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Running title: 25(OH) D mediating TyG index and HTN

Serum 25-hydroxyvitamin D mediates the association of triglyceride-glucose index with hypertension in US adults from NHANES 2001-2018: a national cross-sectional study

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Abstract

This study was designed to explore the mediating role of serum 25-hydroxyvitamin D (25(OH) D) in triglyceride glucose (TyG) index and hypertension (HTN). Study participants were selected from the 2001-2018 National Health and Nutrition Examination Survey. Firstly, we estimated the association between TyG index, and serum 25(OH)D with HTN using weighted multivariable logistic regression model and restricted cubic spline. Secondly, we used generalized additive model to investigate the correlation between TyG index and serum 25(OH)D. Lastly, serum 25(OH)D was investigated as a mediator in the association between TyG index and HTN. There were 14,099 subjects in total. TyG index was positively and linearly associated with HTN risk, while serum 25(OH)D had a U-shaped relationship with prevalence of HTN. When the serum 25(OH)D levels were lower than 57.464 mmol/L, prevalence of HTN decreased with the increase of serum 25(OH)D levels. When serum 25(OH)D levels rise above 57.464 mmol/L, risk of HTN increased rapidly. Based on the U-shaped curve, serum 25(OH)D concentrations were divided into two groups: (<57.464 and ≥57.464 mmol/L). According to the mediation analysis, when serum 25(OH)D levels <57.464 mmol/L, the positive association between TyG index and incident HTN was increased by 25(OH)D. When serum 25(OH)D levels ≥57.464 mmol/L, the negative association between TyG index and incident HTN was increased by 25(OH)D. There was a mediation effect between TyG index and HTN, which was mediated by 25(OH)D. Therefore, we found that the association between serum 25(OH)D levels and TyG index may influence prevalence of HTN.

Key words: Hypertension, TyG index, Mediation analysis, Serum 25-hydroxyvitamin D.

Abbreviations: TyG index: Triglyceride glucose index; Hypertension: HTN; Serum 25-hydroxyvitamin D: Serum 25(OH)D; Insulin resistance: IR; CDC: Centers for Disease Control and Prevention; Family poverty-income ratio: Family PIR; Coronary heart disease: CHD; Diabetes mellitus: DM; Congestive heart failure: CHF; Coronary kidney disease: CKD; Body mass index, BMI; Fast blood glucose: FBG; Uric acid: UA; High-density lipoprotein cholesterol: HDL-C; Blood urea nitrogen: BUN; Glycosylated hemoglobin: HbA1c; Total cholesterol: TC; Triglyceride: TG; Serum creatinine: Scr; Estimated glomerular filtration rate: eGFR; Liquid chromatography-tandem mass spectrometry: LC-MS/MS; Restricted cubic spline, RCS; Total effect: TE; Direct effects: DE; Indirect effects: IE; Odds ratios: ORs; Confidence intervals: CIs; Blood pressure: BP; Systolic blood pressure: SBP; Diastolic blood pressure: DBP;

1. Introduction

Hypertension (HTN) is a common chronic condition that refers to a condition in which blood pressure in the arteries to rise abnormally (1). In terms of morbidity and the leading cause of cardiovascular adverse events risk, HTN is a major global public health challenge (2). The results of a recent study looking at the prevalence of high blood pressure worldwide show that from 1990 to 2019, the number of people aged 30-79 with high blood pressure doubled, from 648 million to 1.278 billion (3). Elevated blood pressure remains the leading cause of death globally, with 10.8 million patients dying from high systolic blood pressure in 2019, accounting for 19.2% of all deaths in 2019 (4, 5). Worldwide, one in five adults has HTN, according to the World Health Organization (6). HTN is one of the major risk factors for cardiovascular disease, which also is especially harmful to the kidney, blood vessel, and brain.

Triglyceride–glucose (TyG) index is a reliable indicator of insulin resistance (IR) based on the logarithmic product of fasting triglycerides and fasting glucose (7). As compared to plasma insulin in the homeostasis model assessment of IR, TyG index is more convenient and accessible in clinical practice (8, 9). The prevalence of IR in the United States is quite high, especially among adults. IR is often closely linked to factors such as obesity, lack of exercise, poor eating habits and genetic factors. According to the Centers for Disease Control and Prevention (CDC), about one-third of American adults are considered IR. The condition is also increasing in children and adolescents, partly due to the increasing prevalence of obesity in this age group (10). Additionally, Vitamin D deficiency or deficiency is common in the United States, especially in the winter or in areas with less sunlight. According to past studies and surveys, about 40 to 60 percent of the U.S. population has varying levels of vitamin D deficiency or deficiency. The condition is more prevalent among certain populations, such as blacks, Latinos and the elderly (11). Previous research has shown that TyG index elevation has been associated with a variety of diseases, such as arterial stiffness, heart failure, coronary artery stenosis, cardiovascular and all-cause mortality (12-15). Vitamin D is a kind of fat-soluble vitamin that is acquired by sunlight exposure or ingestion and primarily regulates calcium and phosphate metabolism. 25-hydroxyvitamin D (25(OH)D) is the primary storage in the body (16, 17). Previous studies have shown that low serum vitamin D levels have been associated with elevated risk of micro-and macrovascular complications, poor outcomes in patients with heart failure, and increased all-

cause and cardiovascular mortality (18-20). Research indicated that HTN and IR interact to increase the risk of diabetes (21). In addition, other studies have shown that drinking orange juice rich in vitamin D3 and probiotics can improve insulin sensitivity and reduce cardiometabolic risk (22). Therefore, there may be a link between vitamin D3, insulin resistance, and high blood pressure. However, the association between TyG index and vitamin D levels and the prevalence of HTN has not been clearly explained. According to our hypothesis, serum 25(OH)D regulates TyG index, thereby reducing the influence of TyG index on the prevalence of HTN. Therefore, in this study, we used the National Health and Nutrition Examination Survey (NHANES) database to explore for the first time the relationship between TyG index, serum 25(OH)D and prevalence of HTN. Additionally, the mediation effect of serum 25(OH)D on TyG index in prevalence of HTN was further explored for the first time.

2. Material and methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES) is a population-based cross-sectional survey designed to collect information on the health and nutrition status of adults and children in the United States of America (23). The people evaluated in this study were the general population in the American. All NHANES protocols are approved by the NCHS Ethics Review Committee prior to data collection (24). The NHANES website provides detailed information about the survey design, methodology, and data (https://www.cdc.gov/nchs/nhanes/).

