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High levels of blood glycemic indicators are associated with chronic kidney disease prevalence in non-diabetic adults: Cross-sectional data from the national health and nutrition examination survey 2005–2016

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ABSTRACT

Objective: Hyperglycemia in individuals with diabetes is associated with chronic kidney disease (CKD); however, little is known about its association with those without diabetes. Our goal was to investigate the association between glycemic indicators and CKD in individuals without diabetes.

Methods: This cross-sectional study included 9610 participants without diabetes who participated in the Health and Nutrition Examination Survey between 2005 and 2016. Exposures included postprandial glucose dip (PGD), fasting blood glucose (FBG), oral glucose tolerance test two-hour blood glucose (OGTT-2HBG), and glycated hemoglobin (HbA1C) levels. Moreover, CKD was defined as an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2 or a urinary albumin-creatinine ratio of $\geq$ 30 mg/g. Two multivariate models were constructed. Interaction effects were also explored.

Results: The mean age of the participants was 46.0 years, with 50.3 % being females. The prevalence of CKD was 12.6 %. In the final multivariable models, the odds ratios (ORs) for CKD were 1.51 (95 % confidence interval [CI]: 1.22,1.88, p < 0.001) for participants in the highest quartile of PGD,1.46 (95 %CI: 1.13,1.87, p = 0.004) for OGTT-2HBG, and 1.33 (95 %CI: 1.04,1.70, p = 0.020) for HbA1C, when compared with the quartile 1. No significant association was observed between FBG levels and CKD in the final model. Additionally, interactions were observed between PGD and body mass index, as well as between PGD and alcohol consumption in relation to CKD.

Conclusion: The study identified that high levels of PGD, OGTT-2HBG, and HBA1C were significantly associated with a high prevalence of CKD in individuals without diabetes.

Introduction

Globally, 10–15 % of adults are affected by chronic kidney disease (CKD), with rising numbers due to an aging population and lifestyle changes that elevate obesity, hypertension, and diabetes mellitus (DM) rates [1–3]. Identifying modifiable risk factors is crucial for reducing the incidence of CKD and improving outcomes.

Glycemic indicators, including fasting blood glucose (FBG), oral glucose tolerance test two-hour blood glucose (OGTT-2HBG), and glycated hemoglobin (HbA1C), have been closely associated with kidney complications in patients with DM [4–6]. Recent systematic reviews and *meta*-analyses [7,8] have further demonstrated that glycemic variability, which reflects fluctuations and changes in glycemic levels, is linked to the onset and progression of CKD in patients with DM. Chen et al. [7] assessed the association between FBG variability and adverse DM-related outcomes. Their findings revealed that FBG variability correlated with renal disease, all-cause mortality, and retinopathy. Furthermore, FBG variability is linked to insulin resistance (IR) [9], a key factor in the development of CKD in individuals without DM [10]. However, the link between these indicators and non-diabetic CKD remains

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unexplored, and whether these associations extend to individuals without DM remains unknown. Moreover, modifiable risk factors including smoking, drinking, and obesity can affect blood glucose levels [11–13] and CKD development [14]. Exploring the potential interaction effects between these modifiable risk factors and glycemic indicators may aid in identifying high-risk groups and formulating personalized CKD prevention and management strategies.

In individuals without DM, the blood glucose level usually increases from approximately 5 mmol/L to 8 mmol/L after consuming 50 g of glucose powder, but then returns to the normal range within two hours due to the regulation of insulin and glucagon [15]. Recent research has demonstrated that the ability to return to normal FBG levels after a two-hour OGTT predicts the risk of DM [16]. Therefore, monitoring this ability is crucial, and the postprandial glucose dip (PGD) is a valuable indicator. A recent study identified a correlation between PGD, metabolic syndrome, and the ten-year risk of cardiovascular disease (CVD) [17]. However, whether PGD is a risk factor for CKD in individuals without DM remains unclear.

To bridge the knowledge gaps identified above, we investigated the associations between PGD, FBG, OGTT-2HBG, HbA1C, and the risk of CKD in a nationally representative sample of American adults without DM. Furthermore, we investigated the potential interaction effects between other modifiable risk factors and glycemic indicators.

Material and methods

Study design and population

The National Health and Nutrition Examination Survey (NHANES) is a periodic cross-sectional survey that generates a nationally representative sample of the noninstitutionalized American civilian population. Utilizing a complex multistage probability sampling design, each NHANES cycle spans two years. Detailed survey design and methods information is available elsewhere [18]. The NHANES protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics Research Ethics Review Board.

The NHANES cycles utilized for this study include 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016. In total, 92,062 individuals participated in the survey. Participants who did not have information on blood glucose and HbA1C levels (n = 78,255) or those with missing data on estimated glomerular filtration ratio (eGFR) and urinary albumin-creatinine ratio (UACR) (n = 169) were excluded. Participants who were pregnant and less than 20 years old (n = 2,956) as well as those who had DM or CKD (n = 1,072) were also excluded. The final analysis included 9, 610 participants with complete datasets. Fig. 1 displays a flowchart of the sample selection process.

Diagnosis of DM

Individuals were classified as having DM if they met any of the following criteria: a self-reported DM diagnosis, HbA1C $\geq$ 6.5 %, a plasma glucose level $\geq$ 200 mg/dL two hours after OGTT, a fasting glucose level $\geq$ 126 mg/dL, or those using oral hypoglycemic agents and/or insulin.

Diagnosis of CKD

The 2012 Kidney Disease: Improving Global Outcomes recommendations were used to define CKD. The diagnosis of CKD was based on the presence of either a low eGFR or albuminuria [19]. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration study formula based on serum creatinine levels [20]. A low eGFR was defined as a rate equal to or less than 60 mL/min/1.73 m². Additionally, albuminuria was defined as a UACR of 30 mg/g or higher. Urinary albumin was assessed using a solid-phase fluorescent

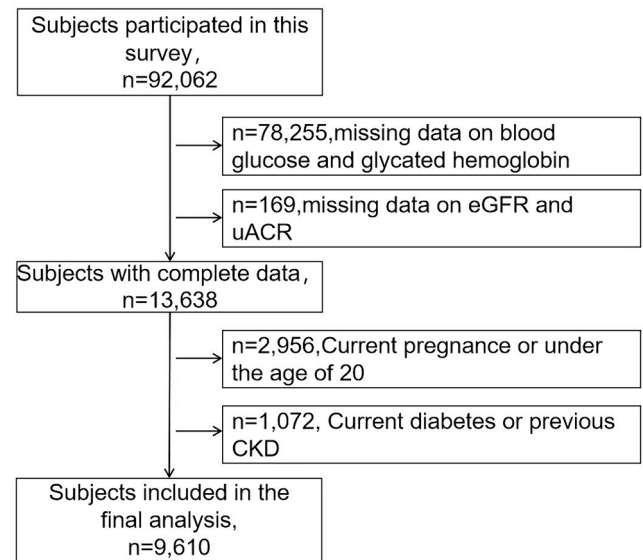## Sample inclusion and exclusion for NHANES 2005 - 2016

Fig. 1. Flowchart of samples' inclusion and exclusion criteria.

immunoassay [21], whereas urinary creatinine was evaluated using an enzymatic method.

