Cardiovascular Diabetology

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How does biological age acceleration mediate the associations of obesity with cardiovascular disease? Evidence from international multi-cohort studies

Lin Hu[1†], Jiayuan Li[1†], Zihuan Tang[1], Peng Gong[1], Zongqi Chang[1], Chen Yang[1], Tianpei Ma[1], Shuang Jiang[1], Chunxia Yang[1*] and Tao Zhang[1*]

Abstract

Background Recent basic biological research found that obesity accelerates biological aging and increases cardiovascular disease (CVD) risk. However, there is still a lack of real-world population evidence. This study aimed to explore the potential mediation roles of biological age acceleration in the associations between different dimensions of obesity characterization and incident CVD.

Methods This international multi-cohort study included participants aged over 45 years with 3 waves longitudinal data from China Health and Retirement Longitudinal Study (CHARLS). China Health and Nutrition Survey (CHNS) was used to develop Klemera-Doubal method-biological age (KDM-BA), and the validation analysis was performed in UK Biobank (UKB) and Hongguang Elderly Health Examination Cohort (HEHEC). Obesity indices including body mass index (BMI), waist circumference (WC), waist height ratio (WtHR), body roundness index (BRI) for body shape; Chinese visceral adiposity index (CVAI), lipid accumulation product (LAP) for visceral fat accumulation; triglyceride-glucose index (TyG) and its derivatives (TyG-BMI, TyG-WC, TyG-WtHR) for metabolic function were used to measure obesity across different dimensions. Biological age acceleration was evaluated by the classic KDM-BA acceleration (KDM-BAacc). Causal mediation analyses assessed the role of biological age acceleration in mediating obesity and incident CVD.

Results In CHARLS, the median follow-up period was 9.00 years, with a baseline age of 58 (52, 65) years. Obesity, KDM-BAacc, and CVD were all significantly associated with each other. For each 1-year increase in KDM-BAacc, the risk of incident stroke, heart disease and CVD increased by 68% (*OR* 1.68, 95% *CI* 1.35–2.09), 35% (*OR* 1.35, 95% *CI* 1.15–1.59), and 44% (*OR* 1.44, 95% *CI* 1.25–1.65), respectively. KDM-BAacc mediated the associations between BMI, WC, WtHR, BRI, CVAI, LAP, TyG-BMI, TyG-WC, TyG-WtHR, with CVD, with the mediation proportions ranging

[†]Lin Hu, Jiayuan Li contributed equally to this work.

*Correspondence:
Chunxia Yang
yangchunxia@scu.edu.cn
Tao Zhang
statzhangtao@scu.edu.cn

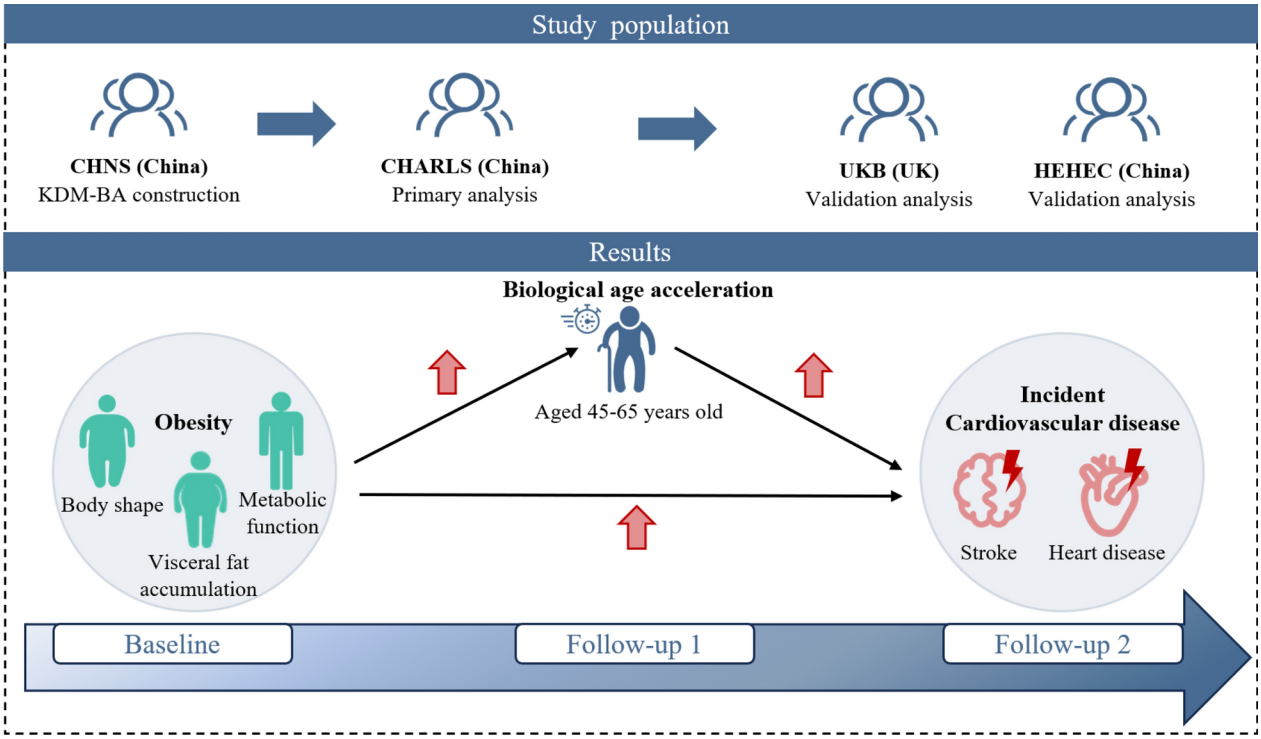
Full list of author information is available at the end of the article

from 10.03 to 25.46%. However, the mediating effect was significant mostly in middle-aged individuals aged 45–65 years. Furthermore, sex differences existed in the mediation mechanisms. Biological age acceleration strongly mediated body shape indices and incident CVD in males, whereas in females, it predominantly mediated visceral fat accumulation and metabolic function dimensions with incident CVD. Similar main results were found in UKB and HEHEC.

Conclusions Biological age acceleration partially mediates the relationship between obesity and incident CVD. This temporal evidence firstly validated the mediation pathway based on international cohorts, emphasizing the importance of addressing biological aging processes in population aged 45–65 years while providing sex-specific obesity intervention strategies to prevent CVD.

Keywords Biological age acceleration, Obesity, Cardiovascular disease, Cohort

Graphical abstract



Background

Cardiovascular diseases (CVD), especially stroke and ischemic heart disease, remain leading causes of morbidity and mortality globally, particularly among older adults [1, 2]. With rapid global aging, CVD prevalence is projected to increase substantially by 2050, posing significant public health challenges [3, 4]. Obesity, a significant modifiable risk factor for CVD [5], is inadequately captured by commonly used indices [6–8]. Therefore, obesity and its metabolic risks should be evaluated from multiple dimensions, including body shape, visceral fat accumulation, and metabolic function.

Recent basic biological research demonstrated that obesity promoted biological aging through chronic inflammation and oxidative stress, impairing endothelial function and accelerating vascular aging [9, 10]. In adipose tissue, abnormal adipokine release and immune cell infiltration further intensify this pro-inflammatory environment [11], hastening aging and heightening the risk of cardiovascular diseases [12–14]. However, research in real-world populations investigating the mediation pathway from obesity to incident CVD through biological age acceleration is still lacking, particularly among middle-aged and older individuals at high risk of CVD.

