

Pulse Pressure Dynamics and Cardiovascular-Kidney-Metabolic Syndrome Progression, Incident Hypertension, and Mortality: A Longitudinal Study from the CHARLS Cohort

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Article

Keywords: Pulse pressure, CKM syndrome, Hypertension, Mortality, Cohort study, CHARLS

Posted Date: August 6th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10471229/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

The cardiovascular-kidney-metabolic (CKM) staging system unifies metabolic, renal, and cardiovascular pathological conditions. Pulse pressure (PP), a simple marker of arterial stiffness reflecting vascular aging, may predict CKM progression. However, it remains unknown whether PP predicts CKM advancement across disease stages, and its longitudinal links with hypertension and mortality are poorly defined. This study evaluated associations of PP with CKM progression, to predict new-onset hypertension and long-term all-cause mortality among middle-aged and elderly Chinese individuals.

Methods

We used data from the China Health and Retirement Longitudinal Study (CHARLS, baseline 2011, follow-up to 2020). PP was calculated as systolic minus diastolic blood pressure. Logistic regression assessed baseline PP and 4-year CKM progression, and 4-year PP change (Δ PP) and new-onset hypertension. Cox models examined baseline PP and all-cause mortality with sequential confounder adjustment. Restricted cubic splines (RCS) modelled nonlinear relationships.

Results

The final sample included 12,853 participants (mean age 58.5 years, 48.5% male), with 1,712 deaths over a median 9-year follow-up. Fully adjusted analyses showed baseline PP predicted CKM progression solely in CKM stage 3 (subclinical cardiovascular disease, CVD; OR = 1.28, 95%CI 1.03–1.59, $P = 0.028$), with no significance for stages 0–2. Each 10 mmHg rise in Δ PP conferred a 4.90-fold higher risk of incident hypertension (OR = 4.90, 95%CI 4.09–5.94, $P < 0.001$). Baseline PP linearly predicted mortality (HR = 1.01 per 10 mmHg, 95%CI 1.005–1.014, $P < 0.001$). RCS revealed a U-shaped PP–mortality curve with the risk nadir at 44 mmHg.

Conclusions

PP exerts stage-specific predictive effects on CKM progression, limited to the subclinical CVD stage. Rising Δ PP strongly predicts incident hypertension, while baseline PP displays a U-shaped mortality association, indicating an optimal PP range for survival. PP serves as a low-cost, non-invasive vascular aging biomarker to support stratified CKM risk assessment among aging Chinese adults.

Research Insights

What is currently known about this topic?

PP is a validated marker of arterial stiffness and vascular aging.

The CKM syndrome framework integrates metabolic, renal, and cardiovascular pathological pathways.

Higher pulse pressure levels are associated with increased hazards of incident hypertension and all-cause death.

What is the key research question?

Does PP predict progressive advancement across successive CKM stages, and how do static baseline PP and dynamic PP changes relate to incident hypertension and long-term mortality?

What is new?

Baseline PP predicts CKM progression exclusively among participants with CKM stage 3 (subclinical CVD).

Four-year longitudinal PP change strongly predicts incident hypertension (OR = 4.90 per 10 mmHg increment).

Pulse pressure displays a U-shaped relationship with all-cause mortality, with the lowest mortality risk observed at approximately 44 mmHg.

How might this study influence clinical practice?

Serial PP monitoring facilitates stratified CKM risk assessment, particularly for patients with subclinical CVD, and enables early identification of individuals at elevated risk of developing hypertension.

Introduction

The American Heart Association (AHA) recently introduced the cardiovascular-kidney-metabolic (CKM) syndrome, an integrated paradigm illustrating overlapping pathological processes of metabolic, renal, and cardiovascular diseases [1]. Unlike traditional approaches that evaluate these conditions in isolation, the CKM paradigm recognizes that adiposity, insulin resistance, hypertension, dyslipidemia, and renal dysfunction constitute a continuous disease spectrum. The AHA CKM staging system stratifies individuals from stage 0 (absence of cardiometabolic risk markers) to stage 4 (established clinical CVD), providing a practical tool for population risk stratification and early intervention [2]. Since its release, accumulating evidence has validated the capacity of this staging framework to predict adverse endpoints including CVD events, heart failure incidence, and all-cause death among diverse populations [3, 4]. Nevertheless, simple, widely accessible biomarkers capable of tracking CKM progression to guide clinical decision-making remain an unmet research priority.

Pulse pressure (PP), defined as SBP minus DBP, directly reflects arterial stiffness and serves as a well-established marker of biological vascular aging [5]. Elevated PP indicates impaired large artery compliance, which imposes excessive pulsatile hemodynamic load on the heart, cerebral vasculature, and kidneys [6]. Whereas mean arterial pressure reflects steady-state tissue perfusion, PP captures dynamic vascular stress exerted on microvascular beds and end organs [7]. Multiple population-based

cohort studies have consistently linked elevated PP to increased risks of hypertension, CVD, stroke, and premature death [8–10]. Notably, a landmark analysis using the Chinese Longitudinal Healthy Longevity Survey (CLHLS) reported a U-shaped PP–mortality relationship among adults aged ≥ 80 years, with the risk nadir ranging from 50 to 60 mmHg [11]. Separately, a prior CHARLS-based study by You et al. revealed that long-term cumulative exposure to elevated PP was strongly linked to stroke incidence (HR = 1.23 per 1-standard deviation increment) [12]. Collectively, these observations underscore the clinical relevance of PP as a low-cost vascular health marker, especially in aging populations with high prevalence of arterial stiffening.

Despite well-documented associations between PP and individual CKM-related components, several critical knowledge gaps persist. First, no prior research has systematically examined whether PP predicts progressive advancement through sequential CKM stages. Although PP correlates with hypertension and CVD—two core components of the CKM framework—it remains unknown whether PP predicts actual stage transitions across the CKM continuum. Given that distinct pathophysiological mechanisms dominate different CKM stages, PP’s predictive performance may vary substantially across disease strata. For instance, metabolic derangements may drive early-stage progression, whereas hemodynamic dysfunction may become more influential in advanced preclinical stages.

Second, although arterial stiffness predicts incident hypertension in select populations [13], the direct longitudinal relationship between PP itself and new-onset hypertension remains inconsistent across studies. Discrepant findings may stem from variations in age distribution, ethnic composition, and measurement of peripheral versus central blood pressure [14]. Furthermore, most existing investigations rely solely on single-timepoint baseline PP rather than dynamic PP changes over years. Whether longitudinal PP trajectories offer additive predictive value for incident hypertension, specifically in middle-aged and elderly Chinese individuals, remains insufficiently investigated to date. Third, while prior work has separately assessed PP and mortality [10], the generalizability of the U-shaped PP–mortality association to the younger, broader CHARLS population requires formal validation. Together, these unresolved questions necessitate a comprehensive longitudinal analysis of static and dynamic PP metrics across the full spectrum of CKM-related adverse outcomes.

To address these gaps, we conducted a prospective cohort analysis using nationally representative CHARLS data. Our three primary study objectives were: (1) to evaluate stage-specific associations between baseline PP and 4-year CKM progression; (2) to quantify the predictive relationship between 4-year Δ PP and incident hypertension; (3) to characterize the association between initial PP levels and all-cause mortality during nine years of follow-up. We hypothesized that PP would exert stage-specific effects on CKM progression, with meaningful predictive value limited to the subclinical CVD stage (CKM stage 3), and that both static baseline PP and longitudinal PP elevation would independently predict incident hypertension and all-cause mortality. By addressing these objectives within a unified analytical framework, we aimed to generate comprehensive evidence supporting the clinical application of PP as a simple biomarker for vascular aging and stratified CKM risk assessment in aging Chinese populations.