Definitions of exposure

In the NHANES, all participants underwent assessments for three glycemic indicators, FBG, OGTT-2HBG, and HbA1C. These indicators were defined as exposures. The aforementioned indicators allowed for the accurate identification of participants with DM who may present with normal HbA1c levels but have abnormal fasting glucose and/or OGTT-2HBG values, thereby ensuring the precise classification of DM in our study population. In addition, we employed PGD as an exposure. The PGD was calculated using the following formula: (OGTT-2HBG − FBG)/ FBG. Exposure was categorized into quartiles. The measurement of HbA1C was performed at the Collaborative Studies Clinical Laboratory at the University of Minnesota (Columbia) using a Tosoh Automated Analyzer HLC-723G8 (Tosoh Medics, Inc., So. San Francisco, CA) [22].

Covariates

Baseline age (years) and body mass index (BMI) were considered continuous variables, with BMI additionally categorized into three weight status groups: underweight or normal weight (<25 kg/m²), overweight (25 to < 30 kg/m²), and obese ($\geq$30 kg/m²) [23]. The BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m²). Sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), educational level (less than high school, high school or equivalent, or college or above), and marital status (married, separated, or never married) were considered categorical variables. The family income-poverty ratio was divided into three categories: below poverty (<1.0), low-to-moderate income (1.1 to 3.0), and above poverty (>3.0). Smoking status was determined based on self-reports, and individuals were classified as never smokers, former smokers, or current smokers. Drinking status was derived from a twenty-four-hour dietary recall, categorizing individuals as non-drinkers, low-to-moderate drinkers (less than two drinks per day for males and less than one drink per day for females), or heavy drinkers (two or more drinks per day for males and one or more drink per day for females). Leisure-time physical activity level was grouped into none (0 times/ week), occasional (1–2 times/week), or frequent ($\geq$3 times/week). Diet quality was assessed using Healthy Eating Index (HEI) scores and

categorized into quartiles. The self-reported health status was classified as very good to excellent, good, or poor to fair. Hypertension was defined as a self-reported hypertension diagnosis, treatment with hypertensive medications, diastolic blood pressure ≥ 90 mmHg, and/or systolic blood pressure ≥ 140 mmHg.

Statistical analysis

All statistical analyses were conducted according to the Centers for Disease Control and Prevention guidelines [18], and we used a suitable sample weight for each participant in the NHANES complex multistage cluster survey design. Categorical variables are presented as percentages with 95 % confidence intervals (95 %CI) and continuous variables are presented as means with 95 %CI. We assessed the differences among the PGD quartiles using analysis of variance for continuous variables and weighted chi-square tests for categorical variables. For UACR (a non-parametric variable), we presented the statistics as medians (P25, P75) and used the Kruskal–Wallis H test for comparison. Multivariate logistic regression analysis was performed to evaluate the association between glycemic indicators and CKD. Three different models were constructed (crude model: unadjusted; model 1: adjusted for age, sex, BMI, race/ethnicity, educational level, marital status, family income-poverty ratio, smoking status, and drinking status; model 2: additionally adjusted for leisure-time physical activity level, HEI scores, self-reported health status, and history of hypertension). Missing data among covariates were imputed using a random forest approach implemented with the R package MissForest [24] fitted with 100 trees.

Restricted cubic spline analysis with four knots (5th, 35th, 65th, and 95th percentiles) was employed to examine the non-linear association between glycemic indicators and CKD using the 25th percentile as a reference. Non-linearity was tested using a likelihood ratio test.

We further stratified the analyses according to sex (male or female),

Table 1
Baseline characteristics of populations with different PGD quartile arrays.