Currently, there is no gold standard for quantifying biological aging process. Different biological age (BA) estimation methods, including epigenetic clocks, Phenotypic Age (PhenoAge), and the Klemera-Doubal method (KDM), may capture distinct dimensions of aging [15]. KDM calculates biological age using routine clinical biomarkers, is accessible and broadly applicable in

epidemiological studies, and correlates with multiple age-related diseases and mortality [16]. We hypothesized that the relationship between obesity and incident CVD was mediated by biological age acceleration. Biological age acceleration refers to the state in which an individual's biological age exceeds their chronological age (CA), indicating faster aging and often associated with a decline in physiological function. In this study, it was calculated as the difference between the CA and classic KDM-biological age (KDM-BA) [17]. Based on longitudinal follow-up data from the China Health and Retirement Longitudinal Study (CHARLS), the UK Biobank (UKB), the Hongguang Elderly Health Examination Cohort (HEHEC), and the China Health and Nutrition Survey (CHNS), we studied the associations between different dimensions of obesity characterization, biological age acceleration, and incident CVD, examined whether and to what extent biological age acceleration mediates the associations of obesity and incident CVD, thereby emphasizing the importance of early-stage health care interventions to reduce CVD occurrence.

Methods

Study population

The primary analysis was based on China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal survey conducted in China established in 2011, and subsequent follow-up surveys were scheduled at biennial intervals [18]. The CHARLS baseline survey utilized multistage stratified probability proportional sampling, with interviews conducted with a nationally representative sample of the Chinese aged 45 years and older. More details of CHARLS were described elsewhere [19]. As blood samples were only collected in waves 1 and 3 [20], we utilized 3 waves data to establish a temporal sequence between obesity and baseline characteristics (wave 1, 2011), biological age acceleration (wave 3, 2015), and incident CVD (wave 5, 2020), leaving a final sample of 4458 participants. To examine reproducibility of the conclusions, we repeated main analyses in UKB and part results in HEHEC. The UKB and HEHEC [21, 22] were both analyzed using different study designs and formed two cohorts each, with UKB1 ($n = 166277$) and HEHEC1($n = 21776$) having large sample sizes, and UKB2 ($n = 7263$) and HEHEC2 ($n = 9701$) having rigorous longitudinal data (see Fig. 1 and Supplementary Material for details).

All participants or their legal representatives provided written informed consent to participate in the baseline and follow-up surveys. CHARLS was approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015), and UKB was approved by the Northwest Multicenter Research Ethics Committee on May 10, 2016 (reference: 16/NW/0274). HEHEC was approved by Ethics Committee of West China Fourth Hospital and West China School of Public Health, Sichuan University (approval number: Gwll2024175), and all participants provided written informed consent [21–23].

Assessment of obesity

Obesity indices (BMI, WC, WtHR, BRI for body shape; CVAI, LAP for visceral fat accumulation; TyG, TyG-BMI, TyG-WC, TyG-WtHR for metabolic function) were used to measure obesity across different dimensions [24, 25], with calculation details provided in Supplementary Material. These obesity indices were standardized and

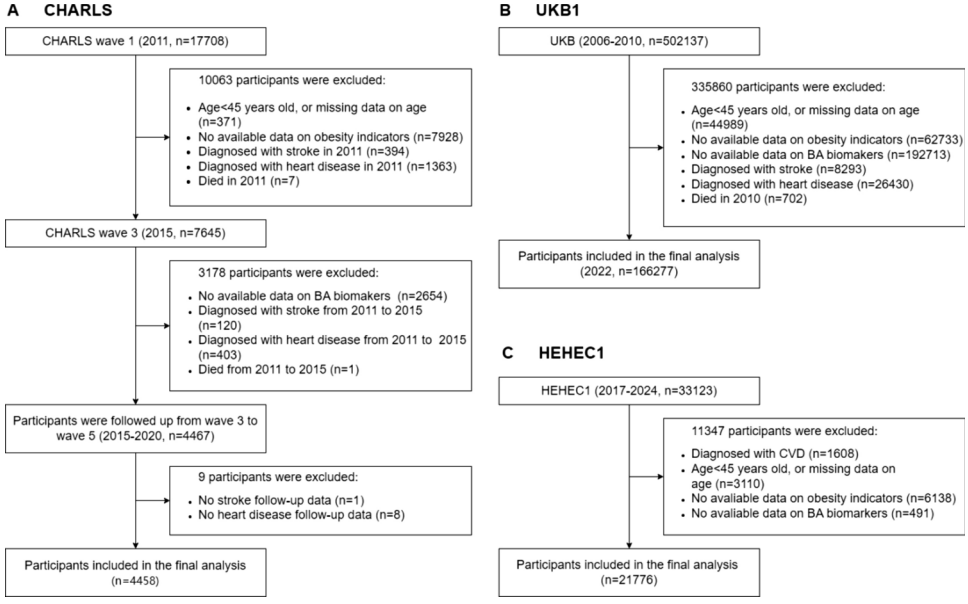


Fig. 1 Flow diagram for participants of CHARLS, UKB1 and HEHEC1. **A**, **B**, and **C** were flow diagrams for CHARLS, UKB1, and HEHEC1, respectively.

also categorized into 3 groups based on tertiles, with the cut-off values provided in Supplementary Material Table S1 for CHARLS. However, according to the Chinese standard, BMI was categorized as underweight and normal (BMI < 24 kg/m^2), overweight (24 ≤ BMI ≤ 28 kg/m^2), and obese (≥ 28 kg/m^2). WC was categorized as normal (< 85 cm for males and < 80 cm for females), abdominal obesity pre-phase (85–90 cm for males and 80–85 cm for females), and abdominal obesity (≥ 90 cm for males and ≥ 85 cm for females) [26].

Development of KDM-BA and KDM-BAacc

The classical KDM was used to construct BA, a validated approach in both Chinese and UK populations, demonstrating effective prediction of age-related health outcomes [27]. Refer to previous studies [28], we trained KDM-BA in the China Health and Nutrition Survey (CHNS) cohort aged 20–79 years, using 12 selected candidate biomarkers, including total cholesterol (TC), triglycerides (TG), albumin, glycated hemoglobin (HBA1C), urea, creatinine, high-sensitivity C-reactive protein (hs-CRP), red blood cell count (RBC), platelet count (PLT), ferritin, transferrin, and systolic blood pressure (SBP), which represent various domains of physical function. Then, projecting the trained KDM-BA onto CHARLS, UKB and HEHEC. As 4 biomarkers (albumin, RBC, ferritin, and transferrin) were unavailable in CHARLS, KDM-BA was computed using the remaining 8 biomarkers. Similarly, ferritin and transferrin were unavailable in UKB, and 6 biomarkers (HBA1C, urea, hs-CRP, RBC, ferritin, transferrin) were unavailable in the HEHEC, so KDM-BA was computed using the remaining biomarkers. The KDM-BA measurements were conducted at wave 3 (2015) in CHARLS, wave 1 (2006–2010) in UKB1 and wave 2 (2012–2013) in UKB2, the first and last year of follow-up during 2017–2024 in HEHEC1 and HEHEC2, respectively. Participants' CAs were recorded concurrently with BA assessments. Correlation(*r*), mean absolute error (*MAE*) and root mean square error (*RMSE*) were used to evaluate KDM-BA accuracy [29].

To adjust for the effect of CA, KDM-BAacc was calculated as the residual from a linear regression of KDM-BA on CA. The final KDM-BAacc was expressed in years to measure biological age acceleration, with a positive value indicating a clinical profile typical of an older individual, while a negative score reflected a younger clinical profile characteristic. KDM-BA calculation was performed by "BioAge" R package [30].

