BMC Public Health

RESEARCH

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The association between visceral adiposity index and long-term all-cause mortality shows age-related disparities: a nationwide cohort study

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Abstract

Background The prevalence of obesity has increased rapidly worldwide over the past few decades and remains a recognized public health concern. However, studies exploring visceral adiposity index (VAI), a sex-specific indicator reflecting visceral fat distribution and function, and long-term mortality are limited. This study aimed to investigate the association of VAI with long-term all-cause mortality among general adults in the United States.

Methods This cohort study used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2018. Participants were linked to National Death Index mortality data through December 31, 2019. Weighted Cox proportional hazards regression model was used to calculate hazard ratios (HRs) and 95% CIs, and restricted cubic spline (RCS) was also conducted.

Results A total of 21,943 US adults (weighted mean age, 46.9 years; 10,921 males [weighted, 49.1%]) were included. During 211,473 person-years of follow-up (median follow-up: 9.3 years), 3326 total deaths occurred. After multivariable adjustments, compared with the 3rd quintile (Q3) of VAI, participants in the 2nd (Q2) and 5th (Q5) quintiles were at a significantly higher risk of all-cause mortality (HR 1.16 [95% CI, 1.00-1.34] and HR 1.15 [95% CI, 1.01–1.31], respectively). RCS revealed a U-shaped relationship of $\log_2$-transformed VAI to all-cause mortality (*P* for nonlinearity < 0.001), with an inflection point of 0.824. Subgroup analysis indicated that there was a significant interaction of VAI with age on all-cause mortality (*P* for interaction = 0.005). Higher VAI levels were associated with higher all-cause mortality in younger adults (Q5 vs. Q3, HR 1.56 [95% CI, 1.12–2.18], *P* = 0.009) rather than older adults (Q5 vs. Q3, HR 1.05 [95% CI, 0.91–1.22], *P* = 0.497).

Conclusions In the nationally representative cohort of US adults, VAI was nonlinearly associated with long-term all-cause mortality and the association showed age-related disparities. A higher VAI was related to a higher mortality risk in younger adults. These findings underscore the importance of appropriate VAI for long-term health outcomes, especially for young adults.

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Keywords Visceral adiposity index, Mortality, Nonlinear, Epidemiology, National Health and Nutrition Examination Survey

Introduction

The prevalence of overweight and obesity has increased rapidly worldwide over the past few decades and remains a recognized public health concern [1]. In Western countries, overweight/obesity has reached epidemic proportions and is the second leading cause of preventable death [2]. It is estimated that about 70% of US adults are classified as overweight or obese, and approximately 19% of children are obese [3]. More than a third of US adults aged ≥ 65 years were obese in 2007–2010 and the number is expected to more than double from 40.2 million to 88.5 million by 2050 [4]. In addition, according to the *World Obesity Atlas 2023*, the prevalence of obesity is anticipated to rise to 24% of the population aged over 5 years and affects nearly 2 billion adults, children and adolescents by 2035, posing an enormous socioeconomic and health threat [5]. Although the etiology of obesity has been hotly debated, which involves biological, psychosocial, socioeconomic, and environmental factors, abundant evidence has uncovered that obesity is an essential and independent risk factor for multiple noninfectious chronic diseases, such as hypertension [6], cardiovascular disease (CVD) [1], cancers [7] and diabetes [8].

Given the substantial burden of obesity, there are several well-established indicators for assessing obesity, including those reflecting overall obesity and different fat distribution. In clinical practice, the most frequently used measure of obesity is body mass index (BMI), defined as weight in kilograms divided by height in meter squared (kg/m^2). Numerous studies have shown a J-shaped association between BMI and risk of morbidity/mortality, that is, very low BMI is also associated with increased mortality [9, 10]. This epidemiological phenomenon of better prognosis among overweight and class I obesity individuals is known as the "obesity paradox" [11]. Although overall obesity is closely related to health, there may be differences in fat distribution with different metabolic risks under the same BMI. Waist circumference (WC) and waist-to-hip ratio (WHR) can reflect fat distribution and thus provide more information beyond BMI. Some organizations and expert panels have recommended that WC should be assessed alongside BMI in clinical evaluation of obesity owing to growing evidence supporting visceral obesity as a marker of cardiovascular risk [1]. Similarly, WHR has been shown to predict cardiovascular mortality independent of BMI [12] and to provide more higher prognostic value than BMI on the likelihood of elevated coronary artery calcification (CAC) [13].

However, indicators such as BMI, WC and WHR only consider anthropometric parameters, but not metabolic parameters. Amato et al. established a sex-specific indicator, the visceral adiposity index (VAI), to indirectly reflect visceral fat distribution and function and found that VAI was superior to BMI and WC in assessing cardiometabolic risk [14]. Several previous studies have also shown positive associations between VAI and blood pressure [15], fasting glucose [16], and insulin resistance [17]. However, studies exploring VAI and long-term mortality have been limited, and the results of some studies are inconsistent [18, 19]. Therefore, further cohort studies with large samples and long follow-up are warranted.

In the present study, based on a nationally representative cohort of US general adults, we aimed to evaluate the association between VAI and long-term all-cause mortality and to assess the optimal VAI value associated with the lowest risk of all-cause mortality if the dose-response relationship was nonlinear.

