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Higher Metabolic Score for Visceral Fat Is Associated With Incident Stroke in Middle Aged and Older Chinese Adults

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Title Page

Title: Higher Metabolic Score for Visceral Fat Is Associated With Incident Stroke in Middle Aged and Older Chinese Adults

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ABSTRACT

Background: Visceral adiposity has been associated with increased cardiovascular risk; however, evidence regarding its relationship with incident stroke in large prospective cohorts remains limited. The metabolic score for visceral fat (METS-VF), which integrates anthropometric and metabolic parameters, has been proposed as a comprehensive indicator of visceral adiposity and metabolic dysfunction. This study investigated the association between METS-VF and incident stroke in a nationally representative cohort of Chinese adults.

Methods: We included 5,031 participants without a history of stroke from the China Health and Retirement Longitudinal Study (CHARLS). Cox proportional hazards regression, restricted cubic spline analyses, receiver operating characteristic curves, and decision curve analyses were performed to evaluate the association between METS-VF and stroke risk, as well as its incremental predictive performance.

Results: During a median follow-up of approximately 7 years, 479 incident stroke events were identified. Compared with participants in the lowest METS-VF quartile, those in the highest quartile had a higher risk of stroke (HR = 1.83; 95% CI: 1.36–2.47; $P < 0.001$). Restricted cubic spline analysis demonstrated a positive association between METS-VF and stroke risk (P for overall < 0.001) without significant departure from linearity (P for nonlinearity = 0.614). Adding METS-VF improved discrimination compared with the basic model (AUC: 0.675 vs 0.630; ΔAUC=0.045, P<0.001), and DCA suggested potential net benefit across part of the evaluated threshold-probability range. Mediation analysis showed no significant indirect effect of ADL-L.

Conclusion: Higher METS-VF was associated with an increased risk of incident stroke among middle-aged and older Chinese adults. METS-VF may serve as a complementary metabolic marker for risk stratification of individuals at higher risk of stroke, although its incremental predictive value and generalizability require further validation in independent cohorts.

Keywords: METS-VF; stroke; risk prediction; Cox regression; CHARLS; visceral adiposity

Introduction

Stroke is a major public health concern worldwide, with its incidence and disease burden continuously increasing over the past decades. According to the latest Global Burden of Disease data, over 93.8 million people were affected by stroke in 2021. The same year saw 11.9 million new cases and 7.3 million deaths from stroke, while the number of disability-adjusted life years (DALYs) lost reached 160.5 million, representing 5.6% of the global total [1]. In China, stroke has become one of the leading causes of death and disability, with more than 26 million prevalent cases and 2.59 million stroke-related deaths reported in 2021, representing 22.1% of all deaths nationwide [2]. Despite advances in early intervention and treatment, the high recurrence rate and long-term functional impairment continue to pose a serious public health challenge [3–5]. These trends underscore the urgent need for potential risk markers to identify individuals at high risk of stroke and support targeted prevention strategies.

In recent years, various metabolic indicators such as the triglyceride-glucose index (TyG), TyG-body mass index (TyG-BMI), Chinese visceral adiposity index (CVAI), and residual cholesterol inflammation index (RCII) have been identified as associations of stroke risk [6–9]. TyG and CVAI have shown predictive value for stroke and obesity-related risk in previous studies [12,38–40]. However, BMI, WC, TyG-related indices, and other composite indicators such as LAP and VAI may not fully capture visceral fat distribution and metabolic dysfunction, particularly in East Asian populations with distinct adiposity and metabolic profiles [10–12,45–48]. These limitations highlight the need for refined indicators that integrate metabolic and anthropometric measures to improve stroke risk prediction. The metabolic score for visceral fat (METS-VF) has recently emerged as an integrated indicator combining anthropometric characteristics and metabolic abnormalities. Compared with single metabolic markers or indices primarily reflecting insulin resistance, METS-VF integrates anthropometric characteristics and metabolic parameters within a unified score, allowing simultaneous assessment of visceral adiposity and metabolic dysfunction. Therefore, METS-VF may provide complementary information beyond traditional obesity indicators or individual metabolic indices.

In comparison, METS-VF is a composite index incorporating age, sex, BMI, waist-to-height ratio, fasting glucose, triglycerides, and HDL-C to estimate visceral adiposity and metabolic dysfunction. It provides a more complete reflection of visceral fat accumulation and metabolic dysregulation [13]. Previous studies have shown that METS-VF performs well in predicting cardiovascular disease, hypertension, and

diabetes [13–16]. A recent CHARLS-based study also reported that higher METS-VF levels were associated with increased risk of cardiovascular disease, including stroke, and that triglycerides partially mediated this association [44]. However, stroke was evaluated only as a component of broader cardiovascular outcomes in previous studies, limiting the ability to characterize stroke-specific associations. Important aspects including prospective time-to-event relationships, dose-response patterns, and incremental predictive performance beyond conventional risk factors remain insufficiently explored. Limitations in activities of daily living (ADL-L) reflect functional decline and frailty and have been associated with incident stroke [49]. Therefore, ADL-L was explored as a potential pathway that might link metabolic dysfunction with stroke risk.

Therefore, this study aimed to investigate the association between METS-VF and incident stroke using data from the China Health and Retirement Longitudinal Study (CHARLS) and to assess its potential utility in stroke risk prediction. By focusing specifically on incident stroke as the primary outcome, this study aims to provide a stroke-specific longitudinal evaluation of METS-VF, including its association with future stroke risk, dose-response relationship, and incremental predictive information beyond conventional risk factors.

Methods

Study Design and Study Population

This study was based on data from CHARLS, a nationally representative cohort designed to assess the economic, social, and health status of the Chinese population [17].

The CHARLS cohort was established using a multistage probability sampling method, selecting participants from 450 communities across 150 counties in 28 provinces. A total of 17,708 individuals residing in 10,257 households were enrolled [17–19]. The baseline survey was conducted between June 2011 and March 2012, targeting individuals aged 45 years or older. Data were collected through standardized face-to-face interviews using structured questionnaires, with follow-up assessments conducted biennially (Wave 2 in 2013, Wave 3 in 2015, and Wave 4 in 2018). The CHARLS study was approved by the institutional review board of Peking University, and all participants provided written informed consent prior to enrollment. The dataset used in this analysis is publicly available on the official CHARLS website. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

Among the 17,708 participants enrolled at baseline, we first excluded 777 individuals younger than 45 years, 5,196 individuals with a self-reported history of stroke at baseline, and 6,548 individuals with missing information required for calculating METS-VF or assessing activities of daily living (ADL). Given that METS-VF is theoretically expected to be positive according to its calculation formula, participants with METS-VF ≤ 0 were considered to have implausible values. To minimize the influence of extreme outliers on nonlinear model fitting, participants with METS-VF values above the 99th percentile were also excluded. These METS-VF-based exclusions resulted in the removal of 154 participants. In addition, multiple imputation was performed for baseline variables with missing values to reduce selection

bias. After imputation, 2 individuals were further excluded due to persistent missing data on educational attainment. Following these screening procedures, a total of 5,031 participants were included in the final analysis, and four waves of follow-up data from 2011 to 2018 were used **(Figure 1)**. Baseline characteristics between participants included in the final analysis and those excluded due to missing information required for METS-VF calculation or ADL assessment were additionally compared to evaluate potential selection bias (**Supplementary Table S2**).