Assessment of incident CVD

The primary outcome for this study was incident CVD. Subjects with heart disease or stroke were defined as suffering from incident CVD. Similar to previous studies, incident CVD in CHARLS was identified based on responses to the questions per wave: "Have you been diagnosed with a heart attack, angina, coronary heart disease, heart failure, or other heart issues?", "Has a doctor diagnosed you with a stroke?", or "Are you currently receiving any of the following treatments (Chinese traditional medicine/Western medicine/Other treatments/None of the above) for stroke, heart disease, or their complications?" [4, 23, 31, 32]. The diagnosis of CVD in the UKB and HEHEC followed the standard of the American Heart Association, with CVD encompassing ischemic heart disease (IHD) (ICD-10: I20–I25) and stroke (ICD-10: I60, I61, I63, I64, I69.0, I69.1, I69.3, and I69.4) [33]. UKB's CVD diagnosis came from the 2022 primary care, hospital admissions, death records, and self-reported medical conditions, and provided each participant with the date of the first occurrence in any source [34]. HEHEC's CVD diagnosis was confirmed by linking the 2023 health examination data to the Medical Record Home Disease Diagnosis Information System managed by the Sichuan Health Information Center.

Assessment of covariates

Based on previous studies, the covariates included in this study were age, sex (male or female), education level (illiteracy, elementary school or below, middle school, or high school or above), marital status (married or others), residential area (rural or urban), smoking pack years, alcohol use (non-drinker, rare drinker, regular drinker), physical activity (yes or no), hypertension (yes or no), diabetes (yes or no), and hyperlipidemia (yes or no) in baseline [35, 36], and see Supplementary Material for details.

Statistical analysis

Descriptive statistics reported the baseline characteristics of participants, with continuous variables reported as median (interquartile range, *IQR*) and categorical variables summarized as count (percentage). Differences in characteristics by incident CVD were tested using Wilcoxon rank test for continuous variables and Chi-square test for categorical variables. The missing proportion for covariates was below 20%. We have identified the missing mechanism [37] before mode or median method was chosen to deal with missing data. Furthermore, we also repeated the primary analysis under different missing data handling methods to ensure results robustness (see sensitivity analyses).

To evaluate the potential mediating role of biological age acceleration (measured by KDM-BAacc) in the association with obesity with incident CVD, we employed a longitudinal design that enabled the determination of temporal ordering. As shown in Fig. 2, we considered three pathways (a: obesity → biological age acceleration; b: biological age acceleration → incident CVD; c: obesity → incident CVD). For path a, multiple linear

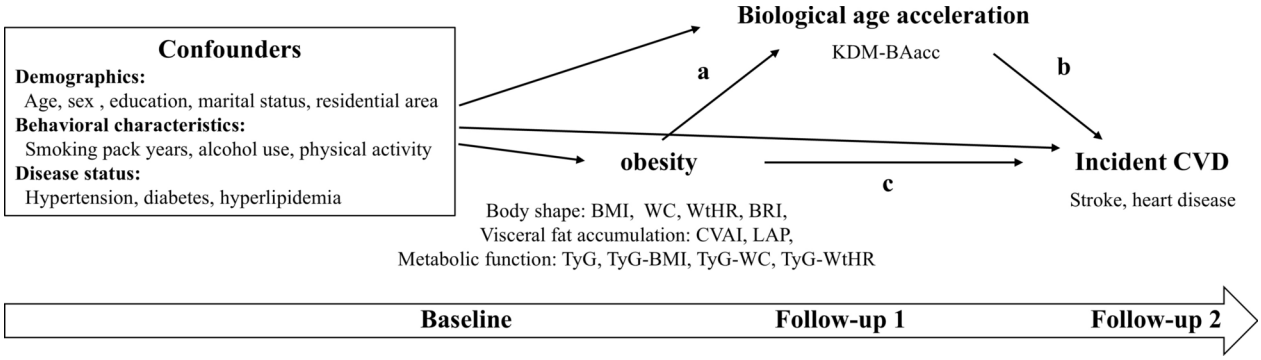


Fig. 2 Causal diagram illustrating postulated causal relationships between obesity, biological age acceleration and incident CVD. In CHARLS, Baseline, Follow-up 1, and Follow-up 2 referred to assessments taken in 2011, 2015, and 2020, respectively.

regression models were used to investigate the associations of obesity with biological age acceleration. The coefficient (β) and 95% confidence interval (95%*CI*) per standard deviation (*SD*) increase in obesity indices were reported. For path b and c, logistic regression models were performed to investigate the associations of obesity and biological age acceleration with incident CVD. The odds ratio (*OR*) and 95%*CI* were reported. Trend test was used to investigate the linear trend of obesity with biological age acceleration and incident CVD. Causal mediation analyses were conducted to assess whether biological age acceleration mediated the relationship between obesity and incident CVD, and to estimate the mediation proportions [38, 39]. The total causal effect (TCE) of obesity on incident CVD was partitioned into the natural direct effect (NDE), which represents the impact of obesity through mechanisms other than biological age acceleration, and the natural indirect effect (NIE), which reflects the effect of obesity via biological age acceleration. The following assumptions were made: there were no unmeasured confounders for paths a, b, and c. Additionally, no confounders of path b were influenced by obesity, given the other confounders [40]. The above analysis was primarily conducted in CHARLS, while the validation analysis was performed with data from UKB and HEHEC. However, due to insufficient follow-up time, incident CVD data could not be obtained, and only path a was validated in HEHEC.

Furthermore, to enhance the validity of our main findings, sensitivity analyses were conducted in CHARLS with regards to nine aspects: (1) Mitigating reverse causation. We excluded individuals who developed CVD within 1 year of biological age acceleration follow-up to mitigate potential reverse causation [41]; (2) Reducing temporal bias. We excluded individuals with biological age acceleration at baseline to mitigate potential temporal bias between obesity and biological aging; (3) Quartile-based categorization. We categorized obesity indices into four groups based on quartiles; (4) AHA-based BMI categorization. BMI was categorized according to the American Heart Association (AHA) criteria, including underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2) [42]; (5) Confounder adjustment for physical activity. Physical activity was included as a confounder, and complete-case analysis was performed to address the missing of physical activity; (6) Medication-based confounder adjustment. We replaced the confounders of hypertension, diabetes, and dyslipidemia with a history of antihypertensive medication, diabetes medication, and dyslipidemia medication, respectively; (7) Validation using PhenoAgeAccel [43] in UKB. PhenoAgeAccel was calculated in UKB with concentrations of albumin, alkaline phosphatase, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean cell volume, red blood cell distribution width, white blood cell count and CA; (8) Assessment of unmeasured confounding. We calculated the *E*-value to evaluate the potential impact of unmeasured confounding. The *E*-value represents the minimum strength of association an unmeasured confounder would need to have with both treatment and outcome, conditional on measured covariates, to fully explain the observed treatment-outcome association [44]; (9) Missing data handling. We repeated the primary analysis using both multiple imputation and complete case analysis to assess the robustness of the results under different missing data handling methods.

Finally, subgroup analyses based on sex and baseline age were conducted to explore potential effect heterogeneity. All statistical analyses were conducted using R 4.3.3, with "medflex" package [45] employed for causal mediation analyses. A two-tailed $P < 0.05$ was considered statistically significant in all tests.

