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Mediating role of arterial stiffness and hemodynamic load in the association between obesity and cardiovascular disease risk: a prospective cohort study

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Research Article

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Abstract

Obesity is a well-established risk factor for cardiovascular disease (CVD), yet the pathways through which excess adiposity translates into cardiovascular injury remain incompletely understood. We addressed this question using longitudinal data from two nationally representative cohorts—CHARLS (n = 5,584) and ELSA (n = 1,989)—with clearly defined temporal ordering: obesity indices measured at baseline, arterial stiffness (estimated pulse wave velocity, ePWV) and hemodynamic load (mean arterial pressure, systolic blood pressure, and diastolic blood pressure) at follow-up, and incident CVD thereafter.Over a 5-year period, 21.3% of CHARLS participants developed CVD. All six obesity indices were positively associated with CVD risk (per-standard-deviation odds ratios: 1.094–1.269). Counterfactual-based mediation analyses revealed that arterial stiffness and hemodynamic load partially mediated these associations, with proportions ranging from 7.3% to 25.6%; mean arterial pressure showed the largest mediating effects (10.5%–25.6%), followed by systolic blood pressure (8.8%–21.7%), ePWV (7.5%–18.8%), and diastolic blood pressure (7.3%–17.8%). Serial mediation supported the sequence of arterial stiffening preceding blood pressure elevation. Notably, mediation was substantially stronger in middle-aged adults (up to 37.8%) and absent in those ≥ 60 years, with findings replicated in ELSA. Collectively, these results underscore the clinical value of early vascular assessment—particularly arterial stiffness evaluation—in obesity-related cardiovascular prevention.

1 Introduction

Obesity has emerged as one of the most pressing public health challenges of the 21st century(1) and constitutes a leading modifiable risk factor for cardiovascular disease (CVD)(2). Yet, while the association between obesity and CVD is well established, the biological pathways linking obesity to cardiovascular injury remain incompletely understood.

The vasculature undergoes progressive structural and functional deterioration with aging, a process characterized by arterial stiffening, endothelial dysfunction, and hemodynamic dysregulation that is driven by chronic inflammation, oxidative stress, and cellular senescence(3, 4). A growing body of evidence indicates that traditional cardiovascular risk factors—including hypertension, diabetes, and vascular calcification—synergistically accelerate this process. Importantly, obesity appears to further compound these effects through metabolic dysfunction, endothelial injury, and progressive arterial remodeling, positioning obesity as a key modifiable upstream driver of vascular deterioration (5, 6). Arterial stiffness, a hallmark of vascular aging, is commonly assessed by pulse wave velocity (PWV), with carotid-femoral PWV considered the gold-standard measure(7). However, its clinical application is constrained by the need for specialized equipment and technical expertise. Estimated pulse wave velocity (ePWV), derived from age and mean arterial pressure, has emerged as a practical and scalable surrogate marker suitable for large epidemiological studies, with demonstrated predictive value for CVD events and mortality independent of traditional risk factors(8). Hemodynamic parameters—including systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP)—capture distinct yet interrelated dimensions of vascular load, reflecting both the steady and pulsatile components of hemodynamic stress imposed on the cardiovascular system. These measures, when integrated within a unified framework, offer an opportunity to disentangle the relative contributions of arterial stiffening versus hemodynamic load to the obesity–CVD pathway. However, it remains unknown whether and to what extent arterial stiffening and hemodynamic load mediate the association between obesity and CVD.

To address these questions, we analyzed longitudinal data from two independent, nationally representative cohorts, the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). Using a counterfactual-based mediation framework with clearly defined temporal sequencing, we quantified the extent to which arterial stiffness (ePWV) and hemodynamic load (MAP, SBP, DBP) mediate the obesity–CVD association, and further evaluated competing serial mediation pathways to determine the temporal ordering of vascular and hemodynamic contributions.

2 Methods

2.1 Study population

The primary analysis drew on data from the CHARLS, a nationally representative prospective cohort of Chinese adults aged 45 years and older. Launched in 2011, CHARLS employs a multistage probability sampling strategy to ensure national representativeness, covering 150 counties across 28 provinces. Detailed descriptions of the study design and sampling procedures have been published previously (9, 10).Baseline data were collected through standardized face-to-face interviews, encompassing comprehensive information on sociodemographic characteristics, lifestyle factors, health status, and anthropometric measurements. Follow-up surveys were conducted biennially, enabling longitudinal tracking of participants' health trajectories. We utilized three waves of data to establish temporal sequencing: baseline sociodemographic and obesity measures from Wave 1 (2011), arterial stiffness and hemodynamic load assessments from Wave 2 (2013), and incident CVD ascertained during Waves 3–5 (2015–2020), yielding an analytical sample of 5,584 participants.

For external validation, we applied an analogous three-wave design to the ELSA: obesity indicators at Wave 2 (2004–2005), arterial stiffness and hemodynamic load measures at Wave 4 (2008–2009), and incident CVD during follow-up from Wave 5 (2010–2011) to Wave 9 (2018–2019), resulting in a validation sample of 1,989 participants.

All participants, or their legal representatives, provided written informed consent for both baseline and follow-up assessments.

2.2 Assessment of obesity

Obesity was assessed across multiple dimensions at baseline using six indices. Body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR) captured body shape; the lipid accumulation product (LAP), triglyceride-glucose index (TyG) and metabolic score for insulin resistance (METS-IR) indicated insulin resistance(11, 12). Calculation details are provided in Supplementary Table S1. All obesity indices were standardized for regression analyses. We also categorized each index into tertiles (T1–T3) based on the distribution within the study sample; cut-off values are reported in Supplementary Table S2. To enhance clinical interpretability and enable comparison with prior Chinese studies, BMI and WC were additionally classified using established Chinese criteria. BMI categories were underweight/normal (< 24 kg/m²), overweight (24–28 kg/m²), and obese (≥ 28 kg/m²). WC categories were normal (< 85 cm for men, < 80 cm for women), pre-abdominal obesity (85–90 cm for men, 80–85 cm for women), and abdominal obesity (≥ 90 cm for men, ≥ 85 cm for women)(9).

