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ORIGINAL RESEARCH

Association of Visceral Adiposity with Nephropathy in Patients with Diabetes Mellitus: Data from Chinese and US Cohorts

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Purpose: This study examined the relationship between the visceral adiposity index (VAI) and diabetic nephropathy (DN) in patients with diabetes mellitus in two cohorts from China and the United States.

Patients and Methods: After screening, 1,949 Chinese participants and 7,158 US participants were included in the analysis. Logistic regression models examined the relationship between VAI and DN. Concurrently, the restricted cubic spline (RCS) model was utilized to investigate the potential nonlinear relationship between VAI and DN. Additionally, segmented logistic regression analysis and subgroup analysis were conducted.

Results: In both cohorts, each unit increase in VAI was associated with a higher prevalence of DN, with a 4% increase (OR=1.04, P<0.001) observed in the Chinese cohort compared to a 3% rise (OR=1.03, P<0.001) in the US cohort. The RCS analysis revealed a nonlinear relationship between VAI and DN, with an inflection point identified at 5. The results of the subgroup analyses demonstrated that the positive correlation between VAI and DN was observed across diverse subgroups. However, the interaction between some subgroups indicated the presence of potential heterogeneity.

Conclusion: A significant positive association was observed between visceral adiposity and DN. Further research is required to elucidate the precise mechanisms by which visceral adiposity and DN are associated and to validate these findings in more diverse populations.

Keywords: visceral adiposity index, diabetes mellitus, nephropathy, inflection point

Introduction

Diabetes Mellitus (DM), a global chronic metabolic disease, is becoming an increasingly significant public health concern, posing a substantial threat to human health. As reported by the International Diabetes Federation, the global prevalence of diabetes among individuals aged 20–79 is estimated to be 10.5% (536.6 million individuals) in 2021, with an anticipated rise to 12.2% (783.2 million individuals) by 2045.[1] Diabetic nephropathy (DN) represents one of the most prevalent microvascular complications of diabetes and is the primary cause of end-stage renal disease, exhibiting a high prevalence and mortality rate.[2–5] DN not only places a significant economic and psychological burden on patients and their families but also presents a formidable challenge to the global public health system.[2,3,6]

The visceral adiposity index (VAI) is a comprehensive assessment tool that utilizes anthropometric and blood biochemical indices to quantify the extent of visceral fat accumulation.[7] It was calculated using waist circumference (WC), body mass index (BMI), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). In recent years, there has been a growing interest in the role of VAI in assessing the risk of metabolic diseases.[8–11] In contrast to subcutaneous fat, visceral fat encircles organs within the abdominal cavity and can secrete many inflammatory factors

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and adipokines. These have been identified as pivotal in the pathogenesis of many metabolic disorders through mechanisms that influence insulin sensitivity, lipid metabolism, and inflammatory responses.[12,13] There is an accumulating body of evidence indicating that the accumulation of visceral fat is associated with an increased risk of developing diabetes and its complications.[12,13]

Visceral adipose tissue is considered an active endocrine organ with elevated metabolic activity and the capacity to secrete a diverse array of bioactive substances compared to subcutaneous fat. These bioactive substances include free fatty acids, inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and adipokines such as resistin, leptin, and lipocalin.[14,15] These substances have the potential to influence insulin sensitivity, the inflammatory response, and vascular endothelial function, which are all associated with the development of DN.[14,15]

The visceral fat accumulation has been linked to an increased risk of developing insulin resistance. Visceral adipocytes are capable of secreting substantial quantities of free fatty acids, which enter the liver and can inhibit insulin signaling through multiple pathways, thereby contributing to the development of insulin resistance.[15–17] Insulin resistance represents a fundamental pathophysiologic mechanism of DM and an important risk factor for the development of DN.[18,19] Insulin resistance results in hyperinsulinemia, which may exacerbate kidney injury by increasing intraglomerular pressure and promoting renal hypertrophy.[20,21] Furthermore, chronic insulin resistance may contribute to the development of renal lesions by activating multiple inflammatory and fibrotic signaling pathways.[22–24] Additionally, visceral adipose-associated inflammatory responses play a pivotal role in the pathogenesis of DN. Visceral adipocytes can secrete various inflammatory factors, including TNF-α and IL-6. These factors are not only involved in the systemic inflammatory response but may also act directly on the kidneys, leading to renal tissue damage and dysfunction.[16,22,25] Moreover, the inflammatory response may also exacerbate renal injury by activating oxidative stress pathways.[25] Furthermore, abnormalities in lipid metabolism associated with visceral fat significantly contribute to DN's pathogenesis. The accumulation of visceral fat can result in lipid metabolism disorders, as evidenced by elevated TG levels and reduced HDL-C levels.[13,26] These lipid abnormalities not only elevate the risk of cardiovascular disease but may also facilitate the development and progression of DN by influencing renal hemodynamics and glomerular filtration barrier function.[27–29]

Nevertheless, despite the examination of numerous studies on the relationship between visceral adiposity and diabetes and its complications,[11,30,31] there remain significant unknowns and controversies surrounding the precise mechanisms, influencing factors, and characteristics of the association between visceral adiposity and nephropathy in diabetic patients across diverse populations. For instance, what is the relationship between the cumulative visceral fat and the incidence of DN? It would be beneficial to ascertain whether there are differences in the effects of visceral adiposity on DN among populations with varying genders, ages, lifestyle habits, and metabolic profiles. The elucidation of these issues is crucial for a comprehensive grasp of the etiology of DN, the refinement of risk assessment models, and the formulation of bespoke intervention strategies.