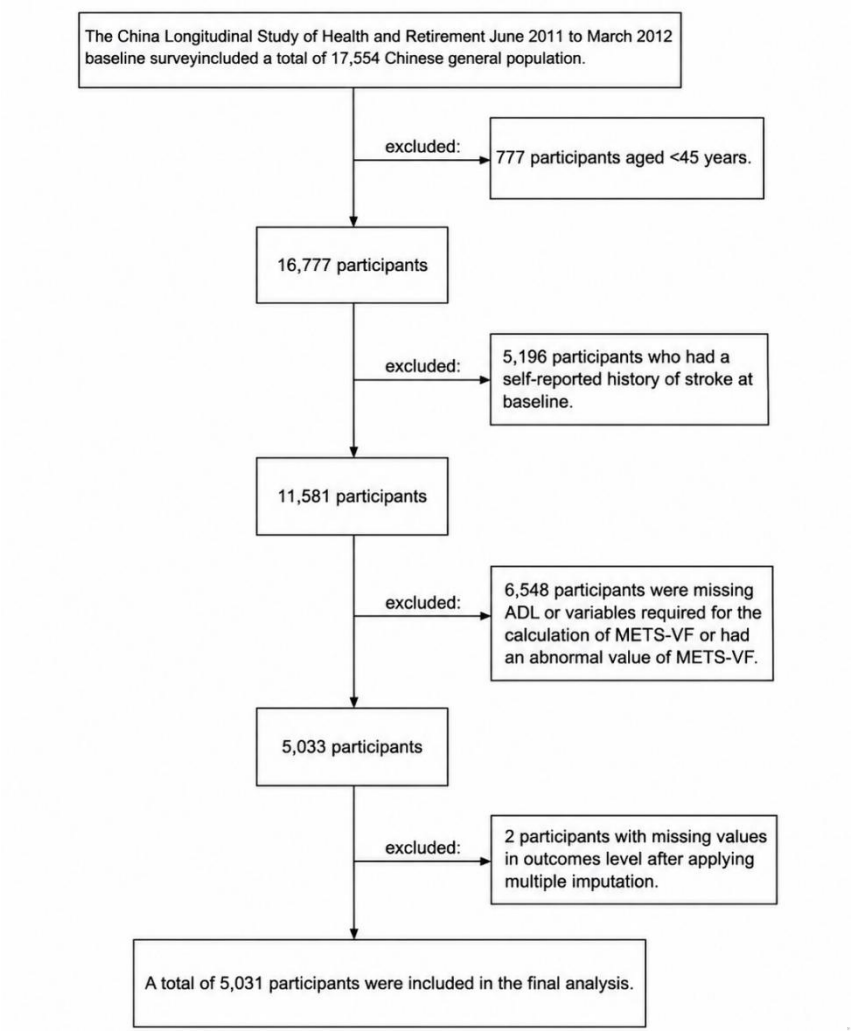


Figure 1. Flowchart illustrating the selection process of study participants.

Study Design

We then examined the association between METS-VF and stroke risk using the following statistical approaches. A Cox proportional hazards regression model was employed to assess the association between METS-VF and incident stroke. To explore potential nonlinear relationships between METS-VF and stroke risk, restricted cubic spline (RCS) analysis was conducted. In addition, receiver operating characteristic (ROC) curves and decision curve analysis (DCA) were used to evaluate model discrimination and potential clinical net benefit. Mediation analysis was performed as

an exploratory analysis to investigate whether (ADL-L) could represent a potential pathway linking METS-VF with incident stroke.

Covariates

Calculation of METS-VF

The exposure variable in this study was METS-VF, an index used to assess visceral fat burden and metabolic health status. METS-VF was calculated using the following formula:

$$\text{METS-VF} = 4.466 + 0.011 \times [\ln(\text{METS-IR})]^3 + 3.239 \times [\ln(\text{WHtR})]^3 + 0.319 \times (\text{sex}) + 0.594 \times \ln(\text{age}),$$

where male = 1 and female = 0 [13].

METS-IR (Metabolic Score for Insulin Resistance) was calculated as:

$$\text{METS-IR} = \ln[(2 \times \text{fasting glucose}) + \text{fasting triglycerides}] \times \text{BMI} / [\ln(\text{HDL-C})]$$ [13].

Waist-to-height ratio (WHtR) was derived as:

$$\text{WHtR} = \text{WC} / \text{height}$$ [13].

Fasting blood glucose (FBG), triglycerides (TG), body mass index (BMI), high-density lipoprotein cholesterol (HDL-C), waist circumference (WC), and height (HT) were all obtained from baseline measurements in the CHARLS study. For analysis, METS-VF was treated as a continuous variable and was also categorized into quartiles (Q1–Q4) to explore its dose–response relationship with stroke risk. In addition, activities of daily living limitations (ADL-L) were included as a covariate and potential

mediator in the analyses.

Stroke Diagnosis

Incident stroke was defined as the occurrence of physician-diagnosed stroke or current stroke treatment reported during follow-up. Participants who reported physician-diagnosed stroke or current stroke treatment during follow-up were classified as having incident stroke events. Information was collected through questionnaire items asking whether the participant had ever been diagnosed with stroke by a physician, whether they were currently receiving treatment for stroke, and the date of diagnosis or the date they became aware of the condition. A "Yes" response to either of the first two questions was used to define incident stroke. The earliest reported date of stroke was recorded as the event time. For participants who reported a stroke, follow-up time was defined as the duration from baseline assessment to the reported date of stroke onset. For those who did not report a stroke during follow-up, follow-up time was calculated from the baseline assessment to the date of the last available survey [42,43].

Data Collection

Baseline data collection included a range of covariates: sociodemographic characteristics (age, sex, educational level, marital status, and residential area), lifestyle factors (smoking and drinking status), clinical parameters (BMI, blood pressure, WC, and HT), medical history (hypertension, diabetes, and dyslipidemia), ADL status, and obesity status [17]. Laboratory measurements comprised total cholesterol (TC), HDL-C, triglycerides (TG), fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) [21].

198 Educational level was categorized as no formal education, primary school,
199 secondary/high school, or college and above. Marital status was grouped as married or
200 other (divorced, unmarried, or widowed). Residential area was classified as urban or
201 rural. Smoking and drinking status were categorized as current smoker or non-smoker,
202 and drinker or non-drinker, respectively.

203 Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, current use of
204 antihypertensive medications, or a self-reported history of hypertension. Diabetes was
205 defined as FBG ≥126 mg/dL (converted to mmol/L by multiplying by 0.0555), HbA1c
206 ≥6.5% (48 mmol/mol), use of glucose-lowering medication, or self-reported physician-
207 diagnosed diabetes. Dyslipidemia was defined as TC ≥240 mg/dL (converted to mmol/L
208 by multiplying by 0.0259), TG ≥150 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL,
209 current use of lipid-lowering agents, or a self-reported history of dyslipidemia.