2.3 Assessment of mediators

Hemodynamic load and arterial stiffness, assessed at Wave 2 (2013), served as the mediators. Hemodynamic load comprised MAP, SBP, and DBP, reflecting steady-state pressure burden; arterial stiffness was captured by ePWV(8, 13).

Resting SBP and DBP were measured three times by trained personnel following a standardized protocol, and the average of the second and third readings was used for analysis. MAP was calculated as DBP + (SBP − DBP)/3.

$$\mathrm{ePWV}=9.587\text{-}0.402\times\mathrm{age}+4.560\times10^{-3}\times\mathrm{age}^{2}\text{-}2.621\times10^{-5}\times\mathrm{age}^{2}\times\mathrm{MBP}+$$

$$3.176\times10^{-3}\times\mathrm{age}\times\mathrm{MBP}\text{-}1.832\times10^{-2}\times\mathrm{MBP}$$

, where $\mathrm{MBP}=\mathrm{DBP}+0.4\times(\mathrm{SBP}\text{-}\mathrm{DBP})$.

All mediators were analyzed as continuous variables in their original clinical units (mmHg for SBP, DBP and MAP; m/s for ePWV) to preserve clinical interpretability.

2.4 Outcome Assessment

The primary outcome was the incidence of CVD over a 5 year follow-up period, from 2015 to 2020. CVD events were defined as physician-diagnosed incident heart disease or stroke, ascertained via standardized biennial questionnaires. The core survey questions included: "Have you been told by a doctor that you have been diagnosed with heart disease, including angina, heart attack, congestive heart failure, and other heart problems?" and "Have you been told by a doctor that you have been diagnosed with a stroke?"

2.5 Covariate Selection

Covariates were selected a priori based on established cardiovascular epidemiological evidence and biological plausibility. To minimize unnecessary adjustment and reduce the risk of collider bias, we further refined our selection using a directed acyclic graph (DAG; Supplementary Figure S1). The final set of confounders included age (years), sex (male/female), educational attainment (elementary school or below, middle school, college or above), marital status (married vs. unmarried), smoking (no, yes), drinking (no, yes), physical activity (inactive, moderate, vigorous), CRP, and history of cancer (yes/no). Consistent with the core assumptions of causal mediation analysis, we avoided adjusting for variables situated on the causal pathway between adiposity and CVD, to eliminate unmeasured confounding affecting exposure-mediator and mediator-outcome associations. This strategy prevents over-adjustment and resultant bias caused by controlling for post-exposure factors.

2.6 Statistical Analysis

Baseline characteristics were summarized as medians with interquartile ranges (IQRs) for continuous variables and as counts with percentages for categorical variables. Chi-square tests and Wilcoxon rank-sum tests were used to assess participants' demographic characteristics by CVD status. Missing covariates were imputed using multiple imputation by chained equations (MICE) with predictive mean matching (5 imputed datasets, 20 iterations); details of missing data before imputation are presented in Supplementary Table S3. DAG was constructed to illustrate hypothesized causal relationships among exposures, mediators, covariates, and outcomes (Supplementary Figure S1).

To evaluate the mediating role of arterial stiffness (ePWV) and hemodynamic load (MAP, SBP, and DBP) in the obesity–CVD association, we employed a longitudinal design with clearly defined temporal ordering of exposure, mediator, and outcome. As shown in Fig. 2, we considered three pathways: (a) obesity → elevated arterial stiffness or hemodynamic load; (b) elevated arterial stiffness or hemodynamic load → incident CVD; and (c) obesity → incident CVD (total effect). For path a, multivariable linear regression was used to estimate associations of obesity indices with each measure of arterial stiffness or hemodynamic load, with regression coefficients (β) and 95% confidence intervals (CIs) reported per standard deviation increase. For paths b and c, multivariable logistic regression was fitted to estimate associations of obesity indices and measures of arterial stiffness or hemodynamic load with incident CVD, with odds ratios (ORs) and 95% CIs reported. Linear trend tests were performed across obesity tertiles. All regression models were adjusted for covariates identified a priori through DAG analysis: age, sex, education level, marital status, smoking status, drinking status, physical activity, CRP, and history of cancer. Causal mediation effects were estimated using the mediation package in R (version 4.3.3) based on quasi-Bayesian Monte Carlo simulations (2,000 iterations), yielding the natural indirect effect (NIE), natural direct

effect (NDE), and total effect (TE). The proportion mediated was calculated as NIE/TE. Serial mediation analyses further estimated the indirect effect through sequential pathways (obesity → M_1 → M_2 → CVD), calculated as the product of the three component path coefficients, with adjustments for prior variables at each step.

The primary analysis was conducted in CHARLS, with key findings externally validated in ELSA. Robustness was assessed through seven sensitivity analyses: (1) bootstrap resampling (2,000 iterations) for mediation effect estimation; (2) exclusion of CVD events within 2 years of mediator assessment to mitigate reverse causation; (3) replacement of Wave 2(2013) mediators with Wave 3(2015) measurements to address temporal bias; (4) categorization of obesity indices into quartiles; (5) categorization of arterial stiffness and hemodynamic load measures by clinical thresholds; (6) adjustment for antidiabetic and lipid-lowering medication use; and (7) complete-case analysis as an alternative to multiple imputation. To assess the impact of unmeasured covariates on the estimates, we calculated the mediational E-values for the NIE and NDE. These values represent the minimum association strength required for an unmeasured confounder with the mediator and outcome to explain the mediation effect under the measured covariates. Effect heterogeneity was explored by sex and baseline age (45–60 years vs. ≥60 years).

3 Results

3.1 Baseline characteristics

Table 1 presents the baseline characteristics of the 5,584 CHARLS participants, stratified by incident CVD status. Among the 5,584 participants,the mean age was 58.9 years (SD 9.1), and 52.7% were female. Over follow-up, 1,189 participants (21.3%) developed CVD—comprising 413 stroke (7.4%) and 901 heart disease (16.1%) cases—while 4,395 (78.7%) remained CVD-free. Median (IQR) values for the ePWV, MAP, SBP, and DBP were 9.5 (8.3–11.0) m/s, 92.2 (83.5–102.0) mmHg, 127.0 (114.0–142.0) mmHg,74.5 (67.0–82.5) mmHg, respectively. Participants who developed CVD differed significantly from those who remained free of the disease across multiple baseline characteristics. In general, participants incident CVD were older, more likely to be female, had lower educational attainment and physical activity levels, were more likely to have never smoked or consumed alcohol, and showed markedly higher obesity indices, CRP levels, arterial stiffness, and hemodynamic load. Baseline characteristics of the ELSA validation cohort are provided in Supplementary Table S4.

