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The combined effects of cardiometabolic index and high-sensitivity C-reactive protein on the risk of new onset stroke in a Chinese national prospective longitudinal cohort study

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Abstract

Background The Cardiometabolic Index (CMI) represents a novel anthropometric measurement, which combines characteristics of adiposity and lipids. Since obesity, lipid metabolism, and inflammation may collectively facilitate the occurrence of stroke, we hypothesize that a combination of elevated levels of the CMI and high-sensitivity C-reactive protein (hs-CRP) increases the risk of future stroke among middle-aged and older Chinese adults.

Methods This study included 8,973 participants aged 45 years or older from the China Longitudinal Study on Health and Retirement (CHARLS), who were stroke-free and underwent baseline evaluations between 2011 and 2012, with followed-up at 2013, 2015 and 2018. The exposures were CMI and hs-CRP, with CMI calculated using the formula [waist circumference (cm)/height (cm)] × [triglycerides (mmol/L)/HDL-C (mmol/L)]. The primary outcome was the occurrence of new-onset stroke events. Cox proportional hazards models and restricted cubic spline (RCS) analyses were conducted to examine the associations between CMI, hs-CRP, and their combined effects on stroke risk. Sensitivity analysis was further implemented to verify the robustness of the results.

Results A total of 629 participants (7.01%) suffered new-onset stroke during follow-up. The risk for stroke increased with each elevating quartile of baseline CMI levels, with adjusted HRs and 95% CIs being 1.27 (0.98–1.66), 1.41 (1.08–1.83), and 1.46 (1.09–1.96) for Q2, Q3, and Q4, respectively. Moreover, participants with levels of hs-CRP ≥ 2 mg/L also had significantly higher stroke incidence compared to those with CRP levels < 2 mg/L (adjusted HR 1.24, 95% CI 1.05–1.47, $p = 0.012$). Specifically, those concurrently with the highest CMI quartile and levels of hs-CRP ≥ 2 mg/L had the highest risk of stroke (adjusted HR 1.90, 95% CI 1.32–2.74). The subsequent sensitivity analyses yielded consistent results, further corroborating the initial findings.

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Conclusions The combination of CMI and hs-CRP exhibited a significant association with stroke risk among middle-aged and older Chinese adults, highlighting the importance of joint assessments of these biomarkers for refining risk stratification and enhancing primary prevention strategies for stroke.

Keywords Cardiometabolic index, hs-CRP, Stroke, CHARLS

Introduction

Stroke is a serious health hazard and a notable cause of acquired disability and mortality worldwide, especially in East Asian countries [1]. The Chinese population faces a 39.3% lifetime risk of stroke, representing a 1.6-fold increase of risk compared with other countries and regions [2]. And based on Global Burden of Disease (GBD), our country exhibits an ascending trend in stroke incidence, prevalence, mortality rates, as well as disability-adjusted life-years [3, 4]. Although substantial efforts have been made, effective remedies against its devastating neurological consequences remain a challenge. Consequently, identifying modifiable risk factors and enhancing stratification of stroke risk is urgently needed.

Obesity is a modifiable metabolic risk factor which poses significant health problems, including increased susceptibility to hypertension, cardiovascular disease, type 2 diabetes, abnormal lipid metabolism, stroke and other numerous comorbidities [5–8]. In the meanwhile, the above factors mutually influence each other and synergistically contribute to the occurrence of stroke, which highlight the importance of obesity and dysmetabolism in stroke. Currently, Body Mass Index (BMI) is a widely used anthropometric index to assess the extent of obesity and is reported to be related with stroke and cardiovascular disease [9, 10]. However, there is limitation of BMI in reflecting the distribution of body fat distribution [11]. And according to previous literature, central adiposity leads to greater risk of stroke rather than general adiposity [12]. Cardiometabolic Index (CMI) is a novel obesity and metabolism-related metric, which combines height and waist circumference and provides a superior capacity to BMI in representing visceral obesity [13]. Besides, CMI integrates parameters of lipids, which are a crucial part in the pathogenesis of stroke [14]. It has emerged as an excellent biomarker for metabolic syndrome [15], diabetes mellitus [16], and cardiovascular disease [17] risk assessment. Particularly, CMI was reported to be independently associated with stroke in cross-sectional studies [18]. However, the evidence regarding the association between CMI and risk of stroke in the general population from longitudinal studies is limited.

In addition, accumulating evidence supports the role of dysregulation of inflammation and immunity in the pathogenesis of the stroke [19]. As an acute phase reactant and biomarker of peripheral inflammation, high-sensitivity C-reactive protein (hs-CRP) has been reported to be associated with higher risk of vulnerable atherosclerotic plaques [20], ischemic stroke [21] and stroke recurrence [22]. Also, both obesity and dyslipidemia was associated with inflammatory state [23, 24], and an raised CMI is related to poorer prognosis in chronic inflammatory conditions, illustrating the conjunct influence of metabolism and inflammation on cardiovascular health [25]. Elevated-CRP levels and CMI may be positive factors in the progression of stroke. However, the combined effect of these two factors on the risk of new-onset stroke in middle-aged and older Chinese adults has not been studied. Therefore, this study will utilise the data of the China Health and Retirement Longitudinal Study (CHARLS) to investigate the combined effect of hs-CRP and CMI on stroke risk.