In light of these considerations, this study aimed to examine the relationship between visceral adiposity and nephropathy in diabetic patients and to contrast the characteristics of this relationship in two distinct cohorts in China and the United States. The impact of visceral adiposity on DN and its differences among different populations were assessed by collecting and analyzing the baseline characteristics, visceral adiposity levels, and the prevalence of DN in diabetic patients in the two cohorts. The results of this study are expected to provide important clues and insights for the in-depth exploration of the pathogenesis of DN and its influencing factors.

Materials and Methods

Study Population

The data for this study were obtained from two cohorts: the cohort data from the Changzhou Third People's Hospital from 2018 to 2023 in China, and the National Health and Nutrition Examination Survey (NHANES) cohort from 1999 to 2018 in the United States, which was obtained from a cross-sectional survey conducted by the Centers for Disease Control and Prevention every two years. This study was conducted according to the ethical principles of the Declaration of Helsinki, and the Ethics Committee of the National Center for Health Statistics approved the US NHANES data. The

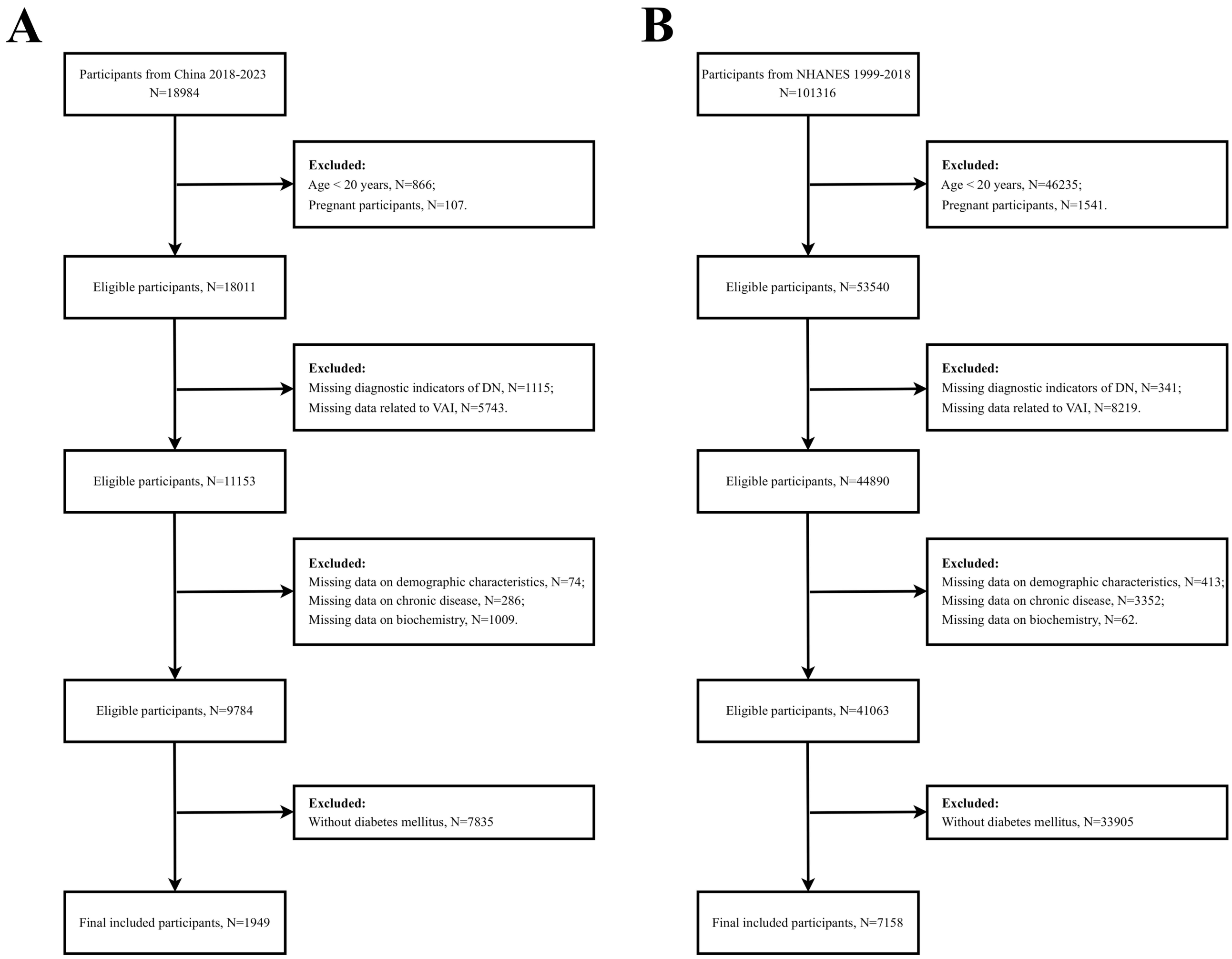

Figure 1 Participant screening flowchart. (**A**) the Chinese cohort; (**B**) the US cohort.

Changzhou Third People's Hospital Ethics Committee approved the Chinese cohort and exempted them from informed consent.

The study initially included 18,984 Chinese participants and 101,316 US participants. To ensure the accuracy and completeness of the study data, a screening process was conducted to exclude the following participants: individuals younger than 20 years of age or in pregnancy, participants lacking data on indicators related to the diagnosis of DN or data on indicators related to the calculation of the VAI, participants with missing demographics, data on chronic diseases, or important biochemical indicators, and non-diabetic patients. After screening, 1,949 Chinese and 7,158 US participants were retained for further analysis (Figure 1).

Disease Assessment

In this study, the definition of DM was based on the following diagnostic criteria: a definitive diagnosis by a healthcare professional; fasting plasma glucose (FPG) ≥ 126 mg/dL; glycosylated hemoglobin (HbA1c) ≥ 6.5%; or the individual is receiving diabetes-related medication or insulin therapy. We selected the urinary albumin to creatinine ratio (UACR) and the estimated glomerular filtration rate (eGFR) to assess renal functional status as core assessment indicators. The eGFR was calculated according to the formula recommended by the Chronic Kidney Disease Epidemiology Collaboration.[32] In diagnosing DN, we adhere to the internationally recognized diagnostic criteria: a UACR of at least 30 mg/g and an eGFR of less than 60 mL/min/1.73 m^2.[33] This approach ensures that the diagnostic results are highly accurate and reliable.