3.2 Associations of obesity indices with incident CVD

Table 2 presents the associations between obesity and incident CVD, estimated using logistic regression models. All six obesity indices were positively associated with CVD risk. On a per-SD basis, the strongest associations were observed for WC (OR 1.269, 95% CI 1.189–1.355), followed by BMI (OR 1.258, 95% CI 1.178–1.342) and WHtR (OR 1.225, 95% CI 1.144–1.312). Insulin resistance–related indices showed comparatively weaker but significant associations: LAP (OR 1.114, 95% CI 1.050–1.183), METS-IR (OR 1.112, 95% CI 1.044–1.184), and TyG (OR 1.094, 95% CI 1.026–1.166). Dose–response analyses using tertiles revealed significant linear trends for all indices (all P for trend < 0.05).

3.3 Associations of obesity with arterial stiffness and hemodynamic load

Table 3 presents the associations of obesity with arterial stiffness (ePWV) and hemodynamic load, estimated using linear regression. All six obesity indices were positively associated with ePWV and with each measure of hemodynamic load (all P < 0.001). The three anthropometric measures—BMI, WC, and WHtR—consistently showed the largest effect sizes. Tertile-based analyses revealed a progressive increase in all arterial stiffness and hemodynamic load measures across ascending tertiles of each obesity index (all P for trend < 0.001).

3.4 Associations of arterial stiffness and hemodynamic load measures with incident CVD

Table 4 presents the associations of ePWV and hemodynamic load with incident CVD. ePWV showed the strongest association (OR 1.124, 95% CI 1.061–1.192, P < 0.001), followed by MAP (OR 1.012, 95% CI 1.007–1.017), DBP (OR 1.011, 95% CI 1.006–1.015), and SBP (OR 1.007, 95% CI 1.004–1.010). All reached significance at P < 0.001.

3.5 Causal mediation analysis

Arterial stiffness and hemodynamic load partially mediated the associations between obesity and incident CVD (Fig. 3; Supplementary Table S5). MAP consistently exhibited the largest mediation proportions (10.5%–25.6%), followed by SBP (8.8%–21.7%), ePWV (7.5%–18.8%), and DBP (7.3%–17.8%). Insulin resistance yielded larger mediation proportions than anthropometric measures, with TyG showing the largest effects overall; among anthropometric indices, WHtR showed the largest effects across all mediators. For most pathways, significant direct effects persisted alongside significant indirect effects, suggesting that arterial stiffness and hemodynamic load capture only part of the obesity–CVD association.

To adjudicate whether arterial stiffening precedes blood pressure elevation or vice versa, we compared two competing serial mediation pathways. As shown in Fig. 4 and Supplementary Table S6–S7, the arterial stiffness-first pathway (obesity → ePWV → hemodynamic load → CVD) consistently outperformed the reverse for MAP (mediation proportions 5.9%–10.0% versus 3.2%–6.8%) and SBP (6.1%–10.8% versus 3.4%–7.2%). For DBP, the two pathways were essentially equivalent (2.3%–4.8% versus 2.5%–5.1%).

3.6 Validation analysis

We externally validated our primary findings in the ELSA cohort (n = 1,989). Consistent with CHARLS, MAP (7.8%–17.4%), SBP (9.7%–17.9%), and ePWV (6.7%–17.6%) each partially mediated the obesity–CVD associations with broadly comparable proportions. DBP showed limited mediation effects, likely reflecting the smaller sample size (Supplementary Table S8–S11).

3.7 Sensitivity analyses

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

1. Non-parametric bootstrap with 2,000 resamples yielded consistent estimates compared with quasi-Bayesian Monte Carlo simulations (Supplementary Table S12).

2. Exclusion of participants who developed CVD within 2 years of exposure assessment produced similar results, ruling out reverse causation (Supplementary Table S13).

3. Using Wave 3 mediators, the mediated proportions for ePWV, MAP, SBP, and DBP were 13.2–21.9%, 15.7–24.8%, 17.2–24.8%, and 9.1–15.1%, respectively (Supplementary Table S14).

(4–5) Categorizing exposures into quartiles or using clinical thresholds for mediators did not alter the findings (Supplementary Table S15–S17).

(6) Additional adjustment for glucose-lowering and lipid-lowering medications yielded unchanged results (Supplementary Table S18).

(7) Complete-case analysis excluding participants with missing covariates confirmed the main findings (Supplementary Table S19).

(8) Mediational E-values consistently exceeded the maximum estimated NIE or NDE for all four mediators, supporting the robustness of the mediation results to potential unmeasured confounding (Supplementary Table S20).

3.8 Subgroup analyses

Subgroup analyses showed that arterial stiffness and hemodynamic load measures mediation of insulin resistance–related indices was stronger in men than in women (Supplementary Table S21-22). Age-stratified analyses further revealed that among participants aged 45–60 years, mediation proportions ranged from 16.8% to 37.8% for ePWV and 10.8% to 29.3% for blood pressure measures, yet no significant mediation was observed in those aged ≥ 60 years (Supplementary Table S23-24).

4 Discussion

This study provides three principal findings. First, we found that the obesity–CVD association is temporally and causally mediated by both arterial stiffness and hemodynamic load, with mediation proportions ranging from 7.3% to 25.6%. Second, this mediation effect is age-dependent and sex-specific, being most prominent in middle-aged adults (45–60 years) and stronger in men for insulin resistance–related indices. Third, we demonstrate that arterial stiffening precedes blood pressure elevation in the obesity–CVD cascade.

