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Association between TyG-BMI and early-onset hypertension: evidence from NHANES

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Early-onset hypertension (EHT) is a growing concern due to its long-term cardiovascular risks. This study investigated the association between the triglyceride glucose-body mass index (TyG-BMI) and EHT in a nationally representative US sample. EHT was defined as physician-reported hypertension diagnosed before age 40. We used weighted logistic regression models to assess the association between TyG-BMI and EHT, adjusting for potential confounders. Mediation analysis was conducted to examine the role of oxidative stress and inflammation markers in this association. We analyzed data from 5193 adults with age under 40 years from the National Health and Nutrition Examination Survey (NHANES) 2009–2018.Participants with EHT had significantly higher TyG-BMI compared to those without EHT ($P < 0.001$). In multivariable analysis, the highest quartile of Ty-BMI was independently associated with 6.47-fold increased odds of EHT (OR: 6.47, 95% CI: 4.35–9.61) compared to the lowest quartile. This association remained significant across subgroups stratified by gender, race, and smoking status. Gamma-glutamyl transferase (GGT) and uric acid were identified as potential mediators. Higher TyG-BMI is significantly associated with EHT. TyG-BMI may serve as a readily available clinical tool for early identification and management of individuals at increased risk for EHT, facilitating timely interventions to mitigate long-term cardiovascular risks.

Keywords Triglyceride glucose-body mass index, Early-onset hypertension, NHANES, Cardiovascular health

Early-onset hypertension (EHT) is a growing public health concern due to its association with increased cardiovascular morbidity and mortality. The prevalence of EHT is increasing worldwide, with estimates ranging from 2 to 16% of the young adult population[1,2]. This rise in EHT is particularly concerning given the long duration of exposure to elevated blood pressure, which can lead to an increased risk of cardiovascular complications later in life[3,4]. Understanding the underlying mechanisms and risk factors associated with EHT is crucial for developing effective prevention and treatment strategies.

The pathogenesis of EHT is multifactorial, involving genetic predispositions, environmental factors, and metabolic disturbances[5]. Among these, insulin resistance has emerged as a pivotal mechanism linking metabolic dysfunction to hypertension[6]. The triglyceride-glucose (TyG) index, a composite marker derived from fasting triglyceride and glucose levels, has been proposed as a reliable surrogate for insulin resistance[7]. Several studies have demonstrated the association between the TyG index and cardiovascular risk factors in both adults[8] and pediatric populations[9], suggesting its potential utility in predicting metabolic and cardiovascular diseases.

The triglyceride glucose-body mass index (TyG-BMI), a recently proposed index calculated as ln [Triglyceride (mg/dl) × FBG (mg/dl)/2] × BMI (kg/m^2), has emerged as a potential surrogate marker for insulin resistance[10]. By incorporating BMI into its calculation, TyG-BMI may more effectively capture the influence of obesity on insulin resistance[11]. This combined measure of obesity and TyG may offer a stronger indicator of insulin resistanc compared to other surrogate markers, as obesity is a well-established risk factor for insulin resistance[11]. Furthermore, several studies have demonstrated that TyG-BMI exhibits superior predictive performance compared to TyG alone in the context of metabolic diseases and cardiovascular disease[12–14].

Despite the established link between insulin resistance and hypertension, the specific relationship between the TyG-BMI index and EHT remains underexplored. While previous studies have examined the associations between TyG-BMI and hypertension, these investigations have primarily focused on older adult populations or general adult populations, with less emphasis on EHT specifically[15,16]. These studies may not fully address the unique risk factors, metabolic characteristics, or lifestyle-related factors that contribute to EHT in younger

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individuals. Furthermore, some previous researches may have not thoroughly explored the complex interplay between insulin resistance and hypertension in younger populations. Understanding whether the TyG-BMI index can serve as a predictive marker for EHT could facilitate early identification and intervention, potentially mitigating long-term cardiovascular risks. Therefore, we hypothesize that higher TyG-BMI is associated with an increased prevalence of EHT in young adults. This study aims to investigate the association between the TyG-BMI index and EHT using data from the National Health and Nutrition Examination Survey (NHANES). By leveraging this comprehensive dataset, we seek to examine whether TyG-BMI index can serve as an independent predictor of EHT.

Methods

Study population

The study utilized data from NHANES, a comprehensive research program conducted by the Centers for Disease Control and Prevention (CDC) aimed at assessing the health and nutritional status of the American population through interviews, examinations, dietary, and laboratory data[17–21]. The NHANES protocol was approved by the Institutional Review Board of the National Center for Health Statistics, adhering to the Declaration of Helsinki, with informed consent obtained from all participants. Our analysis encompassed NHANES public data files spanning from 2009 to 2018. From an initial dataset of 50,086 participants, 14,946 individuals with available triglyceride, fasting plasma glucose (FPG), BMI data were identified. We chose to analyze patients who were under 40 years of age and 6477 were included. We then excluded those subjects who did not know whether they had hypertension in the questionnaire, resulting in 5193 subjects.

Exposure and outcome definitions

In the NHANES questionnaire, subjects were asked: "Have you ever been told by a doctor or other health professional that you had hypertension?" This allowed us to determine whether the subjects had hypertension. BMI was calculated as weight/height^2;

Fasting plasma glucose (FPG) and triglycerides were measured at baseline when the participants provided their blood samples. TyG was calculated as Ln [FPG (mg/dL) × TG (mg/dL)/2], TyG-BMI was calculated as TyG × BMI.

Covariates

Participant characteristics were recorded, encompassing demographics (age, sex, race categorized as Non-Hispanic Black and Other Race) and socioeconomic factors (educational attainment, marital status, and family income-to-poverty ratio). Education levels were grouped as less than high school, high school graduate, some college or associate degree, and bachelor's degree or higher. Marital status was dichotomized as partnered (married or cohabitating) versus single (never married, separated, divorced, or widowed). Family income was assessed relative to the poverty level and categorized into three groups: less than 1, 1 to 3, and greater than 3. Clinical measures, including BMI, smoking status, creatinine, low-density lipoprotein (LDL) cholesterol, albumin, and hemoglobin levels, were also collected from NHANES dataset.