Methods

Study participants and design

This cohort used data from CHARLS survey, which is a prospective longitudinal cohort study conducted to assess the economic, social and health status of individuals aged 45 years and older in China [26]. Briefly, the CHARLS study employed a multistage probability sampling process, encompassing subjects from 450 communities within 150 districts and 28 provinces across China, and finally a total of 17,708 individuals at baseline were investigated between June 2011 and March 2012. Data for CHARLS study was gathered using standardized questionnaires and participants were followed up every two years after baseline survey. The Biomedical Ethics Review Board of Peking University in China (IRB00001052-11015) approved the study and all participants provided written consent prior to their inclusion.

The present study utilized data spanning from 2011 to 2018, including an initial baseline survey conducted between 2011 and 2012, along with three subsequent follow-up surveys in 2013, 2015, and 2018. Initially, 17,708 participants were enrolled at baseline. Among 11,847 adults who had completed the blood sample testing at baseline, and we further excluded those aged < 45 or missing information on age (n = 430), those with preexisting stroke at baseline (n = 318), those with missing values on HDL-C (high-density lipoproteincholesterol), TG (triglyceride) and WHtR (waist-to-height ratio) (n = 1885), those with missing values on hs-CRP (n = 1), and those with missing covariates (n = 240). Ultimately, 8,973 participants were included in the final analysis. The detailed screening process is depicted in Fig. 1. The baseline characteristic differences between the participants included

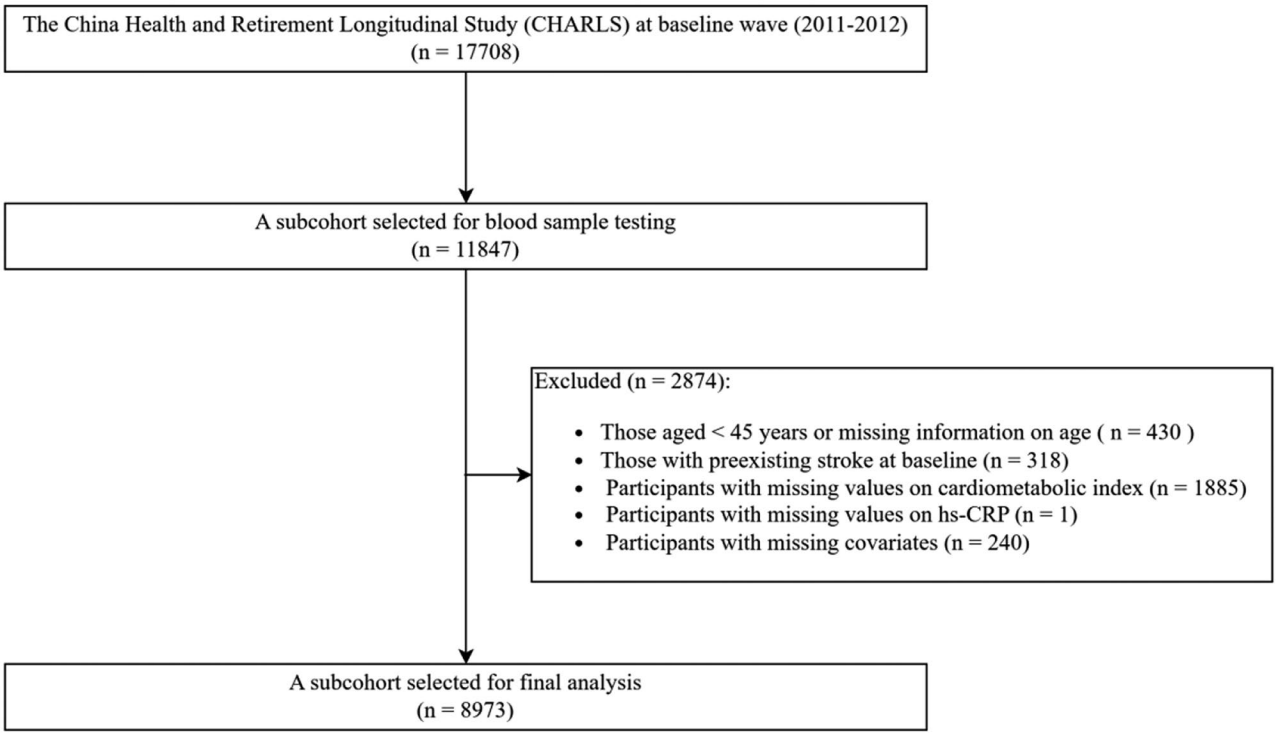

Fig. 1 Flowchart illustrating participant selection in the present study

in the study and those excluded were presented in Table S1.

Assessment of CMI

CMI was calculated as (TG/HDL-c) × WHtR according to the previous literature, while WHtR was calculated as waist circumference (cm)/height (cm) [27].

Assessment of hs-CRP

Baseline fasting and non-fasting venous blood samples were acquired from participants by medically trained staff from the Chinese Center for Disease Control and Prevention (China CDC) and hs-CRP was determined by immunoturbidimetric assay at the Youanmen Center for the Clinical Laboratory of Capital Medical University based on standardized protocol [28]. The concentration of hs-CRP below 2 mg/L is considered indicative of low-grade systemic inflammation [29], and therefore, hs-CRP levels were categorized into two groups: low (<2 mg/L) and elevated (≥2 mg/L) levels.

Ascertainment of new onset stroke events

The primary outcome was new onset stroke events, defined as the occurrence of new-onset stroke during follow-up by a self-reported pattern [30]. Consistent with prior research [31], standardized questions was posed to participants by trained staff: Have you been told by a physician that you have been diagnosed with a stroke? An affirmative answer was considered as having a new onset stroke.