2.2 Covariates

The following covariates were taken into account in the analysis: demographic data (sex (man/women), age, marital status (have a partner/no partner/unmarried), race/ethnicity (Mexican American, other Hispanic American, non-Hispanic black, non-Hispanic white, and other races), family poverty-income ratio (PIR), smoking status (never/former/now), education level (less than high school/high school/more than high school), and alcohol consumption (never/former/mild/moderate/heavy)), physical activities (work and recreational activity), comorbidity data (the history of coronary heart disease (CHD), diabetes mellitus (DM), congestive heart failure (CHF), angina pectoris, coronary kidney disease (CKD), heart attack and

hyperlipidemia), anthropometric data (body mass index (BMI) and waist circumference), dietary data (mean energy intake, mean sodium intake and mean potassium intake) and laboratory data (fast blood glucose (FBG), potassium, uric acid (UA), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen (BUN), sodium, glycosylated hemoglobin (HbA1c), total cholesterol (TC), hemoglobin, potassium, triglyceride (TG), sodium, serum creatinine (Scr), and estimated glomerular filtration rate (eGFR) (25-28). Family PIR refers to ratio of family income to poverty. You can find more information about the NHANES procedures here https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

2.3 Serum 25(OH)D measurements and calculation of TyG index

Expert operators at the Centers for Disease Control and Prevention lab performed the collection and analysis of serum 25(OH)D. Participants were asked to fast for more than eight hours while blood was drawn by a professional. In NHANES 2001-2006, serum 25(OH)D concentrations were measured using the DiaSorin radioimmunoassay kit. Serum 25(OH)D concentrations from 2001-2006 were converted to equivalent values using a regression method based on the liquid chromatography-tandem mass spectrometry (LC-MS/MS) measurements. From 2007-2018, LC-MS/MS was used to measure serum 25(OH)D levels (29, 30). According to the recommendations of CDC, we used the LC-MS/MS–equivalent data for all analyses (31). Details about the procedures can be found on the NHANES website: https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx. Additionally, TyG index was calculated by using the following formulas (8): TyG index = Ln [TG (mg/dL) × FBG (mg/dL)/2].

2.4 HTN ascertainment

In the present study, HTN was diagnosed if one of the following criteria was met: 1) self-reported hypertension, 2) currently taking antihypertensive medication, 3) systolic blood pressure ≥140 mmHg or/and diastolic blood pressure ≥90 mmHg (At least two or more measurements are required at different times and conditions). After resting quietly in a seated position for 5 minutes and after the participant's maximum inflation level has been determined, three consecutive blood pressure (BP) readings are obtained. If a BP measurement is interrupted or incomplete, a fourth attempt may be made. All BP determinations (systolic and diastolic) are taken in the mobile examination center. In individual interviews about various health issues, professionals used

standardized medical condition questionnaires. Participants were asked the following questions: “Because of {SP's} high blood pressure [hypertension], is {he/she} currently taking medicine?”. Additionally, participants were asked the following questions: “Has a doctor or other professional ever told you that you have high blood pressure/hypertension?”. Those who replied "Yes" were considered to have HTN, those who replied "No" were not. Subjects without self-reported hypertension were also considered hypertensive if their systolic blood pressure (SBP) or diastolic blood pressure (DBP) averaged 140 millimeters high or 90 millimeters high (32).

2.5 Statistical analysis

We calculated all data based on the NHANES sample weights. For continuous variables, we used the mean ± standard deviation, and for categorical variables, we used number (percentage, %). Weighted student t-tests were used to calculate continuous variables and weighted chi-square tests to calculate categorical variables in different groups. With the help of restricted cubic spline (RCS) and multivariable logistic regression models, the association of TyG index and serum 25(OH)D with HTN was investigated. In the multivariable logistic regression model 1, adjustments were made for age and sex. Model 2 incorporated additional adjustments for race/ethnicity, education level, smoking, alcohol consumption, marital status, family PIR and DM. Model 3 built upon Model 2 by including further adjustments for the history of CHD, CHF, angina pectoris, heart attack, stroke, hyperlipoidemia and CKD, body mass index, waist circumference, mean energy intake, mean sodium intake, mean potassium intake, sodium, potassium, Hb, FBG, HbA1c, TC, TG, HDL, BUN, UA, serum creatinine and eGFR (33). The generalized additive models were applied in order to evaluate the association of serum 25(OH)D with TyG index, serum 25(OH)D with systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as TyG index with SBP and DBP. Mediating analysis quantifies the degree to which a variable participates in the transmission of change from cause to its effect. In mediation analysis, the association between independent variables (X) and dependent variables (Y) is mediated by mediating variable (M) (34). In the study, the TyG index (X) was the independent variable, HTN (Y) was the outcome variable, and serum 25(OH)D was the mediating variable. Total effect (TE), indirect effect (IE), and direct effect (DE) were used to analyze whether serum 25(OH)D mediated the link between TyG index and HTN. TyG index has the total effect (TE) on HTN that can be divided into direct effect (DE) and indirect effect (IE), respectively. The TE

refers to the effect that the TyG index had on HTN. The IE refers to the effect of the TyG index on HTN through serum 25(OH)D. The DE represents the effect of the TyG index on HTN when controlling for serum 25(OH)D. Based on serum 25(OH)D mediation, we calculated the proportion of IE in TE. Our study used the R version 3.6.4 and SPSS version 22.0 for all statistical analysis. *P*-value < 0.05 was statistically significant.

3. Results

3.1 Baseline characteristics

A total of 87,318 participants were initially enrolled in the NHANES from 2001 to 2018. Among them, individuals without HTN data (n =16,073) were excluded from the study. We further excluded 45,149 individuals due to the absence of TyG index (n=43,629) and serum 25(OH)D (n=1,520). Additionally, 11,997 participants without demographic and biochemical data were excluded. Ultimately, a total of 14,099 individuals were included for data analysis (**Figure 1**). Of these, 5,065 participants self-reported having HTN or taking medications. In **Table 1**, we listed the weighted demographic and medical characteristics of the participants. The prevalence of HTN was found to be present in 42.7% (6,024/14,099) of the population. Subjects in the HTN group were older and had a higher level of BMI, waist circumference, TyG index, serum 25(OH)D, Hb, FBG, HbA1c, TC, TG, BUN, UA and Scr than those in the non-hypertensive group (*P* <0.05). Finally, we also compared the characteristics of the populations between the HTN group and non-hypertensive group after multiple imputation in **Supplementary Table 1**.

3.2 Associations of TyG index and serum 25(OH)D with HTN

The RCS curve shown the positive and linear correlation between TyG index and prevalence of HTN (*P* for nonlinearity =0.890; **Figure 2A**). Additionally, a U-shaped curve association existed between serum 25(OH)D and HTN risk (*P* for nonlinearity =0.005; **Figure 2B**). When the serum 25(OH)D levels was less than 57.464 mmol/L, prevalence of HTN decreased with the increase of serum 25(OH)D level. When serum 25(OH)D levels rise above 57.464 mmol/L, the risk of HTN increased rapidly. Moderate serum 25(OH)D levels reduce the risk of HTN, but too much or too little can adversely affect the prevalence of HTN. Compared with the lowest quartiles (Q1) of TyG index and serum 25(OH)D level, the odds ratios (ORs) with 95% confidence intervals (CIs) for HTN across the quartiles were 1.237 (1.089, 1.405), 1.418 (1.232, 1.632), and 1.616 (1.349,

1.935) for TyG index and 0.961 (0.848, 1.088), 0.908 (0.806, 1.023), and 1.063 (0.934, 1.210) for serum 25(OH)D in model 3 (**Table 2**, and **3**). There were positive and linear connection between TyG index and SBP and DBP (**Figure 3A**, and **3B**). Additionally, serum 25(OH)D level and SBP, and DBP also showed a U-shaped association (**Figure 3C**, and **3D**).