Statistical analysis

We accounted for the complex survey design of NHANES by incorporating sample weights, clustering and stratification to achieve nationally representative estimates[22]. Data analysis was conducted using R software version 4.3.1. Categorical variables were analyzed using Rao-Scott adjusted Chi-square test and continuous variables were analyzed using weighted mean comparisons. We performed a Receiver Operating Characteristic (ROC) curve analysis using the pROC package in R to assess the predictive performance of TyG-BMI for EHT. The area under the ROC curve (AUC) was calculated, and the optimal cutoff threshold was determined using the coords function to maximize the sum of sensitivity and specificity. This threshold was then visually marked on the ROC curve. For analyses with categorical dependent variables, the participants were classified into four groups (Q1, Q2, Q3, Q4) by the quartiles of the TyG-BMI, with Q1 designated as the reference group. The association of the TyG-BMI with EHT among participants was assessed by survey-weighted multivariate logistic regression analysis. Two models were constructed to adjust for possible confounding factors. Model 1 was adjusted for gender, race, age, education level, marital status, smoke history, income level. Model 2 was additionally adjusted for albumin, creatinine, LDL level. Restricted cubic spline (RCS) analysis was employed to explore the potential non-linear relationship between TyG-BMI index and EHT. The association of TyG-BMI values with EHT was analyzed by using subgroups based on gender, race, smoking status, and their interactions were explored. To address the issue of multiple comparisons arising from subgroup analyses, we employed a Bonferroni correction to adjust the p-values. A two-tailed $p < 0.05$ indicated statistical significance. Missing data was present in several variables. The percentages of missing data for most variables were less than 1%, with the exception of Ratio of family income to poverty level (8.21%), systolic blood pressure (4.02%), diastolic blood pressure (4.02%) and LDL (1.17%). To address missing values, we employed multiple imputation using the `mice` package in R. We generated five imputed datasets using 50 iterations. We used the imputed datasets in our logistic regression models, and employed Rubin's rules to pool the regression estimates.

Mediation analysis

Causal mediation analysis, a key technique for understanding causal effects[23,24], was employed in this study to evaluate the mediating roles of various biomarkers. We considered inflammation biomarkers such as neutrophil-to-lymphocyte ratio (NLR), white blood cell count, lymphocyte cell percentage, monocyte cell percentage and neutrophil cell percentage[25–28]. Additionally, oxidative stress biomarkers including gamma-glutamyl transferase (GGT), bilirubin, uric acid were analyzed as potential mediators in the pathway from TyG-BMI to EHT[29–32]. Our

mediation analysis followed a standard three-step procedure[33]. We accounted for the complex survey design of the NHANES data using the `svydesign` function from the `survey` package in R. Initially, we examined the relationship between TyG-BMI and EHT. Next, we explored the associations between TyG-BMI and potential mediators, and between these mediators and the outcome. Finally, both potential mediators and TyG-BMI were included in Cox regression analysis to evaluate direct and indirect effects on EHT. Quasi-Bayesian confidence intervals were estimated using 1000 simulations. These mediation models were fitted using the 'mediation' package in R software.

Results

Characteristics of the study population

A total of 5193 participants were included in the analysis, with a weighted population estimate of 41,809,763(Fig. 1). Participants with EHT ($n = 572$, estimated $N = 4,823,256$) were significantly older (31.23 ± 6.07 vs. 26.94 ± 6.82 years, $p < 0.001$) and had higher BMI (32.85 ± 8.79 vs. 27.42 ± 6.96 kg/m 2, $p < 0.001$) compared to those without EHT ($n = 4621$, estimated $N = 36,986,507$). The EHT group also had a significantly higher proportion of males (57.3% vs. 48.6%, $p = 0.001$), and higher systolic and diastolic blood pressure (SBP: 124.39 ± 14.28 vs. 112.65 ± 10.70 mmHg, $p < 0.001$; DBP: 74.43 ± 13.24 vs. 66.33 ± 10.47 mmHg, $p < 0.001$). Significant differences were observed between the two groups in terms of race/ethnicity, education level, marital status, smoking history, TyG-BMI group, triglyceride level, LDL level, FPG level, TyG-BMI, TyG, creatinine level, albumin level, GGT level, uric acid level, bilirubin level, white blood cell count, and NLR (all $p < 0.05$). No significant differences were observed in hemoglobin, segmented neutrophils percentage, sodium, or potassium levels between the two groups (Table 1).

Association of TyG-BMI with EHT

ROC curve analysis were performed to assess the predictive performance of TyG-BMI for EHT demonstrated an AUC of 0.71 (95%CI: 0.69–0.73), indicating a fair discriminatory ability for predicting EHT. The ROC curve analysis for the TyG demonstrated an AUC of 0.61 (95% CI: 0.58–0.63). These results suggest that the TyG-BMI has a moderate ability to distinguish between hypertensive and non-hypertensive individuals under age of 40 (Fig. 2). RCS analysis indicated a nonlinear relationship between TyG-BMI and EHT (P for nonlinearity = 0.012, P overall 0.015) (Fig. 3).