210 ADL was assessed by asking whether participants had experienced difficulties in
211 the past three months due to health or memory problems in performing six tasks:
212 bathing, dressing, eating, getting in or out of bed, using the toilet, and controlling
213 urination. The assessment method was based on the Katz Index [41]. Participants
214 reporting any difficulty were classified as having ADL limitations (ADL-L). Obesity
215 was defined as a BMI ≥28 kg/m².

216

217 **Statistical Analysis**

218 All statistical analyses were performed using SPSS version 22.0 (IBM Corp.,
219 Chicago, IL, USA) and R software version 4.4.2 (R Foundation for Statistical

Computing, Vienna, Austria). All tests were two-tailed, and a p-value <0.05 was considered statistically significant. Given the very small effect sizes observed in the mediation analysis, results were reported to four decimal places to ensure sufficient precision. METS-VF was analyzed both categorically (quartiles Q1–Q4) and continuously. For continuous analysis, hazard ratios were estimated per 1-standard deviation increase in METS-VF. Continuous variables were described as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as frequencies (percentages). Differences across METS-VF quartiles were assessed using one-way analysis of variance or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables, as appropriate.

Univariate and multivariate Cox proportional hazards regression models were used to evaluate the association between METS-VF and incident stroke. Covariates were adjusted in a stepwise manner: Model 1 adjusted for age and sex; Model 2 further adjusted for marital status, residence, education level, smoking and drinking; Model 3 additionally adjusted for hypertension, diabetes and dyslipidaemia. Because METS-VF incorporates age, sex, BMI, fasting glucose, triglycerides, HDL-C and WHtR, these components were not simultaneously included as covariates to avoid mathematical coupling. However, hypertension, diabetes and dyslipidemia were additionally adjusted in Model 3 because they represent clinically diagnosed metabolic conditions rather than direct mathematical components of METS-VF.

Restricted cubic spline (RCS) modeling was used to assess the shape of the association between METS-VF and stroke risk and to test for nonlinearity. ROC curves

were used to describe model discrimination, and decision curve analysis (DCA) was used to evaluate potential clinical net benefit. Kaplan-Meier curves were used to compare cumulative hazard across METS-VF quartiles, with differences assessed using the log-rank test. Mediation analysis was performed to examine whether ADL-L mediated the association between METS-VF and stroke risk.

To reduce potential bias due to missing baseline covariates, missing values were imputed using the multivariate imputation by chained equations (MICE) method [22]. The imputation model included BMI, SBP, DBP, FBG, TG, HDL-C, WC, height, education level, hypertension, diabetes, dyslipidemia, smoking status, drinking status, and obesity. Missing covariate data were handled using multiple imputation by chained equations (MICE). Five imputed datasets were generated after 10 iterations under the assumption of missing at random (MAR)[23]. Cox regression models were fitted separately within each imputed dataset, and pooled estimates were obtained using Rubin's rules. The proportional hazards assumption was evaluated using Schoenfeld residuals, and no substantial violation was detected.All regression estimates were pooled across five imputed datasets using Rubin's rules.

Sensitivity analyses were performed by excluding variables overlapping with METS-VF components and by additionally removing closely related metabolic conditions to evaluate the robustness of the association.

Results

Baseline Characteristics

A total of 5,031 participants were included in the analysis, with a mean age of 58.7 years and 54.6% being female. **Table 1** presents the characteristics of participants grouped by METS-VF quartiles. Individuals in the highest quartile (Q4) had significantly higher age, BMI, SBP, DBP, and prevalence of diabetes, hypertension, and dyslipidemia compared to those in lower quartiles (all $P < 0.001$). Moreover, Smoking status differed significantly across METS-VF quartiles ($P < 0.001$), whereas the difference in drinking status was not statistically significant ($P = 0.072$). Higher METS-VF quartiles were associated with unfavorable metabolic profiles, including higher BMI, blood pressure, glucose, triglyceride levels, and greater prevalence of hypertension, diabetes, and dyslipidemia. The observed differences in age and sex distributions across quartiles also indicate that population characteristics may influence the relationship between METS-VF and stroke risk. Baseline characteristics between included and excluded participants were additionally compared to assess potential selection bias (**Supplementary Table S2**). Although most demographic characteristics showed comparable distributions, differences were observed for several metabolic conditions, including hypertension, diabetes, and dyslipidemia.

Table 1. Baseline characteristics by METS-VF quantiles

Characteristic	Overall(n=5031)	METS-VF				P value
		Q1(n=1258)	Q2(n=1258)	Q3(n=1257)	Q4(n=1258)	
Age, years (mean±SD)	58.7 ±8.8	56.9 ±8.5	57.6 ±8.3	58.7 ±8.6	61.9 ±8.8	<0.001
45-49	945 (18.8%)	315 (25.0%)	278 (22.1%)	236 (18.8%)	116 (9.2%)	
50-59	1898 (37.7%)	520 (41.3%)	499 (39.7%)	480 (38.2%)	399 (31.7%)	
60-69	1551 (30.8%)	309 (24.6%)	356 (28.3%)	388 (30.9%)	498 (39.6%)	
70-79	567 (11.3%)	106 (8.4%)	118 (9.4%)	134 (10.7%)	209 (16.6%)	
>=80	70 (1.4%)	8 (0.6%)	7 (0.6%)	19 (1.5%)	36 (2.9%)	
Sex						<0.001
Male	2282 (45.4%)	584 (46.4%)	549 (43.6%)	511 (40.7%)	638 (50.7%)	
Female	2749 (54.6%)	674 (53.6%)	709 (56.4%)	746 (59.3%)	620 (49.3%)	
Marital status						0.012
Married	4525 (89.9%)	1148 (91.3%)	1121 (89.1%)	1143 (90.9%)	1113 (88.5%)	
Divorced	26 (0.5%)	7 (0.6%)	10 (0.8%)	7 (0.6%)	2 (0.2%)	
Unmarried	26 (0.5%)	11 (0.9%)	6 (0.5%)	3 (0.2%)	6 (0.5%)	
Widowed	454 (9.0%)	92 (7.3%)	121 (9.6%)	104 (8.3%)	137 (10.9%)	
Residence						<0.001
Urban	1740 (34.6%)	347 (27.6%)	390 (31.0%)	471 (37.5%)	532 (42.3%)	
Rural	3291 (65.4%)	911 (72.4%)	868 (69.0%)	786 (62.5%)	726 (57.7%)	
Education level						0.321
College or above	48 (1.0%)	8 (0.6%)	13 (1.0%)	13 (1.0%)	14 (1.1%)	
Middle or high school	1566 (31.1%)	417 (33.1%)	396 (31.5%)	395 (31.4%)	358 (28.5%)	
Primary school	2007 (39.9%)	499 (39.7%)	510 (40.5%)	487 (38.7%)	511 (40.6%)	
No formal education	1410 (28.0%)	334 (26.6%)	339 (26.9%)	362 (28.8%)	375 (29.8%)	