3.3 25(OH)D mediates the association between TyG index and HTN

Smooth curve fitting shown the roughly n-type correlation between serum 25(OH)D and TyG index. During serum 25(OH)D levels increases, the TyG index increases and then decreases (**Figure 4**). TyG index and HTN were analyzed using mediation analysis to determine whether serum 25(OH)D was a mediator. Based on the U-shaped curve serum 25(OH)D and HTN, we divided serum 25(OH)D concentrations into two groups: (<57.464, and ≥57.464 mmol/L). According to the mediation analysis, when serum 25(OH)D levels <57.646 mmol/L, the positive association between TyG index and incident HTN was increased by serum 25(OH)D. The serum 25(OH)D level was estimated to explain 0.98% of the association between TyG index and HTN (IE: β =0.000642; *P* =0.110; TE: β =0.062454; *P* <0.001; DE: β =0.061812; *P* <0.001) **(Figure 5A)**. When serum 25(OH)D levels ≥57.646 mmol/L, the negative association between TyG index and HTN was increased by serum 25(OH)D. The serum 25(OH)D level was estimated to explain −2.0% of the association between TyG index and HTN (IE: β =−0.00218; *P* =0.002; TE: β =0.10714; *P* <0.001; DE: β =0.10932; *P* <0.001) **(Figure 5B)**.

3.4 Subgroup analysis

Subgroup analyses for the associations of TyG index and serum 25(OH)D with HTN were conducted based on different age (<60/≥60), sex (male/female), DM (no/yes) and BMI (<30/≥30) (**Supplementary Figure 1** and **2**; **Supplementary Table 2** and **3**). A significant positive and liner association between TyG index and HTN was found among subjects who were age <60 years, male or female, with or without DM, and BMI <30 or ≥30 kg/m^2. Additionally, the U-shaped curve associations of serum 25(OH)D with HTN were found among participants who were age <60 or ≥60 year, male or female, with or without DM, and BMI <30 or ≥30 kg/m^2. Additionally, we also demonstrated the effect of serum 25(OH)D-mediated TyG index on HTN based on different age (<60/≥60), sex (male/female), DM (no/yes) and BMI (<30/≥30) (**Supplementary Figure 3** and **4**).

3.5 Sensitivity analysis

In order to avoid bias caused by missing covariate data resulting in potential bias. Therefore, we performed a sensitivity analysis for individuals who were excluded due to missing covariates. Our analysis found that the positive and linear correlation between TyG index and prevalence of HTN (*P* for nonlinearity =0.548; **Supplementary Figure 5A**). Additionally, a U-shaped curve association existed between serum 25(OH)D and HTN risk (*P* for nonlinearity =0.009; **Supplementary Figure 5B**). Compared with the lowest quartiles (Q1) of TyG index and serum 25(OH)D level, the ORs with 95% CIs for HTN across the quartiles were 1.129 (1.003, 1.271), 1.282 (1.131, 1.454) and 1.461 (1.253, 1.705) for TyG index and 0.851 (0.770, 0.940), 0.790 (0.713, 0.874) and 0.850 (0.766, 0.942) for serum 25(OH)D in model 3 (**Supplementary Table 4**, and **5**). When serum 25(OH)D levels <55.208 mmol/L, the positive association between TyG index and incident HTN was increased by serum 25(OH)D. The serum 25(OH)D level was estimated to explain 0.10% of the association between TyG index and HTN (IE: β =0.0004846; *P* =0.010; TE: β =0.04538272; *P* <0.001; DE: β =0.04533426; *P* <0.001) (**Supplementary Figure 6A**). When serum 25(OH)D levels ≥55.208 mmol/L, the negative association between TyG index and HTN was increased by serum 25(OH)D. The serum 25(OH)D level was estimated to explain −2.0% of the association between TyG index and HTN (IE: β =−0.00128; *P* =0.002; TE: β =0.07687; *P* <0.001; DE: β =0.07815; *P* <0.001) (**Supplementary Figure 6B**).

4. Discussion

In this study, the NHANES data was integrated and assessed comprehensively. Firstly, we showed that the TyG index was significantly positively correlated with odds of HTN. Meanwhile, TyG index increases were correlated with increases in SBP and DBP. As found by Wang D et al., the TyG index may be used to predict the risk of HTN as it has a positive dose-response relationship with SBP, DBP and prevalence of HTN from the Dongfeng–Tongji cohort (35). In Mexican adults, Argoty-Pantoja AD et al. also revealed that the TyG index was positively correlated with SBP, and DBP and predicted the incidence of HTN (36). Additionally, among Chinese middle-aged and older adults, Niu ZJ et al. also demonstrated that the TyG index was independently and significantly associated with incidence of HTN (37). This is consistent with our findings. There is still no clear understanding of the mechanism behind the association between the TyG index and change of blood pressure or HTN. HTN and high blood pressure are

caused by systematic inflammation, oxidative stress, and endothelial dysfunction associated with IR (38, 39). Moreover, studies have shown that IR is capable of altering sodium metabolism, activating the sympathetic nervous system and increasing the secretion of vasoactive substances. As a result, blood pressure will rise and HTN will progress (40-42). Additionally, IR is also reported to be associated with obesity and arterial stiffness (43, 44). As a result of these factors, blood pressure may also be affected. Secondly, serum 25(OH)D and risk of HTN was associated in a U-shaped pattern. Additionally, serum 25(OH)D levels were also associated with a U-shaped curve in SBP and DBP. Shen Q et al. suggested that vitamin D deficiency was associated with a higher risk of HTN in non-smoking women of childbearing age (45). Additionally, Ye H et al. also found that adults with HTN who took vitamin D supplements had a lower risk of all-cause mortality, whereas adults with HTN with lower serum 25 (OH)D concentration had higher all-cause mortality (25). There was a non-linear association between serum 25(OH)D concentration and blood pressure discovered by Che J et al. Serum 25(OH)D levels had inversely associated with SBP when concentrations of serum 25(OH)D concentrations <84 nmol/L. Higher serum 25(OH)D concentrations were associated with higher DBP when concentrations of serum 25(OH)D >84 nmol/L (46) . This is also consistent with our findings. There are a number of factors that can contribute to hypotension caused by serum 25(OH)D, but the exact mechanism is unknown. By suppressing the production of renin, serum 25(OH)D reduces blood pressure by downregulating renin-angiotensin-aldosterone system activity (47). By stimulating parathyroid hormone 2 receptors on vascular smooth muscle cells, serum 25(OH)D inhibits the production of parathyroid hormone, which can increase blood pressure. Additionally, calcium deposition in arterial walls increases collagen deposition and vessel stiffness by increasing expression of both receptors of advanced glycation end products and monocyte-macrophage cytokines and interleukin-6 (48). This means that vitamin D deficiency may be an important risk factor for high blood pressure. Therefore, further study of the blood pressure lowering mechanism of vitamin D is now necessary. Finally, we demonstrated for the first time, that the potential protective effect of appropriate serum 25(OH)D levels on the TyG index and the prevalence of HTN in the general U.S. adult population through mediation analysis. Mustafa A et al. founded that when serum 25(OH)D had negative association with TyG index. And, when serum 25(OH)D reached 23-24 ng/ml, the TyG index remains unchanged (49). Liu Z et al. suggested that in patients with metabolic associated fatty liver disease, the TyG index is negatively associated with vitamin D