While previous studies have separately linked obesity to arterial stiffness (14), or blood pressure to CVD(15), few have integrated these pathways within a unified mediation framework. Moreover, most prior mediation analyses relied on cross-sectional data or failed to establish clear temporal ordering, thereby risking reverse causation and overestimation of indirect effects. Our longitudinal design ensures a robust temporal sequence. Importantly, by comparing the two competing serial mediation pathways, we were able to evaluate the temporal sequence between arterial stiffening and blood pressure elevation in the obesity–CVD cascade.

Obesity is intimately linked to increased arterial stiffness (16, 17) through a broad spectrum of metabolic and neurohormonal disturbances that adversely affect vascular structure and function (18). Adipokines such as adiponectin and leptin, secreted by adipose tissue, are closely associated with arterial stiffness (19). In addition, activation of the renin–angiotensin–aldosterone system (20, 21), sympathetic overactivity (22, 23), and sodium retention (24, 25)collectively contribute to sustained blood pressure elevation and endothelial dysfunction. Beyond these hemodynamic disturbances, abnormal adipokine profiles, immune cell dysfunction, and extracellular matrix remodeling are all important contributors to arterial stiffness in individuals with obesity (26, 27). At the vascular level, these alterations impair nitric oxide bioavailability, promote arterial remodeling and vascular senescence, and accelerate arterial stiffening (28–34). The resulting progressive increases in pulsatile load and cardiac afterload may subsequently impair microvascular perfusion and facilitate target-organ injury, thereby increasing susceptibility to cardiovascular events (35, 36).Collectively, these biological processes position arterial stiffness and elevated blood pressure as key intermediate mechanisms linking obesity to CVD—a pathway that our mediation analysis has quantitatively delineated. The larger mediation proportions for the arterial stiffness-first pathway compared with the reverse pathway indicate that obesity-induced metabolic insults may first degrade arterial elasticity, and the resultant stiffening then elevates central blood pressure through early return of reflected waves, thereby increasing cardiac afterload and CVD risk. This temporal sequence has critical clinical implications: it suggests that arterial stiffness may serve as an earlier, more proximal target for intervention than blood pressure per se in obese individuals.

Our finding that arterial stiffness and elevated blood pressure partially mediated the obesity–CVD association in middle-aged participants (aged 45–60 years), but not in those ≥ 60 years, is consistent with previous studies that have established age as a key modifier of the relationships between modifiable risk factors—including obesity, hypertension, and diabetes—and incident CVD, with stronger associations consistently observed in younger populations (37, 38). Mechanistically, middle age is characterized by evolving vascular injury driven by oxidative stress, mitochondrial dysfunction, and accelerated arterial stiffening (39). Although arterial stiffness progressively increases with physiological aging, adiposity appears to accelerate this process from earlier stages of life (40). In older adults, however, decades of cumulative vascular damage, chronic inflammation, frailty, and competing pathological processes may reduce the relative contribution of adiposity-related vascular injury to CVD development (41). Consequently, elevated blood pressure and arterial stiffness in later life may predominantly reflect irreversible vascular remodeling rather than modifiable adiposity-driven injury. Survival bias and competing risks may further attenuate observable mediation effects (42). Clinically, these findings underscore middle age as a critical window for vascular-targeted prevention. Early interventions aimed at reducing adiposity, controlling blood pressure, and slowing arterial stiffening may yield substantial cardiovascular benefits before advanced vascular remodeling becomes established.

The external validation in the ELSA cohort replicated the overall mediation hierarchy with broadly comparable proportions, supporting the generalizability of our findings beyond the Chinese context. Sensitivity analysis, including bootstrap resampling, lagged exposure design, and multiple imputation—consistently supported the robustness of the mediation estimates against reverse causation, missing data, and unmeasured confounding, as detailed in the Results section.

Several limitations warrant consideration. First, CVD events were ascertained via self-reported physician diagnoses, potentially introducing misclassification; however, such bias would likely be non-differential and attenuate estimates toward the null. Second, we lacked repeated measures of mediators across multiple waves, precluding assessment of dynamic changes in ePWV or blood pressure over time and limiting causal inference to the specific timing of our measurements. Third, the CHARLS sample is limited to adults aged ≥ 45 years, which may restrict generalizability to younger populations where the mediation hierarchy might differ. Nevertheless, the consistency across sensitivity analyses and external validation supports the robustness of our conclusions.

5 Conclusion

In summary, our findings establish that arterial stiffness and hemodynamic load serve as partial mediators of the obesity–CVD relationship, with the strongest mediation observed in midlife. Serial mediation analyses provide supportive evidence for the temporal involvement of arterial stiffening preceding blood pressure elevation along this pathway. Collectively, these results underscore the clinical value of early vascular evaluation—especially arterial stiffness measurement—as part of comprehensive risk stratification in obese populations.

Declarations

Ethics approval and consent to participate

CHARLS was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). ELSA received ethical approval from the National Research Ethics Service (07/H0718/30). All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). Data were obtained from the Harmonized CHARLS (Version D, June 2021) and Harmonized ELSA (Version H, September 2025) datasets via the Gateway to Global Aging Data *(https://g2aging.org/)*, with harmonization funded by NIA grants R01 AG030153, RC2 AG036619, and R03 AG043052.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Author contributions

JY conceptualized the study, drafted the manuscript, and prepared the figures. HZ contributed to the critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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Tables