Covariables

At baseline, demographic characteristics (including age, gender, residence, educational level, marital status), risk factors (such as smoking, alcohol consumption, hypertension, diabetes, dyslipidemia, heart disease, chronic kidney disease, cancer, chronic lung disease, depressive symptoms), medical history (including medications for hypertension, diabetes, and lipid-lowering), anthropometric parameters (including body height, weight, waist circumference (WC), and blood pressure measurements (including systolic blood pressure (SBP) and diastolic blood pressure (DBP))were collected through structured questionnaires by trained interviewers. Participants were considered hypertensive if they had an SBP≥140 mmHg, or DBP≥90 mmHg, were using antihypertensive medications, or had a reported history of hypertension. Diabetes was defined as HbA1c≥6.5%, fasting blood glucose (FBG)≥7.0 mmol/L, or self-reported history of diabetes. Hypercholesterolemia was defined as total cholesterol (TC)≥240 mg/dl, LDL≥160 mg/dl, HDL<40 mg/dl, TG≥200 mg/dl, use of lipid-lowering therapy, or self-reported history of hypercholesterolemia. Chronic Kidney Disease was defined as estimated glomerular filtration rate (eGFR)<60mL/min/1.73m^2 or self-reported history of chronic Kidney Disease. BMI was calculated by

dividing the individual's weight by their height squared (kg/m^2) and classified as: underweight (BMI < 18.5 kg/m2), normal weight (18.5 kg/m2 ≤ BMI < 24.0 kg/m2), overweight (24.0 kg/m2 ≤ BMI < 28 kg/m2) and obesity (BMI ≥ 28.0 kg/m2) [32]. Baseline laboratory parameters including TG, HDL-C, TC, creatinine, glucose, and HbA1c were also obtained according to previous reports [33]. We calculated the eGFR utilizing the 2009 creatinine equation provided by the Chronic Kidney Disease Epidemiology Collaboration [34].

Statistical analysis

Descriptive statistics were adopted to depict demographic data. Continuous variables were described by mean ± standard deviation for those normally distributed, while the medians and interquartile ranges were used for those nonnormally distributed. Categorical data were presented as counts and percentages. Baseline characteristics are illustrated according to quantiles of CMI or levels of hs-CRP. Differences between categorical variables were compared using the Chi-squared test or Fisher's exact test, while differences between continuous variables were compared using the t-test, Kruskal–Wallis H test, and analysis of variance (ANOVA), as appropriate.

To determine the relationship between CMI, hs-CRP, and the risk of new-onset stroke, as well as the joint association of CMI and hs-CRP with stroke risk, we employed three stepwise-adjusted multivariable Cox proportional hazards regression models to control for potential confounders, and 95% confidence intervals (CI) and hazard ratio (HR) were reported. Model 1 included adjustment for CMI and hs-CRP. Model 2 included adjustment for CMI, hs-CRP, age, sex, residence, marital status, educational level, smoking status, and drinking status. Model 3 included covariables in Model 2 plus body mass index, diabetes, hypertension, dyslipidemia, chronic kidney disease, cancer, heart disease, lung disease, and depressive symptoms and fasting status. In all models, the quartile 1 group served as the reference. Extreme values were handled using Winsorization. Restricted cubic spline (RCS) analyses (4 knots located at Harrell's recommended percentiles) were adopted to further assess the nonlinear associations of CMI, hs-CRP and the risk of new onset stroke. The incremental predictive value of these biomarkers was evaluated using the C-statistic, net reclassification index (NRI), and integrated discrimination improvement (IDI). Next, different sensitivity analyses were conducted to verify the robustness of the results, including sensitivity analysis 1: excluding individuals with hs-CRP levels > 10 mg/L; sensitivity analysis 2: adjusting for competing risk of deaths using Fine-Gray subdistribution hazard model; sensitivity analysis 3: excluding individuals who experienced a stroke within 2 years; sensitivity analysis 4: excluding non-fasting samples. Finally, multivariable-adjusted models 3 were stratified by potential modifiers; modification was evaluated using the likelihood ratio test comparing models with and without an interaction term between the variable of interest and CMI as well as hs-CRP.

Statistical analyses were carried out with Stata statistical software version 17.0 (StataCorp) and R statistical software version 3.6.1 (R Foundation). $P < 0.05$ was defined as statistically significant (two-tailed).

Results

Participant characteristics

A total of 8,973 subjects were included in the analyses. Baseline characteristics of participants stratified by CMI quartiles are shown in Table 1. The average age of participants at baseline was 59.12 ± 9.26 years old, with 4174 (46.5%) being male. The results demonstrated that participants with higher CMI quartiles tended to be younger, female, living in rural regions, nonsmokers, nondrinkers. Additionally, they had higher rates of hypertension, diabetes, dyslipidemia, heart disease and lower rates of chronic lung disease. Moreover, they were more likely to use medications for hypertension, diabetes, and hyperlipidemia. And a similar trend was noted in SBP, DBP, BMI, WHtR, TG, TC, glucose, HbA1c and hs-CRP. Conversely, the levels of HDL-C, and eGFR were lower in the higher CMI quartile group (all $p < 0.05$). No significant differences were observed in educational level, marital status, prevalence of chronic kidney diseases, cancers and depressive symptoms among the four CMI quartile groups.

In the meanwhile, we also compared baseline characteristics of the participants according to levels of hs-CRP (Table S2). Among the 8,973 respondents included in the analysis, 2,439 (27.18%) had hs-CRP ≥ 2 mg/L. These respondents tended to be older, female, rural residents, married and nonsmokers. They also had an increased proportion of hypertension, diabetes, dyslipidemia, heart disease, chronic kidney disease, chronic lung disease and higher prevalence of medication use of hypertension, diabetes, and hyperlipidemia. Besides, participants with higher levels of hs-CRP exhibited increased levels of SBP, DBP, BMI, WHtR, TG, glucose, HbA1c and CMI. However, they had decreased levels of HDL-C and eGFR. Yet, we did not find any difference in educational level, drinking status, incidence of cancer and depressive symptoms, level of TC and LDL-C between the two groups.