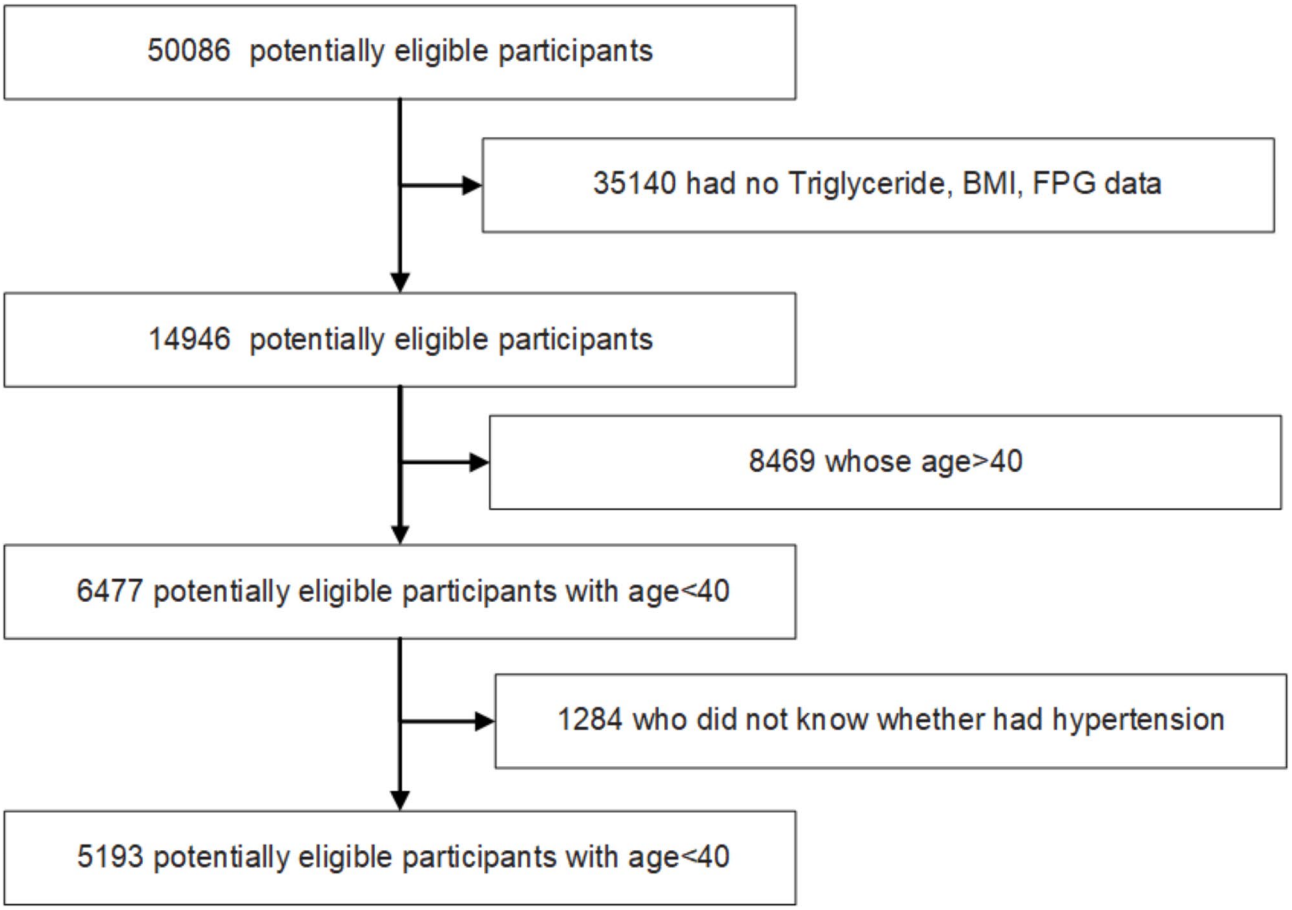

Fig. 1. The flow chart of participants inclusion and exclusion in current study.

Characteristics	Non-EHT ($n=4621$)	EHT ($n=572$)	*P* value
Estimated N	36,986,507	4,823,256	
Age (year)	26.94 (6.82)	31.23 (6.07)	< 0.001
BMI (kg/m^2)	27.42 (6.96)	32.85 (8.79)	< 0.001
Gender (%)			
Male	48.6%	57.3%	0.001
Female	51.4%	42.7%	
SBP (mmHg)	112.65 (10.70)	124.39 (14.28)	< 0.001
DBP (mmHg)	66.33 (10.47)	74.43 (13.24)	< 0.001
Race/ethnicity			
Mexican American	13.9%	9.3%	< 0.001
Other Race	17.6%	14.0%	
Non Hispanic White	56.4%	59.9%	
Non Hispanic Black	12.1%	16.8%	
Education level			
Less than High school	12.2%	15.3%	0.013
High school	19.1%	23.8%	
Some college or associate degree	43.9%	40.8%	
College graduate or above	24.8%	20.1%	
Married state			
Never married/widowed/divorced/separated	54.5%	42.1%	< 0.001
Married/Living with partner	45.5%	57.9%	
Smoke history			
Ever	31.5%	47.3%	< 0.001
Never	68.5%	52.7%	
Ratio of family income to poverty level			
< 1	18.5%	23.8%	0.046
1 ~ 3	45.2%	40.5%	
> 3	36.3%	35.6%	
Diabetes history			
Yes	1.30%	5.90%	< 0.001
No	98.70%	94.10%	
Plasma markers			
Triglyceride (mg/dL)	101.96 (87.08)	132.37 (114.00)	< 0.001
LDL (mg/dL)	103.65 (32.37)	110.85 (32.33)	< 0.001
FPG (mg/dL)	97.33 (18.74)	104.48 (29.97)	< 0.001
TyG-BMI	229.04 (66.48)	283.61 (83.12)	< 0.001
TyG	8.30 (0.64)	8.60 (0.71)	< 0.001
Creatinine (mg/dL)	0.81 (0.21)	0.87 (0.42)	0.001
Hemoglobin (g/dL)	14.34 (1.45)	14.50 (1.65)	0.05
Albumin (g/dL)	4.31 (0.37)	4.25 (0.37)	0.015
GGT (IU/L)	21.29 (21.39)	32.23 (36.59)	< 0.001
Uric acid (mg/dL)	5.26 (1.33)	5.82 (1.48)	< 0.001
Bilirubin (mg/dL)	0.68 (0.35)	0.63 (0.33)	0.011
NLR	1.93 (0.90)	2.09 (1.10)	0.03
White blood cell count ((1000 cells/μL))	6.88 (1.97)	7.36 (2.07)	< 0.001
Segmented neutrophils percent	56.13 (9.08)	57.04 (10.03)	0.141
Sodium (mmol/L)	139.37 (2.11)	139.21 (2.37)	0.172
Potassium (mmol/L)	4.00 (0.30)	4.01 (0.33)	0.76

Table 1. Characteristic of NHANES participants stratified by whether had EHT. All estimates accounted for complex survey designs. All numbers in the table are weighted percentages or means. *NHANES* National Health and Nutrition Examination Survey, *BMI* body-mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TyG* triglyceride-glucose, *LDL* low density lipoprotein cholesterol, *GGT* gamma-glutamyl transferase.