Methods

Study Population

Data for this research were sourced from CHARLS, a nationally representative longitudinal cohort consisting of community-dwelling middle-aged and older adults covering all regions of China. Baseline surveys were conducted in 2011, with study sites including 450 rural and urban communities distributed within 28 Chinese provinces, including an initial enrollment of 17,708 participants. Ethical authorization for the CHARLS project was granted by the Institutional Review Board of Peking University; all study volunteers signed written consent forms ahead of data acquisition.

Study participants were excluded stepwise according to the criteria listed below: (1) loss to follow-up immediately after baseline ($n = 264$), lacking all longitudinal outcome data; (2) missing age information ($n = 8$); (3) death occurring within the baseline survey year ($n = 62$), with zero effective follow-up time; (4) baseline age < 45 years ($n = 502$), consistent with CHARLS's focus on middle-aged and older adults. After these exclusions, 16,872 participants remained eligible for cross-sectional baseline analyses. Sample sizes varied for longitudinal analyses requiring 2015 follow-up measurements and complete covariate data, as detailed in Fig. 1. The exact number of participants included in each analytical model is reported in the corresponding Results section.

Assessment of CKM Syndrome Staging

CKM staging was defined according to the 2023 AHA Presidential Advisory criteria, with minor modifications to accommodate variables available within the CHARLS dataset [1]. **Supplementary Document S1** contains comprehensive criteria defining the five CKM tiers ranging from stage 0 to stage 4. A concise summary is as follows: stage 0 shows no presence of cardiometabolic risks; stage 1 features obesity-related excess fat mass or glucose dysregulation; stage 2 incorporates metabolic disorders with moderate to high hazards and chronic kidney dysfunction; stage 3 marks detectable subclinical cardiovascular lesions; stage 4 stands for fully developed clinical CVD. CKM stage was ascertained at baseline (2011) and the 2015 follow-up using available laboratory and self-reported data. CKM progression was defined as any upward shift in CKM stage from 2011 to 2015.

Assessment of Pulse Pressure

At each survey wave, seated blood pressure was measured three times after a mandatory 5-minute rest using an automated Omron HEM-7112 digital sphygmomanometer [15]. All analytical procedures relied on the average derived from three independent measurements. Baseline PP (2011) was calculated as mean SBP minus mean DBP at the 2011 survey; follow-up PP (2015) was computed identically using 2015 blood pressure values. Four-year PP change (ΔPP) was defined as $PP_{2015} - PP_{2011}$. Physiologically

implausible PP values (< 20 mmHg or > 150 mmHg) were coded as missing, removing 17 participants from all PP-related analyses.

Definitions of Hypertension

Hypertensive status was identified if participants had a mean SBP of at least 140 mmHg, a mean DBP no less than 90 mmHg, self-reported doctor-diagnosed hypertension, or routine intake of antihypertensive agents. Incident hypertension was restricted to participants free of hypertension at baseline (2011) who met hypertension criteria by the 2015 follow-up wave.

Assessment of Mortality

All-cause mortality status was ascertained via the CHARLS dedicated mortality module, combining structured interviews with surviving family members and official local death registry records. Exact death dates were recorded for deceased participants. Survival time was calculated as the interval from the 2011 baseline survey to the recorded death date; for participants who stayed alive or were lost to follow-up, the endpoint was the last follow-up wave conducted in 2020.

Covariates

Covariates were selected based on established cardiovascular epidemiological literature and grouped into four categories: demographic characteristics, lifestyle behaviors, anthropometric and metabolic indices, and pre-existing comorbidities. Demographic variables included chronological age and biological sex. Lifestyle covariates encompassed smoking history (ever/never), alcohol consumption history (ever/never), and educational level (primary or lower, middle school, high school, and college and beyond). Anthropometric measurement including body mass index (BMI), which equals body weight in kilograms divided by height in meters squared. Measured metabolic parameters consisted of eGFR (derived by the CKD-EPI creatinine equation), fasting glucose, triglycerides and high-density lipoprotein cholesterol (HDL-C). Comorbidity covariates included physician-diagnosed hypertension, diabetes, and hypertriglyceridemia.

Missing Data Handling

All covariates except age, sex, and vital status contained varying degrees of missing values. Missing observations were not multiply imputed; instead, case-wise deletion was applied, excluding participants with incomplete variable sets from relevant regression models. Continuous values outside physiologically valid ranges were also coded as missing. Specifically, PP values < 20 mmHg or > 150 mmHg (n = 17) and BMI > 60 kg/m² were flagged as implausible and removed from analysis. Primary analyses did not implement any imputation for exposure or covariate variables, leading to variable

sample sizes across distinct regression models. Sample sizes corresponding to complete-case analyses for all models are detailed in the Results part and figure legends.

Statistical Analysis

Baseline characteristics were summarized as mean $\pm$ SD for continuous variables and n (%) for categorical variables. Intergroup comparisons stratified by PP quartiles adopted one-way ANOVA and chi-square tests for continuous and categorical data, respectively; linear trend across PP quartiles was assessed using linear regression (continuous outcomes) and the Cochran-Armitage test (binary outcomes).

Multivariable logistic regression models with sequential covariate adjustment were constructed to evaluate associations between baseline PP and 4-year CKM progression:

Model 1: Unadjusted crude model

Model 2: Adjusted for age and sex

Model 3: Further adjusted for BMI, smoking, alcohol intake, and education level

Model 4: Fully adjusted for eGFR, fasting glucose, triglycerides, HDL-C, baseline hypertension, and baseline diabetes

Stratified analyses by baseline CKM stage (0, 1, 2, 3) were conducted to test stage-specific PP effects. Statistical interaction between PP and baseline CKM stage was tested via likelihood ratio comparisons of nested models with and without interaction cross-products.

Identical sequential logistic regression frameworks were applied to analyze Δ PP and incident hypertension, with additional adjustment for baseline SBP to isolate the independent effect of longitudinal PP change.

Cox proportional hazards regression models with the same sequential adjustment strategy were used to examine baseline PP and all-cause mortality. The proportional hazards assumption was verified using Schoenfeld residual diagnostics. RCS models were fitted to visualize nonlinear PP–mortality relationships, with the curve nadir identified as the PP value corresponding to the minimum mortality hazard.

Prespecified subgroup stratifications were performed by age (< 60 years vs. $\geq$ 60 years) and sex. Multicollinearity was quantified via variance inflation factors (VIF), with VIF < 5 confirming the absence of severe collinearity.

All statistical analyses were performed using R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Key packages included survival for Cox regression, rms for restricted cubic splines, ggplot2 for

data visualization, and tableone for baseline characteristic table generation. A two-sided P value < 0.05 was defined as the threshold for statistical significance.

Results

Baseline Characteristics

A total of 16,872 participants remained after baseline exclusions (Fig. 1). The overall mean age was 58.5 ± 9.5 years, and 48.5% of participants were male. Sample sizes varied for longitudinal analyses according to follow-up data and covariate completeness: 3,140 participants for the CKM progression analysis, 2,560 for incident hypertension analysis, and 12,853 for all-cause mortality analysis. Baseline characteristics stratified by PP quartiles are presented in Table 1. Participants in the highest PP quartile (Q4) were significantly older (65.7 vs. 55.5 years), exhibited higher SBP (157.0 vs. 112.4 mmHg), lower eGFR (81.0 vs. 93.7 mL/min/1.73m²), and elevated frailty scores (20.7 vs. 15.9) relative to the lowest quartile (all P for trend < 0.001). The prevalence of hypertension, diabetes, metabolic syndrome, and advanced CKM stages increased progressively across ascending PP quartiles (all P for trend < 0.001), whereas grip strength and eGFR displayed consistent declining trends.