Table1(continued)

Characteristic	Overall(n=5031)	METS-VF				P value
		Q1(n=1258)	Q2(n=1258)	Q3(n=1257)	Q4(n=1258)	
Follow up time,years	6.7 ±1.4	6.8 ±1.2	6.8 ±1.2	6.6 ±1.6	6.5 ±1.7	<0.001
Smoking						
No	3070 (61.0%)	729 (57.9%)	794 (63.1%)	814 (64.8%)	733 (58.3%)	<0.001
Yes	1961 (39.0%)	529 (42.1%)	464 (36.9%)	443 (35.2%)	525 (41.7%)	
Drinking						
No	3120 (62.0%)	773 (61.4%)	802 (63.8%)	799 (63.6%)	746 (59.3%)	0.072
Yes	1911 (38.0%)	485 (38.6%)	456 (36.2%)	458 (36.4%)	512 (40.7%)	
ADL-L	769 (15.3%)	145 (11.5%)	171 (13.6%)	189 (15.0%)	264 (21.0%)	<0.001
Obesity	2220 (44.1%)	97 (7.7%)	279 (22.2%)	743 (59.1%)	1101 (87.5%)	<0.001
History of comorbidities						
Hypertension medications	2136 (42.5%)	312 (24.8%)	427 (33.9%)	570 (45.3%)	827 (65.7%)	<0.001
Diabetes medications	896 (17.8%)	128 (10.2%)	160 (12.7%)	232 (18.5%)	376 (29.9%)	<0.001
Dyslipidemia medications	1327 (26.4%)	195 (15.5%)	256 (20.3%)	361 (28.7%)	515 (40.9%)	<0.001
BMI, kg/m2	24.4 ±3.5	20.5 ±2.8	22.5 ±2.3	24.7 ±3.0	30.0 ±3.3	<0.001
SBP, mmHg	130.4 ±21.0	123.4 ±19.3	127.0 ±19.8	132.0 ±20.3	139.3 ±20.9	<0.001
DBP, mmHg	75.7 ±11.9	72.1 ±11.3	74.1 ±11.6	76.8 ±11.5	79.6 ±11.7	<0.001
FBG, mmol/L	6.2 ±2.0	5.8 ±1.6	5.9 ±1.6	6.2 ±1.9	6.8 ±2.6	<0.001
TG, mmol/L	1.5 ±1.2	1.1 ±0.7	1.3 ±0.8	1.6 ±1.1	2.0 ±1.7	<0.001
HDL-C, mmol/L	1.3 ±0.4	1.5 ±0.4	1.4 ±0.4	1.3 ±0.4	1.1 ±0.3	<0.001

Data are presented as mean ± SD or n (%), unless otherwise specified

ADL-L,activities of daily living limitations; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation

[a] P value was based on x^2 or analysis of variance or Kruskal–Wallis rank sum test where appropriate

[b] The METS-VF was calculated using the following formula: METS-VF = 4.466 + 0.011×[ln(METS-IR)]³+ 3.239×[ln(WHtR)]³+ 0.319×sex + 0.594×ln(age),with METS-IR = ln [2×FBG (mg/dl)+ TG(mg/dl)]×BMI(kg/m2) / {ln[HDL-C(mg/dl)]} , and WHtR = WC(cm) / HT(cm).Sex was coded as 1 for men and 0 for women.

Stroke Incidence

Among the 5,031 participants without a history of stroke at baseline, a total of 479 new stroke cases occurred during the 7-year follow-up period. The overall stroke incidence was 9.52% (95% CI: 8.74–10.36), corresponding to 143.04 cases per 10,000 person-years. When stratified by METS-VF quartiles, a progressive increase in stroke incidence was observed across higher quartiles (**Table 2, Figure 2; P for trend < 0.001**). The incidence in Q1 (METS-VF ≤ 6.34) was 5.41% (95% CI: 4.29–6.80), corresponding to 79.78 cases per 10,000 person-years; in Q2 (6.34–6.75), 7.31% (95% CI: 6.00–8.89) and 108.2 cases per 10,000 person-years; in Q3 (6.75–7.08, 10.58% (95% CI: 10.41–10.75) and 160.69 cases per 10,000 person-years; and in Q4 (METS-VF ≥ 7.08), the highest incidence was observed at 14.79% (95% CI: 12.93–16.85), with 227.3 cases per 10,000 person-years. A significant trend was observed (P for trend < 0.001), indicating a positive association between METS-VF and stroke risk.

Table 2. Incidence rate of stroke

METS-VF	Participants(n)	Stroke events(n)	Incidence rate(95%CI)(%)	Per 10,000 person-year
Total	5031	479	9.52(8.74–10.36)	143.04
Q1(≤6.34)	1258	68	5.41(4.29–6.80)	79.78
Q2(6.34-6.75)	1258	92	7.31(6.00–8.89)	108.2
Q3(6.75-7.08)	1257	133	10.58(9.00–12.40)	160.69
Q4(≥7.08)	1258	186	14.79(12.93–16.85)	227.3
P for trend			＜0.001	

METS-VF,metabolic score for visceral fat; CI,confidence interval.Cumulative-incidence 95% CIs were calculated from the displayed event counts using the Wilson method.

Further stratified analysis of stroke incidence by age group and sex (Supplementary Figure S1) showed age and sex related differences in stroke incidence. Stroke incidence generally increased from the 45–49-year age group to the 70–79 year age group and subsequently declined among participants aged ≥80 years. In the 45–49 age group, the incidence was 7.0% in men, 4.2% in women, and 5.3% overall. In the 50–59 age group, the corresponding rates were 9.7%, 8.3%, and 8.9%, respectively. Among participants aged 60–69 years, stroke incidence was 10.9% in men, 12.5% in women, and 11.7% overall. In the 70–79 age group, the incidence was 13.2% in men, 12.5% in women, and 12.9% overall. Among participants aged ≥80 years, the incidence decreased to 10.7% in men, 4.8% in women, and 7.1% overall. The highest overall

stroke incidence was observed in the 70–79 year age group.