Table 1. Baseline characteristics of the participants in CHARLS

Characteristic	CHARLS cohort			
	Overall(n=5,584)	No CVD(n=4,395)	CVD(n=1,189)	P-value
Age,years	58.9±9.1	58.5±9.2	60.4±8.7	<0.001
Male, n (%)	2,639 (47.3%)	2,138 (48.6%)	501 (42.1%)	<0.001
Education, n (%)				0.001
Middle school	1,456 (26.1%)	1,194 (27.2%)	262 (22.0%)	
Elementary school or below	3,991 (71.5%)	3,097 (70.5%)	894 (75.2%)	
College or above	137 (2.5%)	104 (2.4%)	33 (2.8%)	
Smoking status, n (%)				0.007
Never	3,398 (60.9%)	2,648 (60.3%)	750 (63.1%)	
Ever/Current	2,186 (39.1%)	1747 (39.7%)	439 (36.9%)	
Drinking status, n (%)				0.001
Never	3,375 (60.4%)	2,637 (60.0%)	738 (62.1%)	
Ever/Current	2,209 (39.6%)	1,758 (40.0%)	451 (37.9%)	
Married, n (%)	4,724 (84.6%)	3,733 (84.9%)	991 (83.3%)	0.200
Cancer Disease				0.600
Yes	45 (0.8%)	37 (0.8%)	8 (0.7%)	
No	5,539(99.2%)	4,358(99.2%)	1,181(99.3%)	
CRPe	1.0 (0.5,2.0)	0.9 (0.5,2.0)	1.1 (0.6,2.1)	<0.001
Physical activity, n (%)				<0.001
Inactive	2,299 (41.2%)	1,738 (39.5%)	561 (47.2%)	
Moderate	1,568 (28.1%)	1,213 (27.6%)	355 (29.9%)	
Vigorous	1,717 (30.7%)	1,444 (32.9%)	273 (23.0%)	
BMI, kg/m^2	23.0 (20.7,25.5)	22.8 (20.6,25.2)	23.5 (21.3,26.4)	<0.001
WC, cm	84.0 (77.5,91.0)	83.5 (77.0,90.4)	86.1 (79.0,93.8)	<0.001
WHtR	0.5 (0.5,0.6)	0.5 (0.5,0.6)	0.5 (0.5,0.6)	<0.001
LAP	25.7(14.4,45.3)	24.8(13.8,43.9)	30.4(16.6,51.9)	<0.001
METS-IR	2.3 (2.1,2.4)	2.3 (2.1,2.4)	2.3 (2.1,2.5)	<0.001
TyG	8.6 (8.2,9.0)	8.6 (8.2,9.0)	8.6 (8.3,9.0)	0.002
ePWV,m/s	9.5 (8.3,11.0)	9.4 (8.2,10.8)	9.9 (8.8,11.4)	<0.001
MAP,mmhg	92.2(83.5,102.0)	91.5(83.2,101.3)	94.5(84.8,104.7)	<0.001
SBP,mmhg	127.0(114.0,142.0)	126.0(113.5,141.0)	130.0(116.5,145.5)	<0.001
DBP,mmhg	74.5 (67.0, 82.5)	74.5 (66.5,82.5)	75.0 (67.5,83.5)	0.120

***Abbreviation**: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; LAP, lipid accumulation product; METS-IR, metabolic score for insulin resistance; TyG, triglyceride-glucose index; ePWV, estimated pulse wave velocity; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure;CVD, cardiovascular disease*

Table 2. Associations between obesity indices and incident cardiovascular disease in CHARLS

Exposure	Outcome	Association, *OR* (95% *CI*)							
		Per *SD*		Tertile 1	Tertile 2		Tertile 3		*P*trend
BMI	CVD	1.258 (1.178,1.342)	<0.001	Ref	1.346 (1.159,1.563)	<0.001	1.866 (1.517,2.295)	<0.001	<0.001
WC	CVD	1.269 (1.189,1.355)	<0.001	Ref	1.101 (0.904,1.340)	0.339	1.621 (1.395,1.883)	<0.001	<0.001
WtHR	CVD	1.225 (1.144,1.312)	<0.001	Ref	1.251 (1.057,1.482)	0.009	1.570 (1.324,1.862)	<0.001	<0.001
LAP	CVD	1.114 (1.050,1.183)	<0.001	Ref	1.271 (1.073,1.506)	0.006	1.551 (1.309,1.838)	<0.001	<0.001
METS-IR	CVD	1.112 (1.044,1.184)	<0.001	Ref	1.213 (1.031,1.426)	0.020	1.284 (1.091,1.510)	0.003	0.003
TyG	CVD	1.094 (1.026,1.166)	0.006	Ref	1.215 (1.035,1.425)	0.017	1.197 (1.020,1.405)	0.028	0.031

Notes: All models were adjusted for age, sex, education level, marital status, smoking status, drinking status, physical activity, CRP, and history of cancer.The "Per 1-SD increase" column presents the hazard ratio associated with a one-standard-deviation increase in each continuous adiposity index.*Tertile 1 serves as the reference group for categorical analyses.*

Abbreviations:BMI, body mass index;WC, waist circumference; WHtR, waist-to-height ratio; LAP, lipid accumulation product; METS-IR, metabolic score for insulin resistance; TyG, triglyceride-glucose index; CVD, *cardiovascular disease;* OR, odds ratio; CI, confidence interval; SD, standard deviation.

Table 3. Associations of adiposity indices with vascular aging–related measures in CHARLS.