Variable	Total	Q1	Q2	Q3	Q4	P value
n	9610	2502	2377	2547	2184	
Age, years*	46.0(45.35,46.63)	41.3(40.53,42.06)	42.9(41.95,43.84)	47.2(46.26,48.21)	53.3(52.11,54.48)	<0.001
BMI, kg/m^2*	28.5(28.3,28.7)	27.2(26.8,27.5)	28.2(27.9,28.5)	29.2(28.9,29.5)	29.7(29.3,30.1)	<0.001
PGD,mmol/L*	0.11(0.11,0.12)	−0.24(−0.24,-0.23)	0.00(−0.01, 0.00)	0.18(0.18, 0.18)	0.52(0.52, 0.53)	<0.001
FBG,mmol/L*	5.46(5.44,5.48)	5.45(5.43,5.48)	5.38(5.35,5.41)	5.45(5.43,5.48)	5.57(5.54,5.59)	<0.001
OGTT-2HBG,mmol/L*	6.09(6.04,6.13)	4.18(4.14,4.22)	5.39(5.36,5.42)	6.51(6.47,6.54)	8.56(8.50,8.61)	<0.001
HbA1C,%	5.42(5.41,5.43)	5.36(5.34,5.37)	5.36(5.34,5.38)	5.44(5.42,5.46)	5.54(5.52,5.56)	<0.001
eGFR, ml/min/1.73 m^2*	98.90(98.00,99.81)	102.09(100.96,103.22)	101.97(100.57,103.36)	98.34(97.08, 99.59)	92.55(91.03, 94.06)	<0.001
Urinary albumin creatinine ratio, mg/g#	6.38(4.26,11.27)	5.63(3.90, 9.51)	6.09(4.14,10.54)	6.43(4.29,11.30)	7.73(5.00,15.70)	<0.001
Women	50.3(48.2,52.4)	40.0(37.6,42.3)	53.2(51.2,55.3)	53.7(51.6,55.8)	54.8(52.6,57.0)	<0.001
Ethnicity:						0.003
Non-Hispanic white	36.4(33.0,39.9)	36.3(32.7,39.9)	35.2(31.6,38.7)	34.7(30.9,38.5)	40.0(35.7,44.3)	
Non-Hispanic black	23.5(20.7,26.3)	23.0(19.8,26.3)	26.2(23.1,29.2)	24.4(21.3,27.6)	20.1(16.9,23.4)	
Mexican American	18.3(15.6,20.9)	18.0(15.2,20.9)	17.3(14.6,20.1)	19.4(16.5,22.4)	18.2(14.9,21.4)	
Others	21.78(19.5,24.1)	22.63(19.8,25.5)	21.35(18.8,23.9)	21.43(18.5,24.3)	21.71(19.0,24.4)	
Education:						<0.001
Less than high school	25.1(23.1,27.1)	22.4(19.9,24.9)	24.5(22.0,27.1)	25.7(23.2,28.1)	28.0(25.6,30.5)	
High school or equivalent	22.9(21.6,24.1)	25.1(22.5,27.7)	20.1(18.1,22.0)	22.2(20.3,24.1)	24.1(22.1,26.1)	
College or above	52.1(49.6,54.5)	52.5(49.5,55.5)	55.4(52.6,58.2)	52.2(49.3,55.0)	47.8(45.0,50.7)	
Poverty ratio level:						0.002
0–1.0	24.0(22.3,25.7)	26.0(23.6,28.5)	23.5(21.6,25.4)	22.8(20.5,25.2)	23.4(20.9,26.0)	
1.1–3.0	42.3(40.3,44.4)	39.2(36.8,41.6)	40.8(38.5,43.2)	44.3(42.3,46.3)	45.3(42.3,48.4)	
>3.0	33.7(31.7,35.7)	34.8(32.0,37.6)	35.6(33.3,38.0)	32.9(30.5,35.3)	31.3(28.4,34.1)	
Marital status:						<0.001
Married	59.28(56.83,61.73)	56.86(54.78,58.95)	59.02(56.34,61.70)	60.54(58.03,63.06)	60.84(58.25,63.43)	
Separated	20.10(18.92,21.28)	16.93(14.99,18.87)	18.57(16.61,20.52)	20.54(18.77,22.32)	24.90(22.80,27.00)	
Never married	20.62(19.16,22.09)	26.21(23.83,28.58)	22.41(20.03,24.80)	18.91(16.83,21.00)	14.26(12.34,16.19)	
Alcohol drinking:						<0.001
Non-drinker	29.50(28.01,31.00)	21.55(19.60,23.49)	27.36(25.35,29.36)	30.89(28.76,33.03)	39.36(37.23,41.49)	
Low to moderate drinker	47.85(45.81,49.88)	50.12(47.63,52.61)	50.86(48.49,53.22)	47.37(44.91,49.84)	42.49(40.06,44.92)	
Heavy drinker	22.65(21.43,23.87)	28.33(26.13,30.53)	21.79(20.10,23.48)	21.74(20.12,23.36)	18.15(16.25,20.06)	
Smoking status:						<0.001
never	56.7(54.2,59.2)	49.7(47.0,52.3)	60.4(57.8,62.9)	60.0(57.8,62.2)	56.9(54.0,59.9)	
former	21.4(20.1,22.7)	19.2(17.4,20.9)	19.5(17.5,21.5)	21.1(19.1,23.0)	26.3(23.9,28.7)	
current	21.9(20.5,23.3)	31.2(28.7,33.7)	20.1(18.2,22.0)	18.9(17.3,20.6)	16.8(14.3,19.1)	
Leisure time physical activity level:						<0.001
0 times/week	49.4(47.1,51.6)	45.6(43.1,48.1)	47.2(44.7,49.8)	49.0(46.6,51.5)	56.5(53.9,59.1)	
1–2 times/week	13.2(12.2,14.2)	14.9(13.5,16.4)	12.8(11.2,14.4)	13.5(11.8,15.2)	11.2(9.8,12.7)	
≥3 times/week	37.4(35.7,39.2)	39.5(37.1,41.8)	40.0(37.4,42.5)	37.5(35.3,39.6)	32.3(29.8,34.7)	
Healthy eating index score:						<0.001
Quarter 1	28.28(26.77,29.80)	29.51(27.59,31.44)	28.75(26.42,31.08)	28.96(26.78,31.14)	25.56(22.94,28.19)	
Quarter 2	24.89(23.49,26.30)	27.27(25.17,29.38)	25.94(23.64,28.24)	23.43(21.45,25.41)	22.73(20.82,24.64)	
Quarter 3	25.89(24.68,27.09)	24.48(22.83,26.12)	23.58(21.39,25.77)	26.75(24.67,28.82)	29.03(26.82,31.25)	
Quarter 4	20.94(19.68,22.20)	18.74(17.08,20.40)	21.73(19.75,23.71)	20.87(18.94,22.80)	22.67(20.49,24.85)	
Self-reported health:						<0.001
Very good to excellent	20.49(19.24,21.74)	18.51(16.57,20.44)	17.14(15.42,18.86)	20.76(18.90,22.62)	26.15(23.97,28.32)	
Good	37.96(36.3,39.7)	35.96(33.87,38.05)	38.29(36.32,40.26)	38.22(36.24,40.19)	39.60(36.96,42.24)	
Poor to fair	41.5(39.6,43.5)	45.5(42.9,48.1)	44.6(42.1,47.0)	41.1(38.6,43.4)	34.3(31.6,36.9)	
Hypertension	34.6(32.7,36.4)	24.6(22.2,27.1)	29.1(26.8,31.3)	36.9(34.3,39.5)	49.3(46.9,51.7)	<0.001
CKD	12.6(11.5,13.6)	8.5(7.4, 9.7)	9.4(7.8,10.9)	12.3(10.6,14.0)	21.0(18.5,23.5)	<0.001

Variables marked with '*' are represented using means and their corresponding confidence intervals, while variables marked with '#' are described using medians and quartiles. Categorical variables are presented as percentages with confidence intervals. BMI: Body Mass Index, PGD: Postprandial Glucose Dip, FBG: Fasting Blood Glucose, OGTT-2HBG: Oral Glucose Tolerance Test-2 Hour Blood Glucose, HbA1C: Hemoglobin A1c, eGFR: Estimated Glomerular Filtration Rate, CKD: Chronic Kidney Disease.

age (<60 or ≥ 60 years), BMI (<25.0, 25.0–29.9 or ≥ 30), race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or others), alcohol consumption (non-drinker, low-to-moderate drinker, or heavy drinker), and smoking status (never, former, or current). Moreover, p-values for the interaction terms between the glycemic indicators and stratified factors were calculated to estimate the significance of the interactions. To further analyze the robustness of our results, we repeated the regression analyses using non-imputed data.

All our analyses were performed using R version 4.0.5 (https://www. R- project.org, The R Foundation) with the "Survey" package.

Results

Baseline characteristics of participants

The baseline characteristics of the study participants, divided into quartiles based on their PGD indices, are presented in Table 1. A total of 9,610 participants were included, 50.3 % of whom were females. The mean age was 46.0 years. The mean PGD value was 0.11, with a 95 %CI of 0.11 to 0.12. The ranges of PGD index quartiles were <−0.09, ≥ −0.09 to <0.08, ≥0.08 to <0.30, and ≥0.30. Individuals in the highest quartile exhibited poor dietary habits, as indicated by the HEI (25.6 in quartile 4 vs. 29.5 in quartile 1; 95 %CI: 22.9 to 28.2 for quartile 4 and 27.6 to 31.4 for quartile 1). The prevalence of hypertension progressively increased to 50.7 % in the upper quartile (p < 0.001).