Association Between METS-VF and Stroke Risk

To investigate the association between METS-VF and stroke risk, we constructed three Cox proportional hazards regression models (**Figure 2**). In Model 1, adjusted for age and sex, the hazard ratios (HRs) for stroke in Q2, Q3, and Q4 compared with Q1 were 1.35 (95% CI: 0.98–1.84; P = 0.07), 1.99 (95% CI: 1.49–2.67; P < 0.001), and 2.66 (95% CI: 2.01–3.53; P < 0.001), respectively. After further adjustment for potential confounders including marital status, residence, education level, smoking and drinking in Model 2, similar trends were observed, with HRs (95% CI) of 1.35 (95% CI: 0.99–1.85; P = 0.06), 2.00 (95% CI: 1.49–2.68; P < 0.001), and 2.66 (95% CI: 2.00–3.54; P < 0.001) for Q2–Q4, respectively. In Model 3, which additionally adjusted for hypertension, diabetes and dyslipidaemia, the HR for Q2 was 1.24 (95% CI: 0.90–1.70; P = 0.19), while Q3 and Q4 remained significantly associated with increased stroke risk, with HRs of 1.66 (95% CI: 1.23–2.23; P = 0.001) and 1.83 (95% CI: 1.36–2.47; P < 0.001), respectively. These findings indicate that higher METS-VF were consistently associated with increased stroke risk after multivariable adjustment, which persisted across all adjusted models. When METS-VF was analyzed as a continuous variable, each 1-SD increase in METS-VF was associated with a higher risk of incident stroke in the fully adjusted model (HR 1.31, 95% CI 1.16–1.47, P < 0.001). Sensitivity analyses excluding variables overlapping with METS-VF components and further excluding clinically diagnosed metabolic conditions yielded similar results (**Supplementary Table S3**), supporting the robustness of the primary findings. In

addition, comparable estimates were obtained in the complete-case analysis (**Supplementary Table S1**), indicating that the results were not materially influenced by the multiple imputation procedure. Multicollinearity diagnostics showed low GVIF values for all variables included in the fully adjusted model (**Supplementary Table S6**), suggesting that multicollinearity was unlikely to materially influence the regression estimates.

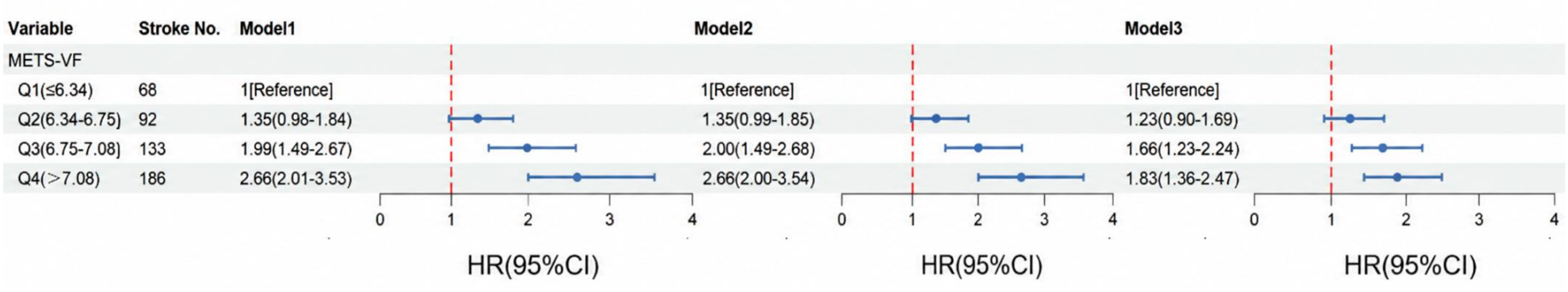


Figure 2. Associations of METS-VF with stroke. Model 1 was adjusted for age, sex. Model 2 was adjusted for age, sex, marital status, residence, education level, smoking, and drinking. Model 3 was adjusted as model 2 plus hypertension, diabetes and dyslipidaemia. METS-VF, metabolic score for visceral fat; Q, quartile; HR, hazard ratio; CI, confidence interval.

352 **Dose Response Association Between METS-VF and Stroke Risk**

353 The RCS model showed a significant overall association between METS-VF and
354 stroke risk (P for overall < 0.001), but there was no statistical evidence of nonlinearity
355 (P for nonlinearity = 0.614; **Figure 3A, B**). The fitted curve suggested increasing stroke
356 risk at higher METS-VF values; however, the visually labeled value of 6.37 in Figure
357 3 should be interpreted descriptively rather than as a statistically validated threshold.

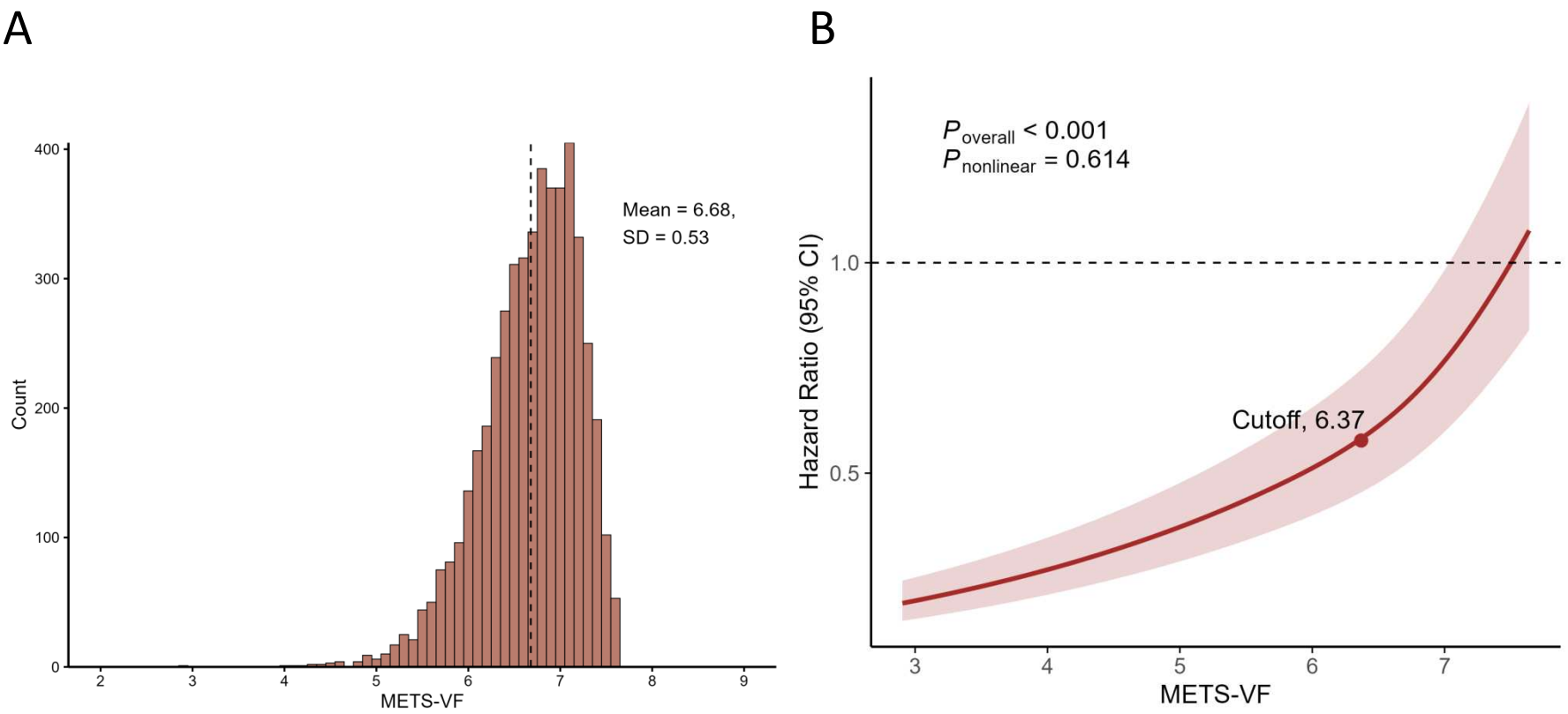


Figure 3. Dose-response association between METS-VF and incident stroke. (A) Distribution of METS-VF. (B) Adjusted hazard ratio for incident stroke across METS-VF values. The model was adjusted for age, sex, marital status, residence, education level, smoking, drinking,hypertension, diabetes and dyslipidaemia. Solid lines indicate HRs and shaded areas indicate 95% CIs. The labeled value of 6.37 is descriptive because the test

for nonlinearity was not statistically significant. METS-VF, metabolic score for visceral fat; HR, hazard ratio; CI, confidence interval.