Table 1
Baseline Characteristics by PP Quartiles

Characteristic	Overall	Q1_Lowest	Q2	Q3	Q4_Highest	p_value
n	13,084	3,300	3,256	3,282	3,246	
Age (years), mean (SD)	59.55 (9.59)	55.47 (7.78)	56.93 (8.21)	60.16 (9.16)	65.69 (9.78)	< 0.001
Sex, n (%)						
Female	6,858 (52.4)	1,796 (54.4)	1,607 (49.4)	1,605 (48.9)	1,850 (57.0)	
Male	6,226 (47.6)	1,504 (45.6)	1,649 (50.6)	1,677 (51.1)	1,396 (43.0)	
BMI (kg/m²), mean (SD)	23.42 (3.83)	23.24 (3.79)	23.28 (3.72)	23.58 (3.74)	23.59 (4.05)	< 0.001
BMI category, n (%)						
Underweight	892 (6.9)	248 (7.6)	207 (6.5)	200 (6.2)	237 (7.5)	
Normal	6,819 (53.1)	1,772 (54.6)	1,787 (55.8)	1,662 (51.4)	1,598 (50.7)	
Overweight	3,701 (28.9)	916 (28.2)	896 (28.0)	991 (30.7)	898 (28.5)	
Obese	1,423 (11.1)	310 (9.6)	312 (9.7)	380 (11.8)	421 (13.3)	
Waist circumference (cm), mean (SD)	85.27 (10.14)	83.95 (9.84)	84.29 (9.80)	85.91 (10.03)	86.93 (10.65)	< 0.001
Systolic BP (mmHg), mean (SD)	131.15 (22.09)	112.40 (11.19)	122.12 (11.55)	133.07 (12.48)	157.02 (18.68)	< 0.001
Diastolic BP (mmHg), mean (SD)	76.04 (11.89)	72.92 (10.76)	74.07 (11.20)	76.53 (11.90)	80.63 (13.08)	< 0.001
Grip strength (kg), mean (SD)	31.53 (10.82)	32.28 (10.79)	32.93 (10.71)	32.15 (10.92)	28.76 (10.46)	< 0.001
Frailty index, mean (SD)	17.52 (12.05)	15.87 (11.22)	15.96 (10.91)	17.51 (11.93)	20.71 (13.21)	< 0.001
Smoking status, n (%)						
Non-smoker	7,852 (60.1)	2,051 (62.2)	1,914 (58.8)	1,886 (57.5)	2,001 (61.7)	
Current smoker	5,220 (39.9)	1,248 (37.8)	1,339 (41.2)	1,393 (42.5)	1,240 (38.3)	

Characteristic	Overall	Q1_Lowest	Q2	Q3	Q4_Highest	p_value
Alcohol use, n (%)						
Non-drinker	7,997 (61.2)	2,058 (62.4)	1,956 (60.2)	1,916 (58.5)	2,067 (63.8)	
Current drinker	5,067 (38.8)	1,238 (37.6)	1,295 (39.8)	1,362 (41.5)	1,172 (36.2)	
Education level, n (%)						
Primary school or below	6,481 (49.7)	1,432 (43.4)	1,440 (44.2)	1,666 (50.8)	1,943 (59.9)	
Middle school	2,794 (21.4)	690 (20.9)	723 (22.2)	675 (20.6)	706 (21.8)	
High school	2,467 (18.9)	745 (22.6)	729 (22.4)	606 (18.5)	387 (11.9)	
College or above	1,340 (10.3)	433 (13.1)	363 (11.2)	335 (10.2)	209 (6.4)	
eGFR (mL/min/1.73m²), mean (SD)	89.02 (18.79)	93.74 (17.26)	93.11 (17.72)	88.27 (18.96)	80.97 (19.32)	< 0.001
TyG index, mean (SD)	8.69 (0.67)	8.62 (0.65)	8.65 (0.67)	8.72 (0.67)	8.76 (0.68)	< 0.001
CHG, mean (SD)	5.33 (0.46)	5.28 (0.43)	5.30 (0.46)	5.36 (0.47)	5.39 (0.47)	< 0.001
CTI, mean (SD)	8.77 (0.85)	8.67 (0.83)	8.70 (0.85)	8.80 (0.84)	8.90 (0.87)	< 0.001
Hypertension, n (%)	6,794 (52.0)	874 (26.5)	1,132 (34.8)	1,867 (56.9)	2,921 (90.0)	< 0.001
Diabetes, n (%)	2,552 (19.6)	488 (14.8)	584 (18.0)	690 (21.1)	790 (24.4)	< 0.001
Prediabetes, n (%)	3,770 (33.2)	898 (30.0)	923 (32.3)	964 (34.4)	985 (35.9)	< 0.001
Dyslipidemia, n (%)	2,729 (21.3)	642 (19.8)	613 (19.2)	755 (23.5)	719 (22.5)	< 0.001
Hypertriglyceridemia, n (%)	2,497 (26.6)	586 (25.0)	572 (24.6)	674 (28.1)	665 (28.4)	0.002
Heart disease, n (%)	2,530 (19.5)	570 (17.4)	553 (17.1)	642 (19.7)	765 (23.7)	< 0.001
Stroke, n (%)	1,093 (8.4)	208 (6.3)	228 (7.0)	283 (8.7)	374 (11.6)	< 0.001

Characteristic	Overall	Q1_Lowest	Q2	Q3	Q4_Highest	p_value
CKD, n (%)	1,977 (25.3)	430 (23.6)	451 (23.7)	489 (24.9)	607 (29.3)	< 0.001
Metabolic syndrome, n (%)	4,043 (31.1)	757 (23.0)	767 (23.6)	1,096 (33.4)	1,423 (44.2)	< 0.001
CKM Stage, n (%)						
Stage 0	71 (0.8)	35 (1.6)	24 (1.0)	12 (0.4)	0 (0.0)	
Stage 1	177 (1.9)	75 (3.4)	62 (2.7)	37 (1.3)	3 (0.1)	
Stage 2	5,745 (54.3)	1,121 (50.5)	1,191 (52.0)	1,628 (57.8)	1,805 (56.7)	
Stage 3	1,254 (11.9)	285 (12.8)	304 (13.3)	304 (10.8)	361 (11.3)	
Stage 4	3,265 (30.9)	705 (31.7)	709 (31.0)	834 (29.6)	1,017 (31.9)	
Clinical CVD, n (%)	3,265 (25.2)	705 (21.5)	709 (21.9)	834 (25.6)	1,017 (31.5)	< 0.001
Subclinical CVD, n (%)	1,977 (15.1)	430 (13.0)	451 (13.9)	489 (14.9)	607 (18.7)	< 0.001

Data are presented as mean (SD) for continuous variables and n (%) for categorical variables. P values were calculated using ANOVA for continuous variables and chi-square tests for categorical variables. P for trend was calculated using linear regression for continuous variables and Cochran–Armitage trend test for categorical variables. BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride-glucose index; CHG, cholesterol-high-density lipoprotein-glucose index; CTI, cardiometabolic index; CKD, chronic kidney disease; CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic; SD, standard deviation.

CKM Stage Progression

Within 3,140 participants with baseline CKM stages 0–3, CKM stage deterioration was observed in 307 cases (9.8%) throughout the 4-year observational period. Progression rates varied markedly by baseline CKM stage: stage 1 demonstrated the highest progression rate (79.6%), followed by stage 0 (46.4%), stage 2 (8.5%), and stage 3 (5.9%). In the full CHARLS sample, baseline CKM stage proportions were stage 0 (0.5%), stage 1 (1.4%), stage 2 (54.8%), stage 3 (12.2%), stage 4 (33.1%); 23.5% of subjects had missing CKM staging data.

Within the overall pooled sample, baseline No meaningful link was identified between PP and the progression of CKM when analyses were adjusted for participants' initial CKM stage (OR per 10 mmHg =

1.04, 95% CI: 0.96–1.14, $P = 0.333$; **Supplementary Table S1**). Baseline CKM stage emerged as the dominant predictor of progression: each one-stage increase reduced progression odds by 89% ($OR = 0.11$, 95% CI: 0.08–0.15, $P < 0.001$), consistent with a ceiling effect, where participants with advanced baseline CKM stages have limited potential for further advancement. Stratified analysis by baseline CKM stage revealed significant stage heterogeneity (Fig. 2; Table 2). Among participants with baseline CKM stage 3, each 10 mmHg higher PP increased the odds of progression to stage 4 by 28% after full adjustment ($OR = 1.28$, 95% CI: 1.03–1.59, $P = 0.028$), whereas no statistically significant correlations were detected among participants with CKM stages 0 to 2 (all $P > 0.10$). The interaction term between PP and baseline CKM stage reached statistical significance (P for interaction = 0.015), formally validating stage-specific effect modification.