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VAI Assessment

TG and HDL-C measurements were conducted after participants had fasted for a minimum of 8.5 hours to ensure the accuracy and reliability of the results. An automated biochemical analyzer was employed to ensure strict control of the experimental conditions and to guarantee the accuracy of the data. BMI was calculated according to the standard formula: weight (kg) divided by height squared (m^2). Moreover, a scientifically validated formula was used to calculate the VAI and further assess the participants' visceral fat accumulation.[7]

The male participants were calculated using the following formula:

$$VAI = \left(\frac{\mathrm{WC(cm)}}{39.68 + (1.88 \times \mathrm{BMI(kg/m^2)})}\right) \times \left(\frac{\mathrm{TG(mmol/L)}}{1.03}\right) \times \left(\frac{1.31}{\mathrm{HDL-C(mmol}/L)}\right)$$

The female participants were calculated using the following formula:

$$VAI = \left(\frac{\mathrm{WC(cm)}}{36.58 + (1.89 \times \mathrm{BMI(kg/m^2)})}\right) \times \left(\frac{\mathrm{TG(mmol/L)}}{0.81}\right) \times \left(\frac{1.52}{\mathrm{HDL-C(mmol}/L)}\right)$$

Covariate Assessment

The covariates included in this study were as follows: gender (categorized as male or female), age (measured in years), marital status (subdivided into cohabitation and solitude), smoking status (whether or not the subject smoked), drinking habits (whether or not the subject had been drinking alcohol), and a history of chronic medical conditions such as hypertension, obesity, and dyslipidemia. Hypertension was defined as a systolic blood pressure of more than 140 mmHg and/or a diastolic blood pressure of more than 90 mmHg or a participant's self-reported history of physician-diagnosed hypertension or current treatment with prescription medications related to hypertension. Obesity was determined by a BMI of 28 kg/m^2 or greater. Dyslipidemia was defined as the presence of any of the following in participants: total cholesterol (TC) levels ≥200 mg/dL, TG levels ≥150 mg/dL, HDL-C levels <50 mg/dL (women) or <40 mg/dL (men), and low-density lipoprotein cholesterol (LDL-C) levels ≥130 mg/dL.

Statistical Analysis

In this study, the Kolmogorov–Smirnov test was employed to assess the normality of continuous variables. As all continuous variables included in the analysis exhibited a non-normal distribution, the median (and the 25th to 75th percentiles) was employed for statistical description, and the Mann–Whitney *U*-test was utilized to compare differences between groups. Categorical variables were subsequently presented as frequencies and percentages, and the chi-square test was employed to assess the statistical significance of observed differences between groups. To investigate the relationship between VAI and nephropathy in diabetic patients, we developed a logistic regression model and calculated the odds ratio (OR) and its 95% confidence interval (CI). To more accurately assess the association and control for potential confounding variables, we constructed progressively multivariable-adjusted models. Specifically, Model 1 was the unadjusted base model; Model 2 incorporated gender and age as adjustment variables based on Model 1; and Model 3 further adjusted for marital status, smoking status, drinking habits, hypertension, obesity, and dyslipidemia based on Model 2. Furthermore, we employed the restricted cubic spline (RCS) model to investigate the potential nonlinear relationship between VAI and nephropathy in diabetic patients. Based on the inflection point values obtained from the RCS analysis, the data were divided into two intervals, and segmented logistic regression analyses were performed to elucidate further the associations between the predictor variables and the results of each segment. To investigate the relationship between VAI and nephropathy in diabetic patients across different subgroups, we conducted subgroup analyses stratified by gender (male/female), marital status (cohabitation/solitude), smoking status (yes/no), drinking habits (yes/no), hypertension status (yes/no), obesity status (yes/no), and dyslipidemia status (yes/no). Additionally, we performed interaction tests to assess the potential modifying effects of these variables on the association between VAI and nephropathy. All statistical analyses were conducted using R 4.4.0 (R Foundation, http://www.R-project.org) and SPSS 23.0 (IBM Corporation, Armonk, NY, USA) software. The generation of graphical representations was facilitated by the use of GraphPad Prism version 9.0 (GraphPad Software, Inc., USA).

Results

Baseline Characteristics of Diabetic Patients in the Chinese Cohort

A total of 1,949 participants from the Chinese cohort were included in this study, comprising 1,192 patients with non-DN and 757 patients with DN. The gender distribution revealed that 62.1% of the participants were male, and 37.9% were female. There was a slight decrease in the proportion of male patients with DN (58.6% vs 64.4%, P = 0.012). The median age was 51 years, with the DN patients exhibiting a higher age (55 vs 49 years, P < 0.001). No significant differences between DN and non-DN patients were observed in marital status, smoking, or drinking habits (all P values > 0.05). The prevalence of obesity was higher in the non-DN group (39.1% vs 30.3%, P < 0.001), and the distribution of hypertension and dyslipidemia was similar between the two groups (P > 0.05). The data revealed that HbA1c, TG, blood urea nitrogen (BUN), creatinine, and UACR were significantly elevated in the DN group relative to the non-DN group, while BMI, WC, TC, HDL-C, and eGFR were diminished (all P values < 0.05). Furthermore, VAI exhibited a similar trend, demonstrating higher levels in the DN group (P < 0.001) (Table 1).