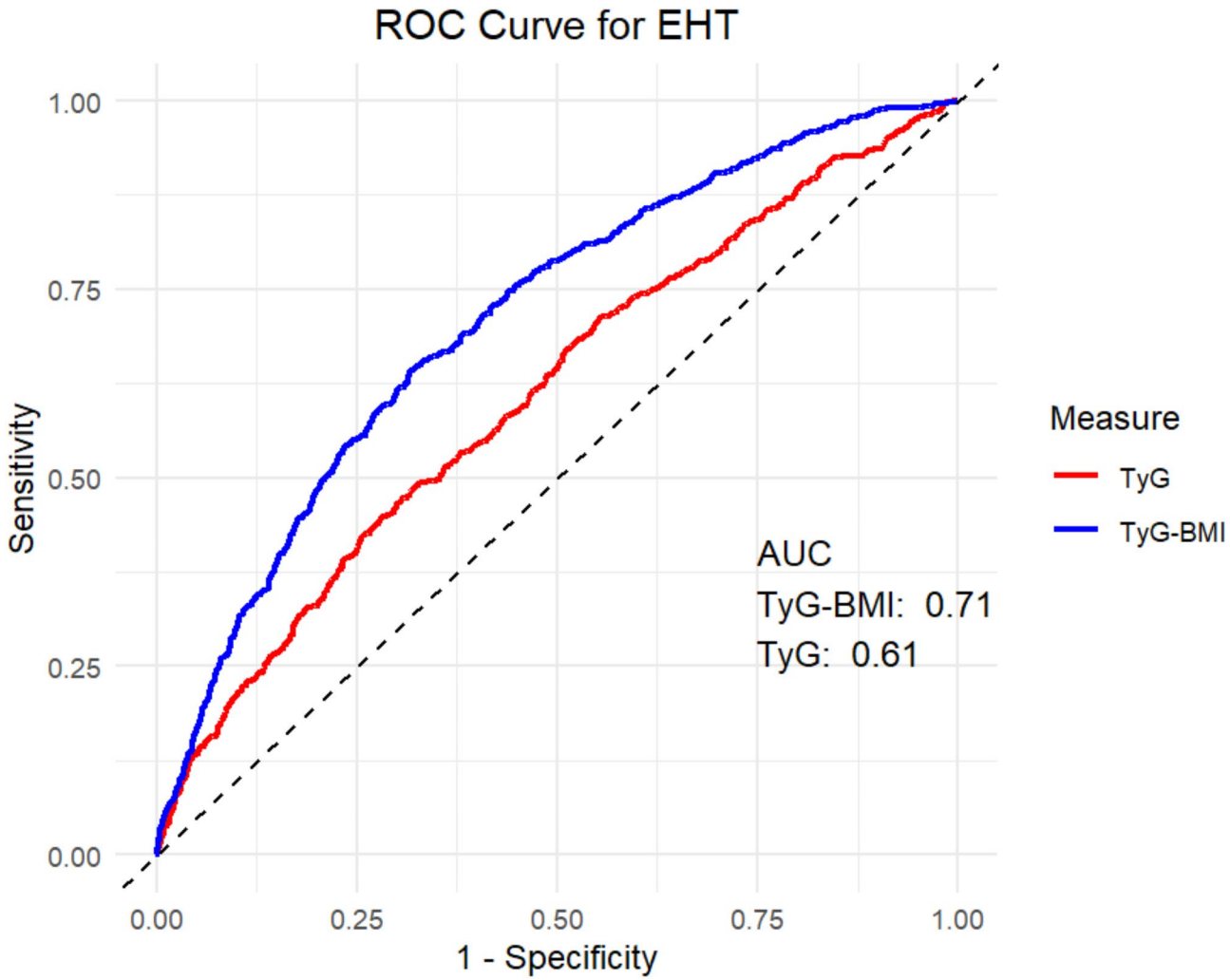

Fig. 2. Receiver operating characteristic (ROC) curve analysis for predicting EHT. This figure displays the ROC curves comparing the predictive performance of two indices: TyG index (represented by the red curve) and TyG-BMI index (represented by the blue curve). The TyG-BMI index shows a higher area under the curve (AUC) (0.71, 95% CI 0.69–0.73) compared to the TyG index (0.61, 95% CI 0.58–0.63), suggesting that incorporating BMI with the TyG index improves the prediction of EHT.

When EHT was defined as hypertension diagnosed before the age of 40 years, the association between TyG-BMI and EHT is presented in Table 2. Compared to the lowest quartile (Q1) in the unadjusted model, the ORs (95% CI) for EHT were 2.02 (1.26–3.22) for Q2, 3.84 (2.54–5.80) for Q3, and 7.96 (5.34–11.86) for Q4 (P for trend < 0.001). After adjusting for potential confounders in Model 1 (gender, race, age, education level, marital status, smoking history, income level), the associations remained significant, although the magnitude of the ORs was attenuated. Further adjustment for albumin, creatinine, and LDL level in Model 2 did not materially change the results. We conducted a sensitivity analysis by removing all 102 participants with diabetes from our primary dataset ($n = 5193$), and re-ran the logistic regression models on the remaining 5091 non-diabetic participants. The results of this sensitivity analysis were largely consistent with our previous findings, confirming the positive association between TyG-BMI and EHT (Table 2).

Table 3 presents the association between TyG-BMI and hypertension diagnosed before the age of 30. Similar to the findings for EHT diagnosed before age 40, a strong positive association was observed between TyG-BMI quartiles and EHT in the unadjusted model. Compared to individuals in the lowest TyG-BMI quartile (Q1), the odds of having hypertension diagnosed before age 30 were significantly higher for those in Q2 [OR (95% CI): 3.77 (1.71–8.34)], Q3 [4.14 (1.98–8.65)], and Q4 [10.92 (5.18–23.01)], with a significant trend across quartiles (P for trend < 0.001). These associations remained statistically significant after adjusting for potential confounders in Model 1 and Model 2.