Results

Population characteristics

Table 1 summarized the characteristics of CHARLS participants stratified by incident CVD. Characteristic of UKB and HEHEC were presented in Supplementary Material Table S2. The characteristics and performance

Table 1 Characteristic analysis in CHARLS

Characteristics	Non-CVD (*N* = 3879)	CVD (*N* = 579)	*P*
Baseline age, median (*IQR*), years	58(51,64)	60(54,65)	**< 0.01**
Follow-up 1 age, median (*IQR*), years	62(55,68)	64(58,69)	**< 0.01**
Female, *n*(%)	2016(51.97)	336(58.03)	**< 0.01**
Urban, *n*(%)	1236(31.86)	176(30.40)	0.48
Education level, *n*(%)			**< 0.01**
Illiteracy	1055(27.20)	177(30.57)	
Elementary school or below	1641 (42.30)	263 (45.42)	
Middle school	842 (21.71)	92 (15.89)	
High school or above	341 (8.79)	47 (8.12)	
Married, *n*(%)	392 (10.11)	61 (10.54)	0.75
Smoking pack years, median(*IQR*)	0.00 (0.00,7.00)	0.00 (0.00, 0.00)	0.14
Alcohol use, *n*(%)			0.92
Non-drinker	2250 (58.00)	338 (58.38)	
Rare drinker	388 (10.00)	60 (10.36)	
Regular drinker	1241 (31.99)	181 (31.26)	
Physical activity, *n*(%)	987 (59.07)	128 (51.20)	**0.02**
Hypertension, *n*(%)	1284 (33.10)	272 (46.98)	**< 0.01**
Diabetes, *n*(%)	484 (12.48)	97 (16.75)	**< 0.01**
Dyslipidemia, *n*(%)	1731 (44.62)	301 (51.99)	**< 0.01**
BMI, median (*IQR*)	22.96 (20.78, 25.35)	23.86 (21.68, 26.59)	**< 0.01**
WC, median (*IQR*)	84.00 (77.60, 90.90)	87.50 (80.60, 94.10)	**< 0.01**
WtHR, median (*IQR*)	0.53 (0.49, 0.58)	0.55 (0.51, 0.60)	**< 0.01**
BRI, median (*IQR*)	3.93 (3.15, 4.94)	4.38 (3.50, 5.43)	**< 0.01**
CVAI, median (*IQR*)	89.85 (65.13, 117.66)	104.03 (78.51, 134.93)	**< 0.01**
LAP, median (*IQR*)	25.51 (13.96, 45.19)	32.72 (19.14, 55.89)	**< 0.01**
TyG, median (*IQR*)	8.56 (8.20, 9.00)	8.67 (8.31, 9.14)	**< 0.01**
TyG-BMI, median (*IQR*)	196.89 (174.24, 223.75)	208.74 (184.26, 238.68)	**< 0.01**
TyG-WC, median (*IQR*)	718.68 (647.88, 804.03)	760.08 (677.28, 849.33)	**< 0.01**
TyG-WtHR, median (*IQR*)	4.57 (4.08, 5.11)	4.82 (4.30, 5.42)	**< 0.01**
KDM-BA, median (*IQR*),years	61.18 (54.79, 67.66)	63.44 (57.74, 69.00)	**< 0.01**
KDM-BAacc, median (*IQR*),years	− 0.72 (− 1.10, − 0.27)	− 0.53 (− 0.90, − 0.04)	**< 0.01**

Bold text in the table represented statistically significant results

IQR interquartile range. Follow-up 1 age referred to the age at the time point used for calculating KDM-BA.

of KDM-BA were shown in the Supplementary Material, and the KDM-BA developed in this study demonstrated good accuracy in *r*, *MAE* and *RMSE*. Among the 4458 participants in CHARLS, the median follow-up period was 9.00 years, the median baseline age was 58 (52, 65) years old, the median KDM-BAacc was − 0.70 (− 1.08, − 0.24) years, and 52.76% were female. A total of 579 (12.99%) participants developed CVD, while 3879 (87.01%) did not develop CVD.

Comparisons of the CVD group with the non-CVD group showed significant differences in age, sex, education level, hypertension, diabetes, hyperlipidemia, 10 obesity indices, KDM-BA and KDM-BAacc (all $P < 0.01$). Compared to the non-CVD group, individuals with CVD were older, more likely female, had lower educational attainment and physical activity, and exhibited significantly higher prevalence of hypertension, diabetes, dyslipidemia, as well as elevated obesity indices and KDM-BA values.

Table 2 Associations between obesity and KDM-BAacc in CHARLS

Obesity	Association, *β*(95%*CI*)				P_{trend}
	Per *SD*	Tertile 1	Tertile 2	Tertile 3	
BMI	0.07 (0.05–0.08)	Ref	0.11 (0.07–0.16)	0.17 (0.10–0.23)	**< 0.01**
WC	0.08 (0.07–0.10)	Ref	0.12 (0.07–0.17)	0.19 (0.15–0.23)	**< 0.01**
WtHR	0.08 (0.06–0.10)	Ref	0.10 (0.05–0.14)	0.21 (0.16–0.25)	**< 0.01**
BRI	0.08 (0.06–0.10)	Ref	0.10 (0.05–0.14)	0.21 (0.16–0.25)	**< 0.01**
CVAI	0.09 (0.07–0.11)	Ref	0.10 (0.06–0.14)	0.21 (0.16–0.26)	**< 0.01**
LAP	0.07 (0.05–0.09)	Ref	0.11 (0.06–0.15)	0.22 (0.17–0.28)	**< 0.01**
TyG	0.10 (0.08–0.12)	Ref	0.07 (0.03–0.11)	0.17 (0.11–0.22)	**< 0.01**
TyG-BMI	0.10 (0.08–0.12)	Ref	0.13 (0.09–0.17)	0.24 (0.19–0.29)	**< 0.01**
TyG-WC	0.12 (0.10–0.14)	Ref	0.12 (0.07–0.16)	0.25 (0.20–0.30)	**< 0.01**
TyG-WtHR	0.12 (0.10–0.14)	Ref	0.10 (0.06–0.15)	0.23 (0.18–0.28)	**< 0.01**

Bold text in the table represents statistically significant results

Associations between obesity and KDM-BAacc

As shown in Table 2, per *SD* rose in the 10 obesity indices were all positively associated with KDM-BAacc in CHARLS. The effects of TyG-WC and TyG-WtHR on KDM-BAacc were the greatest among all indicators, both estimated at 0.12 (0.10–0.14) per *SD*. Consistently, when considered as ordinal variables, the KDM-BAacc increased significantly with the elevated tertile of obesity indices (all $P_{trend} < 0.01$). Compared with the first tertile, the other two tertiles of obesity indices were strongly associated with KDM-BAacc (all $P < 0.01$).

Models adjusted for age, sex, education level, marital status, residential area, smoking pack years, alcohol use, hypertension, diabetes, and hyperlipidemia.

Associations between KDM-BAacc and incident CVD

KDM-BAacc was positively associated with incident CVD in CHARLS. For each 1-year increase in KDM-BAacc, the risk of incident stroke, heart disease and CVD increased by 68% (*OR* 1.68, 95% *CI* 1.35–2.09), 35% (*OR* 1.35, 95% *CI* 1.15–1.59), and 44% (*OR* 1.44, 95% *CI* 1.25–1.65), respectively (Table 3).