Independent predictive value of baseline CMI and hs-CRP for risk of stroke

During the follow-up period from 2013 to 2018, 629 participants (7.01%) suffered new onset stroke. And the Cox proportional hazard models were adopted to explore the relationship between baseline CMI levels,

Table 1 Baseline characteristics according to quantiles of cardiometabolic index (CMI)

	Quantiles of CMI				*P* value
	Q1 (*n* = 2274)	Q2 (*n* = 2257)	Q3 (*n* = 2234)	Q4 (*n* = 2208)	
Age, y	59.54 ± 9.52	59.26 ± 9.45	59.07 ± 9.21	58.59 ± 8.82	0.006
Sex					< 0.001
Man	1248 (54.9)	1075 (47.6)	938 (42.0)	913 (41.3)	
Woman	1026 (45.1)	1182 (52.4)	1296 (58.0)	1295 (58.7)	
Residence					< 0.001
Urban	641 (28.2)	759 (33.6)	822 (36.8)	934 (42.3)	
Rural	1633 (71.8)	1498 (66.4)	1412 (63.2)	1274 (57.7)	
Educational level					0.176
<=Primary school	1642 (72.2)	1585 (70.2)	1569 (70.2)	1512 (68.5)	
Middle school	428 (18.8)	450 (19.9)	445 (19.9)	451 (20.4)	
>=High school	204 (9.0)	222 (9.8)	220 (9.8)	245 (11.1)	
Marital status					0.106
Others	291 (12.8)	282 (12.5)	286 (12.8)	237 (10.7)	
Married/partnered	1983 (87.2)	1975 (87.5)	1948 (87.2)	1971 (89.3)	
Smoking status					< 0.001
Never	1243 (54.7)	1345 (59.6)	1449 (64.9)	1409 (63.8)	
Former	202 (8.9)	183 (8.1)	184 (8.2)	214 (9.7)	
Current	829 (36.5)	729 (32.3)	601 (26.9)	585 (26.5)	
Drinking status					< 0.001
Never	1157 (50.9)	1322 (58.6)	1407 (63.0)	1395 (63.2)	
Former	168 (7.4)	195 (8.6)	209 (9.4)	170 (7.7)	
Current	949 (41.7)	740 (32.8)	618 (27.7)	643 (29.1)	
Hypertension	719 (31.6)	774 (34.3)	1004 (44.9)	1176 (53.3)	< 0.001
Diabetes	221 (9.7)	279 (12.4)	384 (17.2)	664 (30.1)	< 0.001
Dyslipidemia	335 (14.7)	592 (26.2)	958 (42.9)	1978 (89.6)	< 0.001
Heart disease	203 (8.9)	223 (9.9)	283 (12.7)	346 (15.7)	< 0.001
Chronic kidney disease	186 (8.2)	195 (8.6)	191 (8.5)	197 (8.9)	0.848
Cancer	16 (0.7)	20 (0.9)	17 (0.8)	28 (1.3)	0.186
Chronic lung disease	249 (10.9)	237 (10.5)	205 (9.2)	184 (8.3)	0.012
Depressive symptoms	884 (38.9)	856 (37.9)	849 (38.0)	777 (35.2)	0.064
Hypertension medications	261 (11.5)	325 (14.4)	485 (21.8)	647 (29.4)	< 0.001
Diabetes medications	54 (2.4)	54 (2.4)	80 (3.6)	159 (7.2)	< 0.001
Lipid-lowering medications	48 (2.1)	83 (3.7)	101 (4.6)	205 (9.4)	< 0.001
SBP, mm Hg	126.14 ± 21.18	127.24 ± 20.46	131.05 ± 21.82	133.55 ± 21.34	< 0.001
DBP, mm Hg	72.81 ± 12.08	74.10 ± 11.61	76.40 ± 12.36	77.95 ± 12.16	< 0.001
BMI, Kg/m^2	21.52 ± 3.25	22.79 ± 3.61	24.18 ± 3.75	25.65 ± 3.91	< 0.001
BMI categories					< 0.001
Underweight	314 (13.8)	188 (8.3)	74 (3.3)	31 (1.4)	
Normal weight	1573 (69.2)	1341 (59.4)	1064 (47.6)	732 (33.2)	
Overweigh	324 (14.2)	593 (26.3)	803 (35.9)	905 (41.0)	
Obesity	63 (2.8)	135 (6.0)	293 (13.1)	540 (24.5)	
WHtR	0.48 ± 0.09	0.52 ± 0.07	0.55 ± 0.07	0.58 ± 0.06	< 0.001
CMI	0.48 (0.38, 0.58)	0.87 (0.77, 1.00)	1.47 (1.28, 1.69)	3.05 (2.41, 4.54)	< 0.001
TG, mg/dl	64.44 ± 18.00	92.35 ± 22.94	127.52 ± 30.22	239.11 ± 103.21	< 0.001
HDL-C, mg/dl	66.23 ± 13.35	54.19 ± 10.54	46.81 ± 8.73	37.13 ± 8.15	< 0.001
TC, mg/dl	187.82 ± 34.25	189.18 ± 37.20	195.06 ± 38.09	203.65 ± 43.26	< 0.001
LDL-C, mg/dl	110.94 ± 29.69	118.51 ± 33.05	124.18 ± 34.62	113.20 ± 40.36	< 0.001
eGFR, mL/min/1.73 m^2	93.44 ± 14.21	92.49 ± 14.43	91.78 ± 14.93	90.48 ± 15.90	< 0.001
Glucose, mg/dl	102.82 ± 25.30	105.14 ± 28.43	109.56 ± 36.42	124.93 ± 51.84	< 0.001
HbA1c, %	5.15 ± 0.62	5.19 ± 0.69	5.28 ± 0.82	5.47 ± 1.03	< 0.001
Hs-CRP, mg/l	0.76 (0.45, 1.77)	0.89 (0.50, 1.89)	1.11 (0.59, 2.23)	1.38 (0.76, 2.79)	< 0.001
Hs-CRP ≥ 2 mg/l	511 (22.5)	530 (23.5)	622 (27.8)	776 (35.1)	< 0.001