Methods

Study population and design

All data used in this study originated from the National Health and Nutrition Examination Survey (NHANES), a nationally representative program conducted by the National Center for Health Statistics (NCHS). NHANES is a complex, stratified and multistage probability sample to reflect the civilian non-institutionalized resident population information [20]. The detailed descriptions are publicly available from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx). NHANES protocols were approved by the NCHS Research Ethics Review Board before the survey (https://www.cdc.gov/nchs/nhanes/irba98.htm) and each participant provided written informed consent.

For the present analysis, we integrated 10 cycles (20 years) of data from continuous NHANES cohort (1999–2018). Among the 101,316 participants in the total sample, 31,175 participants had VAI data. Participants without mortality data or < 18 years old ($N = 6,871$) were further excluded. We also excluded participants who were pregnant ($N = 701$) or without data on CVD ($N = 1660$) at baseline [21]. Ultimately, a total of 21,943 US adults were included for analysis (Fig. 1).

Definition of VAI

The calculation of VAI included both anthropometric parameters (BMI and WC) and metabolic parameters (triglyceride [TG] and high-density lipoprotein cholesterol [HDL-C]). The calculation formula is as follows: VAI

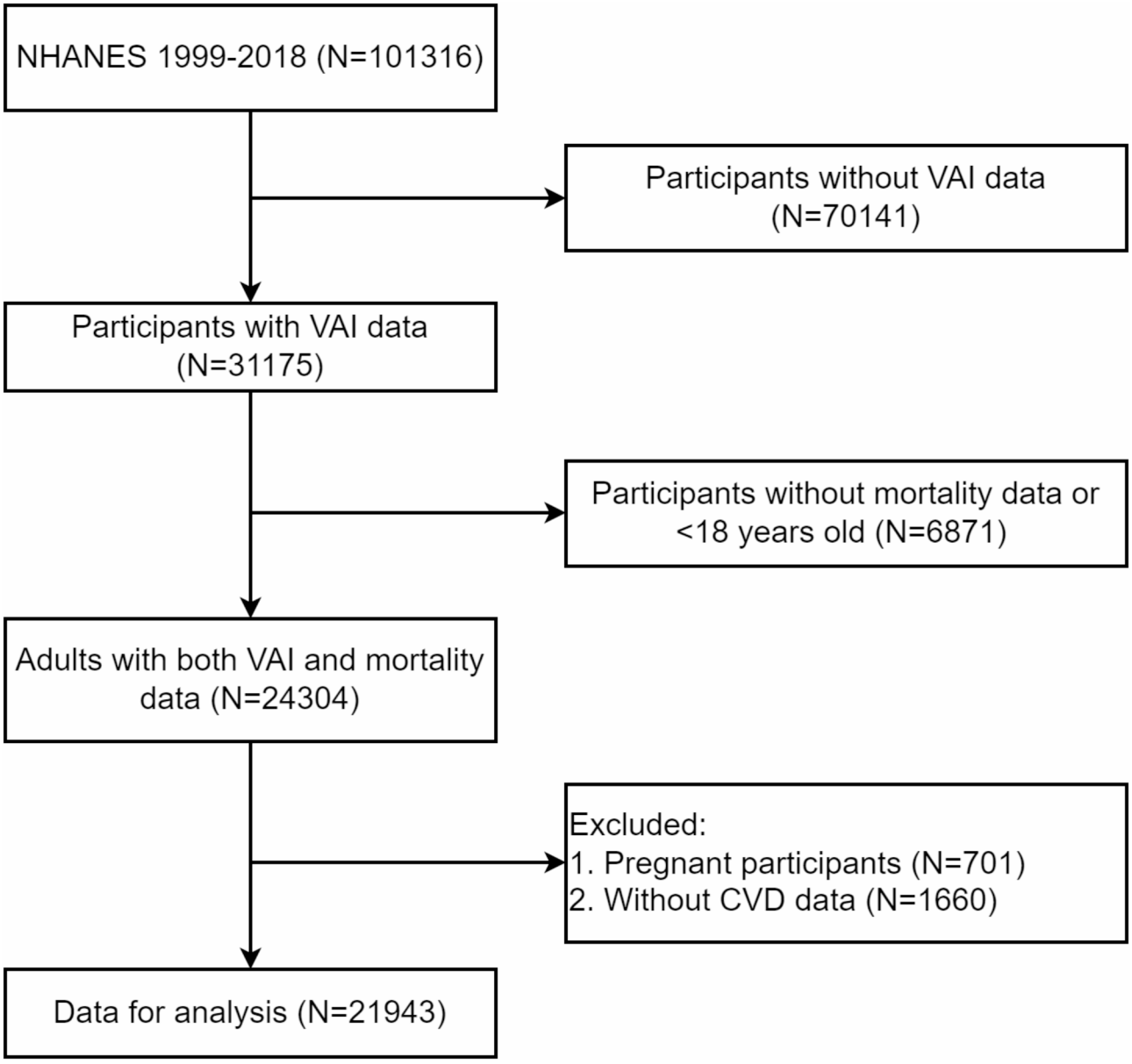

Fig. 1 Flow chart of the study. NHANES, National Health and Nutrition Examination Survey; VAI, visceral adiposity index; CVD, cardiovascular disease