Predictive Utility of METS-VF for Stroke

We systematically evaluated whether adding METS-VF to conventional clinical risk factors improved model discrimination and incremental predictive performance for stroke risk. ROC curve analysis showed that the AUC for Model 1 was 0.630 (95% CI: 0.605–0.655), increased to 0.639 (95% CI: 0.613–0.664) in Model 2, and significantly improved to 0.675 (95% CI: 0.652–0.701; $P < 0.001$) in the model incorporating METS-VF and clinical risk factors in Model 3 (**Figure 4A**), indicating a modest improvement in model discrimination after inclusion of METS-VF-related information.

Further DCA demonstrated (**Figure 4B**) that Model 3 provided higher net benefit than Models 1 and 2 across parts of the clinically relevant threshold-probability range (Figure 4B), suggesting potential incremental predictive performance while recognizing that external validation is required.

Moreover, KM survival analysis (**Figure 5**) revealed a progressive increase in cumulative stroke incidence across METS-VF quartiles, with statistically significant differences between groups (log-rank $p < 0.001$).

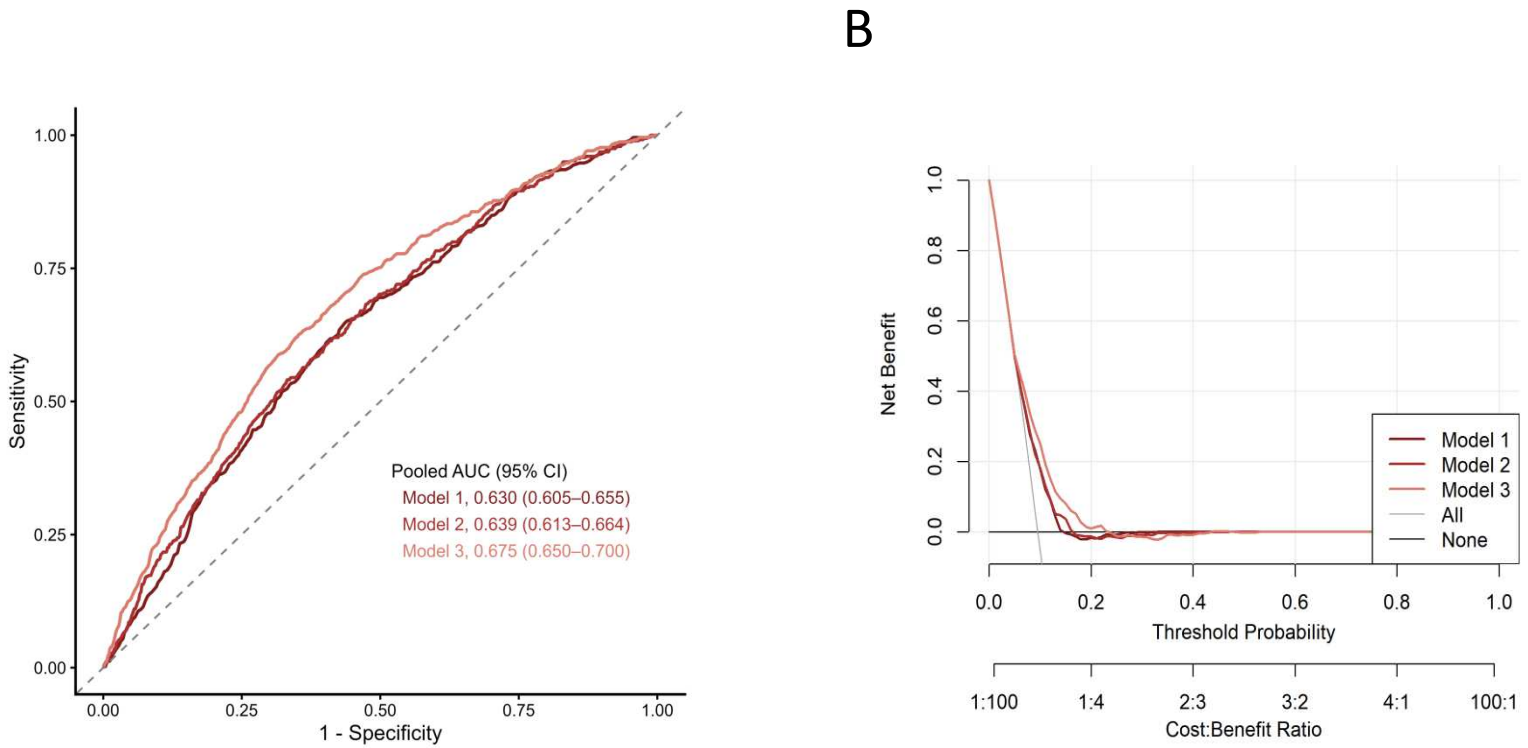


Figure 4. Predictive performance of METS-VF-based models for incident stroke. (A) Receiver operating characteristic curves and area under the curve (AUC) for the three models. (B) Decision curve analysis showing net benefit across threshold probabilities. METS-VF, metabolic score for visceral fat; AUC, area under the curve.