Data was n (%) mean ± SD, or median (IQR)

hs-CPR levels and incidence of new-onset stroke. After adjusting for potential confounders in model 3, the risk of stroke showed an incremental trend across quartiles of CMI (adjusted HR 1.27, 95% CI 0.98–1.66 for Q2; adjusted HR 1.41, 95% CI 1.08–1.83 for Q3; adjusted HR 1.46, 95% CI 1.09–1.96 for Q4; *p*-trend=0.010). Furthermore, baseline CMI was also analyzed as continuous variable, and we found that per 1-unit increase in baseline CMI was related to a 19% higher risk of stroke following adjustment for potential confounding factors in Model 3 (adjusted HR 1.19, 95% CI 1.05–1.35, $p=0.008$). As for hs-CRP, participants with elevated CRP levels also had markedly higher stroke incidence compared to those with lower CRP levels (adjusted HR 1.24, 95% CI 1.05–1.47, $p=0.012$), and every additional unit in the hs-CRP increases risk of stroke by 11% after adjusting for potential confounders in model 3 (adjusted HR 1.11, 95% CI 1.01–1.22, $p=0.030$) (Table 2). Finally, we observed a nonlinear relationship of baseline CMI (p for nonlinearity=0.003) and linear relationship of baseline hs-CRP (p for nonlinearity=0.306) with risk of stroke using RCS analyses (Fig. S1).

Table 2 Independent associations of cardiometabolic index and hs-CRP with risk of stroke ($n=8973$)

	Events/Person-year	HR (95% CI)		
		Model 1	Model 2	Model 3
Categories:				
Cardiometabolic index				
Q1	101/14556.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	137/14406.5	1.36 (1.05–1.76)	1.39 (1.07–1.80)	1.27 (0.98–1.66)
Q3	176/14235.5	1.74 (1.36–2.22)	1.80 (1.41–2.31)	1.41 (1.08–1.83)
Q4	215/13940.0	2.11 (1.66–2.67)	2.23 (1.75–2.84)	1.46 (1.09–1.96)
P value for trend		< 0.001	< 0.001	0.010
hsCRP				
< 2 mg/L	407/42100.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 2 mg/L	222/15038.0	1.43 (1.21–1.69)	1.34 (1.14–1.58)	1.24 (1.05–1.47)
P value		< 0.001	0.001	0.012
Continuous:				
Cardiometabolic index (Ln)	629/57138.0	1.37 (1.24–1.50)	1.42 (1.29–1.56)	1.19 (1.05–1.35)
P value		< 0.001	< 0.001	0.008
Hs-CRP (Ln)	629/57138.0	1.23 (1.12–1.34)	1.17(1.07–1.29)	1.11 (1.01–1.22)
P value		< 0.001	0.001	0.030

Model 1 included cardiometabolic index and hs-CRP

Model 2 included cardiometabolic index, hs-CRP, age, sex, residence, marital status, educational level, smoking status, and drinking status

Model 3 included covariates in Model 2 plus body mass index, diabetes, hypertension, dyslipidemia, chronic kidney disease, cancer, heart disease, lung disease, depressive symptoms, and fasting status

Joint association of CMI and hs-CRP with risk of stroke

Figure 2 showed the relationships between different combinations of CMI and hs-CRP with incidence density of stroke per 1000 person-years. In the lower hs-CRP group, the incidence density of stroke per 1000 person-years increased with rising baseline CMI quartiles, with respective incidence densities of 5.8, 8.5, 11.5, and 13.9. Similarly, in the higher hs-CRP group, the incidence density of stroke per 1000 person-years also increased across the baseline CMI quartiles, with respective incidence densities ranging from 11.3 to 13.1, 14.6, and 18.3. And we found, in the hs-CRP≥2 mg/L group, the incidence density of stroke per 1000 person-years in every quartile of CMI was evidently higher than that in the hs-CRP<2 mg/L group.

Since both CMI and hs-CRP are important predictors of stroke risk, we analyzed their joint effect on the risk of stroke. After adjusting for demographic characteristics, risk factors, and anthropometric parameters, the group with higher CMI quartiles and higher hs-CRP levels exhibited a higher risk of new onset stroke compared to those with the lower CMI quartiles and lower hs-CRP levels. The corresponding adjusted HRs with 95% CIs were as follows: 1.61 (1.18–2.20) for the CMI (Q3) & hs-CRP<2 mg/L group, 1.67 (1.19–2.35) for the CMI (Q4) & hs-CRP<2 mg/L group, 1.72 (1.14–2.60) for the CMI (Q1) & hs-CRP≥2 mg/L group, 1.81 (1.23–2.67) for the CMI (Q2) & hs-CRP≥2 mg/L group, 1.79 (1.23–2.59) for the CMI (Q3) & hs-CRP≥2 mg/L group, and 1.90 (1.32–2.74) for the CMI (Q4) & hs-CRP≥2 mg/L group, respectively (Fig. 3). This result suggests the superior efficacy of the combined index in predicting new onset stroke.