Table 2
Stage-Specific Association Between Pulse Pressure and CKM Progression

Stage	Model	N	Events	OR_CI	P
Stage 1	Unadjusted	98	78 (79.6)	1.72 (0.86–3.62)	0.135
	Model 1	98	78 (79.6)	1.41 (0.67–3.08)	0.377
	Model 2	98	78 (79.6)	1.93 (0.78–5.21)	0.17
	Model 3	98	78 (79.6)	2.13 (0.83–6.06)	0.129
Stage 2	Unadjusted	4108	351 (8.5)	1.14 (1.06–1.22)	< 0.001
	Model 1	4108	351 (8.5)	1 (0.92–1.07)	0.923
	Model 2	4108	351 (8.5)	1 (0.92–1.08)	0.997
	Model 3	4108	351 (8.5)	0.99 (0.89–1.1)	0.839
Stage 3	Unadjusted	1013	60 (5.9)	1.31 (1.14–1.51)	< 0.001
	Model 1	1013	60 (5.9)	1.19 (1.01–1.4)	0.034*
	Model 2	1013	60 (5.9)	1.17 (0.98–1.37)	0.069
	Model 3	1013	60 (5.9)	1.28 (1.03–1.59)	0.028*

Data are presented as n (%) for events. ORs were calculated per 10 mmHg increase in PP. Model 1: adjusted for age and sex; Model 2: further adjusted for BMI, smoking, drinking, and education; Model 3: further adjusted for eGFR, fasting glucose, triglycerides, HDL-C, hypertension, and diabetes. Stage 0 was excluded due to small sample size ($n = 29$). * $P < 0.05$ indicates statistical significance.

Pulse Pressure Change and Incident Hypertension

Over the 4-year follow-up window, 289 new hypertension cases were identified among 2,560 participants free of baseline hypertension, corresponding to a cumulative incidence of 11.3%. Hypertension incidence

rose progressively across ascending Δ PP quartiles, ranging from 2.8% in the lowest quartile to 30.1% in the highest quartile (P for trend < 0.001; Fig. 3A).

In the fully adjusted logistic regression model, each 10 mmHg increment in 4-year Δ PP was associated with a 4.90-fold higher risk of incident hypertension (OR = 4.90, 95% CI: 4.09–5.94, P < 0.001), independent of age, sex, BMI, lifestyle factors, educational attainment, metabolic covariates, and baseline SBP (Table 3). Notably, additional adjustment for baseline SBP strengthened the effect estimate substantially, rising from OR = 3.33 (95% CI: 2.87–3.89) to OR = 4.90 (95% CI: 4.09–5.94), indicating suppression confounding.

Quartile analysis confirmed a clear linear dose–response gradient. Relative to the lowest Δ PP quartile (Q1), Q2 exhibited 3.06-fold higher hypertension odds (OR = 3.06, 95% CI: 1.68–5.76), Q3 exhibited 5.83-fold higher odds (OR = 5.83, 95% CI: 3.35–10.6), and Q4 exhibited 36.8-fold higher odds (OR = 36.8, 95% CI: 21.8–65.8) (Table 4), revealing a prominent linear trend with P for trend less than 0.001.

RCS analysis identified a nonlinear Δ PP–hypertension association (P for nonlinearity < 0.001). The risk curve remained nearly flat for Δ PP values below approximately 40 mmHg, after which odds ratios rose sharply, demonstrating a clear threshold effect (Fig. 3B). ROC curve analysis confirmed excellent discriminatory capacity for the fully adjusted model incorporating Δ PP (AUC = 0.886), significantly superior to a parsimonious model limited to Δ PP, age, and sex (AUC = 0.806, P for difference < 0.001; Fig. 3C).

Table 3
Association Between Pulse Pressure Change (Δ PP) and Incident Hypertension

Model_Label	Adjustment	OR	OR_low	OR_high	OR_CI	P_value
Unadjusted	None	3.491608238	3.017060099	4.067463005	3.49 (3.02–4.07)	< 0.001
Model 1	Age, sex	3.32674807	2.870685745	3.880076686	3.33 (2.87–3.88)	< 0.001
Model 2	Age, sex, BMI, smoking, drinking, education	3.338206345	2.878070192	3.897367295	3.34 (2.88–3.9)	< 0.001
Model 3	Age, sex, BMI, smoking, drinking, education, eGFR, glucose, TG, HDL	3.329843043	2.869692628	3.889681054	3.33 (2.87–3.89)	< 0.001
Model 4	Age, sex, BMI, smoking, drinking, education, eGFR, glucose, TG, HDL, baseline SBP	4.903804546	4.09389667	5.937032882	4.9 (4.09–5.94)	< 0.001

ORs were calculated per 10 mmHg increase in Δ PP. Model 1: adjusted for age and sex; Model 2: + BMI, smoking, drinking, education; Model 3: + eGFR, glucose, TG, HDL; Model 4: + baseline SBP. Δ PP, change in pulse pressure; OR, odds ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglycerides; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Table 4
Dose-Response Relationship Between Δ PP Quartiles and Incident Hypertension

Quartile	OR	OR_low	OR_high	OR_CI	P_value
Q1	1	NA	NA	1.00 (Ref)	-
Q2	3.061872731	1.675208958	5.757053226	3.06 (1.68–5.76)	< 0.001
Q3	5.828222718	3.345652165	10.59964072	5.83 (3.35–10.6)	< 0.001
Q4	36.84095082	21.79279569	65.79953916	36.84 (21.79–65.8)	< 0.001

Adjusted for age, sex, BMI, smoking, drinking, education, eGFR, glucose, TG, HDL, and baseline SBP. Δ PP, change in pulse pressure; OR, odds ratio; CI, confidence interval.

Pulse Pressure and All-Cause Mortality

Over a median follow-up of 9 years, 1,712 all-cause deaths were recorded among 12,853 participants. In fully adjusted Cox proportional hazards models, each 10 mmHg higher baseline PP was independently associated with elevated all-cause mortality (HR = 1.01, 95% CI: 1.005–1.014, $P < 0.001$) after accounting for age, sex, BMI, lifestyle factors, education, metabolic indices, baseline hypertension, and baseline diabetes (Table 5). Age constituted the strongest independent mortality predictor (HR per year = 1.079, 95% CI: 1.070–1.088, $P < 0.001$), followed by male sex (HR = 1.51, 95% CI: 1.26–1.81, $P < 0.001$), smoking history (HR = 1.41, 95% CI: 1.20–1.66, $P < 0.001$), and reduced eGFR (HR per mL/min = 0.987, 95% CI: 0.983–0.991, $P < 0.001$). Higher educational attainment correlated with lower mortality risk (college vs. primary school or below: HR = 0.52, 95% CI: 0.38–0.71, $P < 0.001$). Importantly, baseline hypertension exhibited an inverse association with all-cause mortality (HR = 0.746, 95% CI: 0.642–0.868, $P < 0.001$), a pattern potentially attributable to survivor bias or systematic treatment differences (Fig. 4, **Supplementary Table S2**).

RCS modeling revealed a significant U-shaped nonlinear relationship between baseline PP and all-cause mortality (P for nonlinearity < 0.001 ; Fig. 5A). The mortality risk nadir occurred at approximately 44 mmHg, with mortality risk rising markedly at PP values below 40 mmHg and above 80 mmHg. Kaplan–Meier survival curves stratified by PP quartiles further validated this U-shaped pattern (Fig. 5B). Participants in the highest PP quartile (Q4) displayed significantly inferior survival probabilities relative to lower quartiles (log-rank $P < 0.001$). Median survival was shortest within Q4, with survival curves diverging approximately 4–5 years after baseline and separating progressively over extended follow-up. This U-shaped association remained consistent across all primary and sensitivity analytical models.