Table 1 Baseline Characteristics of Participants with Diabetes Mellitus in the Chinese Cohort

Variables	Total (n = 1949)	Non-DN (n = 1192)	DN (n = 757)	*P*
Gender, n (%)				0.012
Male	1211 (62.1)	767 (64.4)	444 (58.6)	
Female	738 (37.9)	425 (35.6)	313 (41.4)	
Age (years)	51.0 (41.0, 61.0)	49.0 (39.0, 58.0)	55.0 (45.0, 64.0)	<0.001
Marital Status, n (%)				0.957
Cohabitation	1281 (65.7)	784 (65.8)	497 (65.6)	
Solitude	668 (34.3)	408 (34.2)	260 (34.4)	
Smoking, n (%)				0.218
Yes	850 (43.6)	533 (44.7)	317 (41.9)	
No	1099 (56.4)	659 (55.3)	440 (58.1)	
Alcohol, n (%)				0.708
Yes	550 (28.2)	340 (28.5)	210 (27.7)	
No	1399 (71.8)	852 (71.5)	547 (72.3)	
Hypertension, n (%)				0.106
Yes	625 (32.1)	366 (30.7)	259 (34.2)	
No	1324 (67.9)	826 (69.3)	498 (65.8)	
Obesity, n (%)				<0.001
Yes	695 (35.7)	466 (39.1)	229 (30.3)	
No	1254 (64.3)	726 (60.9)	528 (69.7)	
Dyslipidemia, n (%)				0.120
Yes	1618 (83.0)	977 (82.0)	641 (84.7)	
No	331 (17.0)	215 (18.0)	116 (15.3)	
BMI (kg/m^2)	26.50 (24.10, 29.20)	26.70 (24.10, 29.50)	26.20 (24.00, 28.60)	0.004
WC (cm)	92.90 (86.20, 100.70)	93.65 (86.40, 102.00)	91.80 (85.70, 98.70)	<0.001
FPG (mg/dL)	149.58 (129.60, 194.40)	149.40 (129.60, 190.89)	151.20 (129.60, 199.80)	0.456
HbA1c (%)	7.90 (7.00, 9.80)	7.80 (6.90, 9.70)	8.10 (7.00, 9.90)	0.013
TC (mg/dL)	187.98 (160.91, 218.93)	189.15 (162.75, 218.25)	186.44 (158.59, 219.70)	0.290
TG (mg/dL)	168.34 (108.98, 272.89)	163.47 (105.43, 262.48)	178.09 (116.07, 298.58)	0.007
HDL-c (mg/dL)	42.13 (35.56, 48.31)	42.90 (35.94, 48.80)	41.36 (34.78, 47.15)	0.002
Uric acid (mg/dL)	5.50 (4.46, 6.64)	5.51 (4.49, 6.60)	5.47 (4.43, 6.68)	0.737
BUN (mg/dL)	14.84 (12.43, 17.64)	14.34 (12.04, 16.80)	15.68 (12.82, 18.76)	<0.001
Creatinine (mg/dL)	0.78 (0.65, 0.94)	0.77 (0.64, 0.92)	0.80 (0.67, 0.98)	<0.001

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 1949)	Non-DN (n = 1192)	DN (n = 757)	*P*
UACR (mg/g)	24.00 (14.00, 35.00)	16.00 (10.00, 22.88)	37.00 (33.00, 68.00)	<0.001
eGFR (mL/min/1.73m^2)	101.24 (87.35, 114.74)	103.18 (91.10, 117.05)	96.03 (79.39, 112.00)	<0.001
VAI	2.79 (1.67, 4.61)	2.63 (1.59, 4.40)	3.08 (1.81, 4.89)	<0.001

Notes: Data are shown as median (25th, 75th percentiles) or percentages, P <0.05 considered statistically significant.
Abbreviations: DN, diabetic nephropathy; BMI, Body mass index; WC, Waist circumference; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; BUN, Blood urea nitrogen; UACR, Urinary albumin/creatinine ratio; eGFR, Estimated glomerular filtration rate; VAI, Visceral adiposity index.

Baseline Characteristics of Diabetic Patients in the US Cohort

A total of 7,158 participants from the US Cohort were included in this study, comprising 4,389 patients with non-DN and 2,769 patients with DN. The gender distribution revealed that 52.9% of the participants were male and 47.1% were female. Notably, a slightly higher percentage of males were diagnosed with DN (54.4% vs 51.9%, P = 0.040). The median age was 62 years, with patients with DN exhibiting a higher age (67 vs 60 years, P < 0.001). Significant differences were observed between the DN and non-DN groups for marital status, smoking, and alcohol consumption (P < 0.01). The prevalence of hypertension was significantly higher in patients with DN (P < 0.001). The prevalence of obesity and dyslipidemia was similar between the two groups (P > 0.05). Biochemical indices, including WC, FPG, HbA1c, TG, uric acid, BUN, creatinine, and UACR, were significantly elevated in the DN group (all P values < 0.05). Conversely, eGFR was significantly reduced. Additionally, there was a notable trend of higher VAI scores in the DN group (P < 0.001) (Table 2).