Exposure	Mediator	Association, β (95% *CI*)							
		Per 1-SD increase	P value	Tertile 1	Tertile 2	P value	Tertile 3	P value	*P*trend
BMI	ePWV	0.223 (0.194,0.253)	<0.001	Ref	0.325 (0.259,0.390)	<0.001	0.586 (0.488,0.684)	<0.001	<0.001
WC	ePWV	0.197 (0.169,0.226)	<0.001	Ref	0.255 (0.173,0.337)	<0.001	0.429 (0.364,0.495)	<0.001	<0.001
WHtR	ePWV	0.214 (0.183,0.244)	<0.001	Ref	0.218 (0.147,0.288)	<0.001	0.490 (0.417,0.564)	<0.001	<0.001
LAP	ePWV	0.127 (0.098,0.156)	<0.001	Ref	0.184 (0.113,0.256)	<0.001	0.456 (0.383,0.529)	<0.001	<0.001
METS-IR	ePWV	0.113 (0.084,0.142)	<0.001	Ref	0.143 (0.073,0.213)	<0.001	0.321 (0.250,0.392)	<0.001	<0.001
TyG	ePWV	0.123 (0.094,0.152)	<0.001	Ref	0.110 (0.040,0.180)	<0.001	0.298 (0.227,0.369)	<0.001	<0.001
BMI	MAP	2.845 (2.476,3.214)	<0.001	Ref	4.212 (3.388,5.036)	<0.001	7.441 (6.214,8.668)	<0.001	<0.001
WC	MAP	2.552 (2.191,2.913)	<0.001	Ref	3.225 (2.198,4.251)	<0.001	5.547 (4.726,6.368)	<0.001	<0.001
WHtR	MAP	2.737 (2.355,3.119)	<0.001	Ref	2.739 (1.856,3.623)	<0.001	6.299 (5.374,7.225)	<0.001	<0.001
LAP	MAP	1.630 (1.265,1.996)	<0.001	Ref	2.596 (1.701,3.491)	<0.001	6.031 (5.115,6.947)	<0.001	<0.001
METS-IR	MAP	1.455 (1.090,1.819)	<0.001	Ref	1.816 (0.935,2.697)	<0.001	4.166 (3.275,5.056)	<0.001	<0.001
TyG	MAP	1.654 (1.292,2.017)	<0.001	Ref	1.626 (0.747,2.506)	<0.001	4.013 (3.126,4.899)	<0.001	<0.001
BMI	SBP	4.405 (3.847,4.962)	<0.001	Ref	5.857 (4.611,7.103)	<0.001	11.054 (9.198,12.910)	<0.001	<0.001
WC	SBP	3.859 (3.313,4.405)	<0.001	Ref	4.857 (3.305,6.409)	<0.001	8.152 (6.910,9.393)	<0.001	<0.001
WHtR	SBP	4.204 (3.628,4.780)	<0.001	Ref	4.209 (2.875,5.543)	<0.001	9.703 (8.306,11.100)	<0.001	<0.001
LAP	SBP	2.645 (2.093,3.196)	<0.001	Ref	3.636 (2.284,4.988)	<0.001	8.994 (7.611,10.378)	<0.001	<0.001
METS-IR	SBP	2.357 (1.807,2.907)	<0.001	Ref	2.571 (1.241,3.902)	<0.001	6.195 (4.849,7.540)	<0.001	<0.001
TyG	SBP	2.520 (1.972,3.067)	<0.001	Ref	2.396 (1.067,3.725)	<0.001	6.068 (4.729,7.408)	<0.001	<0.001
BMI	DBP	2.065 (1.714,2.417)	<0.001	Ref	3.390 (2.608,4.171)	<0.001	5.634 (4.469,6.799)	<0.001	<0.001
WC	DBP	1.898 (1.555,2.242)	<0.001	Ref	2.408 (1.434,3.383)	<0.001	4.244 (3.465,5.024)	<0.001	<0.001
WHtR	DBP	2.003 (1.641,2.366)	<0.001	Ref	2.004 (1.165,2.843)	<0.001	4.598 (3.719,5.476)	<0.001	<0.001
LAP	DBP	1.123 (0.777,1.469)	<0.001	Ref	2.076 (1.227,2.925)	<0.001	4.549 (3.680,5.418)	<0.001	<0.001
METS-IR	DBP	1.004 (0.659,1.349)	<0.001	Ref	1.438 (0.605,2.271)	<0.001	3.151 (2.309,3.993)	<0.001	<0.001
TyG	DBP	1.221 (0.878,1.564)	<0.001	Ref	1.242 (0.409,2.074)	0.003	2.985 (2.146,3.824)	<0.001	<0.001

Abbreviations:β, standardized regression coefficient; CI, confidence interval; ePWV, estimated pulse wave velocity; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio;LAP, lipid accumulation product; METS-IR, metabolic score for insulin resistance; TyG, triglyceride-glucose index.

Note:All models were adjusted for age, sex, education level, marital status, smoking status, drinking status, physical activity, CRP, and history of cancer.Tertile 1 serves as the reference group for categorical analyses.

Table 4. Associations of Hemodynamic Measures with incident cardiovascular disease in CHARLS.

Mediators	Outcome	*OR* (95% *CI*)	P value
ePWV	CVD	1.124 (1.061,1.192)	<0.001
MAP	CVD	1.012 (1.007,1.017)	<0.001
Systolic pressure	CVD	1.007 (1.004,1.010)	<0.001
Diastolic pressure	CVD	1.011 (1.006,1.015)	<0.001

Abbreviation: OR, odds ratio; CI, confidence interval; ePWV,estimated pulse wave velocity; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease.

Note:All models were adjusted for age, sex, education level, marital status, smoking status, drinking status, physical activity, CRP, and history of cancer.Tertile 1 serves as the reference group for categorical analyses.

Figures

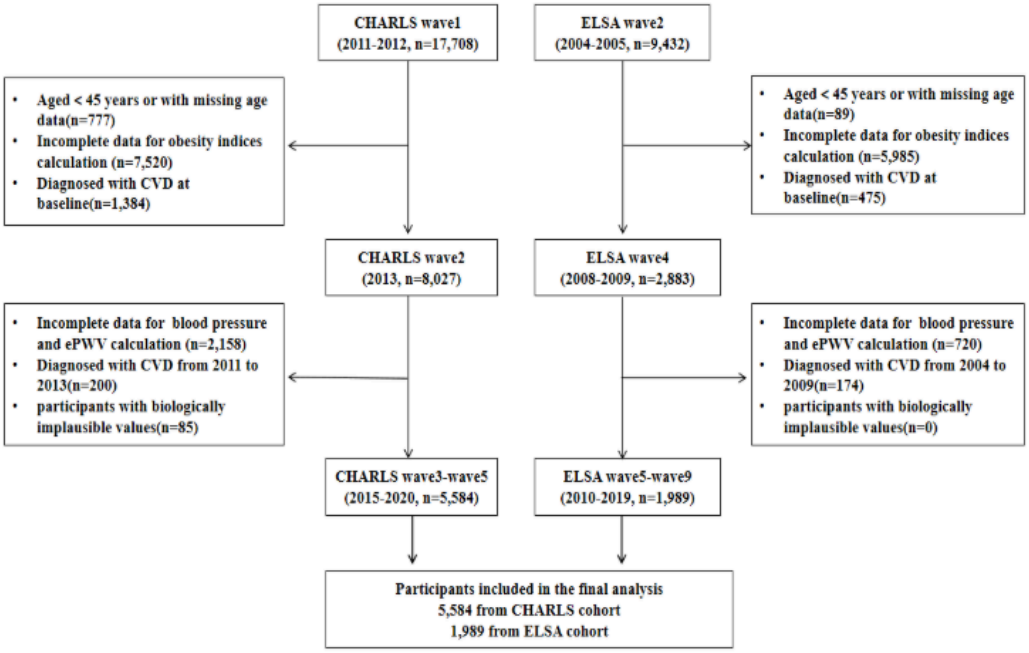


Figure 1

Flowchart of participant selection.