Regarding glycemic indicators, a significant elevation across quartiles was noted. PGD levels varied substantially, ranging from −0.24 mmol/L in quartile 1 to 0.52 mmol/L in quartile 4 (95 %CI: −0.24 to −0.23 for quartile 1 and 0.52 to 0.53 for quartile 4; p < 0.001). The FBG and OGTT-2HBG levels exhibited a similar trend, with the highest values in quartile 4 (p < 0.001). A significant rise in the HbA1C percentages across quartiles was evident (p < 0.001). The mean eGFR was 98.90 mL/min/1.73 m^2 (95 %CI: 98.00 to 99.81), declining from 102.09 mL/min/1.73 m^2 in quartile 1 to 92.55 mL/min/1.73 m^2 in quartile 4 (95 %CI: 100.96 to 103.22 for quartile 1 and 91.03 to 94.06 for quartile 4, p < 0.001). Concurrently, UACR demonstrated an increasing trend in albuminuria across the quartiles (p < 0.001). The overall CKD prevalence rate was 12.6 %, which increased with the rise in the PGD index. Moreover, individuals with the highest PGD index were more likely to be females, non-Hispanic white, less educated, non-drinkers, and current smokers (p < 0.001).

Association between the blood glycemic indicators and CKD

PGD

In the crude model (Table 2), elevated PGD quartiles were significantly associated with a high prevalence of CKD. The odds ratio (OR) for comparing quartile 4 to quartile 1 was 2.84 with a 95 %CI of 2.31 to 3.51, and the p-value for trend was less than 0.001. After adjusting for baseline demographics and lifestyle factors in model 1, this association remained significant (OR for quartile 4 vs. quartile 1 = 1.71, 95 %CI 1.37–2.13, p for trend < 0.001). Further adjustment for physical activity, diet, health status, and hypertension history in model 2 slightly attenuated the association (OR for quartile 4 vs. quartile 1 = 1.51, 95 % CI 1.22–1.88, p for trend < 0.001).

FBG

In the crude model, FBG was less strongly but still significantly associated with CKD (OR for quartile 4 vs. quartile 1 = 1.70, 95 %CI 1.38–2.10, p for trend < 0.001). Adjustments in models 1 and 2 further attenuated this association, with the latter demonstrating a non-significant association.

OGTT-2HBG

The crude model demonstrated a strong association between high OGTT-2HBG and CKD (OR for quartile 4 vs. quartile 1 = 2.81, 95 %CI

Table 2
Univariate and multivariate logistic regression analysis of PGD, FBG, OGTT-2HBG and HbA1C with CKD, respectively.

	Q1	Q2	Q3	Q4	p for trend
PGD					
crude model	ref	1.11 (0.89,1.37) 0.36	1.50 (1.21,1.86) <0.001	2.84 (2.31,3.51) <0.0001	<0.0001
Model 1	ref	1.00 (0.80,1.24) 0.98	1.13 (0.90,1.41) 0.29	1.71 (1.37,2.13) <0.0001	<0.0001
Model 2	ref	0.99 (0.80,1.23) 0.93	1.07 (0.85,1.34) 0.58	1.51 (1.22,1.88) <0.001	<0.001
FBG					
crude model	ref	0.97 (0.76,1.24) 0.82	1.15 (0.90,1.46) 0.26	1.70 (1.38,2.10) <0.0001	<0.0001
Model 1	ref	0.91 (0.71,1.15) 0.41	0.96 (0.74,1.25) 0.75	1.24 (0.98,1.55) 0.07	0.03
Model 2	ref	0.92 (0.73,1.16) 0.46	0.90 (0.70,1.17) 0.44	1.10 (0.87,1.38) 0.43	0.34
OGTT-2HBG					
crude model	ref	1.03 (0.80,1.33) 0.81	1.67 (1.32,2.10) <0.0001	2.81 (2.22,3.56) <0.0001	<0.0001
Model 1	ref	0.93 (0.72,1.21) 0.6	1.27 (1.00,1.61) 0.05	1.68 (1.31,2.16) <0.0001	<0.0001
Model 2	ref	0.92 (0.71,1.19) 0.52	1.20 (0.94,1.53) 0.14	1.46 (1.13,1.87) 0.004	<0.001
HbA1C					
crude model	ref	1.54 (1.23,1.93) <0.001	1.81 (1.39,2.37) <0.0001	2.60 (2.09,3.24) <0.0001	<0.0001
Model 1	ref	1.30 (1.01,1.68) 0.04	1.27 (0.95,1.71) 0.11	1.47 (1.15,1.88) 0.003	0.005
Model 2	ref	1.31 (1.02,1.69) 0.03	1.17 (0.87,1.56) 0.29	1.33 (1.04,1.70) 0.02	0.09

The crude model is a univariate logistic regression model; model1, adjusted for baseline age, sex, BMI, race, education level, marital status, family income-poverty ratio level, smoking and drinking status; model2, additionally adjusted for leisure-time physical activity level, healthy eating index scores, self-reported health status and baseline history of hypertension. PGD: Postprandial Glucose Dip, FBG: Fasting Blood Glucose, OGTT-2HBG: Oral Glucose Tolerance Test-2 Hour Blood Glucose, HbA1C: Hemoglobin A1C, CKD: Chronic Kidney Disease.

2.22–3.56, p for trend < 0.001). This association remained significant but was attenuated in the adjusted models (OR for quartile 4 vs. quartile 1 in model 2 = 1.46, 95 %CI 1.13–1.87, p for trend < 0.001).

3.2.4. HbA1C

HbA1C was significantly associated with CKD in the crude model (OR for quartile 4 vs. quartile 1 = 2.60, 95 %CI 2.09–3.24, p for trend < 0.001). Subsequent model adjustments slightly reduced the strength of this association; however, it remained statistically significant across all models.