Table 2 Baseline Characteristics of Participants with Diabetes Mellitus in the US Cohort

Variables	Total (n = 7158)	Non-DN (n = 4389)	DN (n = 2769)	*P*
Gender, n (%)				0.040
Male	3784 (52.9)	2278 (51.9)	1506 (54.4)	
Female	3374 (47.1)	2111 (48.1)	1263 (45.6)	
Age (years)	62.0 (51.0, 71.0)	60.0 (49.0, 67.0)	67.0 (58.0, 76.0)	<0.001
Marital Status, n (%)				<0.001
Cohabitation	4355 (60.8)	2797 (63.7)	1558 (56.3)	
Solitude	2803 (39.2)	1592 (36.3)	1211 (43.7)	
Smoking, n (%)				0.004
Yes	3674 (51.3)	2193 (50.0)	1481 (53.5)	
No	3484 (48.7)	2196 (50.0)	1288 (46.5)	
Alcohol, n (%)				<0.001
Yes	4324 (60.4)	2721 (62.0)	1603 (57.9)	
No	2834 (39.6)	1668 (38.0)	1166 (42.1)	
Hypertension, n (%)				<0.001
Yes	4483 (62.6)	2482 (56.5)	2001 (72.3)	
No	2675 (37.4)	1907 (43.5)	768 (27.7)	
Obesity, n (%)				0.209
Yes	4904 (68.5)	3031 (69.1)	1873 (67.6)	
No	2254 (31.5)	1358 (30.9)	896 (32.4)	
Dyslipidemia, n (%)				0.065
Yes	5401 (75.5)	3279 (74.7)	2122 (76.6)	
No	1757 (24.5)	1110 (25.3)	647 (23.4)	
BMI (kg/m^2)	30.82 (26.98, 35.80)	30.90 (27.09, 35.86)	30.80 (26.80, 35.70)	0.267
WC (cm)	107.00 (97.43, 117.88)	106.40 (97.10, 117.30)	107.60 (98.00, 118.60)	0.006
FPG (mg/dL)	132.00 (107.00, 171.00)	130.00 (106.00, 160.00)	137.00 (110.00, 189.00)	<0.001

(*Continued*)

Table 2 (Continued).

Variables	Total (n = 7158)	Non-DN (n = 4389)	DN (n = 2769)	*P*
HbA1c (%)	6.70 (6.10, 7.80)	6.60 (6.00, 7.60)	6.90 (6.30, 8.30)	<0.001
TC (mg/dL)	185.00 (157.00, 217.00)	186.00 (159.00, 217.00)	182.00 (154.00, 218.00)	0.010
TG (mg/dL)	156.00 (106.00, 236.00)	152.00 (104.00, 229.00)	163.00 (108.00, 246.00)	<0.001
HDL-c (mg/dL)	45.00 (38.00, 55.00)	45.00 (38.00, 55.00)	45.00 (38.00, 56.00)	0.454
Uric acid (mg/dL)	5.60 (4.60, 6.70)	5.40 (4.50, 6.40)	6.00 (4.90, 7.20)	<0.001
BUN (mg/dL)	14.00 (11.00, 19.00)	13.00 (11.00, 16.00)	17.00 (13.00, 23.00)	<0.001
Creatinine (mg/dL)	0.90 (0.72, 1.10)	0.81 (0.70, 0.97)	1.07 (0.81, 1.35)	<0.001
UACR (mg/g)	12.52 (6.57, 39.23)	8.39 (5.45, 13.82)	61.23 (30.13, 182.80)	<0.001
eGFR (mL/min/1.73m^2)	86.07 (66.72, 101.14)	92.15 (79.01, 104.15)	63.77 (49.55, 92.28)	<0.001
VAI	2.52 (1.50, 4.29)	2.45 (1.45, 4.19)	2.63 (1.56, 4.49)	<0.001

Notes: Data are shown as median (25th, 75th percentiles) or percentages, P <0.05 considered statistically significant.
Abbreviations: DN, diabetic nephropathy; BMI, Body mass index; WC, Waist circumference; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; BUN, Blood urea nitrogen; UACR, Urinary albumin/creatinine ratio; eGFR, Estimated glomerular filtration rate; VAI, Visceral adiposity index.

Relationship Between VAI and DN

In both cohorts, the relationship between VAI and DN was examined using three models: an unadjusted model, an adjusted model for gender and age, and a fully adjusted model. The analysis demonstrated a statistically significant positive correlation between VAI and DN. Following multivariate adjustment, the prevalence of DN increased by 4% for every unit increase in VAI in the Chinese cohort (OR=1.04, P<0.001). The third (OR=1.92) and fourth (OR=1.98) quartiles exhibited statistically significant risk gradients (P<0.001 for trend). The US cohort demonstrated a correlation with each unit increase in VAI, corresponding to a 3% rise (OR=1.03, P<0.001). A 37% increase was observed in the highest quartile group compared to the lowest (P<0.001 for trend) (Table 3).

Table 3 Relationship Between VAI and Nephropathy in Patients with Diabetes Mellitus

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
The Chinese cohort						
VAI (continuous)	1.02 (1.01 ~ 1.04)	0.012	1.04 (1.02 ~ 1.06)	<0.001	1.04 (1.02 ~ 1.06)	<0.001
VAI Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.19 (0.91 ~ 1.55)	0.201	1.24 (0.94 ~ 1.62)	0.124	1.31 (0.96 ~ 1.78)	0.089
Quartile 3	1.58 (1.21 ~ 2.04)	<0.001	1.79 (1.36 ~ 2.34)	<0.001	1.92 (1.38 ~ 2.67)	<0.001
Quartile 4	1.49 (1.15 ~ 1.94)	0.003	1.83 (1.39 ~ 2.40)	<0.001	1.98 (1.42 ~ 2.76)	<0.001
P for trend		<0.001		<0.001		<0.001
The US cohort						
VAI (continuous)	1.01 (1.01 ~ 1.02)	0.020	1.03 (1.02 ~ 1.04)	<0.001	1.03 (1.01 ~ 1.04)	<0.001
VAI Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.10 (0.96 ~ 1.26)	0.184	1.10 (0.96 ~ 1.27)	0.174	1.05 (0.90 ~ 1.23)	0.502
Quartile 3	1.16 (1.01 ~ 1.33)	0.031	1.25 (1.08 ~ 1.44)	0.002	1.13 (0.94 ~ 1.34)	0.189
Quartile 4	1.26 (1.10 ~ 1.44)	<0.001	1.51 (1.31 ~ 1.74)	<0.001	1.37 (1.15 ~ 1.64)	<0.001
P for trend		<0.001		<0.001		<0.001

Notes: Model 1: crude Model 2: adjusted for Gender and Age Model 3: adjusted for Gender, Age, Marital Status, Smoking, Alcohol, Hypertension, Obesity, and Dyslipidemia.
Abbreviations: VAI, Visceral adiposity index; OR, Odds ratio; CI, Confidence interval.