Table 3 demonstrated the incremental predictive value of hs-CRP and CMI when added to the basic model for stroke incidence. The NRI improved to 0.1124 with hs-CRP, 0.0909 with CMI, and achieved the highest NRI of 0.1299 with combined of hs-CRP and CMI ($p<0.05$ for all). The IDI also showed the greatest improvement with combined of hs-CRP and CMI, increasing to 0.0018 ($p=0.003$), compared to 0.0007 with hs-CRP ($p=0.055$) and 0.0012 ($p=0.016$) with CMI.

Sensitivity analyses

Several sensitive assessments were conducted to verify the robustness of our results (Table S3, Fig. S2). First, after excluding individuals with extreme hs-CRP levels, the Cox regression analyses produced similar results to the primary analysis. Next, after adjusting for the competing risk of death using the Fine-Gray subdistribution hazard model, there was no notable change in the

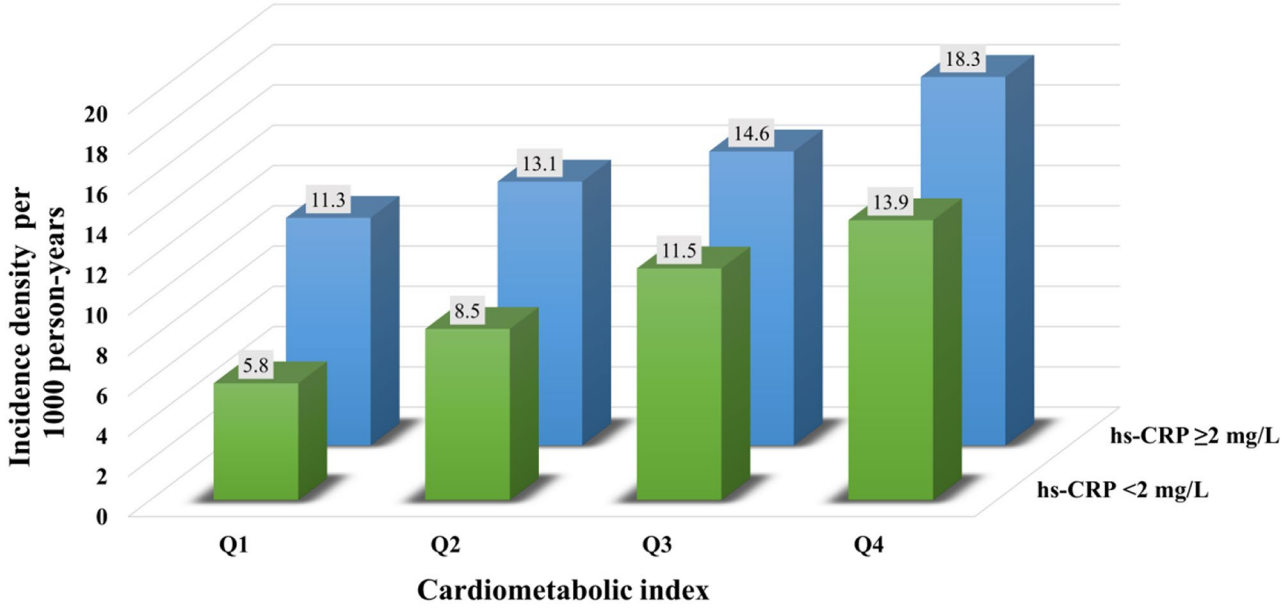

Fig. 2 Incidence density of stroke per person-year by joint of CMI and hs-CRP

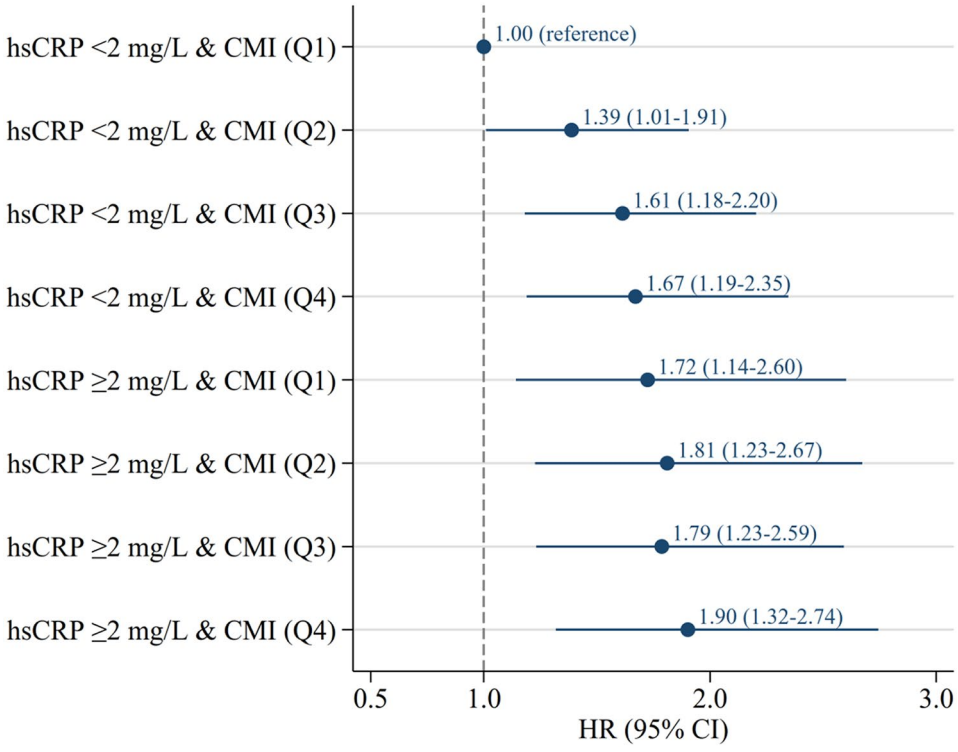

Fig. 3 Joint association of CMI and hs-CRP with risk of stroke. *Model adjusted for age, sex, residence, marital status, educational level, smoking status, and drinking status body mass index, diabetes, hypertension, dyslipidemia, chronic kidney disease, cancer, heart disease, lung disease, depressive symptoms, and fasting status