Associations between obesity and incident CVD

Obesity indices were significantly correlated with incident CVD, and 1 *SD* increase in BMI (*OR* 1.22, 95% *CI* 1.12–1.33), WC (*OR* 1.30, 95% *CI* 1.18–1.42), WtHR (*OR* 1.25, 95% *CI* 1.14–1.38), BRI (*OR* 1.25, 95% *CI* 1.14–1.37), CVAI (*OR* 1.30, 95% *CI* 1.17–1.44), LAP (*OR* 1.10, 95% *CI* 1.01–1.20), TyG (*OR* 1.11, 95% *CI* 1.00–1.24), TyG-BMI (*OR* 1.26, 95% *CI* 1.14–1.38), TyG-WC (*OR* 1.32, 95% *CI* 1.19–1.47), TyG-WtHR (*OR* 1.29, 95% *CI* 1.16–1.44) levels were significantly associated with a greater incident CVD. Except for TyG, the tertile 3 of obesity indices had a stronger association with incident CVD than the other tertiles ($P_{trend} < 0.01$).

The relationship between obesity and stroke or heart disease followed a similar pattern. However, the positive association between obesity and stroke was stronger. TyG-WtHR showed the largest effect (*OR* 1.48, 95% *CI* 1.25–1.74), followed by CVAI (*OR* 1.42, 95% *CI* 1.21–1.66) and TyG-WC (*OR* 1.41, 95% *CI* 1.20–1.66). In contrast, the effect on heart disease was slightly attenuated. LAP, TyG, and heart disease have yet to show a statistically significant association (Table 4).

Causal mediation analysis of KDM-BAacc on associations of obesity with incident CVD

In the causal mediation analysis (Table 5), KDM-BAacc accounted for 10.08%, 10.03%, 11.58%, 10.96%, 11.09%, 25.46%, 13.01%, 13.30%, 15.09% of the associations of BMI, WC, WtHR, BRI, CVAI, LAP, TyG-BMI, TyG-WC, TyG-WtHR with incident CVD, respectively. The proportions mediated through KDM-BAacc were 23.19% and 23.13% for the associations between LAP, TyG, and stroke, respectively, but no mediation effect was found for heart disease. KDM-BAacc mediated the associations between BMI, WC, WtHR, BRI, CVAI, TyG-BMI, TyG-WC, TyG-WtHR, with CVD, stroke, and heart disease. Among them, the mediation proportion of KDM-BAacc was largest in the relationships between TyG-WtHR with CVD, stroke, and heart disease, accounting for 15.09%, 14.02%, and 21.05%, respectively.

Table 3 Associations between KDM-BAacc and CVD in CHARLS

Outcome	*OR* (95% *CI*)	*P*
Stroke	1.68 (1.35–2.09)	**< 0.01**
Heart disease	1.35 (1.15–1.59)	**< 0.01**
CVD	1.44 (1.25–1.65)	**< 0.01**

Bold text in the table represents statistically significant results

Models adjusted for age, sex, education level, marital status, residential area, smoking pack years, alcohol use, hypertension, diabetes, and hyperlipidemia.

Validation analysis

UKB was used to validate the associations between obesity and incident CVD, as well as the mediating effect of KDM-BAacc, with results shown in Fig. 3. In UKB1, the findings were similar to CHARLS. However, the associations between LAP, TyG and heart disease were statistically significant, whereas no significant association with stroke was observed. KDM-BAacc mediated the relationships between WC, WtHR, BRI, CVAI, TyG-WC, TyG-WtHR, with CVD, stroke, and heart disease. The results for UKB2 were presented in Supplementary Material Figure S3, where KDM-BAacc mediated the association between obesity and incident CVD, but with an attenuated effect.

HEHEC was used to validate the associations between obesity and KDM-BAacc, with results presented in Table 6. In HEHEC1, the findings were consistent with those from CHARLS. Per *SD* increase in the 10 obesity indices showed positive associations with KDM-BAacc in HEHEC1. The results for HEHEC2 were shown in Supplementary Material Table S4, where obesity remained associated with KDM-BAacc, though the effect was attenuated.

Sensitivity analysis

The sensitivity analysis was carried out from nine aspects, and the analysis results of each aspect were summarized below.

(1) Mitigating reverse causation. Consistent results were observed after excluding individuals who developed CVD within 1 year of biological age acceleration follow-up (Supplementary Material Figure S4).
(2) Reducing temporal bias. Excluding individuals with baseline biological age acceleration also yielded consistent results, with KDM-BAacc still mediating the association between obesity and incident CVD (Supplementary Material Figure S5).
(3) Quartile-based categorization. The results remained consistent when obesity indices were further categorized into quartiles (Supplementary Material Tables S5–S6).
(4) AHA-based BMI categorization. Similarly, analyses based on BMI categorization according to the American Heart Association (AHA) criteria produced consistent findings (Supplementary Material Tables S7–S8).
(5) Confounder adjustment for physical activity. Additional adjustment for physical activity as a

Table 4 Associations between obesity and incident CVD in CHARLS

Outcome	Obesity	Association, *OR* (95% *CICI*)				
		Per *SD*	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Stroke						
	BMI	1.27 (1.12–1.43)	Ref	1.30 (0.93–1.82)	1.78 (1.12–2.76)	**0.01**
	WC	1.32 (1.13–1.53)	Ref	1.20 (0.74–1.91)	1.99 (1.39–2.88)	**<0.01**
	WtHR	1.36 (1.17—1.58)	Ref	1.62 (1.07–2.48)	2.36 (1.56–3.63)	**<0.01**
	BRI	1.32 (1.15–1.52)	Ref	1.62 (1.07–2.48)	2.36 (1.56–3.63)	**<0.01**
	CVAI	1.42 (1.21–1.66)	Ref	1.36 (0.89–2.09)	2.00 (1.31–3.08)	**<0.01**
	LAP	1.14 (1.01–1.28)	Ref	2.01 (1.32–3.08)	2.29 (1.43–3.70)	**<0.01**
	TyG	1.25 (1.06–1.48)	Ref	1.15 (0.78–1.69)	1.25 (0.81–1.95)	0.33
	TyG-BMI	1.35 (1.18–1.55)	Ref	2.14 (1.42–3.29)	2.48 (1.59–3.94)	**<0.01**
	TyG-WC	1.41 (1.20–1.66)	Ref	1.65 (1.08–2.54)	2.50 (1.62–3.91)	**<0.01**
	TyG-WtHR	1.48 (1.25–1.74)	Ref	1.73 (1.15–2.65)	2.10 (1.34–3.32)	**<0.01**
Heart disease						
	BMI	1.17 (1.06–1.29)	Ref	1.28 (1.01–1.62)	1.61 (1.16–2.21)	**<0.01**
	WC	1.23 (1.10–1.37)	Ref	1.39 (1.03–1.87)	1.48 (1.15–1.91)	**<0.01**
	WtHR	1.18 (1.06–1.32)	Ref	1.08 (0.83–1.42)	1.23 (0.93–1.63)	0.14
	BRI	1.19 (1.07–1.32)	Ref	1.08 (0.83–1.42)	1.23 (0.93–1.63)	0.14
	CVAI	1.21 (1.08–1.36)	Ref	1.25 (0.95–1.65)	1.50 (1.12–2.02)	**0.01**
	LAP	1.01 (0.90–1.12)	Ref	1.37 (1.05–1.81)	1.39 (1.01–1.91)	0.05
	TyG	1.02 (0.90–1.16)	Ref	1.16 (0.89–1.50)	1.01 (0.74–1.39)	0.86
	TyG-BMI	1.17 (1.05–1.30)	Ref	1.19 (0.91–1.56)	1.42 (1.06–1.91)	**0.02**
	TyG-WC	1.21 (1.07–1.36)	Ref	1.27 (0.97–1.67)	1.54 (1.15–2.07)	**<0.01**
	TyG-WtHR	1.17 (1.04–1.33)	Ref	1.18 (0.89–1.56)	1.49 (1.11–2.02)	**0.01**
CVD						
	BMI	1.22 (1.12–1.33)	Ref	1.31 (1.06–1.61)	1.75 (1.31–2.31)	**<0.01**
	WC	1.30 (1.18–1.42)	Ref	1.38 (1.05–1.80)	1.76 (1.41–2.20)	**<0.01**
	WtHR	1.25 (1.14–1.38)	Ref	1.23 (0.97–1.56)	1.56 (1.22–1.99)	**<0.01**
	BRI	1.25 (1.14–1.37)	Ref	1.23 (0.97–1.56)	1.56 (1.22–1.99)	**<0.01**
	CVAI	1.30 (1.17–1.44)	Ref	1.25 (0.98–1.60)	1.73 (1.34–2.24)	**<0.01**
	LAP	1.10 (1.01–1.20)	Ref	1.54 (1.21–1.97)	1.70 (1.29–2.25)	**<0.01**
	TyG	1.11 (1.00–1.24)	Ref	1.17 (0.93–1.47)	1.12 (0.85–1.47)	0.39
	TyG-BMI	1.26 (1.14–1.38)	Ref	1.49 (1.18–1.90)	1.79 (1.38–2.33)	**<0.01**
	TyG-WC	1.32 (1.19–1.47)	Ref	1.38 (1.08–1.76)	1.93 (1.49–2.50)	**<0.01**
	TyG-WtHR	1.29 (1.16–1.44)	Ref	1.35 (1.06–1.72)	1.71 (1.31–2.23)	**<0.01**