status. Vitamin D deficiency may be associated with a high TyG index (50). Jia Y et al. also found that high TyG index is a risk factor for vitamin D deficiency in T2DM. Therefore, proper supplementation of vitamin D in these patients may improve IR (51). Additionally, Vitamin D deficiency increases the risk for T2DM, which might be related to IR (52). This explains why when serum 25(OH)D D levels are <57.464 mmol/L, the positive association between TyG index and incident HTN was mediated by serum 25(OH)D. As mentioned above, TyG index has been regarded as a reliable and novel indicator of IR. Dhas Y et al. revealed that sufficient serum 25(OH)D concentration may lower the risk of development of IR (53). This is consistent with our results. Mechanistically, low serum 25(OH)D levels may promote the occurrence of HTN through multiple pathways. Firstly, the important role of serum 25(OH)D in calcium homeostasis and vasodilation has been widely studied, and its deficiency may lead to vascular dysfunction and HTN. In addition, the effect of serum 25(OH)D on insulin sensitivity is also one of the potential mechanisms. IR is closely related to the TyG index, which may further aggravate metabolic disorders through serum 25(OH)D deficiency, thereby leading to HTN. Finally, based on the findings of this study, the potential benefits of serum 25(OH)D intervention are especially significant for patients with high IR, as indicated by an elevated TyG index. The association between serum 25(OH)D levels and TyG index may influence prevalence of HTN. When serum 25(OH)D levels ≥57.464 mmol/L, serum 25(OH)D level showed a positive correlation with HTN risk and mediated a negative connection between TyG index and HTN risk. In our study, observations suggested that increased serum 25(OH)D levels appeared to attenuate the relationship between the TyG index and HTN risk. Consequently, for individuals with a notably elevated TyG index, a more proactive approach to vitamin D supplementation might be beneficial.

NHANES employs a complex, multistage sampling design to represent the diversity of the U.S. population. However, our study had several major limitations. Firstly, NHANES data relies primarily on participants' self-reported information, including health conditions, dietary habits, and behaviors. This can introduce biases such as recall bias, social desirability, and subjective interpretation, affecting the accuracy and reliability of the data. Secondly, NHANES is a cross-sectional study, meaning data collection is conducted at a specific point in time. Therefore, the study was a cross-sectional assessment of the levels of TyG index and serum 25(OH)D and

monitoring the continuous state of levels of TyG index and serum 25(OH)D is difficult. Therefore, NHANES cannot establish causal association of TyG index and serum 25(OH)D with prevalence of HTN. Thirdly, we studied the effect of serum 25(OH)D levels mediating the relationship between TyG index and HTN, and were unable to assess the effect of vitamin D intake on the relationship between TyG index and HTN. Fourthly, mediation analysis also could not clarify the causality between serum 25(OH)D concentrations and the TyG index. Finally, the diversity of geographic regions, diet, and lifestyle determines the "mediation variable" in mediation analysis might synergistically affect multiple factors.

5. Conclusions

In summary, TyG index was positively and linearly associated with HTN and serum 25(OH)D was U-shaped related to HTN. When vitamin D levels ≥57.464 mmol/L, serum 25(OH)D level showed a positive correlation with HTN risk and mediated a negative connection between TyG index and HTN risk. Therefore, increased serum 25(OH)D levels appeared to attenuate the relationship between the TyG index and HTN risk. These observations indicated a potential interaction between serum 25(OH)D levels and the TyG index in relation to HTN risk.

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Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships.

Authorship

Jing Lu and Mengying Cao contributed to hypothesis development and manuscript preparation. Jing Lu and Xiaoxue Zhang contributed to the study design. Mengying Cao and Wenhao Zhong undertook data analyses. Jie Yuan and Yunzeng Zou drafted and revised the manuscript. All authors approved the final draft of the manuscript for publication.

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the National Center for Health Statistics obtained institutional review board. Written informed consent was obtained from all subjects/patients.

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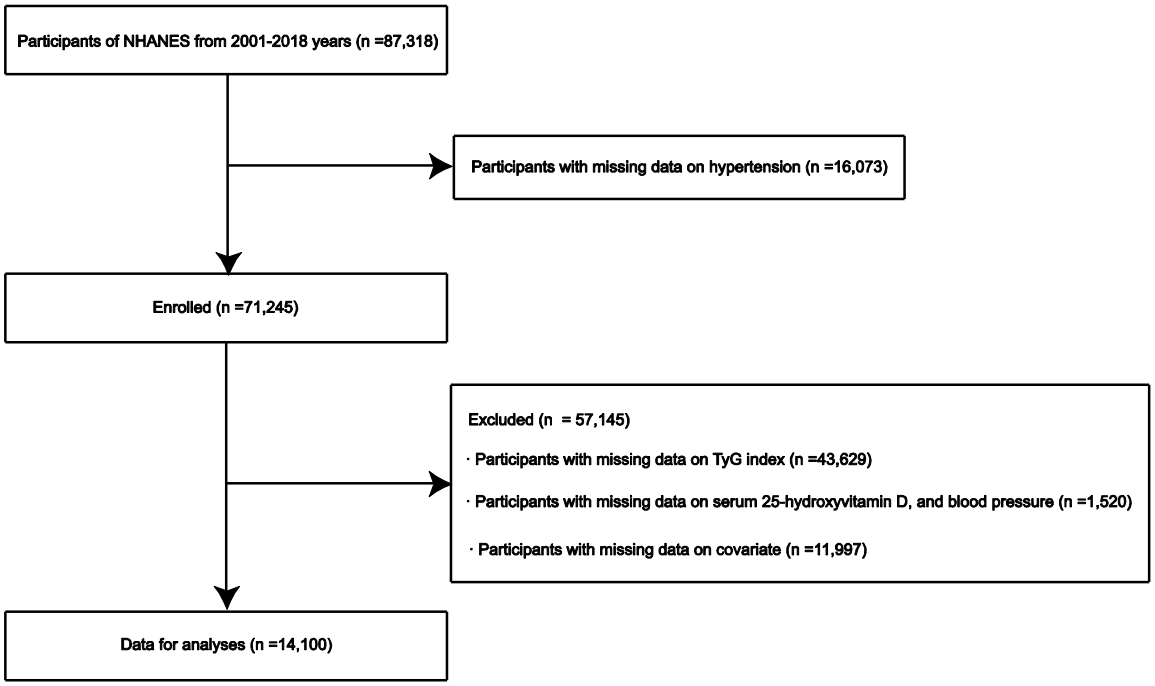

Figure 1. Study flow chart.