associations between the studied variables and stroke risk. Then we excluded those individuals who experienced a stroke within 2 years ($n=50$), The risk for stroke increased with each elevating quartile of baseline CMI levels, with adjusted HRs and 95% CIs being 1.28 (0.97–1.68), 1.49 (1.14–1.96), and 1.46 (1.08–1.98) for Q2, Q3, and Q4, respectively. Moreover, participants with levels of hs-CRP ≥ 2 mg/L also had significantly higher stroke incidence compared to those with hs-CRP levels < 2 mg/L (HR 1.22, 95% CI 1.03–1.46). Last, of the

Table 3 Incremental predictive value of hs-CRP and CMI

	C Statistics		NRI (Continuous)		IDI	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Basic model	0.6882 (0.6675–0.7090)	< 0.001	Reference		Reference	
+ hs-CRP (Ln)	0.6899 (0.6694–0.7105)	< 0.001	0.1124 (0.0293–0.1955)	0.008	0.0007 (0.000-0.0015)	0.055
+ Cardiometabolic index (Ln)	0.6914 (0.6709–0.7120)	< 0.001	0.0909 (0.0079–0.1739)	0.032	0.0012 (0.0002–0.0022)	0.016
+ hs-CRP (Ln) + cardiometabolic index (Ln)	0.6926 (0.6721–0.7130)	< 0.001	0.1299 (0.0469–0.2129)	0.002	0.0018 (0.0006–0.0029)	0.003

8973 blood sample in our analysis, 90.2% were fasting, 8.2% were non-fasting, and 1.6% had an unknown fasting status. To eliminate the influence of food on the accuracy of our study outcomes, a sensitivity analysis was conducted excluding participants who had not fasted. Similar results were obtained and are consistent with previous reports, indicating that non-fasting CRP and lipid profiles possess good predictive value [35, 36]. These results indicated that the associations were not influenced by potential confounding factors in the current analysis.

Subgroup analysis

The association of CMI, hs-CRP with the incidence of stroke was further evaluated in subgroup analyses. The results showed a significant association between high hs-CRP levels and stroke risk in those aged over 65 (p for interaction = 0.034) (Fig. S3). However, in subgroup analysis stratified by sex, smoking status, hypertension, diabetes, dyslipidemia, heart disease and BMI, no statistically significant interaction was found (Fig. S4-10). Besides, there was no interaction between CMI and hs-CRP with respect to the risk of stroke (p for interaction = 0.347).

Discussion

The present study explored the associations between CMI, hs-CRP, and the combined effect of CMI and hs-CRP, with risk of new onset stroke in a large national prospective longitudinal analysis of middle-aged and older Chinese adults. Our data revealed that individual elevated CMI, hs-CRP levels, as well as combined elevated CMI and hs-CRP levels conferred a higher risk for future stroke. The predictive effect was particularly prominent for combined elevated CMI and hs-CRP levels, which was robust even after adjusting for other established stroke risk factors. Our findings indicated that baseline CMI and levels of hs-CRP could serve as reliable markers for assessing stroke risk stratification, providing significant insights for clinical practice and public health initiatives.

Obesity serves as a significant risk factor for diabetes, hyperlipidemia and hypertension. Besides, adipocytes produce various physiologically active substances, including leptin, adiponectin, tumor necrosis factor, plasminogen activator inhibitor-1, which collectively contribute to the progression of inflammation and atherosclerosis, ultimately leading to stroke and cardiovascular disease [37, 38]. And the relationship between obesity and increased stroke risk has already been well-documented [8]. BMI and WC are conventional indicators of obesity in predicting stroke. A systemic review and meta-analysis included 24 studies with 5,798,826 subjects found that higher BMI was linked to an elevated overall risk of stroke, yielding a combined relative risk value of 1.25 [37]. Furthermore, the results of a Chinese cohort study showed that higher WC levels were linked to an increased risk of stroke, with each SD rise in WC corresponding to a 24% elevation in stroke risk [39]. However, BMI has limitations in providing comprehensive information about body composition and body fat distribution. Similarly, WC, while useful, is inadequate for differentiating between visceral adipose tissue and abdominal subcutaneous adipose tissue, and its accuracy may be influenced by variables such as age and height [40, 41]. Given these limitations, neither of them precisely indicates obesity when predicting stroke risk. The WHtR, a practical and age-sensitive metric considering both height and central adiposity, was proved to be a more beneficial alternative than BMI and WC for assessing stroke-related risk factors, including hypertension, diabetes, dyslipidaemia, metabolic syndrome, and cardiovascular disease [42]. And its role in predicting stroke risk deserves further investigation.