Subgroup analyses of the association between TyG-BMI and EHT

Subgroup analyses were performed to explore the potential effect modification of the association between TyG-BMI and EHT by gender, race and smoking status (Table 4). The positive association between higher TyG-BMI

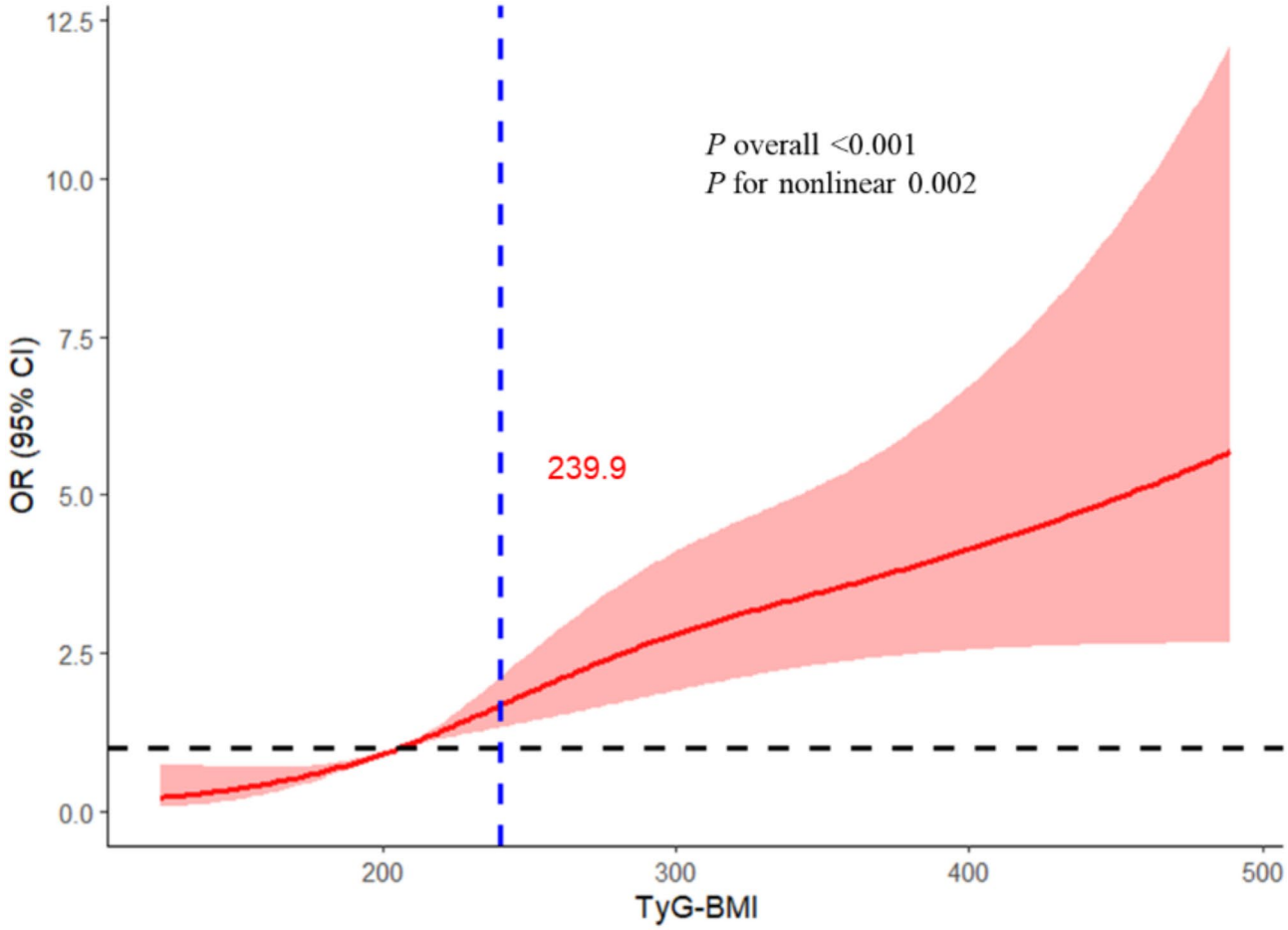

Fig. 3. Non-linear association between TyG-BMI and EHT assessed by restricted cubic spline analysis. The analysis reveals a statistically significant overall association between TyG-BMI and EHT ($P < 0.001$) and confirms a non-linear relationship (P for non-linearity = 0.002). The vertical blue dashed line marks the identified TyG-BMI breakpoint at 239.9.

TyG-BMI	Cases	*N*	Non-adjusted model		Model1		Model2	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
All participants								
Quartile 1	1298	47	Ref		Ref		Ref	
Quartile 2	1298	87	2.02(1.26–3.22)	0.003	1.66(1.05–2.64)	0.031	1.74(1.11–2.75)	0.016
Quartile 3	1298	148	3.84(2.54–5.80)	< 0.001	2.72(1.76–4.21)	< 0.001	3.06(2.01–4.69)	< 0.001
Quartile 4	1299	290	7.96(5.34–11.86)	< 0.001	5.56(3.70–8.21)	< 0.001	6.47(4.35–9.61)	< 0.001
P for trend				< 0.001		< 0.001		< 0.001
Participants without diabetes								
Quartile 1	1273	46	Ref		Ref		Ref	
Quartile 2	1272	81	1.95(1.19–3.20)	0.008	1.61(0.99–2.62)	0.051	1.69(1.04–2.73)	0.033
Quartile 3	1273	140	3.92(2.56–6.03)	< 0.001	2.79(1.78–4.36)	< 0.001	3.14(2.03–4.85)	< 0.001
Quartile 4	1273	268	7.75(5.26–11.40)	< 0.001	5.54(3.73–8.05)	< 0.001	6.43(4.41–9.41)	< 0.001
P for trend				< 0.001		< 0.001		< 0.001

Table 2. The relationships between TyG-BMI and EHT (hypertension diagnosed before age of 40). Survey sample weights were taken into consideration in the Cox models accompanying the NHANES data. It examines the association of TyG-BMI level with EHT. Model 1 was adjusted for gender, race, age, education level, marital status, smoke history, income level. Model 2 was additionally adjusted for albumin, creatinine, LDL level. Data was shown as HR (95% CI). *Ref* reference, *OR* odds ratios, *CI* confidence interval, *EHT* early-onset hypertension.