Bold text in the table represents statistically significant results

Models adjusted for age, sex, education level, marital status, residential area, smoking pack years, alcohol use, hypertension, diabetes, and hyperlipidemia.

confounder did not alter the observed associations (Supplementary Material Tables S9–S12).

(6) Medication-based confounder adjustment. Replacing hypertension, diabetes, and dyslipidemia with history of antihypertensive medication, diabetes medication, and dyslipidemia medication, respectively, yielded similarly robust results (Supplementary Material Tables S13–S16).

(7) Validation using PhenoAgeAccel in UKB. In the UKB, analyses using PhenoAgeAccel to measure biological age acceleration demonstrated consistent associations with larger effects (Supplementary Material Figures S6–S7).

(8) Assessment of unmeasured confounding. *E*-value results indicated that only unmeasured confounding with an *OR* exceeding the corresponding *E*-value could alter the observed associations among obesity indices, KDM-BAacc, and incident CVD. However, given the extensive adjustment for measured confounders, the presence of such influential unmeasured confounding was unlikely (Supplementary Material Table S17).

(9) Missing data handling. Results of the missing data mechanism test were provided in the Supplementary Material. Both the multiple imputation and complete case analyses yielded consistent results (Supplementary Material Tables S18–S25).

Subgroup analyses

Subgroup analyses showed that KDM-BAacc mediated body shape indices were more significantly associated with incident CVD in males. In contrast, KDM-BAacc

Table 5 Causal mediation analysis of KDM-BAacc on associations of obesity with incident CVD

Outcome	Obesity	*OR* (95% *CI*), per *SD*			Mediation proportion (%)
		TCE	NDE	NIE	
Stroke					
	BMI	1.28 (1.16–1.42)	1.25 (1.12–1.39)	1.03 (1.01–1.05)	**11.11**
	WC	1.32 (1.15–1.51)	1.27 (1.1–1.46)	1.04 (1.02–1.06)	**14.18**
	WtHR	1.37 (1.19–1.57)	1.32 (1.14–1.52)	1.04 (1.01–1.06)	**11.99**
	BRI	1.33 (1.18–1.49)	1.28 (1.14–1.45)	1.03 (1.01–1.06)	**11.86**
	CVAI	1.43 (1.22–1.66)	1.37 (1.17–1.60)	1.04 (1.02–1.07)	**11.77**
	LAP	1.15 (1.04–1.28)	1.11 (1.00–1.24)	1.03 (1.01–1.05)	**23.19**
	TyG	1.25 (1.05–1.49)	1.19 (1.00–1.42)	1.05 (1.02–1.08)	**23.13**
	TyG-BMI	1.37 (1.22–1.55)	1.32 (1.16–1.49)	1.04 (1.02–1.07)	**13.33**
	TyG-WC	1.41 (1.21–1.65)	1.34 (1.14–1.57)	1.06 (1.02–1.09)	**16.17**
	TyG-WtHR	1.48 (1.26–1.74)	1.40 (1.18–1.66)	1.06 (1.02–1.09)	**14.02**
Heart disease					
	BMI	1.17 (1.07–1.29)	1.15 (1.05–1.27)	1.02 (1.00–1.03)	**10.79**
	WC	1.23 (1.10–1.37)	1.20 (1.07–1.35)	1.02 (1.01–1.04)	**10.72**
	WtHR	1.19 (1.06–1.33)	1.16 (1.03–1.30)	1.02 (1.01–1.04)	**13.03**
	BRI	1.19 (1.07–1.32)	1.17 (1.05–1.30)	1.02 (1.01–1.04)	**11.77**
	CVAI	1.21 (1.08–1.37)	1.18 (1.05–1.34)	1.03 (1.01–1.04)	**13.05**
	LAP	1.01 (0.92–1.12)	0.99 (0.89–1.10)	1.02 (1.01–1.04)	–
	TyG	1.02 (0.89–1.16)	0.99 (0.86–1.12)	1.03 (1.01–1.05)	–
	TyG-BMI	1.18 (1.06–1.31)	1.15 (1.03–1.28)	1.03 (1.01–1.04)	**15.91**
	TyG-WC	1.21 (1.08–1.36)	1.17 (1.04–1.32)	1.03 (1.01–1.06)	**17.14**
	TyG-WtHR	1.17 (1.04–1.33)	1.13 (1.00–1.29)	1.03 (1.01–1.06)	**21.05**
CVD					
	BMI	1.22 (1.13–1.33)	1.20 (1.10–1.30)	1.02 (1.01–1.03)	**10.08**
	WC	1.30 (1.18–1.43)	1.26 (1.15–1.39)	1.03 (1.01–1.04)	**10.03**
	WtHR	1.25 (1.14–1.38)	1.22 (1.11–1.35)	1.03 (1.01–1.04)	**11.58**
	BRI	1.25 (1.14–1.37)	1.22 (1.11–1.34)	1.02 (1.01–1.04)	**10.96**
	CVAI	1.30 (1.17–1.44)	1.26 (1.14–1.40)	1.03 (1.01–1.05)	**11.09**
	LAP	1.10 (1.02–1.19)	1.07 (0.99–1.16)	1.02 (1.01–1.04)	**25.46**
	TyG	1.11 (1.00–1.24)	1.07 (0.96–1.20)	1.04 (1.02–1.06)	34.66
	TyG-BMI	1.26 (1.15–1.38)	1.22 (1.12–1.34)	1.03 (1.01–1.05)	**13.01**
	TyG-WC	1.32 (1.19–1.47)	1.28 (1.15–1.42)	1.04 (1.02–1.06)	**13.30**
	TyG-WtHR	1.29 (1.16–1.44)	1.24 (1.11–1.38)	1.04 (1.02–1.06)	**15.09**

"–" indicated suppression effect and was not reported. Bold indicated statistically significant proportion mediated. Models adjusted for age, sex, education level, marital status, residential area, smoking pack years, alcohol use, hypertension, diabetes, and hyperlipidemia.

mediated visceral fat accumulation and metabolic function indices were more significantly associated with incident CVD in females, especially for stroke. In the individuals aged ≥ 65 in baseline, although most obesity indices were associated with incident CVD, no mediating effect by KDM-BAacc was found. The mediating effect of KDM-BAacc was significant in the population aged 45–65 years (Supplementary Material Figures S8–S10).