RCS Analysis

Figure 2 illustrates the findings of the RCS analyses examining the correlation between VAI and nephropathy in diabetic patients for the Chinese and US cohorts, respectively. All models were adjusted for potential confounding variables, including gender, age, marital status, smoking status, alcohol consumption, hypertension, obesity, and dyslipidemia. The findings indicate a statistically significant positive correlation between VAI and DN in both cohorts. In the Chinese cohort (Figure 2A), the prevalence of nephropathy exhibited a gradual increase with rising VAI levels, showing a highly statistically significant correlation (P < 0.001). This relationship exhibited a nonlinear trend (P-Nonlinear < 0.001), with the inflection point occurring at a VAI value 5. In the US cohort (Figure 2B), the nonlinear relationship between VAI and the proportion of nephropathy was also significant (P-Nonlinear = 0.036), with the inflection point located at a VAI value of 5. Similarly, the prevalence of nephropathy was found to increase significantly with increasing VAI (P < 0.001).

Segmented Logistic Regression Analysis of the Effect of VAI Level on DN

In the Chinese cohort, the segmented logistic regression analysis results indicated a 20% increase in the prevalence of nephropathy for each unit increase in VAI levels below 5 (OR = 1.20, P < 0.001). In contrast, when the VAI level was equal to or greater than 5, there was no statistically significant change in the prevalence of nephropathy for each unit increase (OR = 1.02, P = 0.180). The segmented logistic regression analysis results for the US cohort were comparable to those observed in the Chinese cohort. A 6% increase in the prevalence of nephropathy was observed for each unit increase when the VAI level was less than 5 (OR = 1.06, P = 0.017). In contrast, when the VAI level was greater than or equal to 5, no significant change was noted in the prevalence of nephropathy for each unit increase (OR = 1.00, P = 0.870) (Table 4).

Subgroup Analysis

As illustrated in Figures 3 and 4, subgroup analyses adjusted for confounding variables demonstrated that the trend of positive association between VAI and DN remained robust across most subgroups (all P < 0.05). Interaction analyses revealed statistically significant interactions for specific subgroups in the Chinese cohort. Specifically, drinking status (interaction P = 0.002) and dyslipidemia (interaction P = 0.004) showed statistically significant heterogeneity of effects. In contrast, no significant interactions were observed for the other stratification variables (all P interactions > 0.05).

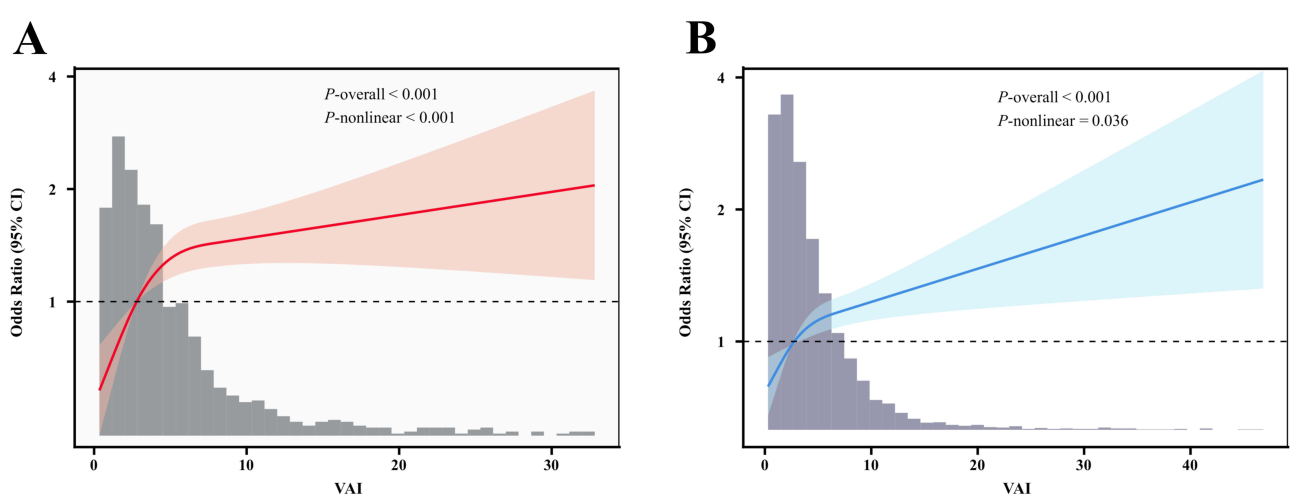

Figure 2 Restricted cubic spline fitting for the association between VAI and nephropathy in patients with diabetes mellitus. (**A**) the Chinese cohort; (**B**) the US cohort. The solid line displays the odds ratio, with the 95% CI represented by shading. The bar graph is a VAI histogram, denoting the distribution of the VAI values. They were adjusted for gender, age, marital status, smoking, alcohol, hypertension, obesity, and dyslipidemia.

Abbreviations: VAI, Visceral adiposity index; CI, Confidence interval.

Table 4 Segmented Logistic Regression Analysis of the Effect of VAI Level on Nephropathy

Variables	OR (95% CI)	*P*
The Chinese cohort		
VAI (< 5)	1.20 (1.09 ~ 1.31)	<0.001
VAI (≥ 5)	1.02 (0.99 ~ 1.04)	0.180
The US cohort		
VAI (< 5)	1.06 (1.01 ~ 1.11)	0.017
VAI (≥ 5)	1.00 (0.99 ~ 1.02)	0.870

Note: ORs were adjusted for Gender, Age, Marital Status, Smoking, Alcohol, Hypertension, Obesity, and Dyslipidemia.
Abbreviations: VAI, Visceral adiposity index; OR, Odds ratio; CI, Confidence interval.

