic patients. They reported that the risk of all-cause mortality (HR, 1.62 [95% CI, 1.36, 1.94]) in the highest tertile of NPAR was significantly higher than that in the lowest tertile of NPAR [27], and Li X et al. [15] further employed RCS regression analysis to establish a J-shaped association between NPAR and all-cause mortality. Additionally, in another single-center observational study [18], researchers utilized a two-segment Cox proportional hazards model to evaluate the turning point between NPAR and all-cause mortality, with similar results verified in the studies by Jing Y [19] and

Chen J [20]. Ji W et al. [28] also reported that higher NPAR was associated with an increased risk of metabolic syndrome in the US adult, suggesting that this association was partly mediated by serum uric acid and the TyG index. Moreover, another cross-sectional investigation revealed that elevated NPAR was independently linked to an increased incidence of Diabetic Retinopathy (DR) [16]. Tan J et al. [29] conducted a 13-year multicenter retrospective cohort study of 83,776 T2DM patients and found that higher NPAR levels were closely related to prolonged hospital stays in T2DM patients. Furthermore, another predictive model for elderly T2DM patients with heart failure demonstrated that NPAR was an independent predictor of 30-day readmission risk [30]. Of note, Li J et al. [31] reported a positive correlation between NPAR and an increased risk of CKD, including a nonlinear association was identified between the two. In Tan J et al.'s research [32], NPAR was found to be significantly associated with increased all-cause mortality and cardiovascular mortality in DN patients, with gender-based differences in this correlation noted. Consistent with our findings, Li H et al. [17] also observed a positive correlation between NPAR and DN. It is worth emphasizing that, based on an expanded sample size, we further identified a specific inflection point for NPAR through RCS analysis, and the two-stage linear regression results validated the presence of different correlations on either side of the turning point. Interestingly, subgroup analysis revealed an interaction between educational level and NPAR, potentially due to lifestyle variations such as diet and physical activity. Further investigation is warranted to explore this relationship.

While the precise mechanisms through which NPAR influences the prevalence of DN remain unclear, from a pathophysiological perspective, NPAR, as a novel indicator reflecting inflammation and metabolic dysregulation in the body, its elevation indicates abnormal activation of the body's inflammatory and immune responses, which plays a key role in the development and progression of DN. Under hyperglycemic conditions, the formation of Advanced Glycation End Products (AGEs) increases significantly [33]. These AGEs, after binding to the Receptor for Advanced Glycation End Products (RAGE), activate the nuclear factor κB (NF-κB) signaling pathway, triggering the release of large amounts of pro-inflammatory cytokines such as TNF-α and IL-6. This, in turn, results in functional impairment and structural alterations in renal tubular epithelial cells, glomerular mesangial cells, and podocytes [34]. Additionally, elevated levels of inflammatory factors such as TNF-α and IL-6 also trigger the inflammatory cascade, promoting the synthesis and deposition of extracellular matrix and accelerating the process of renal fibrosis [35]. In peripheral cells, neutrophils are known to contribute to DN pathogenesis [36], while albumin, as the primary plasma protein, influences the transport and distribution of various substances in the body[10]. Collectively, these findings suggest that NPAR may affect the prevalence of DN through inflammatory mechanisms.

This study further focused on the changes in NPAR within the context of diabetes, supplemented the existing knowledge on the nonlinear association between NPAR and the prevalence of DN, observed a J-shaped relationship between NPAR and DN, and pinpointed the inflection point of NPAR. Additionally, we adjusted for multiple confounding factors and employed subgroup analysis and sensitivity analysis to confirm the reliability of the results. Notwithstanding these efforts, this study has certain limitations. Firstly, as a cross-sectional study, similar to other investigations of this nature, it is unable to determine

the temporal sequence of events, and thus, the causal relationship between the study factors cannot be established. Future research should aim to clarify the causal direction through cohort studies or interventional trials. Secondly, although multiple confounding factors were adjusted for, it is still not possible to exclude the influence of all potential confounding variables. Specifically, this study did not incorporate detailed medication information of patients, precluding the determination of the potential interference of drugs on the results. In conclusion, based on the findings of this study, NPAR holds promise as a potential biomarker for the early screening and disease monitoring of DN. Future research can delve into the underlying mechanisms and pathways through which NPAR impacts the development of DN and explore novel therapeutic strategies for DN by modulating NPAR-related inflammatory pathways.