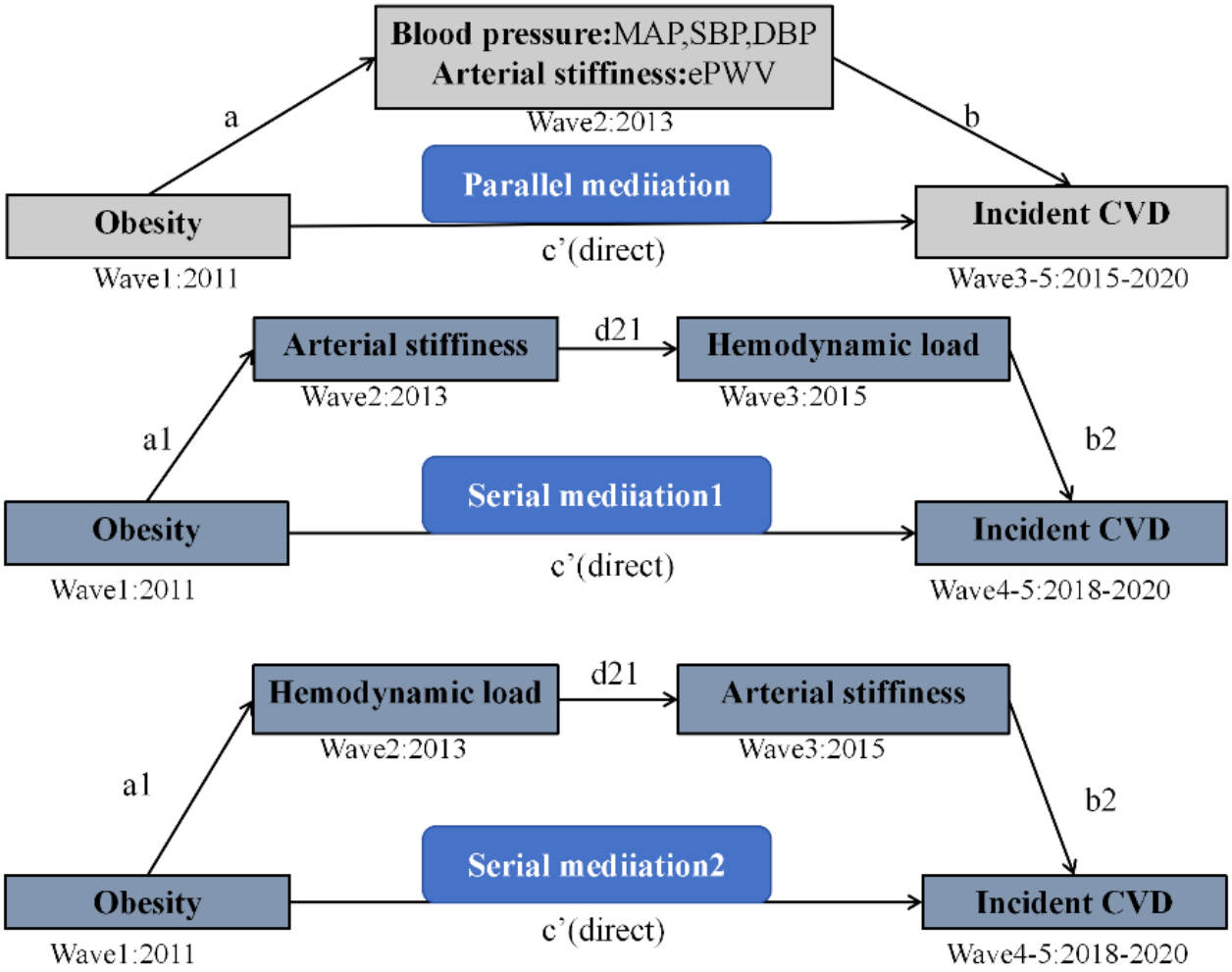


Figure 2

Causal diagram illustrating postulated causal relationships between obesity, arterial stiffness, hemodynamic load, and incident cardiovascular disease in CHARLS.