Discussion

The findings of this prospective international multicohort study first suggested that biological age acceleration partially mediated the associations of obesity across multiple dimensions and incident CVD. However, this mediating effect was only observed in individuals aged 45–65 years. Furthermore, we found that the mechanisms underlying the associations between obesity, biological age acceleration, and incident CVD differed slightly between sex. Biological age acceleration more strongly mediated the associations between body shape indices and incident CVD in males, whereas in females, visceral fat accumulation and metabolic function dimensions played a more prominent role in the development of biological age acceleration and incident CVD.

Although only a few studies have explored the mediating role of biological age acceleration in the relationship between obesity and incident CVD, our findings aligned with those recent studies. For instance, Li et al. found that biological age acceleration partially mediated the association between unhealthy lifestyles and incident CVD [46]. However, their study focused on a composite unhealthy lifestyle score derived from 5 lifestyle factors,

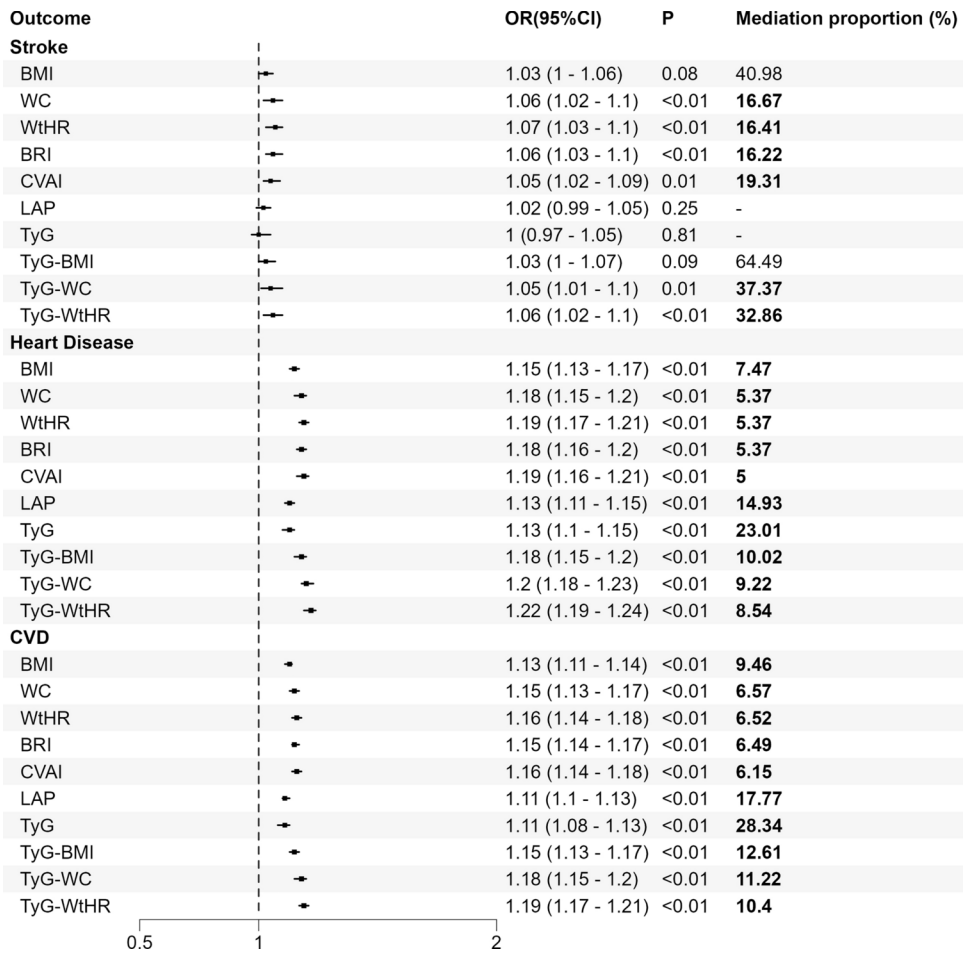


Fig. 3 Associations between obesity, KDM-BAacc and incident CVD in UKB1. "-" indicated suppression effect and was not reported. Bold indicated statistically significant proportion mediated. Models adjusted for age, sex, education level, residential area, smoking pack years, physical activity, hypertension, diabetes, and hyperlipidemia.

including BMI, rather than focusing on obesity. Similarly, Sun et al. identified epigenetic age acceleration as a potential molecular link between childhood BMI and subclinical atherosclerosis, a condition closely related to CVD [13]. Notably, our sensitivity analysis using PhenoAge in the UKB cohort further validated these findings, underscoring the robustness of the observed mediating role of biological age acceleration. Building on these studies, our study offered new insights into the temporal links between obesity, biological age acceleration, and incident CVD by incorporating multidimensional obesity indices and temporal sequence designs, while providing evidence from multiple cohorts to support disease prevention and interventions.

Previous human and animal studies have highlighted chronic inflammation as a central link between obesity, biological age acceleration, and incident CVD. Inflammaging, a persistent low-grade systemic inflammation [47], promotes lipid and fibrous component deposition in arterial walls, forming plaques whose instability and rupture can trigger thrombosis, leading to severe events such as myocardial infarction and stroke [48]. Obesity exacerbates inflammaging through the senescence-associated secretory phenotype (SASP) [49], where senescent cells secrete pro-inflammatory cytokines and proteases, disrupting tissue homeostasis and biological age acceleration [50]. At the cellular level, shared features of obesity and aging, including mitochondrial dysfunction, redox imbalance, and impaired autophagy, drive cellular senescence and reinforce inflammation [10]. This pro-inflammatory environment fosters a vicious cycle among obesity, insulin resistance, and age-related cardiovascular diseases by promoting immune cell infiltration into insulin-responsive tissues, increasing oxidative stress, and reducing insulin receptor expression [51]. Consequently, elevated glucose, lipids, free fatty acids, and reactive oxygen species (ROS) contribute to metabolic syndrome and endothelial dysfunction, accelerating cardiovascular aging and disease progression [11].

Table 6 Associations between obesity and KDM-BAacc in HEHEC1

Obesity	Association, *β* (95% *CI*)				P_{trend}
	Per *SD*	Tertile 1	Tertile 2	Tertile 3	
BMI	0.06 (0.05–0.06)	Ref	0.08 (0.07–0.10)	0.13 (0.11–0.16)	**< 0.01**
WC	0.05 (0.04–0.06)	Ref	0.04 (0.02–0.06)	0.09 (0.07–0.10)	**< 0.01**
WtHR	0.04 (0.03–0.05)	Ref	0.05 (0.03–0.07)	0.09 (0.07–0.10)	**< 0.01**
BRI	0.04 (0.03–0.05)	Ref	0.06 (0.04–0.08)	0.10 (0.08–0.12)	**< 0.01**
CVAI	0.05 (0.04–0.05)	Ref	0.07 (0.05–0.09)	0.10 (0.07–0.12)	**< 0.01**
LAP	0.09 (0.08–0.10)	Ref	0.07 (0.05–0.09)	0.10 (0.08–0.13)	**< 0.01**
TyG	0.09 (0.08–0.10)	Ref	0.06 (0.04–0.08)	0.09 (0.07–0.12)	**< 0.01**
TyG-BMI	0.08 (0.07–0.09)	Ref	0.07 (0.05–0.09)	0.15 (0.13–0.17)	**< 0.01**
TyG-WC	0.07 (0.06–0.08)	Ref	0.08 (0.06–0.10)	0.14 (0.12–0.16)	**< 0.01**
TyG-WtHR	0.07 (0.06–0.08)	Ref	0.07 (0.05–0.09)	0.13 (0.11–0.15)	**< 0.01**

Bold text in the table represents statistically significant results

Models adjusted for age, sex, education level, marital status, alcohol use, hypertension, diabetes, and hyperlipidemia.