Table 5
Association Between Baseline Pulse Pressure and All-Cause Mortality

Model	N	Events	Adjustment	HR_per_10	HR_CI	P_formatted
Unadjusted	12853	1712	None	1.028	1.028 (1.025– 1.030)	< 0.001
Model 1	12853	1712	Age, sex	1.006	1.006 (1.003– 1.009)	< 0.001
Model 2	12853	1712	Age, sex, BMI, smoking, drinking, education	1.006	1.006 (1.004– 1.009)	< 0.001
Model 3	12853	1712	Age, sex, BMI, smoking, drinking, education, eGFR, glucose, TG, HDL, hypertension, diabetes	1.01	1.010 (1.005– 1.014)	< 0.001

HRs were calculated per 10 mmHg increase in baseline PP. Model 1: adjusted for age and sex; Model 2: + BMI, smoking, drinking, education; Model 3: + eGFR, glucose, TG, HDL, hypertension, diabetes. HR, hazard ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglycerides; HDL, high-density lipoprotein.

Subgroup and Sensitivity Analyses

Stratified subgroup analyses by age (< 60 vs. ≥60 years) and sex demonstrated consistent PP–CKM progression and PP–mortality associations across all strata, with no statistically significant interaction terms detected (all P for interaction > 0.10; **Supplementary Figure S1**). These results confirm that the stage-specific predictive value of PP for CKM progression and its U-shaped mortality association are robust across distinct age and sex subgroups. For the ΔPP–incident hypertension relationship, subgroup stratification yielded qualitatively consistent dose–response patterns across all pre-specified strata (**Supplementary Figure S2**).

Sensitivity analyses using multiply imputed CKM staging data generated results materially consistent with primary analyses (OR = 0.96, 95% CI: 0.92–1.00, P = 0.056). Additional sensitivity tests excluding participants with implausible PP values, individuals receiving baseline antihypertensive medication, or those with pre-existing baseline CVD did not meaningfully alter core effect estimates (all P > 0.05), verifying the robustness of our primary findings (**Supplementary Table S3**).

Discussion

In this longitudinal analysis of a nationally representative cohort of 12,853 middle-aged and older Chinese adults, we systematically evaluated the associations between pulse pressure dynamics and

multiple CKM syndrome-related outcomes. Three key findings emerged. First, the predictive capacity of baseline pulse pressure (PP) for CKM progression was stage-specific, with significant effects only observed among participants with baseline CKM stage 3 (subclinical CVD). In this subgroup, each 10 mmHg increment in PP corresponded to a 28% higher odds of advancing to clinical CVD (stage 4). Second, the 4-year change in PP (Δ PP) strongly and independently predicted incident hypertension; each 10 mmHg rise in Δ PP conferred a 4.90-fold higher risk, even after adjustment for baseline systolic blood pressure. Third, baseline PP displayed a U-shaped relationship with all-cause mortality, with the risk nadir at approximately 44 mmHg, indicating an optimal survival-preserving PP range. Collectively, these results demonstrate that PP dynamics provide complementary prognostic information for stratified CKM risk assessment across successive disease stages.

Stage-Specific Association of PP with CKM Progression

The stage-specific relationship between baseline PP and CKM progression merits careful interpretation. After full multivariable adjustment, PP was not independently associated with overall CKM progression, as baseline CKM stage dominated disease transition risk—a pattern consistent with a ceiling effect. Individuals with advanced baseline CKM stages have limited room for further progression, while early-stage CKM deterioration is driven predominantly by metabolic rather than hemodynamic disturbances [16]. The highest progression rate observed in stage 1 further underscores the primacy of metabolic dysfunction in early CKM transitions. Notably, elevated PP independently increased the odds of progression from subclinical CVD (stage 3) to overt clinical CVD (stage 4), implying that arterial stiffness captured by elevated PP acts as a critical driver of incident cardiovascular events once subclinical vascular damage has developed [17]. Restricted cubic spline (RCS) models confirmed a linear PP effect restricted exclusively to this high-risk subgroup.

This stage-dependent gradient aligns with the established conceptual framework of CKM syndrome, which posits divergent dominant pathophysiological pathways across disease stages [18]. Early CKM progression is primarily metabolically mediated, whereas transitions from subclinical to clinical CVD are accelerated by vascular and hemodynamic impairment [19, 20]. The statistically significant interaction between PP and baseline CKM stage formally validates this heterogeneous association. From a clinical perspective, PP monitoring delivers incremental prognostic value specifically for patients with subclinical CVD to identify those at elevated risk of subsequent clinical cardiovascular events.

Δ PP as a Strong Predictor of Incident Hypertension

Our analysis identified Δ PP as a robust independent predictor of incident hypertension among middle-aged and older Chinese adults. This correlation remained robust following adjustment for baseline SBP and comprehensive metabolic, lifestyle, and demographic confounders, with each 10 mmHg 4-year PP increase associated with a nearly fivefold elevation in hypertension risk. RCS modeling revealed a prominent threshold effect near 40 mmHg: mild PP elevations over time were not linked to meaningful hypertension risk, yet vascular decompensation beyond this critical threshold triggered rapid hypertensive onset [21]. The clear dose–response gradient across Δ PP quartiles and excellent

discriminatory performance of the fully adjusted model (AUC = 0.886) further support the clinical utility of serial PP trajectory monitoring for hypertension risk screening.

Several observations from this analysis warrant emphasis. First, the predictive effect of Δ PP remained independent of baseline SBP; in fact, adjustment for baseline SBP strengthened the magnitude of the odds ratio from 3.33 to 4.90, indicative of suppression confounding. This confirms that Δ PP captures progressive hemodynamic deterioration unreflected by single-timepoint blood pressure measurements. The RCS curve remained flat for Δ PP values below ~ 40 mmHg, after which risk rose steeply. This threshold phenomenon may reflect the gradual accumulation of arterial stiffness, which only translates to clinically meaningful hypertension risk once vascular reserve is exhausted. Clinically, this finding suggests that modest longitudinal PP elevations carry minimal hypertensive risk, whereas a > 40 mmHg 4-year PP increase constitutes a critical warning sign requiring intensified surveillance and lifestyle intervention.

U-Shaped Relationship Between PP and All-Cause Mortality

Consistent with prior CLHLS-based epidemiological evidence [11], we detected a pronounced U-shaped association between baseline PP and all-cause mortality, with risk minimized at approximately 44 mmHg. This nonlinear pattern reinforces a core clinical principle for vascular health management in older populations: for PP, “lower is not always better”. Low PP may signal reduced cardiac output or advanced physical frailty, while high PP marks severe arterial stiffening; both extremes correlate with unfavorable long-term survival [22]. Importantly, our results replicate this U-shaped curve within a younger middle-aged and older cohort with extended 9-year follow-up, substantially broadening the generalizability of this nonlinear risk relationship across age groups.

The counterintuitive inverse relationship between hypertensive status and all-cause death (HR = 0.746, $p < 0.001$) aligns with consistent reports of the hypertension paradox in older adult longitudinal cohorts [23–25]. Three interrelated mechanisms may explain this phenomenon: (1) treatment bias—individuals diagnosed with hypertension receive routine antihypertensive therapy and regular medical surveillance, which improves overall survival [26]; (2) reverse causation—undiagnosed severe chronic illness suppresses blood pressure and concurrently elevates mortality risk [22]; (3) survival bias—individuals surviving to advanced age represent a physiologically resilient subset capable of tolerating chronic hypertension without premature events [27]. Critically, PP retained independent predictive value for mortality even after accounting for hypertension status, demonstrating that PP quantifies subclinical vascular aging beyond the binary clinical diagnosis of hypertension [28].