= [WC (cm)/(39.68 + (1.88×BMI)] × [TG (mmol/L)/1.03] × [1.31/HDL-C (mmol/L)] for men; and VAI = [WC (cm)/(36.58 + (1.89×BMI)] × [TG (mmol/L)/0.81] × [1.52/HDL-C (mmol/L)] for women [14, 22, 23]. In NHANES, TG and HDL-C were detected by standardized assays in mobile examination centers. Detailed laboratory procedures for the collection and processing of blood specimens have been described elsewhere [24] and can also be available from NHANES laboratory data files (https://www.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Laboratory%26CycleBeginYear=2017).

Assessment of covariates

Demographic information in this study, including age, gender, race, education level and family income to poverty ratio and medical history information, including hypertension, diabetes and CVD, as well as lifestyle information, including smoking status and alcohol intake, were obtained via standardized interviews or questionnaires. Laboratory tests, including TG and HDL-C, were determined in NHANES mobile examination centers.

Hypertension was defined as the systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, self-reported history of hypertension or taking antihypertensive medications [25]. Diabetes was defined as the fasting plasma glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%

(48 mmol/mol), 2 h glucose in Oral Glucose Tolerance Test (OGTT) ≥ 200 mg/dL, self-reported history of diabetes or taking anti-hyperglycemic medications [26]. In NAHNES, CVD was a composite event of congestive heart failure, coronary heart disease, angina pectoris, heart attack and stroke [27]. Smoking status was categorized as never, former or current smokers according to whether an individual had smoked > 100 cigarettes in their lifetime and/or still smoked at the time of the survey [20]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [28].

Ascertainment of mortality

Mortality data was ascertained using NHANES Mortality File linked to the National Death Index through December 31, 2019. This approach has been described in previous studies and is generally accepted [20, 21, 29]. The outcome in the present study was mortality from all causes. Follow-up time was calculated from the day of standard biochemical measurement to the death date or December 31, 2019, whichever occurred first.

Statistical analysis

According to NHANES analytic guidelines, sample weights, strata, and clustering should be included in the statistical analysis to produce accurately nationally representative estimates [30]. Descriptive statistics for continuous variables were expressed as weighted mean (standard error [SE]) or weighted median (25th percentile, 75th percentile) as appropriate. Descriptive statistics for categorical variables were represented by weighted percentages (SE). SE was obtained using the Taylor series linearization.

Quintiles of VAI levels were determined based on the distribution in the study population. Besides, since VAI had a positive skewed distribution and extreme values, $\log_2$-transformation was also performed to improve the normality of the data [31]. The weighted multivariable Cox proportional hazards regression model was conducted to assess the hazard ratios (HRs) and 95% CIs. Model 1 was the unadjusted model. Model 2 was adjusted for age (continuous), gender (male or female) and race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race). Model 3 was the same as Model 2 with additional adjustments for education level (< 9th grade, 9-11th grade, high school, college, or graduate or above), family income to poverty ratio (continuous), hypertension (yes or no), diabetes (yes or no), smoking status (never, former, or current smoker), drinking status (yes or no), eGFR (continuous) and CVD (yes or no). To minimize the loss of sample size owing to the missing covariates, multiple imputation by chained equations was performed [32]. The associations of the quintiles of VAI with mortality were examined using the third quintile (Q3) as the reference group as Q3 was associated with the lowest risk of all-cause mortality based on the Cox regression model. Furthermore, to explore the dose-response relationship between VAI and mortality, restricted cubic spline (RCS) regression with 3 default knots at the 10th, 50th and 90th percentiles of VAI was conducted for visualization [27]. The nonlinearity was obtained using the likelihood ratio test. Next, a piecewise Cox regressions was employed to assess all-cause mortality below and above the inflection points identified by RCS with $\log_2$-transformed VAI as a continuous variable.

Subgroup analyses were also performed with multivariable adjustments (Model 3, fully-adjusted model) based on participants' age, gender, diabetes, CVD, smoking status, BMI and eGFR at baseline, under the premise of a significant interaction effect. Interaction tests were conducted by adding multiplicative interaction terms in the multivariable models. A significant "*P* for interaction" in the subgroup analysis indicated that the effect of VAI on mortality varied depending on the variable that divided the participants' subgroups. To account for multiplicity in the subgroup analyses, Bonferroni-corrected *P* values were used for multiple testing and the significance level $P = 0.05$ was divided by seven, i.e., 0.007.