This study revealed that biological age acceleration partially mediated the association between obesity and CVD in 45–65 years old individuals, consistent with previous studies [52]. However, in individuals aged 65 years and above, this mediating effect was no longer significant. This may indicate that middle age and early older age represent a critical period where obesity promotes biological age acceleration, thereby increasing CVD risk. While in older adults, cumulative vascular damage and chronic pathological states dominate, prolonged exposure to cardiovascular risk factors and inflammation shifts the primary CVD risk from biological age acceleration to these cumulative pathological changes [53, 54].

Commonly used BMI cannot distinguish the distribution of adipose tissue, such as subcutaneous and visceral fat [32], or detect metabolic abnormalities like insulin resistance [36]. These factors all play critical roles in the development of CVD [55]. To address these limitations, this study evaluated obesity across multiple dimensions, including body shape, visceral fat accumulation, and metabolic function, providing a more comprehensive exploration of the mechanisms linking obesity, biological age acceleration, and incident CVD. The results showed distinct sex-based mechanisms in incident CVD. Body shape was a stronger determinant in males, while visceral fat accumulation and metabolic dysfunction played a more pronounced role in females, particularly in driving biological age acceleration and stroke. These differences can be explained by that males tend to accumulate fat in the abdominal region, reflecting a predisposition to abdominal obesity [56]. In contrast, hormonal changes in women, especially after menopause [57], drive visceral fat deposition and metabolic dysfunction, exacerbating CVD risk through mechanisms such as altered insulin kinetics, glucose and lipid metabolism, and myocardial substrate utilization [58, 59]. Furthermore, this study confirmed that combining TyG with obesity indices offers a better assessment of IR and CVD risk than using the TyG alone, particularly TyG-WtHR [60]. Controlling obesity through healthy lifestyle is expected to be an effective approach to mitigating biological age acceleration and reducing CVD incidence.

This study has several strengths. It is the first to investigate the mediation pathway linking obesity, biological age acceleration, and its impact on incident CVD. The unique longitudinal design enhances the reliability of the findings by capturing temporal relationships. By incorporating multiple obesity indices across different dimensions, this study provides a deeper understanding of the mechanisms involved. Furthermore, the inclusion of multiple international prospective cohorts, along with large samples and rigorous study designs, ensures the generalizability and robustness of the results.

Several limitations of this study should be acknowledged. First, the diagnosis of CVD in CHARLS was self-reported based on the doctor's diagnosis, which may introduce some bias. However, this method aligned with approaches used in many previous studies and is reasonably accurate. The results were further validated using electronic medical records in the UKB supporting reliability. Second, although multiple confounders were adjusted for and *E*-values were calculated to assess the potential impact of unmeasured confounding, the possibility of residual confounding cannot be completely eliminated. Third, due to data limitations, the constructed BA included only a few routine clinical biomarkers and the specific BA biomarkers varied slightly across the three study cohorts, which may affect the interpretability of biological age acceleration. Nevertheless, the KDM-BA applied in this study has been found to be associated with pro-inflammatory pathways and remained an important factor in the development of obesity and CVD [15]. Future studies incorporating multi-omics data could provide a more comprehensive understanding of the underlying mechanisms [61]. Fourth, many participants were excluded due to the longitudinal design, which reduced the sample size. To address this, findings were validated across multiple cohorts with different samples, demonstrating the robustness of the results. However, we also observed that cohorts with rigorous longitudinal designs tended to have a higher median age, thereby attenuating

the effect, as explained previously. We suggest that cohort should enhance follow-up monitoring, particularly in middle-aged populations, to better study and intervene in aging-related effects during earlier life stages. Finally, prospective studies in more diverse populations are still needed to confirm the validity of these findings.

Conclusion

In conclusion, this study was the first to provide temporal evidence that biological age acceleration partially mediates the relationship between obesity and incident CVD across multiple international cohorts. These findings emphasized the importance of addressing biological aging processes in the population aged 45–65 years. The observed sex differences underscore the importance of developing sex-specific strategies. Integrating anti-aging strategies with obesity interventions could play a crucial role in reducing health inequalities and prevent CVD in later life.

Abbreviations

CVD	Cardiovascular disease
CA	Chronological age
BA	Biological age
CHARLS	China Health and Retirement Longitudinal Study
CHNS	China Health and Nutrition Survey
UKB	UK Biobank
HEHEC	Hongguang Elderly Health Examination Cohort
KDM-BA	KDM-biological age
KDM-BAacc	KDM-BA acceleration
BMI	Body mass index
WC	Waist circumference
WHtR	Waist height ratio
BRI	Body roundness index
LAP	Lipid accumulation product
CVAI	Chinese visceral adiposity index
TyG	Triglyceride-glucose
TyG-BMI	Triglyceride-glucose-body mass index
TyG-WC	Triglyceride-glucose-waist circumference
TyG-WHtR	Triglyceride-glucose-waist height ratio
TC	Total cholesterol
TG	Triglycerides
HBA1C	Glycated hemoglobin
hs-CRP	High-sensitivity C-reactive protein
RBC	Red blood cell count
PLT	Platelet count
SBP	Systolic blood pressure
MAE	Mean absolute error
RMSE	Root mean square error
IQR	Interquartile range
OR	Odds ratio
SD	Standard deviation
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02770-0.

Supplementary Material 1.

Acknowledgements

All authors thank the original data collectors, depositors, copyright holders, and funders of China Health and Retirement Longitudinal Study, UKB, and HEHEC. This research has been conducted using the UKB resource under application number 203528.

Author contributions

LH, TZ, JYL and CXY were responsible for the study design. LH, JYL, ZHT, PG, ZQC, CY and TPM collated the data. LH and TZ performed the statistical analysis and interpretation. LH, ZHT, PG and SJ drafted the manuscript and conducted the literature search. LH drafted the main manuscript. TZ, JYL and CXY contributed to manuscript revisions. All authors reviewed and approved the submitted version of the manuscript.

Funding

This research work was funded by National Key R&D Program of China (2022YFC3600600), Sichuan Science and Technology Program (2024ZYD0102, 2025YFHZ0069), Chengdu Science and Technology Program (2024-YF05-01784-SN), and Sichuan Preventive Medicine Association (SYYXH202403).The funders played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

Data supporting this study's results are available from the official websites of the China Health and Retirement Longitudinal Study (http://charls.pku.edu.cn), UK Biobank (https://www.ukbiobank.ac.uk/), and HEHEC. HEHEC is also available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate

CHARLS was approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015), and UKB was approved by the Northwest Multicenter Research Ethics Committee on May 10, 2016 (reference: 16/NW/0274). HEHEC was approved by Ethics Committee of West China Fourth Hospital and West China School of Public Health, Sichuan University (approval number: Gwll2024175), and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

All authors declare no disclosure of interest for this contribution.

Author details

[1]Department of Epidemiology and Health Statistics, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, Sichuan, People's Republic of China

Received: 7 February 2025 / Accepted: 2 May 2025
Published online: 14 May 2025

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