Moreover, obesity is closely linked to abnormal lipid metabolism, and lipids play a complex role in the development of stroke. TG is crucial for lipid exchange between lipoprotein CM (chylomicrons) and VLDL (very low-density lipoproteins), as well as cholesterol exchange in lipoprotein LDL (low-density lipoproteins) and HDL. Elevated TG levels enhance lipid exchange activity, leading to a rise in compact LDL levels, a decrease in HDL levels, subsequently increasing atherogenic factors, and ultimately contributing to the development of stroke [43]. Conversely, HDL-C facilitates reverse cholesterol transport, exerting an anti-atherogenic effect, and increased HDL-C levels alleviate carotid plaque instability and stroke risk [44]. Recent studies have established TG/HDL-C as a novel marker for LDL molecular particle size, revealing that a higher ratio of TG/HDL-C correlates with a heightened risk of atherosclerosis [45], stroke [46], and progressive infarction [47]. CMI is a novel index that integrates obesity and lipid metabolism metrics by utilizing WHtR and TG/HDL-C. Prior research has shown that CMI exhibits superior predictive ability

for cardiovascular diseases and stroke risk factors, such as hypertension and diabetes, as mentioned above. Additionally, CMI has been proved to be independently correlated with the risk of ischemic stroke and stroke risk among rural residents. Nevertheless, research examining the connection between CMI and the overall stroke risk in the general populace remains scarce. The current study has addressed the previously identified deficiency and demonstrated a statistically significant positive association between CMI and the risk of future stroke, with each 1-unit increase in baseline CMI was associated with a 19% elevated risk of stroke after adjusting for potential confounding factors.

The inflammatory response and immune regulation are widely acknowledged to be crucial factors in the pathogenetic process of stroke [48]. And as an extensively studied inflammation biomarker which often used in vascular risk prediction, hs-CRP was also proved to be associated with risk of stroke [49, 50]. Consistent with previous studies, we discovered that individuals with higher levels of hs-CRP (≥2 mg/L) had a 1.24 times greater probability of stroke compared to those with lower levels (<2 mg/L), and each additional unit of hs-CRP increased the risk of stroke by 11%. Obesity contribute to the development of stroke by influencing lipid metabolism and inflammatory responses [50], and lipids may further exacerbate stroke risk via inflammatory pathways. The intricate interplay between obesity, lipids, and inflammation highlights their potential combined effects as powerful predictors of stroke. Based on this, we investigated the effectiveness of combining CMI and hs-CRP in predicting stroke and found that the combination of the highest CMI quartiles with higher hs-CRP levels was the strongest indicator of new-onset stroke. Hs-CRP has been reported to influence the development of obesity by directly impacting body weight, insulin sensitivity, and glucose homeostasis through the regulation of central leptin effects and hypothalamic signaling [51]. Moreover, hs-CRP is directly associated with highly atherogenic oxidized LDL-C, facilitating monocyte adhesion and transmigration into the vessel wall, as well as catalyzing the polarization of macrophages towards a proinflammatory phenotype, thus contributing to atherosclerosis [52]. And obesity, reduced insulin sensitivity, glucose abnormalities, and atherosclerosis are all factors that enhance the risk of stroke. The synergistic effects of obesity, dyslipidemia, and inflammation may explain the superior effect of combining the highest CMI quartiles with higher hs-CRP levels in predicting the risk of stroke.

Strengths and limitations

The strength of this study lies in being the largest population-based prospective study to explore the intricate relationships among obesity, lipid metabolism, inflammation, and stroke risk. Besides, the study is well-designed, employing survey instruments based on the best international practices, and it has been harmonized with numerous other studies, enabling the provision of nationally representative data for middle-aged and older Chinese adults [26]. However, certain limitations exist in this study. Firstly, relying on self-reported stroke events may have introduced bias and resulted in the omission of undiagnosed stroke cases. Nevertheless, the use of detailed questionnaires by trainees from advanced training centers, combined with multiple follow-up visits, may help to reduce this deficiency. Besides, the reliability of self-reported outcomes has been reported in previous literature, offering a degree of certainty in their accuracy [53, 54]. Secondly, as this study is observational in nature, we are unable to establish a causal link between CMI, hs-CRP, and the risk of stroke. Further clinical trials are necessary to validate the results. Thirdly, multiple covariates such as dietary habits, genetic predisposition, and other inflammatory markers may be significant in predicting new-onset stroke, which is worthy of further exploration. Finally, our study employs data derived from a single Chinese population, hence the results may not generalize to other ethnic groups. Additional external validation is required to validate the results further.

Conclusions

In summary, by utilizing data gathered from a national cohort of Chinese adults in a large prospective study, we found that the combination of CMI and hs-CRP levels was significantly associated with increased stroke risk, thereby highlighting the coexposure effect of obesity, lipid metabolism, and inflammation on the occurrence of stroke. This discovery has the potential to improve the accuracy of clinical markers used for stratifying stroke risk, and interventions targeting these risk factors may offer promise for reducing stroke incidence.

Abbreviations

ANOVA	Analysis of variance
BMI	Body Mass Index
CHARLS	China Longitudinal Study on Health and Retirement
CI	Confidence intervals
CM	Chylomicrons
CMI	Cardiometabolic Index
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoproteincholesterol
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
LDL	Low-density lipoproteins
RCS	Restricted cubic spline
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglyceride
VLDL	Very low-density lipoproteins
WC	Waist circumference
WHtR	Waist-to-height ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
Study conception and design: WZ and JZ, manuscript writing: FL and WZ, statistical analysis: YH and FL, manuscript revision: AY and MX, Study supervision: WZ and JZ.

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Data availability
The datasets used in the present study are available from the corresponding author on reasonable request.

Declarations

Informed consent
The study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). Written informed consent was obtained from all participants involved in this study.

Competing interests
The authors declare no competing interests.

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