In addition, a series of sensitivity analyses were also conducted to assess the robustness of our results. First, to exclude the potential effect of multiple imputation, we re-performed the Cox regression analysis without multiple imputation. Second, we used a directed acyclic graph (DAG) for identifying potential confounders to guide the modeling strategy [33]. Third, we excluded participants who died during the first 2 years of follow-up ($n = 421$) to reduce the potential reverse causation bias [21]. Fourth, we further included BMI or WC in the regression model (Model 3) respectively to explore whether the relationship between VAI and mortality was influenced by BMI or WC. In addition, we also plotted the receiver operating characteristic (ROC) curves and compared the area under the curve (AUC) of VAI ($\log_2$-transformed), BMI, and WC at 9.3 years (median follow-up in this study) to evaluate the predictive performance of VAI for all-cause mortality compared to BMI and WC. Fifth, to assess whether the association between VAI and all-cause mortality was consistent among participants with and without unhealthy lifestyle habits such as smoking and alcohol drinking and chronic medical history such as CVD, we also plotted RCS curves excluding participants with smoking, alcohol drinking, and history of CVD, respectively. Sixth, considering the long follow-up time, we excluded participants with more than 10 years of follow-up ($n = 9872$) and re-performed the statistical analysis only in participants with less than 10 years of follow-up. Finally, to reduce the impact of extreme values,

participants with extreme values (> 95%, or < 5%) of VAI were excluded.

Statistical analysis in the present study considered the complex design of NHANES and was performed using Stata 16.0 (StataCorp LLC, College Station, TX) and R 4.2.3. There was no evidence for violation of the proportional hazards assumption for VAI and mortality (using *estat phtest* command in Stata). A *P* value (two-tailed) < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study

A comparison of the characteristics of participants with and without multiple imputation is shown in Supplementary Table S1 (see Additional file 1). All variables showed no significant difference before and after imputation (all $P > 0.05$), suggesting that imputation did not significantly affect the values of the variables.

A total of 21,943 participants, representing 205.1 million US non-institutionalized adults, were included, and 49.1% of them were males. The mean age of the study participants was 46.9 years. During 211,473 person-years of follow-up (median follow-up, 9.3 years; maximum follow-up, 20.8 years), 3326 total deaths occurred. Participants with higher VAI levels were more likely to be older, non-Hispanic White, less educated, poorer and had a higher proportion of hypertension, diabetes and CVD (all $P < 0.05$). Besides, these participants also showed higher BMI, WC and TG levels as well as lower HDL-C and eGFR levels (all $P < 0.05$). The detailed baseline characteristics of the participants are summarized in Table 1.

Table 1 Baseline characteristics of the study population, according to quintiles of visceral adiposity index[a]

Characteristic	Overall (*n* = 21943)	Quintiles of visceral adiposity index					
		Q1 (*n* = 4388)	Q2 (*n* = 4389)	Q3 (*n* = 4389)	Q4 (*n* = 4389)	Q5 (*n* = 4388)	*P* value
Age, yrs	46.9 (0.2)	43.5 (0.4)	45.8 (0.4)	47.1 (0.4)	49.0 (0.3)	49.5 (0.3)	< 0.001
Gender, %							0.015
Male	49.1 (0.3)	51.9 (0.9)	48.0 (1.0)	47.2 (1.0)	49.1 (0.9)	49.1 (1.0)	
Female	50.9 (0.3)	48.1 (0.9)	52.0 (1.0)	52.8 (1.0)	50.9 (0.9)	50.9 (1.0)	
Race, %							< 0.001
Mexican American	8.2 (0.5)	6.2 (0.6)	7.0 (0.6)	8.8 (0.7)	9.4 (0.7)	9.6 (0.7)	
Other Hispanic	5.5 (0.5)	4.6 (0.5)	5.3 (0.6)	5.6 (0.5)	6.3 (0.7)	6.0 (0.8)	
Non-Hispanic White	68.6 (1.0)	64.7 (1.3)	67.3 (1.3)	68.6 (1.3)	69.8 (1.3)	73.1 (1.3)	
Non-Hispanic Black	10.9 (0.6)	17.2 (1.0)	13.8 (0.8)	10.0 (0.6)	7.6 (0.5)	5.2 (0.4)	
Other Race	6.8 (0.3)	7.3 (0.6)	6.6 (0.6)	7.0 (0.5)	6.9 (0.5)	6.1 (0.5)	
Education level, %							< 0.001
Less than 9th grade	6.0 (0.3)	3.7 (0.4)	4.9 (0.3)	6.0 (0.4)	7.6 (0.5)	8.0 (0.5)	
9-11th grade	11.3 (0.4)	8.6 (0.5)	10.0 (0.6)	11.7 (0.7)	12.3 (0.7)	14.2 (0.6)	
High school	24.1 (0.5)	20.1 (0.9)	24.4 (0.9)	24.0 (0.9)	25.1 (1.0)	27.2 (1.2)	
College	30.8 (0.5)	30.2 (1.0)	31.1 (0.9)	31.7 (1.0)	30.1 (1.0)	30.9 (1.0)	
Graduate or above	27.8 (0.8)	37.4 (1.4)	29.6 (1.2)	26.6 (1.2)	24.9 (1.2)	19.7 (1.0)	
Hypertension, %	36.7 (0.5)	24.7 (0.9)	31.4 (1.0)	36.4 (1.1)	42.4 (1.1)	49.7 (1.0)	< 0.001
Diabetes, %	14.0 (0.4)	6.1 (0.4)	8.7 (0.5)	12.9 (0.6)	17.3 (0.8)	25.6 (0.9)	< 0.001
Smoker, %							< 0.001
Never	53.3 (0.6)	59.9 (1.1)	56.3 (1.1)	53.1 (1.1)	51.6 (1.2)	44.8 (1.1)	
Former	25.4 (0.5)	22.9 (0.9)	24.4 (1.0)	26.0 (1.0)	25.3 (1.0)	28.7 (0.9)	
Current	21.3 (0.5)	17.2 (0.8)	19.3 (0.8)	20.9 (0.9)	23.1 (0.9)	26.5 (0.8)	
Alcohol user, %	77.4 (0.6)	82.0 (0.8)	78.7 (0.9)	76.4 (1.1)	76.3 (1.1)	73.5 (1.1)	< 0.001
CVD, %	8.2 (0.3)	5.0 (0.4)	6.4 (0.4)	8.3 (0.6)	10.1 (0.6)	11.7 (0.6)	< 0.001
Income to poverty ratio	2.98 (0.03)	3.17 (0.04)	3.05 (0.04)	2.97 (0.04)	2.90 (0.04)	2.81 (0.04)	< 0.001
eGFR, mL/min/1.73m^2	95.94 (0.31)	99.84 (0.47)	96.83 (0.48)	95.77 (0.51)	93.97 (0.47)	92.98 (0.46)	< 0.001
BMI, kg/m^2	28.71 (0.08)	25.38 (0.12)	27.35 (0.14)	29.00 (0.13)	30.54 (0.16)	31.59 (0.13)	< 0.001
WC, cm	98.38 (0.21)	88.73 (0.30)	94.34 (0.37)	99.20 (0.32)	103.50 (0.37)	106.95 (0.32)	< 0.001
TG, mmol/L	1.19 (0.82, 1.75)	0.62 (0.50, 0.73)	0.91 (0.78, 1.05)	1.20 (1.04, 1.37)	1.61 (1.39, 1.85)	2.54 (2.11, 3.30)	< 0.001
HDL-C, mmol/L	1.39 (0.01)	1.79 (0.01)	1.51 (0.01)	1.35 (0.01)	1.21 (0.01)	1.03 (0.01)	< 0.001
VAI	1.46 (0.89, 2.48)	0.59 (0.46, 0.71)	1.01 (0.91, 1.12)	1.49 (1.36, 1.65)	2.27 (2.03, 2.53)	4.10 (3.37, 5.53)	< 0.001