Non-linear analyses

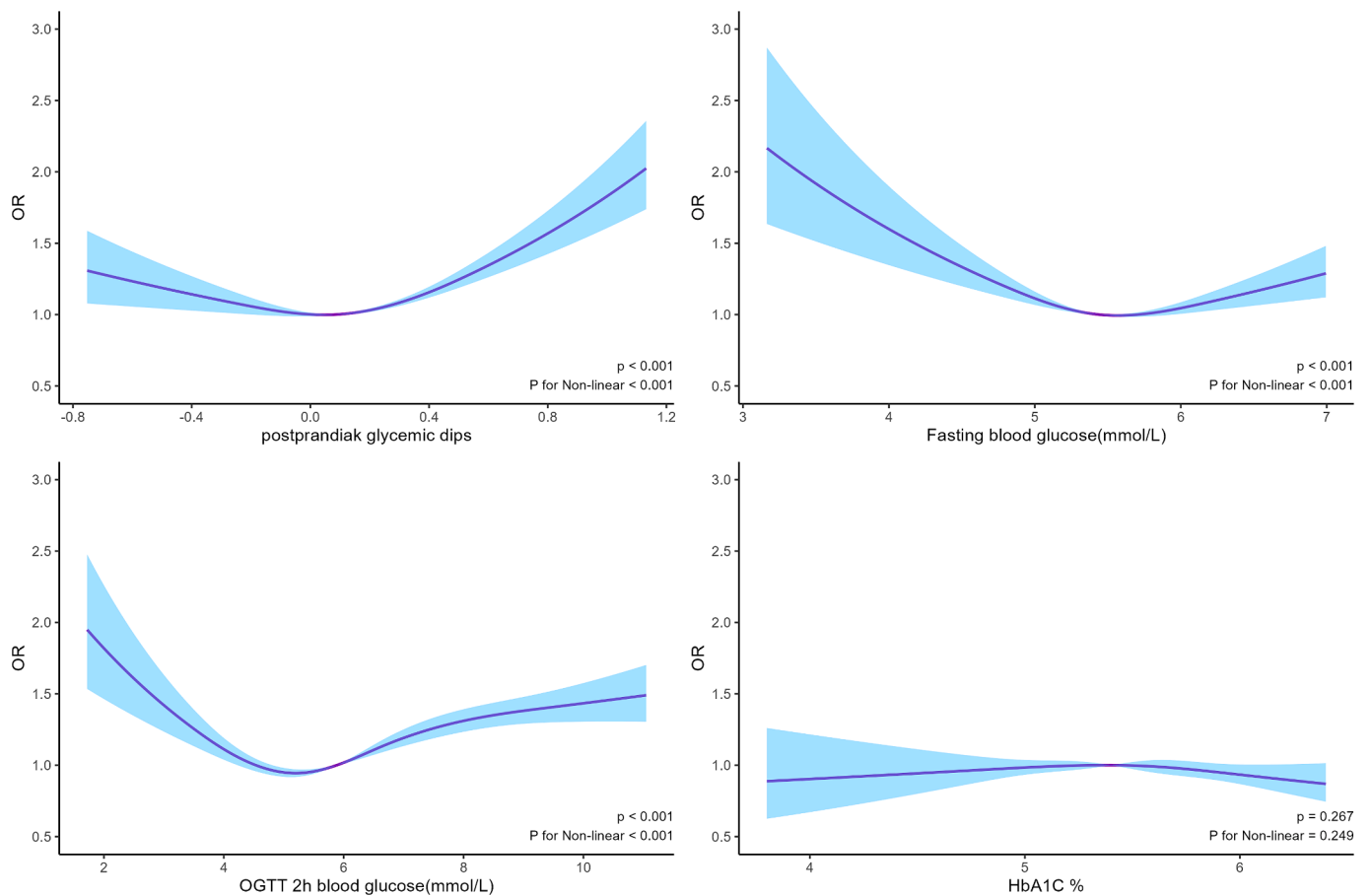Fig. 2 illustrates the results of the non-linear analysis. Three glycemic

Fig. 2. Non-linear Associations of Glycemic Indicators with Chronic Kidney Disease. Curves represent the odds ratio (OR) for chronic kidney disease across different glycemic indicators. The shaded areas denote 95% confidence intervals. The x-axis shows glycemic indicator levels, and the y-axis shows the prevalence OR. P-values indicate the significance of the non-linear relationship.

indicators, PGD, FBG, and OGTT-2HBG, exhibited U-shaped associations with CKD risk (all p-values for non-linearity < 0.001). No significant non-linear association was observed between CKD and HbA1C (p for non-linearity = 0.267).

Subgroup analyses

In the subgroup analyzes detailed in Table 3, the associations of PGD, FBG, OGTT-2HBG, and HbA1C with CKD were explored.

In the sex-stratified analysis, males in the quartile 4 of PGD exhibited a high prevalence of CKD (OR = 1.64, 95 %CI 1.14–2.34, p = 0.01) compared to females (OR = 1.33, 95 % CI 0.98–1.81, p = 0.06). For HbA1C, the second quartile was significantly associated with CKD in females (OR = 1.44, 95 % CI 1.03–2.02, p = 0.03). A significant interaction between sex and FBG levels in relation to CKD was observed, with males displaying a high prevalence in the quartile 4 (p for interaction = 0.03).

In age-stratified analyses, participants aged < 60 years in the highest quartile of PGD demonstrated a significant association with CKD (OR = 1.62, 95 %CI 1.21–2.15, p = 0.001). A similar pattern was observed in the age group for OGTT-2HBG (OR = 1.46, 95 %CI 1.07–2.00, p = 0.02). No significant interactions with age were observed.

The BMI subgroup analyses revealed that participants with a BMI ≥ 30 had a noticeably high prevalence of CKD in the quartiles 3 and 4 of PGD (OR = 1.91, 95 %CI 1.25–2.93, p = 0.003; OR = 2.13, 95 %CI 1.40–3.24, p < 0.001, respectively) and OGTT-2HBG (OR = 2.21, 95 % CI 1.41–3.48, p < 0.001; OR = 2.57, 95 %CI 1.59–4.16, p < 0.001, respectively). A significant interaction between BMI and PGD was

observed in relation to CKD (p = 0.02).

In the ethnicity-stratified analyses, Mexican-American participants demonstrated a high prevalence of CKD in the highest quartiles across all glycemic indicators: PGD (OR = 2.32, 95 %CI 1.16–4.64, p = 0.02), FBG (OR = 3.28, 95 %CI 1.40–7.65, p = 0.01), OGTT-2HBG (OR = 2.41, 95 % CI 1.37–4.22, p = 0.003) and HbA1C (OR = 2.02, 95 %CI 1.05–3.91, p = 0.04). Conversely, non-Hispanic white participants had a low prevalence in the quartile 2 of OGTT-2HBG (OR = 0.68, 95 %CI 0.49–0.95, p = 0.02). No significant interactions were observed.

When stratified by lifestyle factors, low to moderate drinkers and heavy drinkers in the highest quartile of PGD demonstrated a significantly increased prevalence of CKD (OR = 1.86, 95 %CI 1.37–2.52, p < 0.001; OR = 1.98, 95 %CI 1.18–3.30, p = 0.01, respectively). A significant interaction between alcohol consumption and PGD in terms of CKD prevalence was observed, particularly among heavy drinkers (p for interaction = 0.03). Among participants who never smoked, PGD and HbA1C in quartile 4 were significantly associated with an elevated prevalence of CKD (OR = 1.56, 95 %CI 1.14–2.13, p = 0.01; OR = 1.59, 95 %CI 1.13–2.25, p = 0.01, respectively), while current smokers had the lowest prevalence in the quartile 2 of FBG (OR = 0.40, 95 %CI 0.22–0.75, p = 0.004). No significant interactions were identified between smoking habits.

When stratified by hypertension status, both hypertensive and non-hypertensive participants exhibited a similar pattern of increased CKD prevalence in the highest quartile of PGD (OR = 1.59, 95 %CI 1.12–2.24, p = 0.01; OR = 1.46, 95 %CI 1.10–1.94, p = 0.01, respectively). Moreover, hypertensive participants in the highest quartile of OGTT-2HBG had a significantly elevated prevalence of CKD (OR = 1.51, 95

Table 3
Subgroup analysis of pgd, fbg, ogtt-2hbg, hba1c and ckd risk.