Discussion

This study investigated the correlation between VAI and DN by analyzing data from diabetic patients in Chinese and US cohorts. The findings demonstrated a significant positive correlation between VAI and DN in both cohorts. Specifically, in the Chinese cohort, each unit increase in VAI was associated with a 4% increase in the prevalence of DN, while in the US cohort, this increase was 3%.

The RCS analysis revealed a nonlinear relationship between VAI and DN, with an inflection point identified at 5. This finding provides a new reference point for identifying high-risk groups in clinical practice. A significant increase in nephropathy was observed with each unit increase in VAI levels when the VAI level was less than 5. Conversely, when the VAI level was greater than or equal to 5, the trend of increasing nephropathy prevalence was no longer significant. These findings indicate that prompt intervention may prove more effective in averting the onset and progression of DN when VAI levels are low.

Furthermore, the present study analyzed the relationship between VAI and DN in different subgroups. The results demonstrated that positive correlations between VAI and DN were pervasive across gender, marital status, smoking, alcohol consumption, hypertension, obesity, and dyslipidemia subgroups. However, some of the interactions between subgroups indicated the potential for heterogeneity. For instance, the correlation between VAI and DN was not statistically significant in the non-obese and non-dyslipidemic subgroups in the US cohort. In contrast, in the Chinese cohort, there was an interaction between the drinking and dyslipidemic subgroups. These findings underscore the necessity of conducting studies in diverse populations to enhance comprehension of the association between VAI and DN and to devise tailored prevention strategies for specific populations.

The underlying mechanisms responsible for the observed differences between the two cohorts are attributable to the multifaceted interaction of numerous factors. With regard to metabolic phenotypic heterogeneity, the median VAI of the US cohort was significantly lower than that of the Chinese cohort, despite higher WC levels. This discrepancy may be attributable to the negatively weighted relationship between WC and BMI in the formula used to calculate the VAI (median BMI 30.82 in the US population vs 26.50 kg/m² in the Chinese population). Additionally, the TG/HDL-C moderated the compensatory effect on WC. Furthermore, the presence of co-morbid confounding effects may have exacerbated this discrepancy, with the significantly higher prevalence of hypertension in the US cohort (62.6% vs 32.1%) suggesting that its blood pressure-mediated glomerular hyperfiltration mechanism may have partially masked the direct pathologic effects of visceral fat deposition.[34] Of particular interest is the potential effect of gene-environment interaction, as available evidence suggests that insulin resistance in East Asian populations is more likely to be regulated by visceral fat distribution.[35] In contrast, systemic metabolic disturbances induced by chronic high-fat diets in Western populations may weaken the specific association between visceral adiposity and DN.[36] Furthermore, discrepancies in study design must be considered. The

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Subgroup	N	Adjusted OR (95% CI)	*P* value	*P* for interaction
Overall	1949	1.04 (1.02, 1.06)	<0.001	
Gender				0.272
Male	1211	1.04 (1.02, 1.07)	0.001	
Female	738	1.02 (1.00, 1.05)	0.090	
Marital Status				0.308
Cohabitation	1281	1.03 (1.01, 1.05)	0.017	
Solitude	668	1.05 (1.01, 1.09)	0.006	
Smoking				0.796
Yes	850	1.04 (1.01, 1.07)	0.010	
No	1099	1.03 (1.01, 1.06)	0.013	
Alcohol				0.002
Yes	550	1.10 (1.05, 1.16)	<0.001	
No	1399	1.02 (1.00, 1.04)	0.052	
Hypertension				0.589
Yes	625	1.05 (1.01, 1.10)	0.028	
No	1324	1.03 (1.01, 1.05)	0.004	
Obesity				0.332
Yes	695	1.02 (0.99, 1.05)	0.140	
No	1254	1.05 (1.02, 1.08)	0.001	
Dyslipidemia				0.004
Yes	1618	1.03 (1.01, 1.05)	0.001	
No	331	2.33 (1.38, 3.93)	0.002	

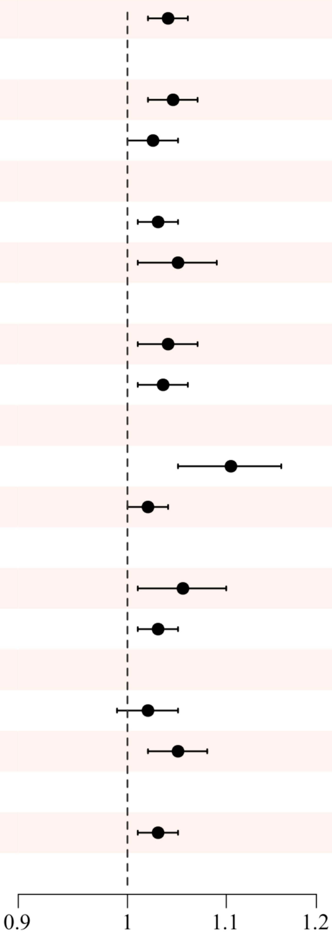

Figure 3 Subgroup analysis of the association between VAI and nephropathy in patients with diabetes mellitus in the Chinese cohort. Adjusted variables: gender, age, marital status, smoking, alcohol, hypertension, obesity, and dyslipidemia. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis.
Abbreviations: VAI, Visceral adiposity index; OR: Odds ratio; CI, Confidence interval.

cross-sectional data from NHANES in the United States exhibited substantial disparities in causal inference validity compared to the single-center retrospective study in China. This discrepancy may be attributable to potential health worker bias, stemming from the concentration of the included population in tertiary care centers. These methodological discrepancies could have further compromised the cross-cohort comparability of the results.