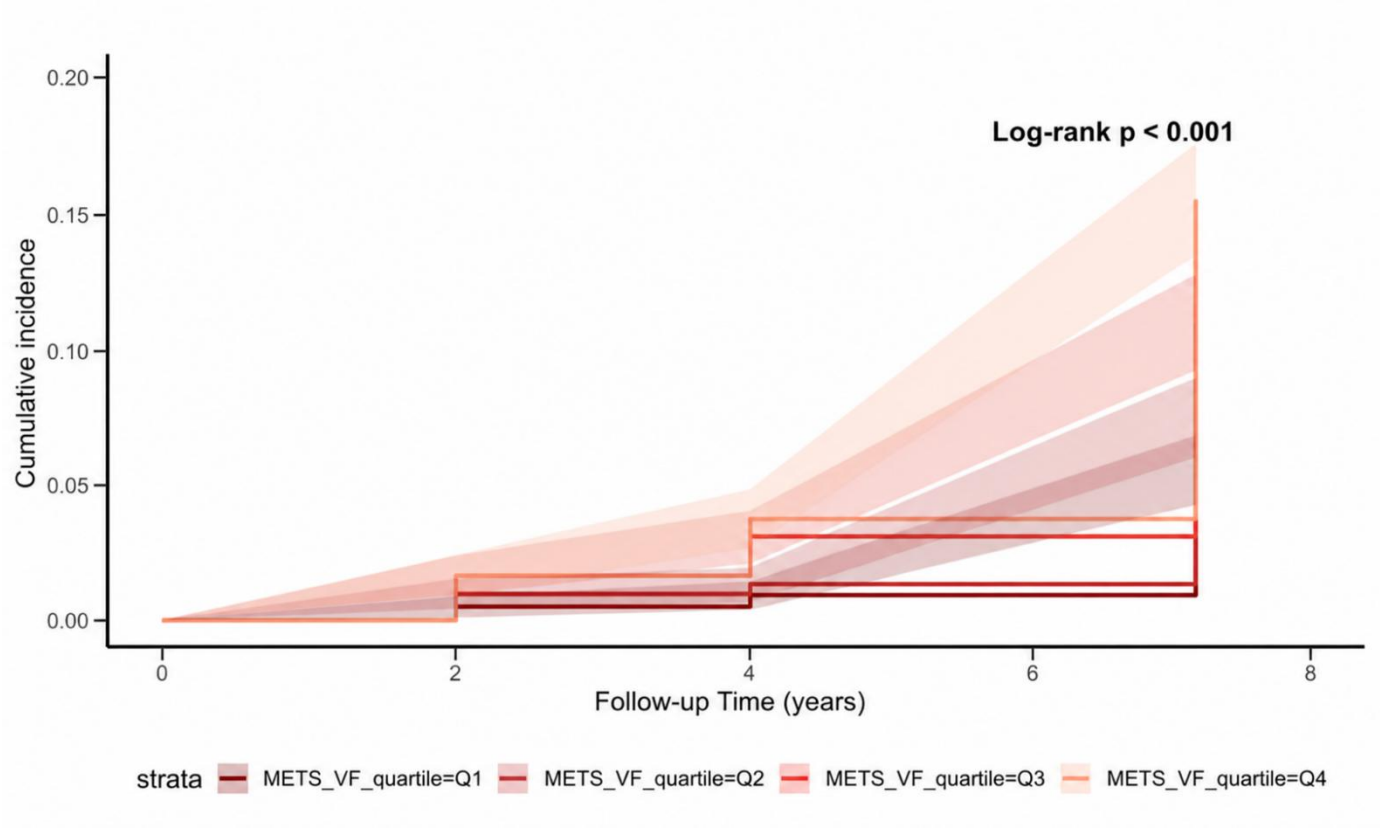


Figure 5. Cumulative incidence of stroke stratified by METS-VF quartiles.

The Kaplan–Meier curves show the cumulative incidence of incident stroke across four quartiles of METS-VF. Participants in the highest quartile (Q4) had significantly higher stroke risk compared with those in lower quartiles. Shaded areas represent 95% confidence intervals. The difference

between groups was statistically significant (Log-rank test, $p < 0.001$).

ADL Mediation Analysis

Although baseline analyses indicated a statistical difference in ADL-L across METS-VF levels ($P < 0.05$), this may have been confounded by factors such as age, sex, and other variables. Therefore, a mediation analysis was conducted using a model adjusted for age, sex, marital status, place of residence, education level, smoking, alcohol consumption, hypertension, diabetes, dyslipidemia, and BMI. As shown in **Figure 6**, the average causal mediation effect (ACME) of METS-VF on stroke through ADL-L was 0.0002 (95% CI: –0.0006 to 0.0000; P = 0.89), and the average direct effect (ADE) was 0.0010 (95% CI: –0.0019 to 0.0000; P = 0.47). The total effect was 0.0013 (95% CI: –0.0020 to 0.0000; P = 0.50), with a mediation proportion of 19.1% (95% CI: –183.3% to 158.0%; P = 0.85). These results suggest that ADL-L did not exhibit a significant mediating effect in the association between METS-VF and stroke risk.

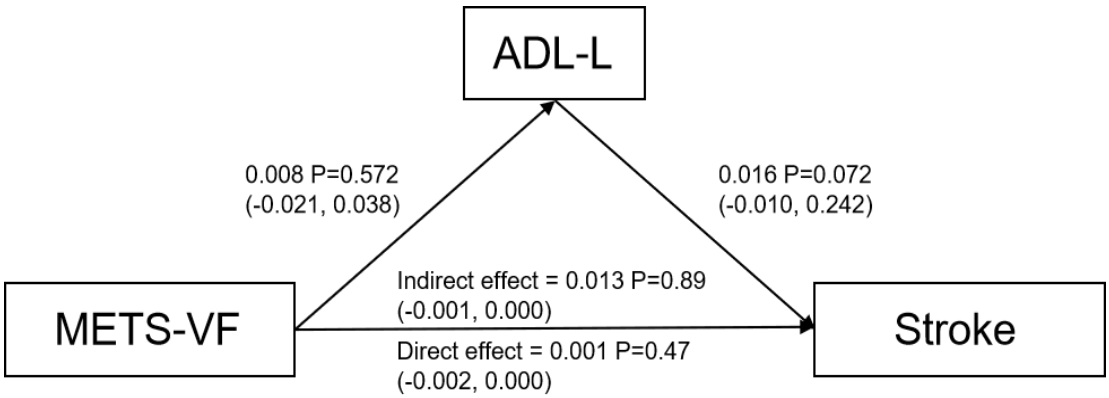


Figure 6. Path diagram of the association between METS-VF and ADL-L as a mediator.Notes: 95 % CI in the parentheses are shown. Models control for age, gender, marital status, residence, education level, smoking, drinking, hypertension, diabetes and dyslipidaemia.

Discussion

This study systematically evaluated the longitudinal association between METS-VF and incident stroke in a nationally representative cohort of middle-aged and older Chinese adults. We found that higher METS-VF levels were significantly associated with increased stroke risk, independent of demographics, lifestyle factors, and chronic conditions. Restricted cubic spline analysis further supported an increasing association between METS-VF and stroke risk, although no statistically significant nonlinear relationship was observed. Mediation analysis did not support a significant role of ADL-L. Together, these findings suggest that METS-VF may provide supplementary information for identifying individuals at elevated stroke risk, particularly when used alongside conventional clinical risk factors. These findings should, however, be interpreted in the context of the moderate discriminatory performance observed in the present study and the need for external validation before broader clinical application.