Abbreviations: NHANES, National Health and Nutrition Examination Surveys; 25(OH)D, 25-hydroxyvitamin D; HTN, hypertension.

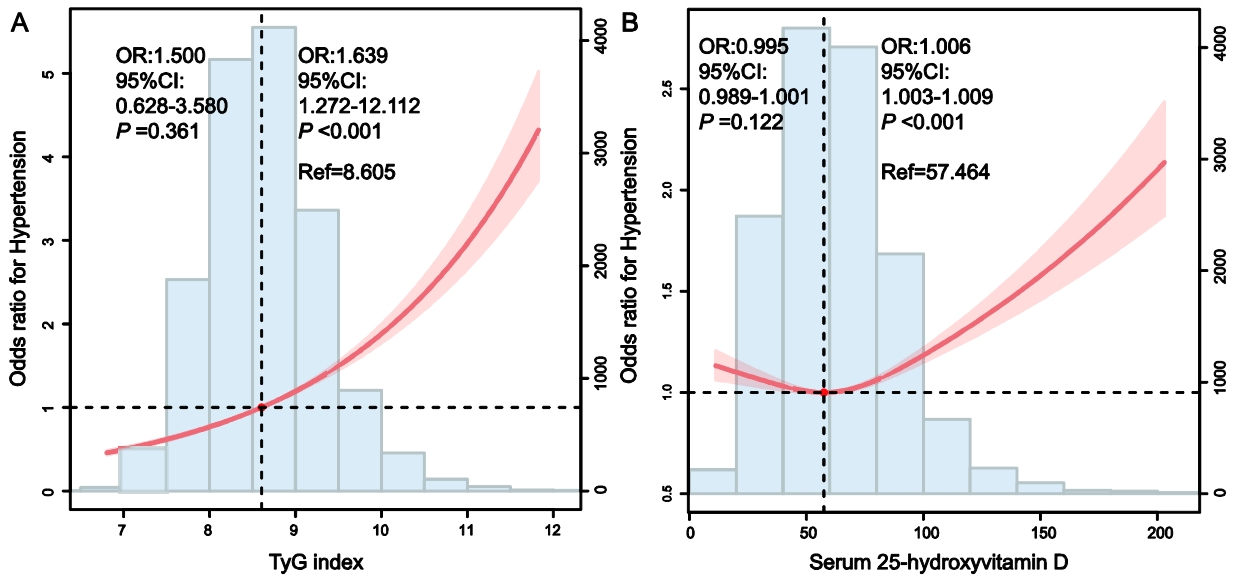

Figure 2. The RCS plots of associations of (A) TyG index and (B) serum 25(OH)D with prevalence of HTN.

Abbreviations: RCS, restricted cubic spline; TyG index, triglyceride-glucose index; HTN, hypertension; 25(OH)D, 25-hydroxyvitamin D.

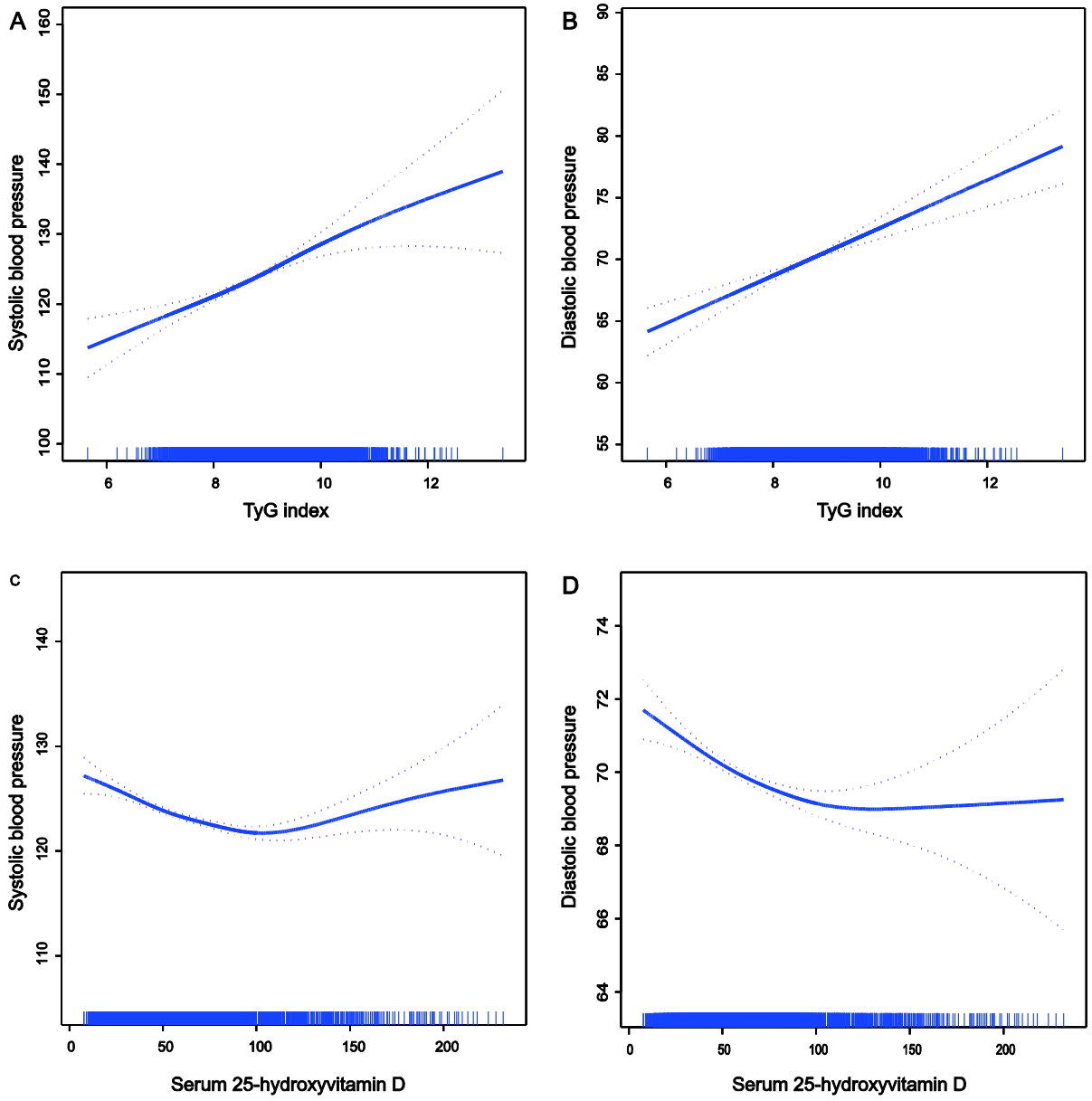

Figure 3. The association of TyG index and serum 25(OH)D with SBP, and DBP. (A) The association between TyG index and SBP; (B) The association between TyG index and DBP; (C) The association between serum 25(OH)D and SBP; (D) The association between serum 25(OH)D and DBP.