Comparison with Previous Studies

Our findings extend existing literature on PP dynamics and cardiometabolic outcomes in four distinct, novel ways. First, we replicated the U-shaped PP–mortality association originally observed in the oldest-old CLHLS population within a broader middle-aged and older adult cohort with prolonged follow-up,

verifying consistent nonlinear risk patterns across age spectrums [11]. Second, our results complement prior CHARLS analyses linking cumulative vascular burden to stroke risk, collectively establishing PP as a generalized cardiovascular prognostic biomarker [12]. Third, although prior investigations have evaluated cross-sectional PP and hypertension associations across diverse populations [29, 30], our study provides unique longitudinal evidence that dynamic PP trajectories predict incident hypertension with far larger effect sizes than static blood pressure metrics, highlighting the superiority of serial PP measurements for tracking progressive arterial dysfunction. Fourth, this work is among the first to systematically characterize stage-specific PP effects across the full AHA-defined CKM continuum, generating novel evidence to support stratified cardiometabolic risk stratification protocols.

Clinical Implications

Our analyses yield three translational clinical implications for precision cardiometabolic risk management. First, PP exhibits stage-limited prognostic utility: it only improves risk prediction for patients with subclinical CVD (CKM stage 3), with negligible incremental value during early metabolic CKM stages. Second, serial tracking of PP trajectories enables early identification of individuals at high hypertension risk; a 4-year PP increase exceeding 40 mmHg warrants targeted lifestyle modification and intensified blood pressure monitoring. Third, the U-shaped mortality curve underscores a shift away from aggressive blood pressure lowering toward maintenance of moderate PP levels (~ 44 mmHg) in aging populations. Contextualized interpretation of PP by CKM disease stage aligns with evolving precision vascular care paradigms among middle-aged and elderly individuals.

Strengths and Limitations

This study possesses several methodological strengths. First, we leveraged a large, nationally representative CHARLS sample with up to 9 years of longitudinal follow-up, providing sufficient statistical power to detect stage-specific and nonlinear associations. Second, we simultaneously evaluated three distinct CKM-related outcomes within a unified analytical framework, enabling holistic characterization of PP's clinical utility. Third, comprehensive adjustment for a broad panel of demographic, lifestyle, metabolic, and comorbidity confounders strengthens causal inference. Fourth, complementary statistical approaches—including logistic regression, Cox proportional hazards models, and restricted cubic splines—deliver robust, mutually supportive evidence for all reported associations.

Several limitations require acknowledgment. First, the 4-year follow-up window for CKM progression may underestimate long-term PP-mediated disease transitions, particularly slow early-stage metabolic deterioration. Second, CKM staging was operationalized using available CHARLS laboratory and self-reported data rather than gold-standard clinical assessments, which may introduce minor classification misclassification, especially for subclinical CVD (stage 3). Third, the limited number of stage 3 progression events reduced statistical precision in this subgroup analysis, though primary results remained stable across multiple sensitivity tests. Fourth, we lacked time-varying data on antihypertensive medication use across follow-up waves, a factor that could alter PP trajectories and incident hypertension risk. Fifth, external validation in younger adults or non-Chinese ethnic populations

is required to confirm broader generalizability. Lastly, similar to all observational cohort investigations, thorough adjustment for multiple covariates cannot completely rule out residual confounding from unmeasured factors.

Conclusions

In conclusion, this nationwide longitudinal CHARLS cohort study demonstrates divergent stage-dependent associations between PP dynamics across the CKM disease continuum. Longitudinal PP elevation strongly predicts incident hypertension, whereas baseline PP exhibits a U-shaped correlation with all-cause mortality risk, with optimal survival at approximately 44 mmHg. These findings validate PP as an inexpensive, non-invasive biomarker of vascular aging to support stratified cardiometabolic risk evaluation in middle-aged and elderly Chinese individuals. Subsequent investigations are needed to externally validate the present results using separate study cohorts and dissect the mechanistic pathways linking progressive PP changes to CKM advancement, particularly the role of arterial stiffness in driving transitions from subclinical to clinical cardiovascular disease.

Abbreviations

ANOVA

analysis of variance

BMI

body mass index

CKD

chronic kidney disease

CKD-EPI

Chronic Kidney Disease Epidemiology Collaboration

CKM

cardiometabolic stage

eGFR

estimated glomerular filtration rate

HDL-C

high-density lipoprotein cholesterol

LDL-C

low-density lipoprotein cholesterol

PP

pulse pressure

SD

standard deviation

CHD

coronary heart disease

HR

hazard ratio
OR
odds ratio
95%CI
95% confidence interval
GLU
fasting glucose
TG
triglycerides
BP
blood pressure
SBP
systolic blood pressure
DBP
diastolic blood pressure
CHARLS
China Health and Retirement Longitudinal Study

Declarations

Ethics approval and consent to participate

The CHARLS study protocol was approved by the Institutional Review Board of Peking University. All participants provided written informed consent before baseline data collection. All procedures complied with the Declaration of Helsinki.

Consent for publication

Not applicable (all analyses used de-identified public cohort data without individual identifiable information).

Competing interests

The authors declare that they have no competing interests.

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Funding

No funding was received for this study.

Author Contribution

WF and JX conceived and designed the study; ZSZ performed statistical analysis; LCQ drafted the manuscript; WF revised the manuscript critically for intellectual content; All authors read and approved the final manuscript.

Acknowledgement

We thank all participants of the CHARLS cohort and the research team at Peking University for data collection and maintenance. DeepSeek-V4 was used for language polishing and grammar checking during manuscript preparation. All revisions were reviewed and approved by the authors, who assume full responsibility for the final manuscript.

Data Availability

CHARLS datasets are publicly available from the China Health and Retirement Longitudinal Study official website (<https://charls.pku.edu.cn/>). The analytic code generated during this study is available from the corresponding author upon reasonable request.