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; WC, waist circumference; TG, triglycerides; HDL-C, High-density lipoprotein cholesterol; VAI, visceral adiposity index

[a] Data were presented as weighted mean (SE) or weighted median (25th percentile, 75th percentile) for continuous variables as appropriate and weighted percentages (SE) for categorical variables

Table 2 Association of VAI with all-cause mortality in NHANES 1999–2018

Outcome	Quintiles of VAI, adjusted HR (95% CI)				
	Q1	Q2	Q3	Q4	Q5
	≤ 0.803	0.803–1.232	1.232–1.827	1.827–2.862	> 2.862
Total No.[a]	4388	4389	4389	4389	4388
Deaths No.[a]	428	601	671	756	870
Model 1	0.73 (0.62, 0.85) ***	0.94 (0.80, 1.10)	1 [Reference]	1.20 (1.03, 1.40) *	1.39 (1.22, 1.59) ***
Model 2	0.95 (0.81, 1.12)	1.04 (0.91, 1.20)	1 [Reference]	1.12 (0.97, 1.29)	1.36 (1.20, 1.54) ***
Model 3	1.14 (0.96, 1.34)	1.16 (1.00, 1.34) *	1 [Reference]	1.04 (0.90, 1.21)	1.15 (1.01, 1.31) *

Abbreviations: VAI, visceral adiposity index; HR, hazard ratio; CI, confidence interval

[a] Unweighted No

Model 1: unadjusted model. Model 2: adjusted for age (continuous), gender (male or female) and race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race). Model 3: adjusted for Model 2 plus education level (< 9th grade, 9-11th grade, high school, college, or graduate or above), family income to poverty ratio (continuous), hypertension (yes or no), diabetes (yes or no), smoking status (never smoker, former smoker, or current smoker), drinking status (yes or no), eGFR (continuous) and CVD (yes or no)

* $P < 0.05$, *** $P < 0.001$

Association of VAI with all-cause mortality

Participants were divided into five groups by quintiles of VAI: Q1 ≤ 0.803 ($n = 4388$), 0.803 < Q2 ≤ 1.232 ($n = 4389$), 1.232 < Q3 ≤ 1.827 ($n = 4389$), 1.827 < Q4 ≤ 2.862 ($n = 4389$), Q5 > 2.862 ($n = 4388$). Multivariable Cox regression analysis showed that participants in the third quintile (Q3) had the lowest HR values in the fully-adjusted model (Model 3), so Q3 was used as the reference group. Compared with Q3, the HRs with 95% CIs for all-cause mortality across the quintiles were 1.14 (0.96, 1.34), 1.16 (1.00, 1.34), 1.04 (0.90, 1.21) and 1.15 (1.01, 1.31) in the fully-adjusted model, suggesting that the association of VAI with all-cause mortality was nonlinear (Table 2).