TyG-BMI	Cases	*N*	Non-adjusted model		Model1		Model2	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Quartile 1	798	14	Ref		Ref		Ref	
Quartile 2	797	40	3.77(1.71–8.34)	0.001	3.39(1.55–7.44)	0.002	3.53(1.59–7.86)	0.002
Quartile 3	796	49	4.14(1.98–8.65)	< 0.001	3.58(1.67–7.63)	0.001	4.02(1.87–8.63)	< 0.001
Quartile 4	798	107	10.92(5.18–23.01)	< 0.001	9.19(4.43–19.06)	< 0.001	11.07(5.29–23.17)	< 0.001
P for trend				< 0.001		< 0.001		< 0.001

Table 3. The relationships between TyG-BMI and EHT (hypertension diagnosed before age of 30). Survey sample weights were taken into consideration in the Cox models accompanying the NHANES data. It examines the association of TyG-BMI level with hypertension. Model 1 was adjusted for gender, race, age, education level, marital status, smoke history, income level. Model 2 was additionally adjusted for albumin, creatinine, LDL level. Data was shown as HR (95% CI). *Ref* reference, *OR* odds ratios, *CI* confidence interval.

Subgroup	TyG-BMI							*P* for interaction
	Q1	Q2		Q3		Q4		
	OR	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
Gender								
Male	Ref	2.04 (1.05–3.97)	0.079	3.72 (1.90–7.25)	< 0.001	7.73 (4.06–14.71)	< 0.001	0.758
Female	Ref	1.79 (0.96–3.32)	0.133	3.56 (2.14–5.89)	< 0.001	7.84 (4.95–12.43)	< 0.001	
Race/ethnicity								
Non-Hispanic White	Ref	1.91 (0.99–3.68)	0.132	4.77 (2.59–8.77)	< 0.001	9.35 (5.02–17.39)	0.037	0.119
Other Race	Ref	2.19 (1.26–3.82)	0.014	2.81 (1.74–4.55)	< 0.001	6.55 (4.16–10.31)	0.038	
Smoke								
Ever	Ref	1.72 (0.89–3.28)	0.184	3.06 (1.64–5.68)	< 0.001	4.89 (2.58–9.27)	0.021	0.608
Never	Ref	2.19 (1.10–4.38)	0.004	4.03 (2.31–7.06)	< 0.001	10.71 (6.02–19.05)	0.019	

Table 4. Subgroup analysis of the associations between TyG-BMI and EHT. Survey sample weights were taken into consideration in the Cox models accompanying the NHANES data. It examines the association of TyG-BMI level with EHT by using subgroups based on sex, BMI level, race, smoking status, marital status and the interaction with TyG-BMI. Data was shown as HR (95% CI). *Ref* reference, *HR* hazard ratio, *CI* confidence interval, *EHT* early-onset hypertension.

quartiles and EHT was observed across all subgroups. Men in the highest TyG-BMI quartile (Q4) had a 7.73-fold increased odds of EHT compared to those in the lowest quartile (Q1) [OR (95% CI): 7.73 (4.06–14.71), $p < 0.001$]. Similarly, women in the highest quartile had 7.84-fold increased odds of EHT [OR (95% CI): 7.84 (4.95–12.43), $p < 0.001$]. The interaction between gender and TyG-BMI was not statistically significant (*P* for interaction = 0.758). The association between TyG-BMI and EHT was consistent across different racial/ethnic groups. Compared to Q1, the ORs (95% CI) for EHT in Q4 were 9.35 (5.02–17.39) for Non-Hispanic White, and 6.55 (4.16–10.31) for Other Races (both $p < 0.001$). The interaction between race/ethnicity and TyG-BMI was not statistically significant (*P* for interaction = 0.119). Both ever and never smokers showed a positive association between TyG-BMI and EHT. The ORs (95% CI) for EHT in the highest TyG-BMI quartile compared to the lowest were 4.89 (2.58–9.27) for ever smokers and 10.71 (6.02–19.05) for never smokers (both $p < 0.001$). The interaction between smoking status and TyG-BMI was not statistically significant (*P* for interaction = 0.608).

Mediation analysis

Our analysis revealed a significant mediating role for both GGT ($P = 0.028$) and uric acid ($P = 0.024$) in the pathway between TyG-BMI and EHT. Specifically, we found that: GGT mediated 3.2% of the total effect of TyG-BMI on EHT. This suggests that a portion of the increased risk of EHT associated with higher TyG-BMI is explained by elevated GGT levels. Uric acid mediated 7.8% of the total effect of TyG-BMI on EHT. This indicates that higher uric acid levels also contribute to the association between TyG-BMI and EHT. These findings are summarized in Table 5, which provides detailed information on the mediation analysis results, including estimated proportions and confidence intervals. Figure 4 visually depicts the mediation pathways for GGT and uric acid.

Discussion

Our study, using a large, representative sample from the NHANES database, demonstrated a significant and independent association between TyG-BMI and the prevalence of EHT. The positive association persisted even after adjusting for established risk factors for hypertension, including age, sex, race, socioeconomic factors, and

Indicators	Proportion of mediation effect (95% CI)	*P*-value
Inflammation biomarkers		
NLR	0.016 (-0.011 ~ 0.232)	0.232
White blood cell (1000 cells/μL)	0.006 (-0.033 ~ 0.688)	0.688
Neutrophils cell percent (%)	-0.001 (-0.006 ~ 0.920)	0.920
Oxidative stress biomarkers		
GGT	0.032 (0.011 ~ 0.028)	0.028
Uric acid	0.078 (0.016 ~ 0.024)	0.024
Bilirubin	0.002 (-0.025 ~ 0.720)	0.720

Table 5. Mediation analysis of the influence of indicators on the interaction between TyG-BMI and EHT. *CI* confidence intervals, *NLR* neutrophil-to-lymphocyte ratio, *GGT* gamma-glutamyl transferase, *EHT* early-onset hypertension.