Abbreviations: SBP, systolic blood pressure; TyG index, triglyceride-glucose index; DBP, diastolic blood pressure; 25(OH)D, 25-hydroxyvitamin D.

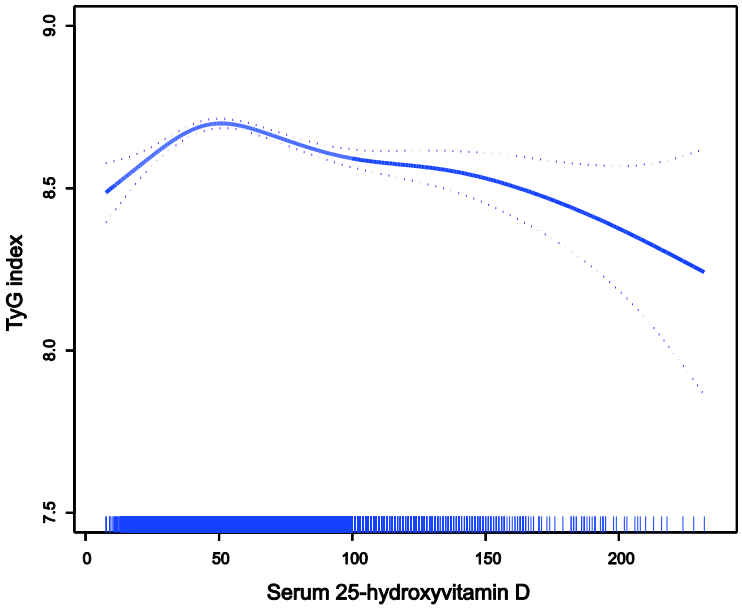

Figure 4. The association between serum 25(OH) D and TyG index.

Abbreviations: TyG index, triglyceride-glucose index; 25(OH)D, 25-hydroxyvitamin D.

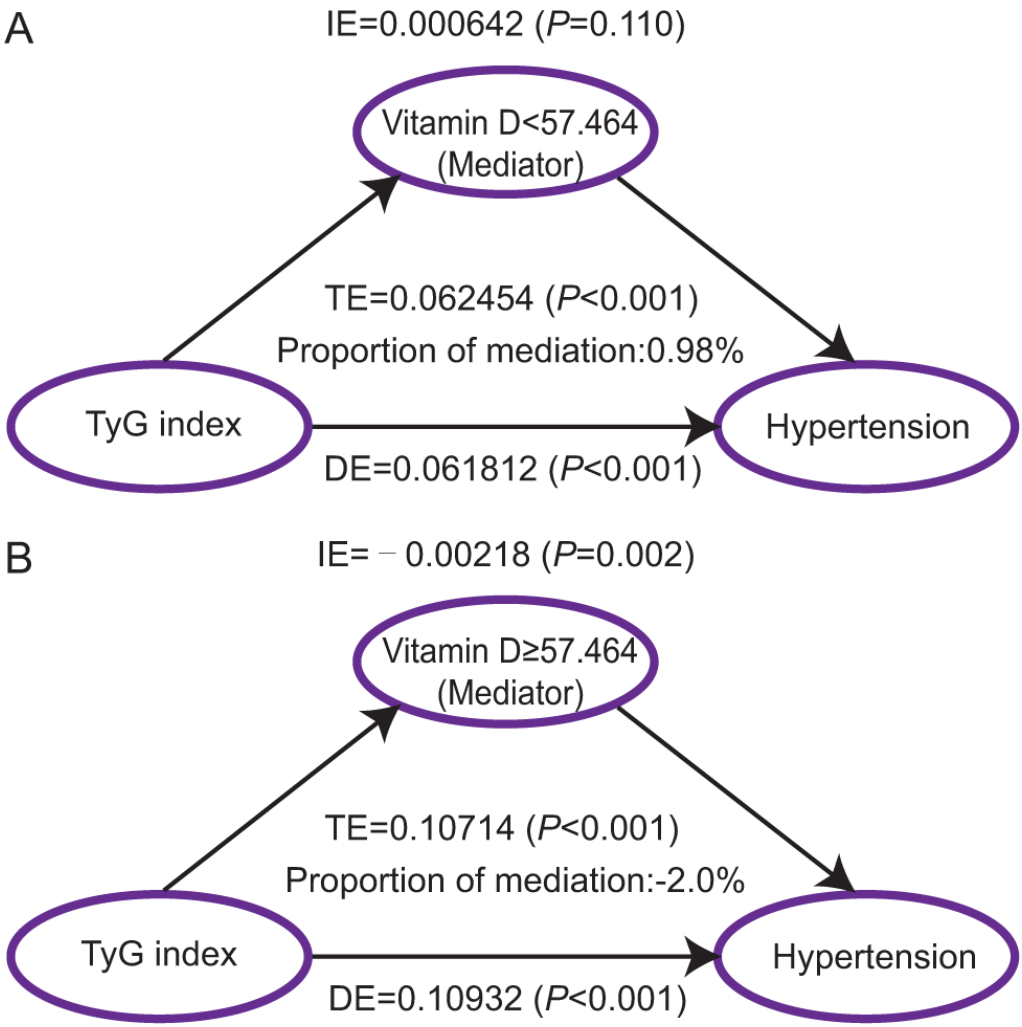

Figure 5. Mediation analysis of serum 25(OH)D on the interaction between TyG index and hypertension. (A) Mediation models of serum 25(OH)D (<57.464), TyG index, and hypertension: direct effect (TE =0.062454; *P* <0.001) of TyG index (exposure) toward hypertension (outcome), and 25(OH)D medication proportion is 0.98%; indirect effect (IE =0.000642; *P* =0.110) of TyG index (exposure) toward 25(OH)D (mediator) and effect hypertension (DE =0.061812; *P* <0.001), from 25(OH)D (mediator) toward hypertension (outcome). (B) Mediation models of serum 25(OH)D (≥57.464), TyG index, and hypertension: direct effect (TE =0.10714; *P* <0.001) of TyG index (exposure) toward hypertension (outcome), and 25(OH)D medication proportion is -2.0%; indirect effect (IE =-0.00218; *P* =0.002) of TyG index (exposure) toward 25(OH)D (mediator) and effect hypertension (DE =0.10932; *P* <0.001), from 25(OH)D (mediator) toward hypertension (outcome).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HTN, hypertension.

Supplementary materials

Supplementary Figure 1. Subgroup analysis for the association between TyG index and hypertension based on (A) age, (B) sex, (C) DM, and (D) BMI.

Abbreviation: DM, diabetes mellitus; TyG index, triglyceride-glucose index; BMI, body mass index.

Supplementary Figure 2. Subgroup analysis for the association between serum 25(OH) D and hypertension based on (A) age, (B) sex, (C) DM, and (D) BMI.

Abbreviation: DM, diabetes mellitus; serum 25-hydroxyvitamin D, serum 25(OH) D; BMI, body mass index.