In addition, RCS plot was consistent with the above results and revealed that the association of $\log_2$-transformed VAI with all-cause mortality was nonlinear (U-shaped) (P for nonlinearity < 0.001), with the inflection point of 0.824,, equivalent to a VAI of 1.770 (Fig. 2). Then we used 2-piecewise Cox regression analysis with a $\log_2$-transformed VAI of 0.824 as the inflection point (Additional file 1: Supplementary Table S2). The results showed that, consistent with the cubic splines, when VAI was below the inflection point, each 1-fold increase in VAI was significantly associated with a 14% decrease (HR 0.86 [95% CI, 0.77–0.96], $P = 0.007$) in all-cause mortality.

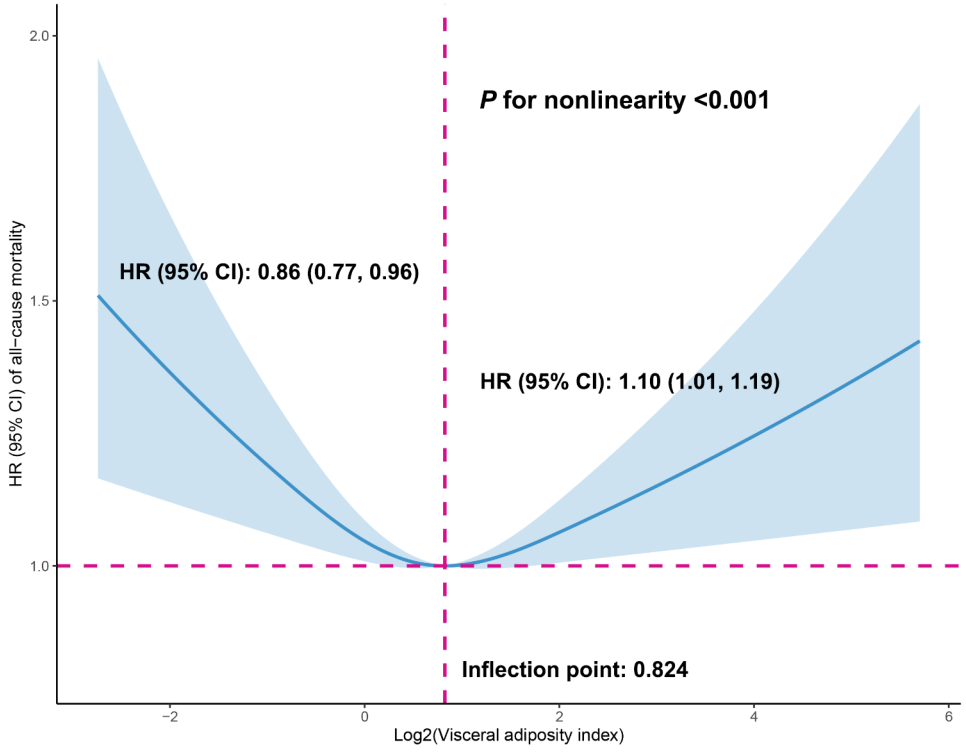

Fig. 2 Hazard ratios (95% CIs) of $\log_2$-transformed VAI with all-cause mortality in all analytical participants. Analysis was adjusted for age (continuous), gender (male or female), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race), education level (< 9th grade, 9-11th grade, high school, college, or graduate or above), family income to poverty ratio (continuous), hypertension (yes or no), diabetes (yes or no), smoking status (never, former, or current smoker), drinking status (yes or no), eGFR (continuous) and CVD (yes or no) (Model 3)

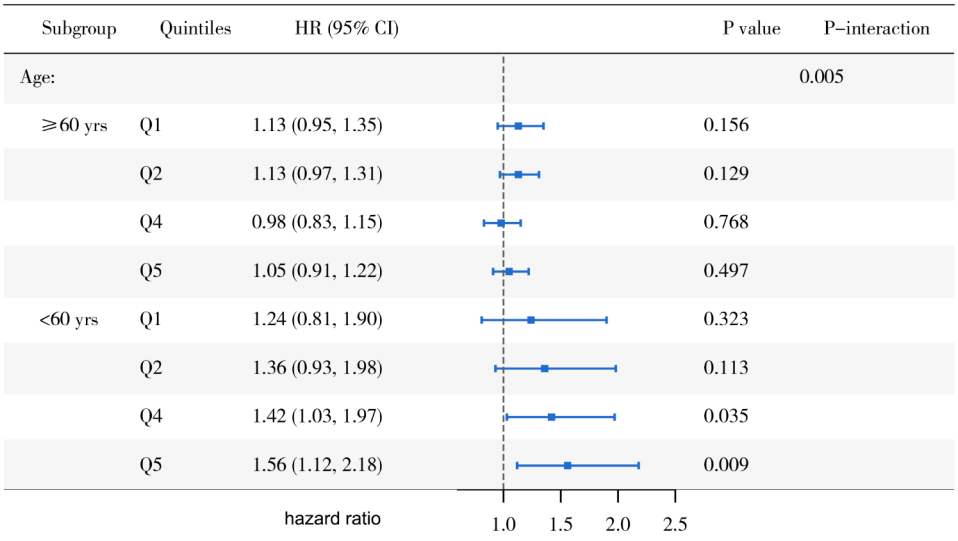

Fig. 3 Subgroup analysis for the association of VAI with all-cause mortality. Analysis was adjusted for age (continuous), gender (male or female), race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, or other race), education level (< 9th grade, 9-11th grade, high school, college, or graduate or above), family income to poverty ratio (continuous), hypertension (yes or no), diabetes (yes or no), smoking status (never, former, or current smoker), drinking status (yes or no), eGFR (continuous) and CVD (yes or no) (Model 3) when they were not the strata variables

However, each 1-fold increase in VAI was associated with a 10% increase (HR 1.10 [95% CI, 1.01–1.19], $P = 0.029$) in all-cause mortality when VAI exceeded the inflection point.