	Q1	Q2	p	Q3	p	Q4	p	p for trend	p for interaction
PGD									
sex									0.29
Men	ref	1.04(0.75,1.44)	0.81	1.13(0.80,1.61)	0.47	1.64(1.14,2.34)	0.01	0.01	
Women	ref	0.92(0.65,1.30)	0.63	0.93(0.67,1.31)	0.69	1.33(0.98,1.81)	0.06	0.04	
Age, years									0.41
<60	ref	0.92(0.69,1.23)	0.58	1.08(0.78,1.50)	0.62	1.62(1.21,2.15)	0.001	0.002	
≥60	ref	1.05(0.70,1.57)	0.83	0.96(0.65,1.43)	0.85	1.33(0.90,1.97)	0.15	0.13	
BMI, kg/m^2									0.02
<25.0	ref	0.76(0.53,1.09)	0.14	0.78(0.51,1.20)	0.26	1.36(0.95,1.95)	0.10	0.17	
25.0–29.9	ref	1.12(0.79,1.60)	0.52	0.77(0.50,1.18)	0.22	1.35(0.92,2.00)	0.13	0.28	
≧30	ref	1.33(0.83,2.13)	0.23	1.91(1.25,2.93)	0.003	2.13(1.40,3.24)	<0.001	<0.001	
Ethnicity:									0.46
Non-Hispanic white	ref	0.83(0.59,1.17)	0.28	0.90(0.65,1.24)	0.51	1.26(0.92,1.72)	0.14	0.09	
Non-Hispanic black	ref	1.13(0.72,1.75)	0.59	0.96(0.61,1.52)	0.86	1.51(0.94,2.42)	0.09	0.17	
Mexican American	ref	1.35(0.58,3.11)	0.47	2.29(1.20,4.36)	0.01	2.32(1.16,4.64)	0.02	0.003	
Others	ref	0.98(0.57,1.69)	0.94	1.05(0.63,1.77)	0.84	1.73(1.04,2.88)	0.04	0.03	
Alcohol drinking:									0.03
Non-drinker	ref	0.97(0.64,1.48)	0.88	1.01(0.67,1.52)	0.98	1.02(0.68,1.52)	0.94	0.88	
Low to moderate drinker	ref	1.09(0.78,1.51)	0.6	1.04(0.72,1.51)	0.83	1.86(1.37,2.52)	<0.001	<0.001	
Heavy drinker	ref	0.77(0.45,1.33)	0.34	1.05(0.63,1.75)	0.86	1.98(1.18,3.30)	0.01	0.01	
Smoking status:									0.69
never	ref	1.13(0.84,1.50)	0.42	1.08(0.78,1.50)	0.65	1.56(1.14,2.13)	0.01	0.01	
former	ref	0.92(0.58,1.47)	0.74	0.93(0.61,1.41)	0.71	1.39(0.88,2.18)	0.15	0.14	
current	ref	0.65(0.42,1.02)	0.06	1.02(0.60,1.73)	0.94	1.35(0.80,2.28)	0.26	0.21	
Hypertension									0.9
no	ref	0.95(0.67,1.34)	0.75	1.05(0.74,1.51)	0.77	1.59(1.12,2.24)	0.01	0.01	
yes	ref	1.02(0.73,1.42)	0.91	1.07(0.78,1.46)	0.68	1.46(1.10,1.94)	0.01	0.01	
FBG									
sex									0.03
Men	ref	0.92(0.57,1.48)	0.74	0.88(0.56,1.39)	0.59	1.34(0.87,2.05)	0.18	0.07	
Women	ref	0.97(0.71,1.32)	0.84	0.97(0.72,1.31)	0.86	0.93(0.70,1.25)	0.64	0.65	
Age, years									0.96
<60	ref	0.94(0.68,1.31)	0.73	0.94(0.69,1.30)	0.72	1.25(0.94,1.65)	0.12	0.15	
≥60	ref	0.90(0.62,1.31)	0.56	0.86(0.59,1.24)	0.41	0.96(0.69,1.35)	0.82	1	
BMI, kg/m^2									0.05
<25.0	ref	0.84(0.59,1.20)	0.33	0.69(0.46,1.04)	0.07	0.78(0.52,1.18)	0.23	0.16	
25.0–29.9	ref	0.76(0.50,1.17)	0.21	0.99(0.62,1.59)	0.96	1.40(0.95,2.08)	0.09	0.02	
≧30	ref	1.11(0.73,1.68)	0.63	1.03(0.67,1.59)	0.89	1.13(0.71,1.78)	0.61	0.69	
Ethnicity:									0.24
Non-Hispanic white	ref	1.04(0.73,1.50)	0.81	1.00(0.70,1.42)	1	1.12(0.81,1.55)	0.5	0.52	
Non-Hispanic black	ref	0.62(0.38,1.00)	0.05	0.60(0.35,1.03)	0.06	0.82(0.48,1.39)	0.44	0.45	
Mexican American	ref	2.20(0.77,6.24)	0.14	2.36(1.02,5.46)	0.04	3.28(1.40,7.65)	0.01	0.001	
Others	ref	0.82(0.49,1.36)	0.43	0.79(0.48,1.33)	0.37	0.89(0.52,1.53)	0.67	0.78	
Alcohol drinking:									0.15
Non-drinker	ref	0.94(0.64,1.40)	0.77	1.07(0.72,1.60)	0.73	0.92(0.64,1.33)	0.65	0.76	
Low to moderate drinker	ref	0.89(0.60,1.31)	0.54	0.78(0.53,1.15)	0.21	1.08(0.76,1.54)	0.65	0.58	
Heavy drinker	ref	0.84(0.50,1.42)	0.51	0.74(0.42,1.28)	0.28	1.27(0.73,2.20)	0.39	0.35	
Smoking status:									0.07
never	ref	0.89(0.65,1.22)	0.47	1.02(0.77,1.37)	0.87	1.12(0.82,1.54)	0.47	0.3	
former	ref	1.23(0.73,2.06)	0.43	1.31(0.73,2.36)	0.36	1.38(0.81,2.36)	0.23	0.26	
current	ref	0.82(0.49,1.38)	0.45	0.40(0.22,0.75)	0.004	0.89(0.56,1.42)	0.62	0.43	
Hypertension									0.56
no	ref	0.98(0.69,1.37)	0.89	0.98(0.68,1.42)	0.92	1.31(0.95,1.80)	0.1	0.14	
yes	ref	0.84(0.60,1.19)	0.33	0.82(0.59,1.13)	0.22	0.96(0.70,1.31)	0.79	0.94	
OGTT-2HBG									
sex									0.13
Men	ref	0.99(0.71,1.36)	0.93	1.32(0.87,2.01)	0.19	1.65(1.13,2.41)	0.01	0.004	
Women	ref	0.82(0.56,1.19)	0.28	1.08(0.77,1.50)	0.66	1.25(0.91,1.73)	0.17	0.04	
Age, years									0.56
<60	ref	0.82(0.57,1.17)	0.27	1.14(0.84,1.53)	0.39	1.46(1.07,2.00)	0.02	0.003	
≥60	ref	1.08(0.71,1.65)	0.71	1.30(0.88,1.92)	0.18	1.47(0.95,2.26)	0.08	0.04	
BMI, kg/m^2									0.11
<25.0	ref	0.68(0.45,1.03)	0.07	0.90(0.60,1.36)	0.61	1.10(0.74,1.64)	0.62	0.42	
25.0–29.9	ref	0.94(0.60,1.48)	0.79	1.04(0.65,1.65)	0.87	1.30(0.83,2.04)	0.24	0.11	
≧30	ref	1.51(0.93,2.45)	0.09	2.21(1.41,3.48)	<0.001	2.57(1.59,4.16)	<0.001	<0.001	
Ethnicity:									0.64
Non-Hispanic white	ref	0.68(0.49,0.95)	0.02	1.07(0.75,1.53)	0.71	1.24(0.88,1.74)	0.21	0.03	
Non-Hispanic black	ref	1.16(0.70,1.95)	0.56	1.16(0.75,2.49)	0.5	1.47(0.87,2.49)	0.15	0.16	
Mexican American	ref	1.12(0.56,2.27)	0.74	2.03(1.08,3.81)	0.03	2.41(1.37,4.22)	0.003	0.001	
Others	ref	1.08(0.52,2.26)	0.83	1.15(0.65,2.02)	0.63	1.45(0.76,2.76)	0.25	0.15	