However, it should be noted that the present study has limitations. First, due to the limitations of the cross-sectional design, this paper only describes the nonlinear association between VAI and DN, not the causal time series relationship. Despite the application of logistic regression analysis and multivariate adjustment modeling to control for potential confounding variables, it is acknowledged that observational studies are inherently unable to exclude the influence of unmeasured confounding variables on outcomes. Accordingly, future interventional studies, such as randomized controlled trials, must further elucidate the causal relationship between visceral adiposity and DN. Secondly, some selection bias may still exist despite the relatively large sample size. For instance, the individuals who participated in the NHANES and Changzhou Third People's Hospital cohorts may not fully represent the overall population, particularly about specific population characteristics (eg, age, gender, ethnicity, etc). that may differ. This may result in the study results being less generalizable. It would be beneficial for future studies to consider including a more diverse range of population samples to enhance the representativeness and generalizability of the results. Furthermore, this study employed a formula based on WC, BMI, TG, and HDL-C to assess VAI. Although this formula has been widely validated and is highly correlated with MRI-measured visceral fat, some measurement errors may still exist. For instance, the measurement of WC may be

Subgroup	N		Adjusted OR (95% CI)	*P* value	*P* for interaction
Overall	7158		1.02 (1.01, 1.04)	<0.001	
Gender					0.721
Male	3784		1.02 (1.01, 1.04)	0.010	
Female	3374		1.03 (1.01, 1.05)	0.003	
Marital Status					0.207
Cohabitation	4355		1.01 (1.00, 1.03)	0.013	
Solitude	2803		1.04 (1.02, 1.06)	0.001	
Smoking					0.207
Yes	3674		1.02 (1.01, 1.04)	0.005	
No	3484		1.03 (1.01, 1.05)	0.004	
Alcohol					0.700
Yes	4324		1.02 (1.01, 1.04)	0.008	
No	2834		1.03 (1.01, 1.05)	0.003	
Hypertension					0.263
Yes	4483		1.03 (1.01, 1.05)	0.001	
No	2675		1.02 (1.00, 1.04)	0.013	
Obesity					0.488
Yes	4904		1.02 (1.01, 1.04)	0.001	
No	2254		1.02 (1.00, 1.04)	0.051	
Dyslipidemia					0.371
Yes	5401		1.02 (1.01, 1.04)	<0.001	
No	1757		1.05 (0.85, 1.30)	0.662	

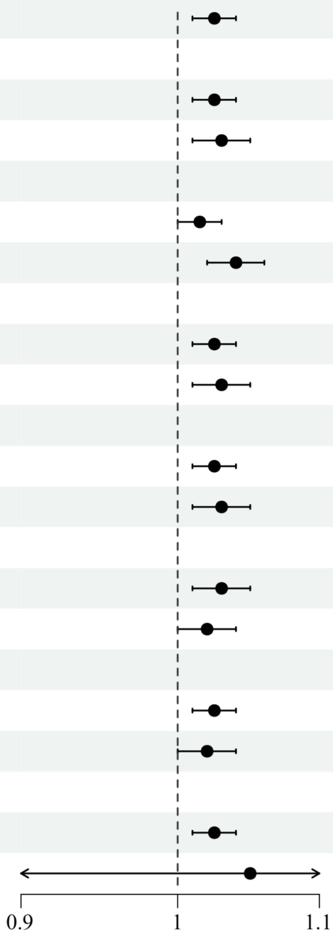

Figure 4 Subgroup analysis of the association between VAI and nephropathy in patients with diabetes mellitus in the US cohort. Adjusted variables: gender, age, marital status, smoking, alcohol, hypertension, obesity, and dyslipidemia. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis.

Abbreviations: VAI, Visceral adiposity index; OR: Odds ratio; CI: Confidence interval.

influenced by many factors, including individual body size and respiratory status. Additionally, BMI, as a marker of obesity, may not accurately reflect the distribution and composition of visceral fat. It would be beneficial for future studies to consider utilizing more precise visceral fat measurement techniques, such as computed tomography or magnetic resonance imaging, to gain a more accurate understanding of the relationship between visceral adiposity and DN. Moreover, due to limitations in the available data, this study did not differentiate between type 1 and type 2 diabetes mellitus. Therefore, future studies must be further validated to determine the specific type of diabetes mellitus. Furthermore, in examining the underlying mechanisms of the relationship between visceral adiposity and DN, this study primarily relied on existing literature reviews and theoretical assumptions rather than direct validation through biological experimentation. Consequently, the explanations of these mechanisms remain somewhat hypothetical and uncertain. Future studies should conduct additional biological experiments and mechanism studies to understand better the specific mechanisms underlying the association between visceral adiposity and DN.

Conclusion

Higher levels of VAI (which reflect abnormal accumulation of visceral fat) were significantly associated with the prevalence of DN by a mechanism that may be related to the pathologic processes of insulin resistance and chronic inflammation. However, the disease-predictive efficacy of VAI may be significantly influenced by race-specific metabolic characteristics and the type of study design. Consequently, future validation of this study's findings in prospective multiracial cohorts is warranted.

Data Sharing Statement

The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/). The Chinese cohort data utilized and analyzed in the present study are accessible from the corresponding author upon justified request.

Institutional Review Board Statement

The studies involving humans in US cohort were approved by the National Center for Health Statistics Ethics Review Board. The participants provided their written informed consent to participate in this study. As NHANES is a publicly accessible database, the Changzhou Third People's Hospital Ethics Committee granted approval to waive ethical review and approved the study protocol (02A-A2024018). The Changzhou Third People's Hospital Ethics Committee approved the Chinese cohort study (02A-A20230023).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this study.

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