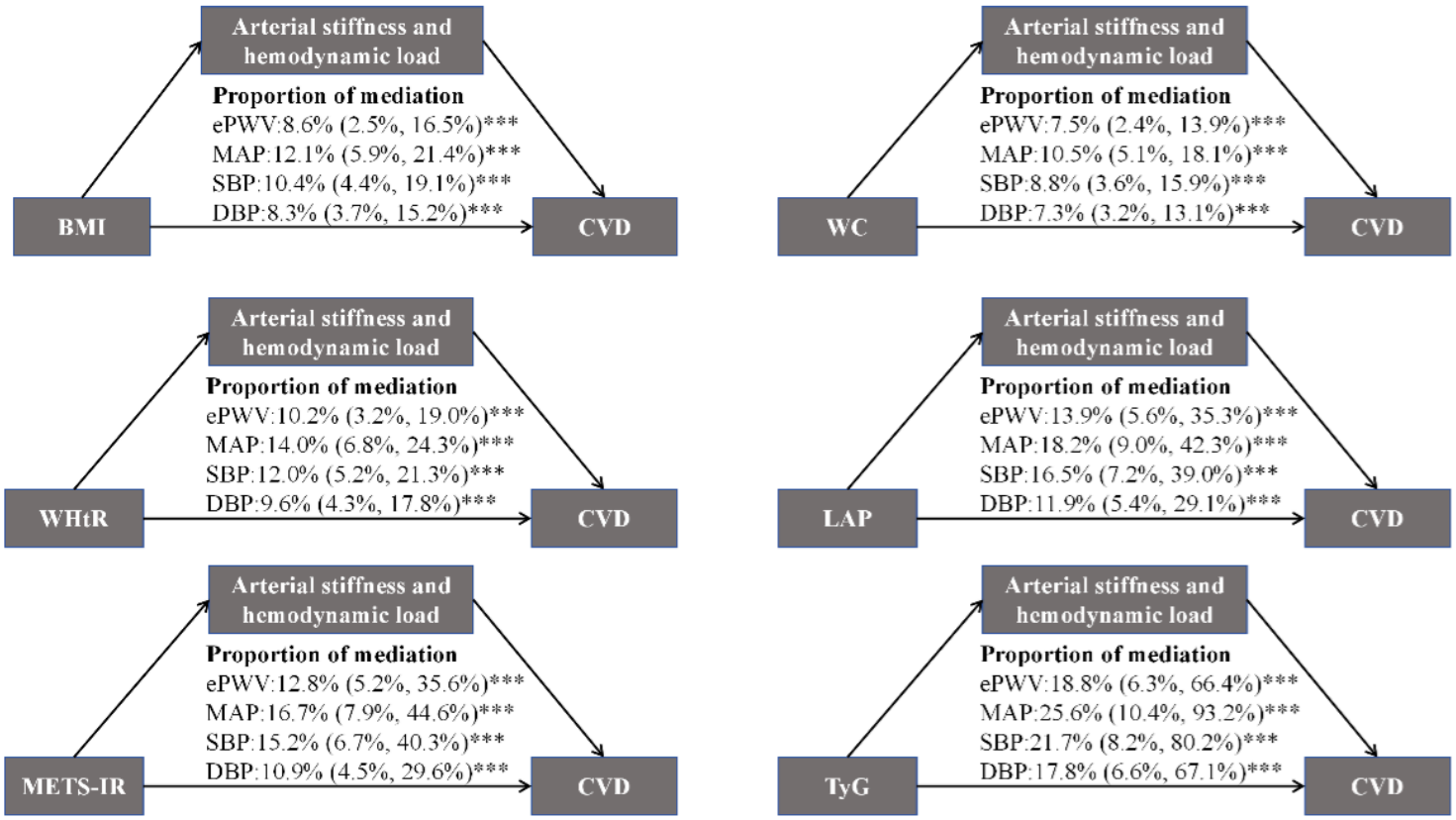


Figure 3

Mediation effect of arterial stiffness and hemodynamic load on the association between obesity and CVD risk in CHARLS.

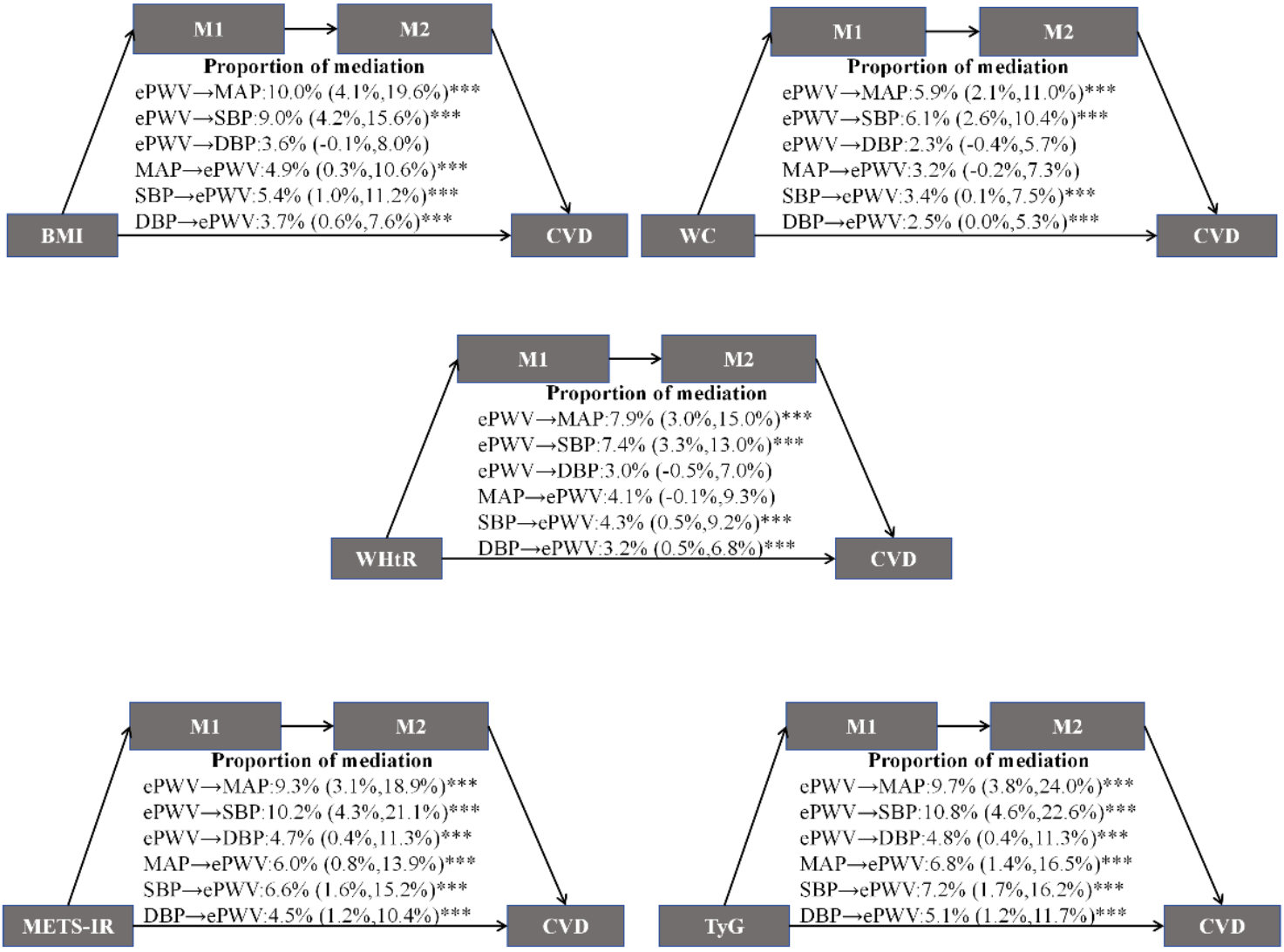


Figure 4

Serial mediation effect of arterial stiffness and hemodynamic load on the association between obesity and CVD risk in CHARLS .

Supplementary Files

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