Table 3 (*continued*)

	Q1	Q2	p	Q3	p	Q4	p	p for trend	p for interaction
Alcohol drinking:									0.28
Non-drinker	ref	0.88(0.55,1.40)	0.58	1.11(0.71,1.72)	0.64	1.07(0.70,1.63)	0.77	0.51	
Low to moderate drinker	ref	0.90(0.60,1.35)	0.60	1.20(0.82,1.77)	0.34	1.63(1.12,2.35)	0.01	0.001	
Heavy drinker	ref	0.94(0.57,1.56)	0.81	1.13(0.67,1.92)	0.65	1.80(1.10,2.93)	0.02	0.02	
Smoking status:									0.99
never	ref	0.85(0.59,1.22)	0.37	1.10(0.80,1.51)	0.56	1.35(0.95,1.91)	0.09	0.01	
former	ref	0.82(0.47,1.40)	0.46	1.19(0.79,1.78)	0.41	1.40(0.90,2.19)	0.14	0.04	
current	ref	1.00(0.59,1.71)	0.99	1.26(0.70,2.25)	0.43	1.36(0.79,2.34)	0.27	0.22	
Hypertension									0.71
no	ref	0.80(0.54,1.18)	0.25	1.22(0.85,1.75)	0.28	1.40(0.97,2.03)	0.07	0.02	
yes	ref	1.03(0.69,1.54)	0.87	1.22(0.84,1.76)	0.29	1.51(1.05,2.18)	0.03	0.01	
HbA1C									
sex									0.08
Men	ref	1.18(0.80,1.74)	0.40	1.03(0.68,1.56)	0.90	1.41(0.94,2.10)	0.09	0.10	
Women	ref	1.44(1.03,2.02)	0.03	1.36(0.92,2.01)	0.12	1.32(0.92,1.88)	0.13	0.33	
Age, years									0.59
<60	ref	1.35(1.00,1.83)	0.05	1.05(0.70,1.55)	0.83	1.31(0.93,1.85)	0.13	0.34	
≧60	ref	1.24(0.86,1.78)	0.25	1.31(0.84,2.03)	0.23	1.44(1.02,2.04)	0.04	0.05	
BMI, kg/m^2									0.44
<25.0	ref	1.63(1.09,2.46)	0.02	1.39(0.88,2.19)	0.16	1.26(0.80,1.97)	0.32	0.64	
25.0–29.9	ref	1.22(0.79,1.89)	0.36	1.05(0.63,1.74)	0.86	1.37(0.93,2.01)	0.11	0.14	
≧30	ref	1.07(0.69,1.67)	0.76	1.02(0.65,1.60)	0.93	1.23(0.80,1.88)	0.33	0.33	
Ethnicity:									0.07
Non-Hispanic white	ref	1.47(1.02,2.11)	0.04	1.54(0.99,2.40)	0.05	1.55(1.10,2.19)	0.01	0.02	
Non-Hispanic black	ref	1.13(0.64,1.99)	0.67	0.96(0.58,1.61)	0.89	0.89(0.52,1.54)	0.68	0.47	
Mexican American	ref	1.37(0.72,2.62)	0.33	1.04(0.50,2.15)	0.92	2.02(1.05,3.91)	0.04	0.05	
Others	ref	1.10(0.60,2.03)	0.75	0.67(0.34,1.32)	0.24	1.14(0.65,2.01)	0.63	0.88	
Alcohol drinking:									0.18
Non-drinker	ref	1.50(0.90,2.51)	0.12	1.55(0.93,2.61)	0.09	1.43(0.83,2.47)	0.2	0.35	
Low to moderate drinker	ref	1.09(0.79,1.50)	0.60	1.03(0.69,1.53)	0.9	1.23(0.88,1.72)	0.22	0.26	
Heavy drinker	ref	1.55(0.99,2.43)	0.05	0.80(0.43,1.51)	0.49	1.53(0.90,2.59)	0.11	0.43	
Smoking status:									0.47
never	ref	1.39(1.00,1.94)	0.05	1.14(0.77,1.68)	0.50	1.59(1.13,2.25)	0.01	0.03	ref
former	ref	0.99(0.63,1.54)	0.95	1.14(0.66,1.94)	0.64	0.98(0.61,1.57)	0.93	0.98	ref
current	ref	1.65(0.89,3.04)	0.11	1.45(0.80,2.65)	0.22	1.43(0.78,2.61)	0.25	0.45	ref
Hypertension									0.18
no	ref	1.56(1.09,2.23)	0.02	1.53(1.04,2.24)	0.03	1.39(0.96,2.00)	0.08	0.14	
yes	ref	1.08(0.76,1.54)	0.65	0.93(0.62,1.39)	0.71	1.21(0.88,1.68)	0.23	0.22	

All models were adjusted for baseline age, sex, race, education level, marital status, family income-poverty ratio level, drinking and smoking status, leisure-time physical activity level, healthy eating index scores, self-reported health status, baseline history of hypertension. BMI: Body Mass Index, PGD: Postprandial Glucose Dip, FBG: Fasting Blood Glucose, OGTT-2HBG: Oral Glucose Tolerance Test-2 Hour Blood Glucose, HbA1C: Hemoglobin A1C.

%CI 1.05–2.18, p = 0.03). However, the interaction between the hypertension status and these indicators was not significant.