Conclusion

This study represents the first systematic confirmation that the NPAR, a composite biomarker reflecting both inflammatory activity and nutritional metabolic status, exhibits a J-shaped nonlinear association with the risk of DN, with a critical threshold identified at 14.48. Specifically, when NPAR is equal to or exceeds 14.48, each unit increase is significantly associated with elevated DN risk. In contrast, no statistically significant association is observed when NPAR is below this threshold. Given its ease of measurement and cost-effectiveness, NPAR holds promise as a practical biomarker for clinical application. The identified threshold provides a quantifiable reference for risk stratification and clinical decision-making. In clinical practice, it is recommended to maintain NPAR below 14.48 to mitigate DN risk. For individuals with NPAR values exceeding 14.48, proactive renal function evaluation should be implemented to enhance early detection and timely intervention of DN. This approach is particularly valuable for renal health monitoring among diabetic patients in primary healthcare settings.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The NHANES datasets are available for download from the NHANES home website (https://www.cdc.gov/nchs/nhanes/index.htm).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JP-L: Conceptualization, methodology, supervision, and project administration.

YJ-Z, JJ-Q and JY-F: Writing—original draft preparation.

YJ-Z, JJ-Q, JY-F, HT-Z, JE-L, SX, LX-F, and J-Z: Writing—reviewing and editing.

YJ-Z and JJ-Q: Software.

YJ-Z, JJ-Q, JY-F and LX-F: Formal analysis and validation.

YJ-Z, JJ-Q, JY-F, HT-Z, and J-Z: Data curation.

All authors: All authors read and approved the final manuscript.

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Figures

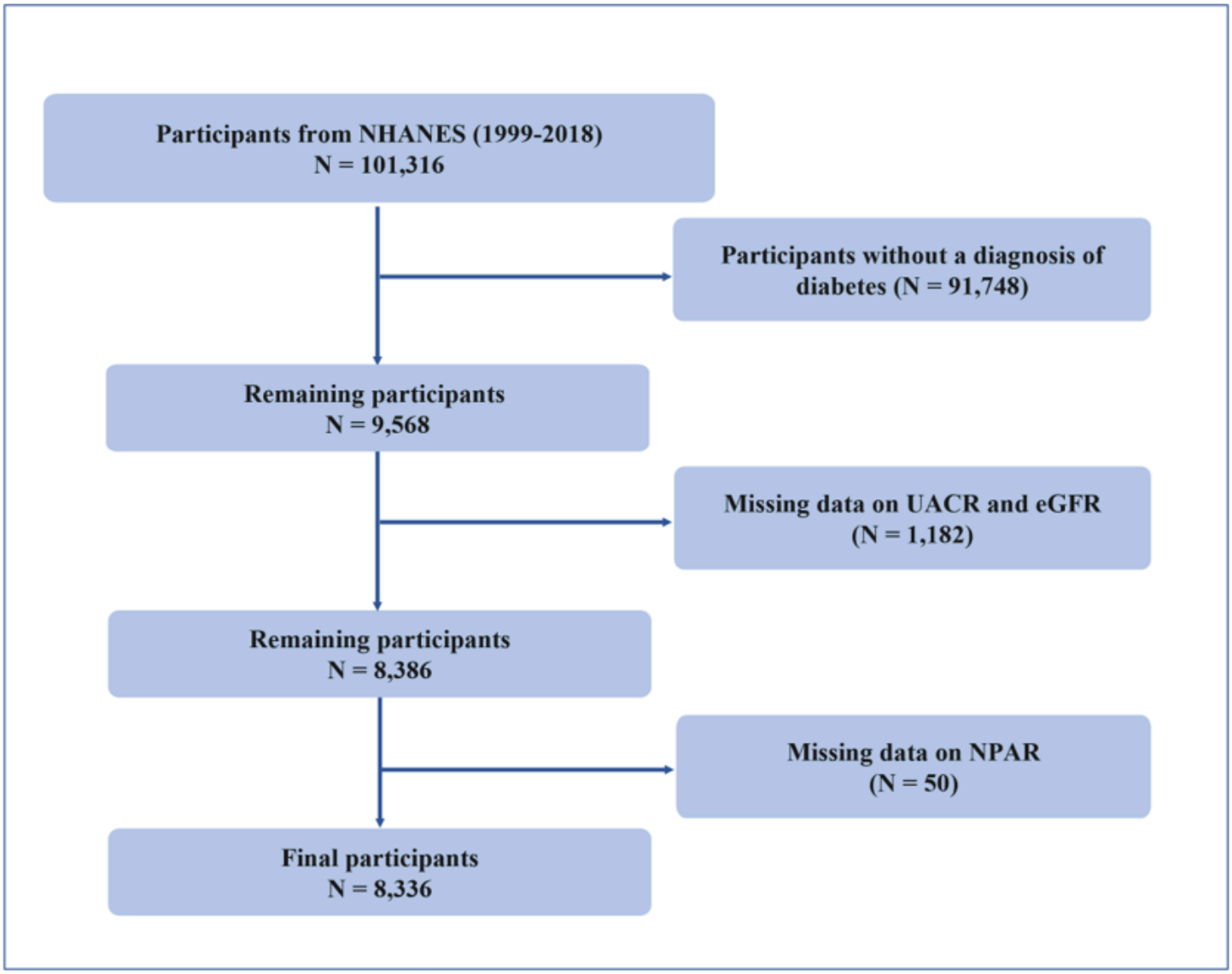


Figure 1

Study population screening flowchart.