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Figures

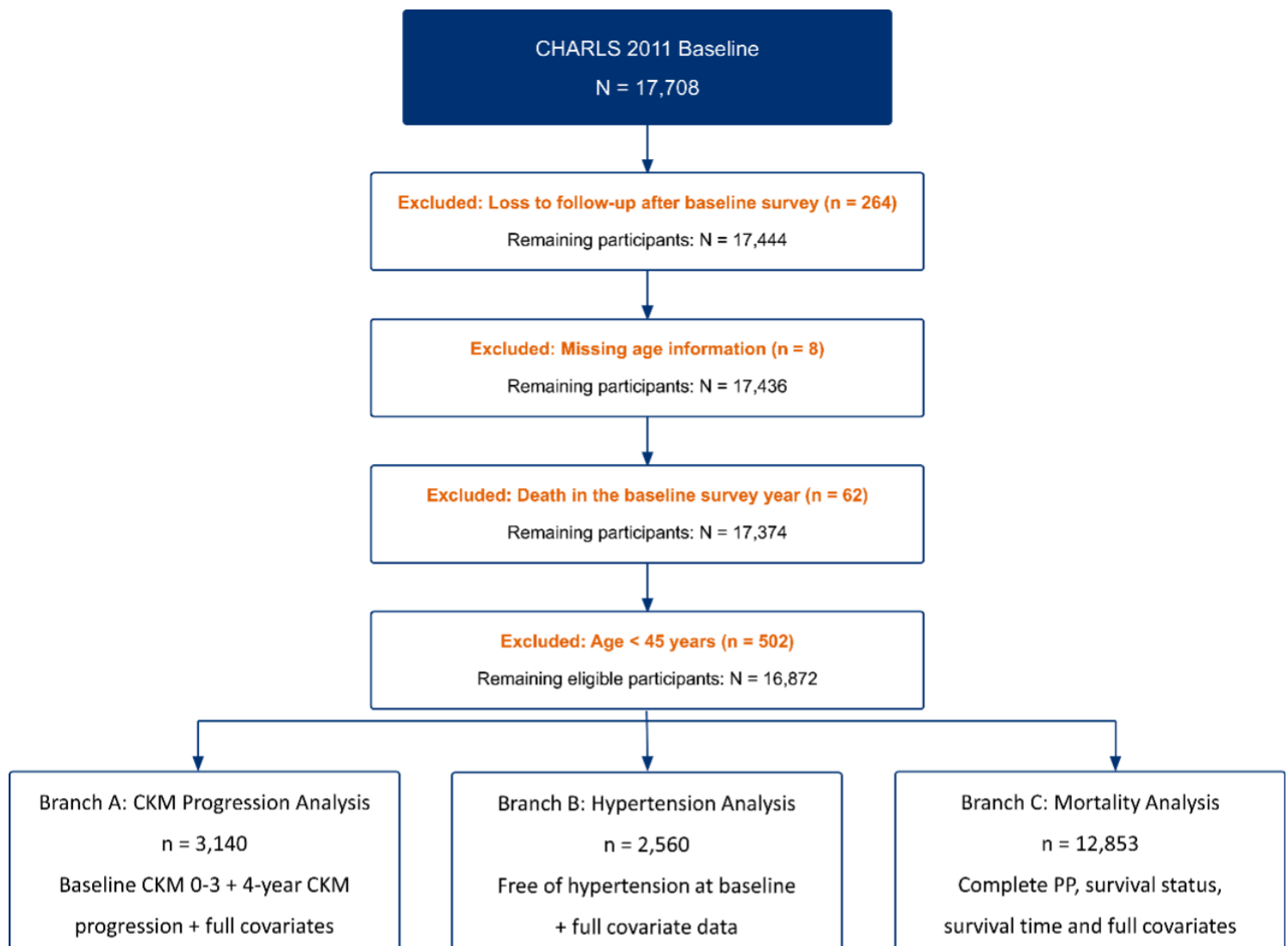


Figure 1

Flowchart showing participant selection from the CHARLS 2011 baseline cohort. After sequential exclusion of participants lost to follow-up, with missing age data, deceased in baseline year, or aged <45

years, the remaining eligible population was stratified into three analytic subcohorts for CKM progression, incident hypertension, and all-cause mortality analyses, respectively.

Stage-Specific Association Between PP and CKM Progression

Adjusted for age, sex, BMI, lifestyle, metabolic factors

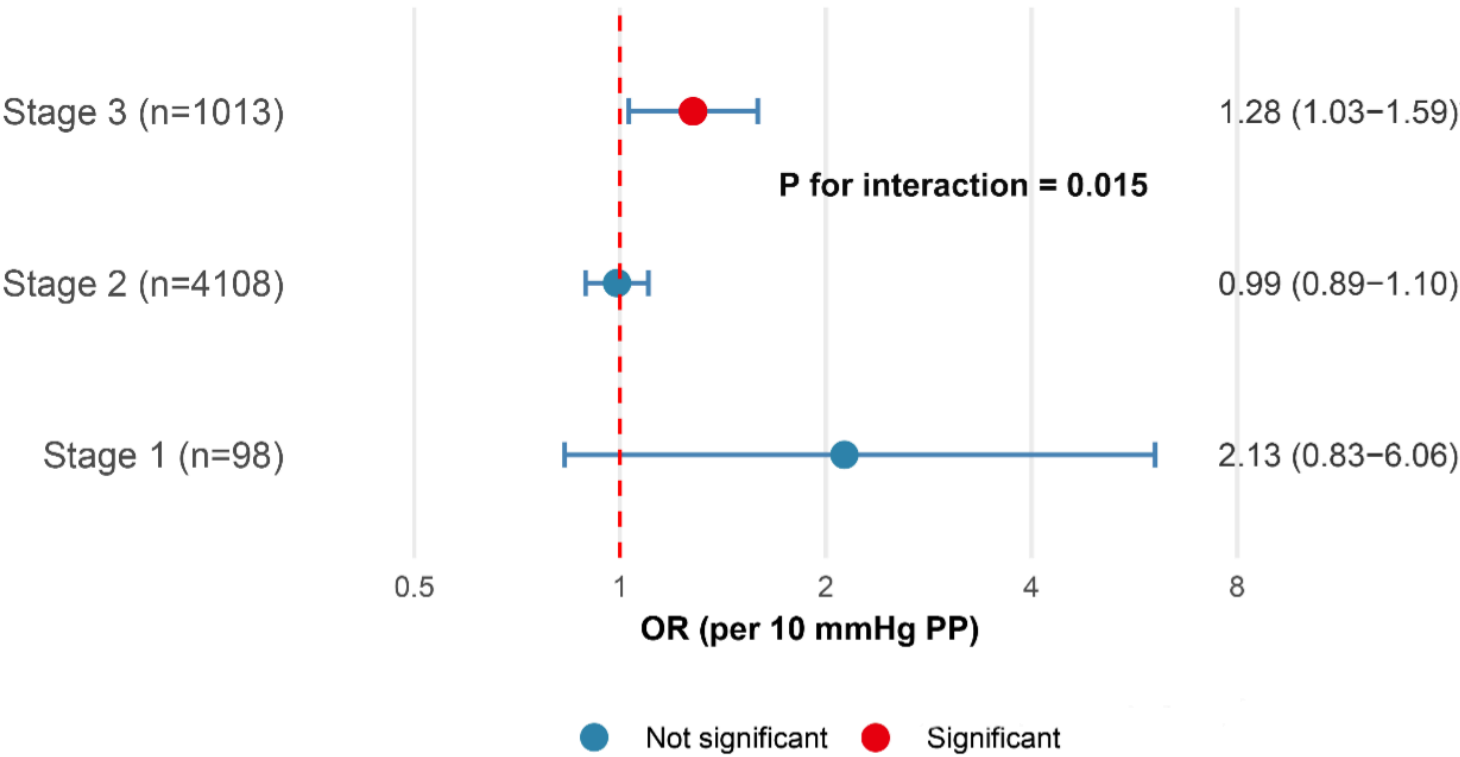


Figure 2

Forest plot of stage-specific associations between baseline pulse pressure (per 10 mmHg) and CKM progression. ORs were adjusted for age, sex, BMI, smoking, drinking, education, eGFR, fasting glucose, triglycerides, HDL cholesterol, hypertension, and diabetes. The dashed vertical line indicates OR = 1. Error bars represent 95% CIs. P for interaction = 0.015. CKM, cardiovascular-kidney-metabolic; PP, pulse pressure; OR, odds ratio; CI, confidence interval.