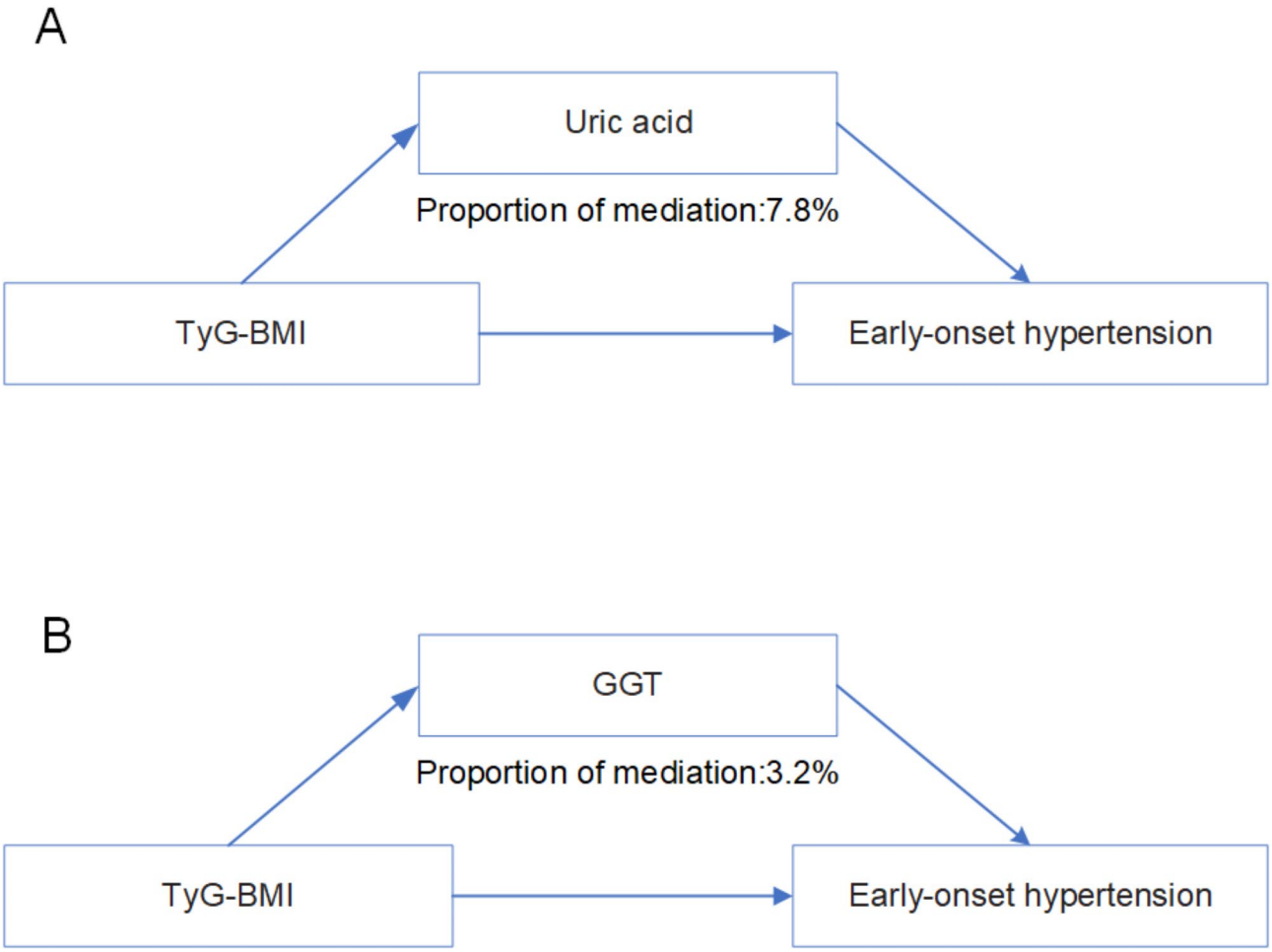

Fig. 4. Mediation analysis demonstrating the roles of uric acid and Gamma-glutamyl transferase (GGT) in the association between TyG-BMI and EHT. This figure illustrates the results of the mediation analyses examining uric acid (**A**) and GGT (**B**) mediate the relationship between TyG-BMI and EHT. The proportion of the total effect of TyG-BMI on EHT that is mediated by each biomarker is indicated. These analyses reveal that both uric acid (7.8%) and GGT (3.2%) significantly mediate the association between TyG-BMI and EHT.

smoking status. Notably, we observed a dose-response relationship, with individuals in the highest quartile of TyG-BMI having 6.47-fold increased odds of EHT compared to those in the lowest quartile. This relationship remained consistent across subgroups stratified by gender, race, and smoking status. Furthermore, our mediation analysis suggested that elevated GGT and uric acid, markers of oxidative stress, may play mediating roles in the pathway between TyG-BMI and EHT.

Our findings are consistent with a growing body of literature demonstrating a strong link between TyG-related indices and hypertension[34,35]. These findings support the notion that elevated triglyceride and glucose levels, reflecting insulin resistance, contribute to the development of hypertension early in life. Furthermore, our study adds to the emerging evidence suggesting that TyG-BMI might be a superior predictor of cardiometabolic risk compared to TyG alone[36]. This is plausible, as TyG-BMI directly incorporates BMI, a major risk factor for both insulin resistance and hypertension. However, research directly comparing the predictive performance of TyG and TyG-BMI for EHT specifically is limited and warrants further investigation. Our study focuses specifically on EHT, a demographic often overlooked in traditional hypertension research. Most previous studies have either focused on older populations or have not specifically stratified by age of hypertension onset. RCS analysis in our study indicated a nonlinear relationship between TyG-BMI and EHT. This finding aligns with recent studies that have demonstrated a similar non-linear association between triglyceride-glucose related indices and cardiovascular outcomes[37,38]. Our findings highlight the importance of early risk assessment and emphasize the potential role of TyG-BMI as a readily available screening tool in young adults, where traditional risk factors might not be as prominent.