Subgroup analysis stratified by age group

Interaction tests revealed that only the age group (older adults [≥ 60 years], or younger adults [< 60 years]) had a significant interaction with VAI on all-cause mortality (P for interaction = 0.005). Thus, subgroup analysis for the association of VAI with all-cause mortality stratified by age (≥ 60 or < 60 years) were further performed and illustrated in Fig. 3. Compared with participants in Q3, participants in Q4 and Q5 had a significantly higher risk of all-cause mortality among younger (aged < 60 years) adults (HR 1.42 [95% CI, 1.03–1.97], $P = 0.035$ and 1.56 [95% CI, 1.12–2.18], $P = 0.009$, respectively), rather than older (aged over 60 years) adults (HR 0.98 [95% CI, 0.83–1.15], $P = 0.768$ h 1.05 [95% CI, 0.91–1.22], $P = 0.497$, respectively), suggesting an age-related disparity in the relationship between VAI and all-cause mortality.

Sensitivity analyses

In the sensitivity analyses, we first re-performed the statistical analysis using data without covariates multiple imputation, and the association between VAI and all-cause mortality remained unchanged (Additional file 1: Supplementary Table S3). Second, we used the DAG method to re-select covariates and determined 6 covariates that were further included in the regression models, including age, gender, race, diabetes, smoking status and drinking status (Supplementary Fig. S1). The results still did not change (Supplementary Table S4). After excluding participants who died within the first 2 years of follow-up, VAI was also nonlinearly related to all-cause mortality (Supplementary Table S5). The same occurred when we further adjusted BMI or WC in the regression model (Supplementary Table S6), indicating that the relationship between VAI and all-cause mortality was independent of BMI or WC. Besides, after multivariable adjustments (model 3), the AUC values of VAI, BMI and WC at 9.3 years (median follow-up) were similar (VAI vs. BMI vs. WC, 0.8859 vs. 0.8860 vs. 0.8859, all $P > 0.05$) (Supplementary Fig. S2). Furthermore, RCS curves illustrated that the nonlinear (U-shaped) relationship between VAI and all-cause mortality still held after excluding participants with smoking (Supplementary Fig. S3), alcohol drinking (Supplementary Fig. S4) or history of CVD (Supplementary Fig. S5) at baseline. In addition, participants in Q5 was also associated with a higher risk of all-cause mortality after excluding participants with > 10 years of follow-up (Supplementary Table S7). Finally, when we excluded participants with extreme values (> 95%, or < 5%) of VAI, the nonlinear association still remained unchanged (Supplementary Table S8).

Discussion

In the large sample cohort of US nationally representative population, we found that VAI, an indicator reflecting visceral fat of the body, was nonlinearly associated with all-cause mortality in the general adults after multivariable adjustments. The risk of death was lowest at a $\log_2$-transformed VAI of 0.824, which was equivalent to a VAI of 1.770. Both higher or lower VAI values were

associated with a higher risk of death. Subgroup analysis revealed that the association showed age-related disparities. Specifically, higher VAI levels were associated with higher all-cause mortality in younger adults rather than older adults.

To our knowledge, this is one of the first studies to explore the relationship of VAI to long-term mortality in the US general population. The most paramount finding of this study was that VAI had a nonlinear association with all-cause mortality and the inflection point was also determined. Since the calculation of VAI is easy, this study further underscores the potential importance of VAI management to help physicians identify high-risk individuals.

Previous cross-sectional and case-control studies have identified the relationships between VAI and recognized cardiovascular risk factors, such as blood pressure [15], fasting glucose [16], blood lipids [34], worsen renal function [35] and insulin resistance [17]. However, prospective studies on the associations between VAI and human health outcomes were inconsistent. Tamosiunas and colleagues found that VAI was positively associated with all-cause mortality among middle-aged and elderly Lithuanians [18]. Similarly, in a study of 464 prevalent hemodialysis patients, VAI was associated with a higher risk of a composite event of death and new-onset cardiovascular events [36]. However, another study in patients with chronic kidney disease indicated a J-shaped association between VAI and all-cause death and the risk of death was higher in patients with visceral fat deficiency than those with excessive visceral fat deposition [19]. Most of these studies included participants with specific diseases [19, 36] or specific age groups [18] and did not cover the entire general population, thus, differences in the study population might partly explain the different conclusions. Based on the weighted Cox regression and cubic splines, we found a nonlinear relationship between VAI and long-term mortality among the US general adults. Besides, the risk of all-cause mortality declined as VAI increased when VAI was below 1.770, whereas higher VAI was associated with increased all-cause mortality when VAI exceeded the inflection point, again demonstrating a nonlinear relationship. In addition to the large sample and long follow-up, we also extended this relationship to the entire general population and identified the inflection point of VAI on mortality.