Sensitivity analysis

During the sensitivity analyses, the results from the non-imputed data aligned with those from our main analyses across both the crude (Table S1) and final models (Tables S2-S5).

Discussion

In this study, we investigated the association between glycemic indicators and the prevalence of CKD in a representative American adult population without DM. Our findings revealed significant correlations between elevated PGD, OGTT-2HBG, HbA1C and CKD, particularly among overweight, obese individuals, and habitual drinkers. Additionally, our non-linear analyses revealed a U-shaped relationship between PGD, FBG, OGTT-2HBG, and CKD.

To our knowledge, this is the first study to investigate the association between PGD and CKD. Our study aligns with the findings of Sun et al. [17], who identified significant correlations between PGD and metabolic disorders as well as CVD in a cohort of Chinese participants. This similarity highlights the broad relevance of postprandial glucose fluctuations in metabolic health. Continuous glucose monitoring (CGM) enables real-time tracking of blood sugar levels, thereby facilitating a detailed understanding of glucose variability. To assess the impact of long-term glycemic variability on various health outcomes in patients with DM, a *meta*-analysis synthesized data from 75 studies involving more than 2 million participants [7]. The analysis revealed significant associations between high variability in FBG levels and renal disease. Two recent *meta*-analyses suggested that the glycemic variability may be linked to an increased risk of complications and mortality associated with DM [8,25]. Unlike complex CGM technology, our study used a simple yet effective measure, the PGD index, to assess blood glucose fluctuations.

When examining the relationship between traditional glycemic indicators and CKD, we discovered no significant association between FBG levels and CKD after full multivariable adjustments. This observation is consistent with the current evidence. For instance, Vieira et al. [26] conducted a secondary analysis of the Systolic Blood Pressure Intervention Trial with 9,361 non-diabetic participants, which demonstrated no significant correlation between impaired fasting glucose (IFG) and an increased risk of deteriorating kidney function or albuminuria. Similarly, a Mendelian randomization analysis, which exploits genetic variants to assess causal relationships between exposures and outcomes, noted no causal association between FBG and CKD development in non-diabetic populations, despite using a genetic risk score derived from nine fasting glucose-related genetic variants [27]. Conversely, an earlier *meta*-analysis of nine studies investigating the link between prediabetes and the incidence of CKD identified a significant association between IFG and CKD [28]. Variations in study results could be attributed to differences in sample sizes, CKD definitions, and study populations.

Further research is needed to elucidate this association in non-diabetic populations. Regarding OGTT-2HBG and HbA1C, our findings align with those of previous studies. In a prospective cohort study involving 6,445 non-diabetic individuals over 40 years of age in China, Li et al. [29] demonstrated that impaired glucose tolerance and elevated HbA1C levels significantly increased the risk of CKD. Collectively, our data suggest that OGTT-2HBG and HbA1C may be more indicative of CKD development than FBG levels.

The subgroup analyses revealed several noteworthy patterns. The association between PGD and CKD varied according to the BMI, particularly among obese participants who exhibited a high risk of CKD in the highest PGD quartile, indicating a potential interaction between BMI and PGD in influencing the risk of CKD. The interaction with BMI is biologically plausible as accumulating evidence [13,30] suggests that obese individuals are highly susceptible to the harmful effects of erratic glucose levels owing to existing metabolic disturbances. This susceptibility is likely due to a combination of factors, including increased insulin resistance, a heightened inflammatory response, and altered adipokine profiles in obese individuals [13]. These factors can exacerbate renal stress caused by significant postprandial glucose fluctuations [31], thereby increasing the risk of CKD progression. This finding underscores the need for targeted strategies to manage postprandial glucose levels, particularly in patients with obesity, to mitigate the heightened risk of CKD. Additionally, another interesting interaction was observed between alcohol consumption and PGD. The data revealed that heavy drinking had a significantly pronounced association with the risk of CKD in the context of PGD. This finding suggests a potential vulnerability specific to alcohol concerning the renal effects of glycemic variability. The underlying mechanisms may involve alcohol-induced alterations in glucose metabolism and insulin sensitivity [32]. Heavy alcohol consumption can disrupt liver function, which is crucial for regulating blood glucose levels. This disruption can lead to erratic glucose fluctuations, particularly after a meal. Additionally, alcohol can directly affect kidney function by altering renal blood flow and inducing oxidative stress [33]. When the harmful effects of alcohol are combined with a high magnitude of PGD index, the risk of developing CKD can increase. Therefore, carefully monitoring and managing the postprandial glucose levels in individuals who consume alcohol is important.

Understanding the mechanisms linking serum glycemic indicators and CKD in non-diabetic individuals is crucial for developing effective strategies to prevent and manage CKD, particularly in populations at risk of unstable glucose levels. Constant hyperglycemia can lead to glomerular hyperfiltration, which increases pressure in the glomeruli of the kidney and eventually worsens renal function [34]. Increased blood glucose levels, particularly postprandial glucose levels, are always accompanied by insulin resistance. Insulin resistance aggravates oxidative stress and inflammation, both of which play key roles in the onset and progression of kidney damage. Moreover, insulin resistance directly affects endothelial function and arterial stiffness [10], further compromising renal blood flow and filtration. In addition to these mechanisms, previous research has demonstrated that significant fluctuations in blood glucose levels, as reflected partially by PGD, can damage the endothelial cells lining blood vessels [35]. When blood glucose levels fluctuate dramatically, endothelial cells experience stress, which further increases inflammation and oxidative stress in the kidney. Therefore, while avoiding high blood glucose levels to maintain kidney function is crucial, maintaining stable serum glucose levels is equally critical.

Our study has some limitations that need to be acknowledged. First, we did not include patients with a family history of DM, which is known to heavily influence personal glycemic traits [36]. However, we attempted to mitigate this limitation by excluding patients with DM. Second, our exclusion criteria did not allow us to exclude individuals with prediabetes identified by an HbA1c cutoff <6.5. As a result, confounding factors for prediabetes may still be present in our findings. Third, owing to the cross-sectional nature of our study, we were unable

to establish causality between the observed associations. In future research, a longitudinal design should be employed to investigate the temporal nature of the relationship between glycemic indicators and CKD. Fourth, while we were able to adjust for the daily eating quality indicated by the HEI, we were unable to account for long-term eating habits that have been identified as important factors in renal health [37]. Finally, we did not include potential confounders such as kidney-damaging drugs in our models.

Conclusions

In a nationally representative sample of American adults without DM, PGD was significantly associated with a high prevalence of CKD. This association is influenced by factors such as obesity and alcohol consumption. Avoiding large fluctuations between the postprandial and FBG may help reduce the risk of CKD in individuals without DM. Further research is needed to identify the specific target values for PGD.

CRediT authorship contribution statement

Lu Jin: Writing – original draft, Formal analysis. **Xing Wang:** Writing – original draft, Data curation. **Yun Liu:** Formal analysis. **Qiulian Xiang:** Writing – review & editing, Project administration. **Ruiou Huang:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2024.100347.

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