Prior research has established strong links between obesity, insulin resistance, and stroke, but traditional measures such as BMI and WC provide limited predictive power[25,26]. Recently, TyG and its derivatives have been applied to capture insulin resistance and predict stroke. For example, Huo et al. reported that TyG mediated the association between BMI and stroke, and that combining TyG with BMI improved predictive accuracy (AUC = 0.602) [6], while Wang et al. showed that TyG-CVAI was positively associated with incident stroke and outperformed single indices [8]. Unlike these indices, METS-VF integrates BMI, WC, TG, and FBG into a composite score that better reflects visceral adiposity and metabolic dysfunction [27,28]. Evidence from both

NHANES and CHARLS cohorts has suggested associations between METS-VF and stroke [13,24], consistent with our findings. In the present study, The METS-VF-based models showed modest discrimination, and DCA suggested potential incremental decision-analytic value within part of the evaluated threshold-probability range. Additionally, incremental discrimination analyses using IDI and NRI showed consistent improvement after incorporating METS-VF into the prediction model (**Supplementary Table S4**). These findings support further investigation of METS-VF as a risk-stratification marker rather than a standalone prediction tool. Therefore, METS-VF should currently be considered as a supplementary risk marker rather than a replacement for established clinical assessment approaches. These findings support further evaluation of METS-VF as a risk-stratification marker rather than establishing superiority over other indices. Because METS-VF incorporates several metabolic components, adjustment for related clinical conditions may raise concerns regarding mathematical coupling or overadjustment. To address this issue, we performed sensitivity analyses using alternative adjustment strategies. The observed associations remained consistent across models, suggesting that the association between METS-VF and incident stroke was robust and was unlikely to be explained by model specification or multicollinearity.

The observed association is biologically plausible. METS-VF reflects visceral fat–related metabolic abnormalities, which may contribute to stroke through several mechanisms. Insulin resistance, a key component of METS-VF, impairs glucose utilization and promotes endothelial dysfunction, atherosclerosis, and neurovascular

452 impairment [29,32]. At the cellular level, mitochondrial ROS overproduction triggered by
453 TNF-α activates the ASK1–JNK pathway, disrupting insulin signaling and aggravating
454 vascular injury [30]. In addition, METS-VF incorporates lipid disturbances, including
455 high TG and low HDL-C, which may enhance platelet activity, thrombin generation,
456 and reduce fibrinolysis, thereby creating a prothrombotic environment [31].
457 Inflammatory markers such as hs-CRP have been shown to mediate stroke recurrence
458 and poor outcomes [33], while composite indices like SIRI are also linked to
459 cardiovascular events [34]. Thus, METS-VF likely captures the combined effects of
460 insulin resistance, lipid abnormalities, oxidative stress, and inflammation, providing a
461 possible biological mechanisms for the observed link with stroke. This
462 multidimensional nature distinguishes METS-VF from simpler anthropometric indices
463 and may contribute to its potential predictive utility. Recent evidence further suggests
464 that persistent inflammatory activation may contribute to residual cardiovascular risk
465 even after conventional metabolic risk factors have been considered, supporting the
466 biological plausibility of METS-VF as an integrative metabolic marker[50].

467 Given that ADL reflects functional capacity and may mediate metabolic effects on
468 vascular outcomes, we tested ADL-L as a potential mediator. We hypothesized that
469 impaired ADL could reduce physical activity and increase sedentary behavior, thereby
470 worsening metabolic dysregulation and vascular injury [35,36]. Possible explanations
471 include reliance on self-reported questionnaires, which are prone to subjective bias, and
472 the stronger direct effects of metabolic dysfunction that may trigger stroke
473 independently of functional decline. Future studies should incorporate more sensitive

mediators, such as hs-CRP, arterial stiffness, or neuroimaging biomarkers, to clarify biological pathways linking metabolic burden and stroke. It would also be valuable to investigate lifestyle behaviors, such as diet and physical activity patterns, which may interact with metabolic risk and functional limitations to influence stroke incidence. Although ADL-L was evaluated as a potential mediator based on the temporal sequence of baseline exposure and subsequent stroke follow-up, reverse causality and residual confounding cannot be completely excluded. Therefore, the mediation findings should be interpreted cautiously and regarded as exploratory rather than conclusive evidence of a causal pathway.

Our study has several strengths. First, CHARLS is a large, nationally representative cohort with repeated follow-up, enabling temporal assessment of incident stroke. Second, we used complementary statistical approaches, including Cox regression, RCS, ROC analysis, DCA, Kaplan-Meier analysis, and mediation analysis, to evaluate association, dose-response pattern, discrimination, and potential incremental predictive performance. Third, METS-VF was examined as both a continuous and categorical exposure, allowing assessment across its distribution.

Several limitations should be acknowledged. Stroke events were self-reported, which may introduce misclassification, although prior studies have shown acceptable validity [37]. In addition, CHARLS did not provide sufficiently detailed stroke subtype information for this analysis; therefore, we were unable to determine whether the association differed between ischemic and hemorrhagic stroke. Residual confounding cannot be excluded, and a single baseline measurement of metabolic indicators may not

capture longitudinal changes in exposure. Missing covariates were handled using multiple imputation, and pooled estimates across imputed datasets were used in the revised analysis. In addition, although baseline characteristics between included and excluded participants were compared, differences in some metabolic characteristics suggested that selection bias related to missing information could not be completely excluded. Nevertheless, residual confounding cannot be completely excluded. the complete-case sensitivity analysis yielded estimates in the same direction but with wider uncertainty. Finally, the discriminatory performance of the models was moderate, and external validation and formal assessment of incremental predictive value are needed before clinical implementation. In addition, although METS-VF improved discrimination when added to the constructed clinical models, comparisons with established stroke risk prediction tools were not performed. Future studies should evaluate whether METS-VF provides incremental value beyond validated risk scores. Moreover, because this study was conducted in a Chinese middle-aged and older population, the applicability of METS-VF for other ethnic groups and healthcare settings remains uncertain and requires validation in diverse populations.

In conclusion, higher METS-VF was independently associated with an increased risk of incident stroke in a nationally representative cohort of middle-aged and older Chinese adults. The association was significant overall, with no statistical evidence of nonlinearity. METS-VF may provide additional information for stroke risk stratification, but its incremental predictive value, optimal clinical application, and generalizability require further validation.

Incident stroke was identified based on participants' self-reported physician diagnosis or treatment information rather than adjudicated clinical records. Although this approach has been widely adopted in CHARLS-based studies, outcome misclassification cannot be completely excluded.

Declarations

Ethical approval

This study was a secondary analysis of de-identified data from the China Health and Retirement Longitudinal Study (CHARLS). The original CHARLS study was approved by the Institutional Review Board of Peking University, and all participants provided written informed consent before enrollment. The present study used publicly accessible, de-identified CHARLS data and involved no new recruitment, participant contact, or intervention. No separate ethical approval for this secondary analysis is claimed.

Consent to participate

Not applicable to the present secondary analysis. Written informed consent was obtained from participants in the original CHARLS study.

Clinical trial registration

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Third-party material

No third-party figures, images, tables, or supplementary materials are reproduced or adapted in this manuscript.

Competing interests

The authors declare that they have no competing interests.

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Data availability

The datasets analysed during the current study are available through the China Health and Retirement Longitudinal Study (CHARLS) data repository: https://charls.charlsdata.com/pages/data/111/en.html

Access to the datasets requires registration and approval in accordance with the CHARLS data use policy.

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Author contributions:

D.-Z.K., L.-Y.Z. contributed to study design. Z.-Y.C., J.-J.H. and Y.Z. wrote the first draft. Y.-B.H., J.-J.Z. and F.-X.L. did the data analysis and statistical analysis. All authors read and approved the final manuscript.

Supplementary Material:

Table S1-S6

Figure S1

Supplementary Files

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- Supplementary.docx