Although the specific mechanisms underlying VAI and mortality are not fully elucidated, several mechanisms and explanations have been proposed. First, as mentioned above, VAI has a clear relationship with cardiovascular risk factors [15, 16, 34]. Therefore, an excessive VAI (reflecting excess visceral fat) can influence the aforementioned risk factors and thus lead to higher mortality. Second, the calculation of VAI incorporates both anthropometric and metabolic parameters and may indirectly reflect other non-classical risk factors, such as altered adipocytokines production, enhanced lipolysis and increased plasma free fatty acids, which can induce inflammatory responses in a variety of cells and increase the release of inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 [14, 37], thereby increasing mortality. Third, studies have shown that VAI is positively associated with sedentary time [38] and tobacco use [39, 40], and negatively associated with standing and walking time [38]. These findings suggest that increased VAI may reflect poorer lifestyle and health status, which is recognized as an important predictor of mortality. Fourth, abundant evidence demonstrates that visceral obesity increases the risk of cancers, such as colorectal, pancreatic and gastroesophageal cancers, and thus increases the risk of death [41]. Nevertheless, too low VAI level, reflecting little visceral fat or overall fat, may also be harmful and increase the risk of certain health problems. Adipose tissue plays multiple roles such as energy storage, maintenance of body temperature, organ protection and hormone production [42]. Too little visceral fat is associated with diseases such as muscle wasting and malnutrition, suggesting that low VAI may also predict poor health. A deeper exploration of fat distribution and function will undoubtedly contribute to a better understanding of the relationship between obesity and health.

Our study also revealed that there was a significant interaction of VAI with age on all-cause mortality. Specifically, the positive association between VAI and death was observed in younger adults rather than older adults. A systematic review of 12 cohorts revealed that high visceral adipose tissue (VAT) areas appeared to be associated with increased all-cause mortality in individuals younger than 65 years, possibly mediated by metabolic complications rather than independent effects, and this relationship was weak and might disappear in older adults [43]. Similarly, a large cohort study declared that overall and abdominal obesity were associated with higher mortality risk in younger adults, whereas this association was null or inverse in older adults [44]. That is, the adverse effects of obesity on mortality risk were apparent only in younger adults. Our findings were consistent with these studies and suggested that although visceral obesity was consistently associated with health outcomes in adults, aging might potentially modify this association [41].

The present study has several strengths. First, the nationally representative data from NHANES cohort enabled us to generalize our findings to a broader population. Besides, the multiple models and a series of sensitivity analyses ensured the robustness of the results. Nevertheless, several limitations should also be

acknowledged. First, in NHANES, biochemical test was performed only once in each participant, thus, we were unable to assess the impact of changes in VAI over time on the outcome. Second, as with all observational studies, the possibility of residual and unknown confounders could not be completely excluded, although a range of confounders were adjusted. Third, VAI is derived from anthropometric and metabolic indicators and has not been clinically classified or defined with a clear cut-off value in clinical practice. Although our study provides an inflection point of VAI for mortality, how to utilize this inflection point and explore its applicability in different populations certainly warrants further research. Fourth, the subgroup analysis in this study was a post hoc analysis and should be considered exploratory and interpreted with caution [21]. Fifth, the observational study design limited the causal inferences. Finally, this study aimed to explore the relationship between VAI and all-cause mortality and we found that this nonlinear association was independent of BMI or WC, which are commonly used obesity-related measures, and therefore VAI was useful in predicting mortality. However, given the comparable discriminative performance for all-cause mortality among the three parameters as indicated by AUC values at 9.3 years, as well as the simplicity and accessibility of BMI and WC, the incremental value of VAI relative to these established anthropometric measures merits further investigation.

Conclusions

Our study showed that VAI was nonlinearly associated with all-cause mortality in US adults. Higher VAI levels were associated with higher all-cause mortality in younger adults (< 60 years) rather than older adults. These findings highlight the important role of appropriate VAI on long-term health outcomes and the modification role of aging. Further studies are warranted to validate our findings in other populations.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
TG	Triglyceride
VAI	Visceral adiposity index
VAT	Visceral adipose tissue
WC	Waist circumference
WHR	Waist-to-hip ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22428-6.

Supplementary Material 1

Acknowledgements

The authors would like to thank all the National Health and Nutrition Examination Survey (NHANES) staff and participants for providing the publicly available data.

Author contributions

Q.S., S.W. and L.W. conceived the study design. Q.S. and S.W. wrote the manuscript. S.W., X.H., and L.G. did the statistical analysis. H.W. and Q.Y. provided critical revisions of the draft. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The datasets used and/or analysed during the current study are available from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx).

Declarations

Ethics approval and consent to participate

The NHANES protocol was approved by the NCHS Research Ethics Review Board (Protocol #98-2018) (https://www.cdc.gov/nchs/nhanes/irba98.htm) and was consistent with the Declaration of Helsinki. Each participant signed the written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 23 October 2023 / Accepted: 21 March 2025
Published online: 03 April 2025

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