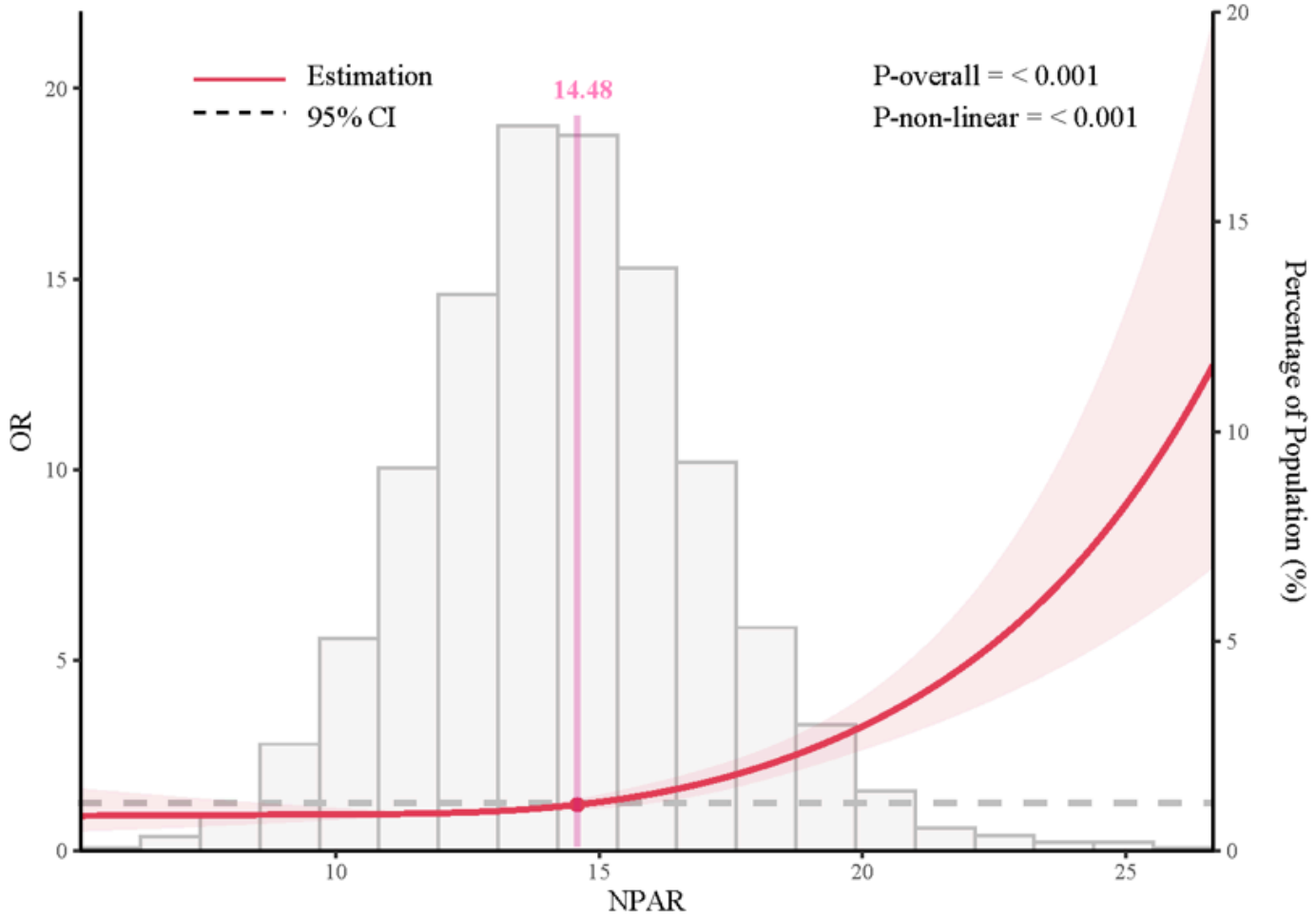


Figure 2

The dose–response association between the NPAR and Diabetic Nephropathy.

All abbreviations are listed in Table 1. Restricted cubic splines were adjusted for age, sex, height, weight, ethnicity, education, marital status, PIR, drinking status, smoking status, CHD history and hypertension history.

Supplementary Files

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- Supplementarytable.docx