Supplementary Figure 3. Mediation analysis of serum 25(OH)D on the interaction between TyG index and hypertension based on different age and sex. (A) age <60 and serum 25(OH)D <57.464, (B) age <60 and serum 25(OH)D ≥57.464, (C) age ≥60 and serum 25(OH)D <57.464, (D) age ≥60 and serum 25(OH)D ≥57.464, (E) male and serum 25(OH)D <57.464, (F) male and serum 25(OH)D ≥57.464, (G) female and serum 25(OH)D <57.464 and (H) female and serum 25(OH)D ≥57.464.

Abbreviation: TyG index, triglyceride-glucose index; serum 25-hydroxyvitamin D, serum 25(OH) D.

Supplementary Figure 4. Mediation analysis of serum 25(OH)D on the interaction between TyG index and hypertension based on different BMI and with or without DM. (A) without DM and serum 25(OH)D <57.464, (B) without DM and serum 25(OH)D ≥57.464, (C) with DM and serum 25(OH)D <57.464, (D) with DM and serum 25(OH)D ≥57.464, (E) BMI <30 and serum 25(OH)D <57.464, (F) BMI <30 and serum 25(OH)D ≥57.464, (G) BMI≥30 and serum 25(OH)D <57.464 and (H) BMI≥30 and serum 25(OH)D ≥57.464.

Abbreviation: TyG index, triglyceride-glucose index; serum 25-hydroxyvitamin D, serum 25(OH) D; DM, diabetes mellitus; BMI, body mass index.

Supplementary Figure 5. The RCS plots of associations of (A) TyG index and (B) serum 25(OH)D with prevalence of HTN.

Abbreviations: RCS, restricted cubic spline; TyG index, triglyceride-glucose index; HTN, hypertension; 25(OH)D, 25-hydroxyvitamin D.

Supplementary Figure 6. Mediation analysis of serum 25(OH)D on the interaction between TyG index and hypertension after multiple imputation. (A) Mediation models of serum 25(OH)D

(<57.464), TyG index, and hypertension: direct effect (TE =0.0458272; *P* <0.001) of TyG index (exposure) toward hypertension (outcome), and 25(OH)D medication proportion is 0.98%; indirect effect (IE =0.0004846; *P* =0.010) of TyG index (exposure) toward 25(OH)D (mediator) and effect hypertension (DE =0.0453426; *P* <0.001), from 25(OH)D (mediator) toward hypertension (outcome). (B) Mediation models of serum 25(OH)D (≥57.464), TyG index, and hypertension: direct effect (TE =0.07687; *P* <0.001) of TyG index (exposure) toward hypertension (outcome), and 25(OH)D medication proportion is -2.0%; indirect effect (IE =-0.00128; *P* =0.002) of TyG index (exposure) toward 25(OH)D (mediator) and effect hypertension (DE =0.07815; *P* <0.001), from 25(OH)D (mediator) toward hypertension (outcome).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HTN, hypertension.

Supplementary Table 1. Characteristics of the study population after multiple interpolation.

Supplementary Table 2. Subgroup analysis of TyG index with prevalence of hypertension.

Supplementary Table 3. Subgroups analysis of serum 25(OH) D with prevalence of hypertension.

Supplementary Table 4. Adjusted ORs for associations between TyG index and prevalence of hypertension after multiple interpolation.

Supplementary Table 5. Adjusted ORs for associations between serum 25(OH)D and prevalence of hypertension after multiple interpolation.

Table 1. Characteristics of the study population.

Variable	Overall (14,099)	Non-Hypertension (8,075)	Hypertension (6,024)	*P*-value
Age, years	47.60 ± 0.26	42.04 ± 0.28	56.74 ± 0.27	<0.001
Sex, %				0.232
Male	7024 (49.8%)	4025 (28.5%)	2999 (21.3%)	
Female	7075 (50.2%)	4050 (28.7%)	3025 (21.5%)	
Race, %				<0.001
Mexican American	2289 (16.2%)	1511 (10.7%)	778 (5.5%)	
Other Hispanic	1070 (7.6%)	670 (4.8%)	400 (2.8%)	
Non-Hispanic White	6916 (49.1%)	3858 (27.4%)	3058 (21.7%)	
Non-Hispanic Black	2690 (19.1%)	1281 (9.1%)	1409 (10.0%)	
Other race	1134 (8.0%)	755 (5.4%)	379 (2.7%)	
Family PIR	3.10 ± 0.03	3.11 ± 0.04	3.08 ± 0.04	0.514
Education level, %				
Less than high school	3274 (23.2%)	1693 (12.0%)	1581 (11.2%)	
High school	1311 (9.3%)	693 (4.9%)	618 (4.4%)	
More than high school	9514 (67.5%)	5689 (40.4%)	3825 (27.1%)	
Marital status, %				<0.001
Having a partner	8757 (62.1%)	5037 (35.7%)	3720 (26.4%)	
No partner	2988 (21.2%)	1269 (9.0%)	1719 (12.2%)	

Unmarried	2354 (16.7%)	1769 (12.5%)	585 (4.1%)	
				<0.001
DM, %				
No	11429 (81.1%)	7310 (51.8%)	4119 (29.2%)	
Yes	2670 (18.9%)	765 (5.4%)	1905 (13.5%)	
				<0.001
Smoker, %				
No	7548 (53.5%)	4575 (32.4%)	2973 (21.1%)	
Former	3693 (26.2%)	1708 (12.1%)	1985 (14.1%)	
Now	2858 (20.3%)	1792 (12.7%)	1066 (7.6%)	
				<0.001
Alcohol user, %				
Never	1825 (12.9%)	967 (6.9%)	858 (6.1%)	
Former	2467 (17.5%)	1100 (7.9%)	1357 (9.6%)	
Mild	4982 (35.3%)	2780 (19.7%)	2202 (15.6%)	
Moderate	2128 (15.1%)	1386 (9.8%)	742 (5.3%)	
Heavy	2697 (19.1%)	1832 (13.0%)	865 (6.1%)	
				<0.001
CHD, %				
No	13502 (95.8%)	7946 (56.4%)	5556 (39.4%)	
Yes	597 (4.2%)	129 (0.9%)	468 (3.3%)	
				<0.001
CHF, %				
No	13690 (97.1%)	8008 (56.8%)	5682 (40.3%)	

Yes	409 (2.9%)	67 (0.5%)	342 (2.4%)	
				<0.001
Angina pectoris, %				
No	13723 (97.3%)	8002 (56.8%)	5721 (40.6%)	
Yes	376 (2.7%)	73 (0.5%)	303 (2.1%)	
				<0.001
Heart attack, %				
No	13490 (95.7%)	7939 (56.3%)	5551 (39.4%)	
Yes	609 (4.3%)	136 (1.0%)	473 (3.4%)	
				<0.001
Stroke, %				
No	13583 (96.3%)	7967 (56.5%)	5616 (39.8%)	
Yes	516 (3.7%)	108 (0.8%)	408 (2.9%)	
				<0.001
Hyperlipidemia, %				
No	3773 (26.8%)	2758 (19.6%)	1015 (7.2%)	
Yes	10326 (73.2%)	5317 (37.7%)	5009 (35.5%)	
				<0.001
CKD, %				
No	11645 (82.6%)	7421 (52.6%)	4224 (30.0%)	
Yes	2454 (17.4%)	654 (4.6%)	1800 (12.8%)	
				<0.001
Work activity, %				