The observed association between elevated TyG-BMI and EHT in our study is biologically plausible and aligns with current understanding of hypertension pathogenesis. A key mechanism underlying this association is likely insulin resistance, a metabolic disorder characterized by impaired glucose uptake and utilization by the body's cells[39]. Insulin resistance is closely linked to obesity, elevated triglycerides, and hyperglycemia, all components integrated within the TyG-BMI index[40].Obesity, particularly abdominal obesity, is a well-established driver of insulin resistance. Adipose tissue, especially visceral fat, releases inflammatory cytokines and free fatty acids that interfere with insulin signaling pathways[41]. Elevated triglycerides, often seen in obesity and insulin resistance, further contribute to endothelial dysfunction, oxidative stress, and vascular inflammation, all of which can lead to increased vascular tone and hypertension. Our findings reveal that both GGT and uric acid significantly mediate the relationship between TyG-BMI and EHT, with GGT explaining 3.2% and uric acid explaining 7.8% of the total effect. Although these proportions might seem modest at first glance, they are clinically relevant because they pinpoint specific pathways through which elevated TyG-BMI contributes to the development of EHT[42,43]. GGT, a marker of oxidative stress, and uric acid, a pro-inflammatory mediator, are both modifiable factors that can be influenced by lifestyle interventions and/or targeted therapies[44–46]. These findings highlight the potential for interventions aimed at reducing oxidative stress and inflammation to mitigate the adverse effects of elevated TyG-BMI on EHT risk[47]. Further, the relatively small proportions suggest that other pathways independent of GGT and uric acid, such as direct effects of insulin resistance, endothelial dysfunction, and other oxidative stress pathways, may play more substantial roles in mediating the relationship between TyG-BMI and EHT, warranting further investigation[48,49]. Our study provides a foundation for the development of tailored interventions to address the specific mechanisms underlying EHT in individuals with elevated TyG-BMI.The robust association between TyG-BMI and EHT identified in our study, particularly among younger adults, carries important clinical implications. Early identification of individuals at risk for EHT is critical for effective prevention and management of long-term cardiovascular complications[50]. TyG-BMI, calculated from routinely collected clinical data (fasting glucose, triglycerides, and BMI), provides a readily available and cost-effective tool for early risk stratification in clinical practice. Our findings underscore the importance of addressing modifiable risk factors, particularly obesity and metabolic disturbances, in young adults to mitigate the risk of developing EHT. Lifestyle interventions targeting weight loss through dietary modification and increased physical activity have been shown to improve insulin sensitivity and reduce blood pressure[51]. Moreover, the use of TyG-BMI as a screening tool could help identify individuals who might benefit from more aggressive lifestyle interventions or even earlier pharmacological interventions, such as metformin, which has been shown to improve insulin sensitivity and reduce cardiovascular risk[52].

Our study suggests that TyG-BMI is a promising screening tool for EHT due to its ease of calculation using routinely collected clinical data (fasting plasma glucose, triglycerides, and BMI), eliminating the need for additional testing. TyG-BMI can be readily integrated into routine health assessments, as the required data is often collected during standard physicals and blood work. Given its simplicity and low cost, TyG-BMI presents a potentially cost-effective strategy for early risk stratification and intervention. However, further studies comparing its cost-effectiveness to other established risk factors are needed.

There are some limitations in the present study. The cross-sectional nature of the NHANES data limits our ability to draw definitive conclusions about causality. While our findings strongly suggest an association between TyG-BMI and EHT, the temporal relationship between these factors remains unclear. Therefore, while our mediation analysis provides valuable insights into potential pathways linking TyG-BMI and EHT, the results should be interpreted as reflecting associations rather than proven causal mechanisms. It's possible that undiagnosed or preclinical hypertension might influence metabolic parameters, including triglyceride and glucose levels[53]. Despite adjusting for a wide range of potential confounders, residual confounding cannot be entirely ruled out. Unmeasured or imperfectly measured factors could still influence the observed association. The reliance on self-reported hypertension diagnosis in NHANES, while a common limitation in large-scale epidemiological studies[54], introduces the possibility of misclassification bias. Furthermore, our results should be primarily interpreted and applied within a non-diabetic context, due to the limited representation of diabetic individuals in our study. This limits our ability to draw conclusions about the association between TyG-BMI and EHT in diabetic populations. Therefore, caution should be exercised when applying our findings to such populations.

Despite these limitations, our study has several strengths. Most notably, we leveraged data from NHANES, a large, nationally representative survey known for its high-quality data collection and rigorous methodology[55]. The large sample size provided sufficient statistical power to detect significant associations and conduct subgroup analyses. Furthermore, our robust statistical analysis, including multiple adjustments for potential confounders

and the use of survey weights, enhances the generalizability and internal validity of our findings. Focusing on individuals under 40 allows our study to specifically target EHT, isolating relevant environmental risk factors with fewer confounding variables. This approach can reveal unique etiologies and intervention opportunities specific to younger populations, potentially informing tailored public health strategies. Additionally, it enhances the ability to capture contemporary lifestyle influences and provides a foundation for longitudinal studies on hypertension's development over time. Our study provides a foundation for future research in this area. Prospective studies are warranted to confirm the causal link between TyG-BMI and EHT, exploring whether elevated TyG-BMI precedes the development of hypertension. Intervention studies designed to reduce TyG-BMI, such as through lifestyle modifications or pharmacological interventions, would provide valuable insights into the potential for mitigating EHT risk. Further investigation into the specific molecular mechanisms linking TyG-BMI to hypertension, including the roles of inflammation, oxidative stress, and endothelial dysfunction, is also crucial for identifying novel therapeutic targets.

Conclusion

In conclusion, our study highlights the association between elevated TyG-BMI and an increased prevalence of EHT in a nationally representative sample of US adults. Our findings suggest that targeting TyG-BMI and related mediators may contribute to EHT. Further, this study emphasizes the need for longitudinal studies to understand the causal relationship between TyG-BMI and EHT. Given the substantial long-term cardiovascular risks associated with EHT, incorporating TyG-BMI into routine clinical practice could facilitate early intervention strategies, emphasizing lifestyle modifications and potentially even earlier pharmacotherapy for those at highest risk. This proactive approach has the potential to mitigate the growing burden of cardiovascular disease attributable to EHT.

Data availability

The original data of this study have been deposited on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).The code and data generated during the study were available from the corresponding author on reasonable request.

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Author contributions

W L and C G contributed to conceptualization. C G contributed to data curation, formal analysis and methodology. J Z contributed to investigation and project administration. W L and C G wrote the main manuscript text. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The research has followed the Tenets of the Declaration of Helsinki. Ethical considerations have been rigorously followed, with all data sourced from the publicly available NHANES, which obtained informed consent from all participants and received ethical approval from the NCHS Research Ethics Review Board.

Additional information
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