No	7163 (50.8%)	3907 (27.7%)	3256 (23.1%)	
Yes	6936 (49.2%)	4168 (29.6%)	3768 (19.6%)	
Recreational activity, %				<0.001
No	8111 (57.5%)	4199 (29.8%)	3912 (27.7%)	
Yes	5988 (42.5%)	3876 (27.5%)	2112 (15.0%)	
BMI, kg/m^2	28.82 ± 0.09	27.59 ± 0.10	30.86 ± 0.12	<0.001
Waist circumference, cm	98.91 ± 0.22	95.10 ± 0.25	105.19 ± 0.28	<0.001
SBP, mmHg	121.15 ± 0.23	114.37 ± 0.19	132.31 ± 0.35	<0.001
DBP, mmHg	70.38 ± 0.19	68.73 ± 0.19	73.11 ± 0.29	<0.001
Mean energy intake, kcal	2133.37 ± 9.21	2186.76 ± 10.91	2045.48 ± 13.69	<0.001
Mean sodium intake, mg	3506.24 ± 15.32	3557.95 ± 19.38	3421.10 ± 25.37	<0.001
Mean potassium intake, mg	2716.76 ± 15.06	2744.96 ± 18.14	2670.34 ± 19.48	0.001
Sodium, mmol/L	139.25 ± 0.06	139.24 ± 0.06	139.27 ± 0.08	0.630
Potassium, mmol/L	4.05 ± 0.01	4.04 ± 0.01	4.05 ± 0.01	0.425
TyG index	8.62 ± 0.01	8.49 ± 0.01	8.84 ± 0.01	<0.001

Serum 25(OH)D, mmol/L	68.12 ± 0.56	67.56 ± 0.57	69.05 ± 0.73	0.020
Hb, g/dl	14.45 ± 0.03	14.47 ± 0.03	14.41 ± 0.03	0.073
FBG, mg/dl	105.14 ± 0.36	100.26 ± 0.33	113.19 ± 0.68	<0.001
HbA1c, %	5.57 ± 0.01	5.42 ± 0.01	5.83 ± 0.02	<0.001
TC, mg/dl	195.26 ± 0.54	193.72 ± 0.60	197.80 ± 0.81	<0.001
TG, mg/dl	131.06 ± 1.34	119.57 ± 1.63	149.98 ± 2.01	<0.001
HDL-C, mg/dl	54.01 ± 0.21	54.73 ± 0.26	52.82 ± 0.31	<0.001
BUN, mg/dl	13.46 ± 0.07	12.61 ± 0.07	14.86 ± 0.11	<0.001
UA, mg/dl	5.49 ± 0.02	5.26 ± 0.02	5.87 ± 0.02	<0.001
Scr, mg/dl	0.89 ± 0.00	0.86 ± 0.00	0.94 ± 0.01	<0.001
eGFR, mL/min/1.73m^2	94.17 ± 0.33	99.56 ± 0.37	85.30 ± 0.42	<0.001

Abbreviations: family PIR, family poverty income ratio; DM, diabetes mellitus; CHD, coronary heart disease; CHF, Congestive heart failure; CKD, coronary kidney disease; BMI, body mass index; SBP, systolic blood pressure; Diastolic blood pressure, DBP; TyG index, triglyceride-glucose index; Serum 25(OH)D, serum 25-hydroxyvitamin D; Hb, hemoglobin; FBG, fast blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; BUN, blood urea nitrogen; UA, urid acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate.

Table 2. Adjusted ORs for associations between TyG index and prevalence of hypertension.

TyG index	Model 1	Model 2	Model 3
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Q1	Ref.	Ref.	Ref.
Q2	1.314 (1.174, 1.472) ***	1.439 (1.280, 1.616) ***	1.237 (1.089, 1.405) **
Q3	1.689 (1.510, 1.889) ***	1.892 (1.682, 2.128) ***	1.418 (1.232, 1.632) ***
Q4	2.384 (2.131, 2.666) ***	2.427 (2.145, 2.747) ***	1.616 (1.349, 1.935) ***
P for trend	<0.001	<0.001	<0.001

Abbreviations: Q1, 5.646–8.183; Q2, 8.184–8.605; Q3, 8.606–9.052; Q4, 9.053–13.405; TyG, triglyceride-glucose index; ** $P < 0.01$; *** $P < 0.001$; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty income ratio, diabetes mellitus, smoke status, and drink status. Model 3 was adjusted for model 2 variables plus work activity, recreational activity, the history of coronary heart disease, congestive heart failure, angina pectoris, heart attack, stroke, hyperlipoidemia and chronic kidney diseases, body mass index, waist circumference, mean energy intake, mean sodium intake, mean potassium intake, sodium, potassium, hemoglobin, fast blood glucose, glycosylated hemoglobin, total cholesterol, triglyceride, high density lipoprotein-cholesterol, blood urea nitrogen, urid acid, serum creatinine, and estimated glomerular filtration rate.

Table 3. Adjusted ORs for associations between serum 25(OH)D and prevalence of hypertension.

Serum 25(OH)D	Model 1	Model 2	Model 3
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Q1	Ref.	Ref.	Ref.
Q2	0.667 (0.599, 0.743) ***	0.801 (0.715, 0.897) ***	0.961 (0.848, 1.088)
Q3	0.620 (0.556, 0.691) ***	0.783 (0.696, 0.880) ***	0.908 (0.806, 1.023)
Q4	0.637 (0.572, 0.711) ***	0.810 (0.719, 0.913) ***	1.063 (0.934, 1.210)
P for trend	<0.001	0.001	0.223

Abbreviations: Q1, 7.57–44.7 nmol/L; Q2, 44.8–60.8 nmol/L; Q3, 60.9–77.8 nmol/L; Q4, 77.9–232 nmol/L; Serum 25(OH)D, serum 25-hydroxyvitamin D; ***$P < 0.001$; OR, odd ratio; CI, confidence interval. Model 1: age and sex. Model 2: model 1 variables plus race/ethnicity, education level, marital status, family poverty income ratio, diabetes mellitus, smoke status, and drink status. Model 3 was adjusted for model 2 variables plus work activity, recreational activity, the history of coronary heart disease, congestive heart failure, angina pectoris, heart attack, stroke, hyperlipoidemia and chronic kidney diseases, body mass index, waist circumference, mean energy intake, mean sodium intake, mean potassium intake, sodium, potassium, hemoglobin, fast blood glucose, glycosylated hemoglobin, total cholesterol, triglyceride, high density lipoprotein-cholesterol, blood urea nitrogen, urid acid, serum creatinine, and estimated glomerular filtration rate.