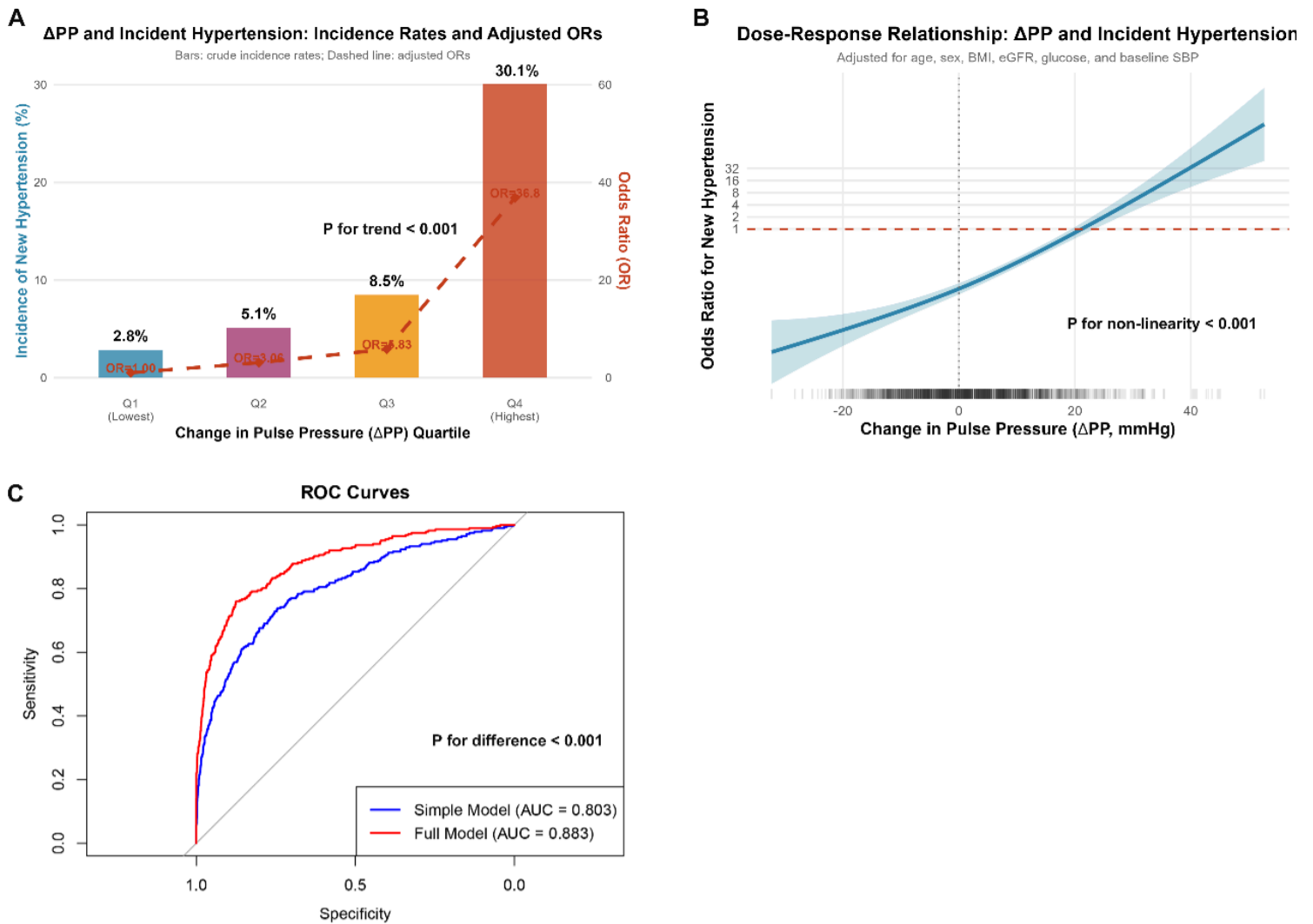


Figure 3

Associations between 4-year change in pulse pressure (ΔPP) and incident hypertension. (A) Incidence rates of new hypertension by ΔPP quartile. **(B)** Dose-response relationship between ΔPP and incident hypertension using restricted cubic splines (P for non-linearity < 0.001), showing a threshold effect at approximately 40 mmHg. The shaded area represents the 95% confidence interval. **(C)** ROC curves comparing the predictive performance of the simplified model ($AUC = 0.803$) and the full model ($AUC = 0.883$). ΔPP, change in pulse pressure; OR, odds ratio; CI, confidence interval; AUC, area under the curve; SBP, systolic blood pressure.

Cox Regression: Predictors of All-Cause Mortality

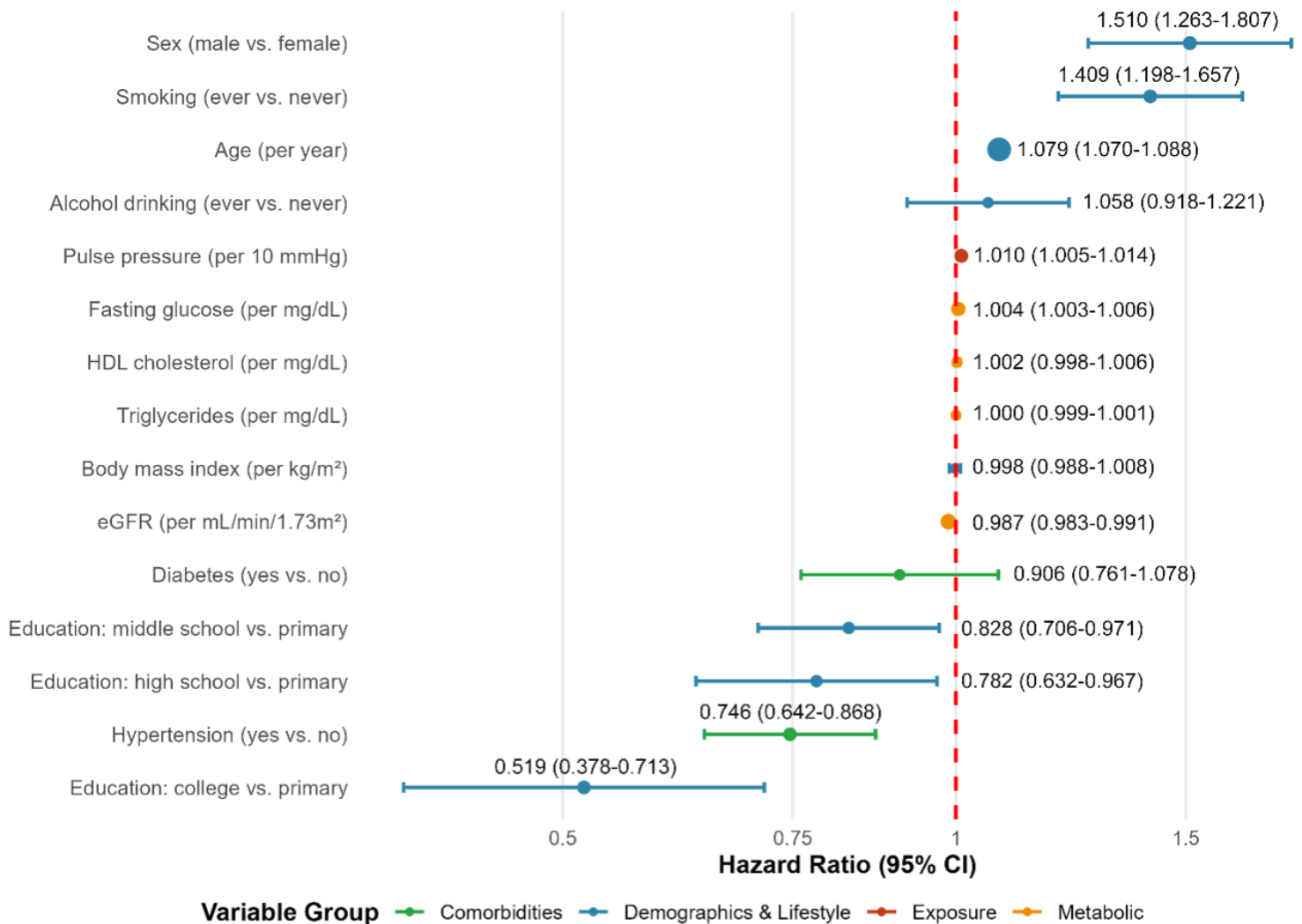


Figure 4

Forest plot showing the adjusted hazard ratios (HRs) for all-cause mortality from the fully adjusted Cox proportional hazards model. Each variable is represented by a point estimate (HR) with corresponding 95% confidence intervals (error bars). The dashed vertical line indicates the null value (HR = 1). Variables with confidence intervals entirely to the right of the null line indicate significantly increased mortality risk, while those to the left indicate reduced risk. Pulse pressure (per 10 mmHg) was significantly associated with increased mortality risk (HR = 1.010, 95% CI: 1.005–1.014, $P < 0.001$). Age (HR = 1.079 per year, 95% CI: 1.070–1.088, $P < 0.001$), male sex (HR = 1.510, 95% CI: 1.263–1.807, $P < 0.001$), and smoking (HR = 1.409, 95% CI: 1.198–1.657, $P < 0.001$) were also independent risk factors. Higher education levels and eGFR were associated with lower mortality risk. The model was adjusted for all variables shown in the figure. HR, hazard ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

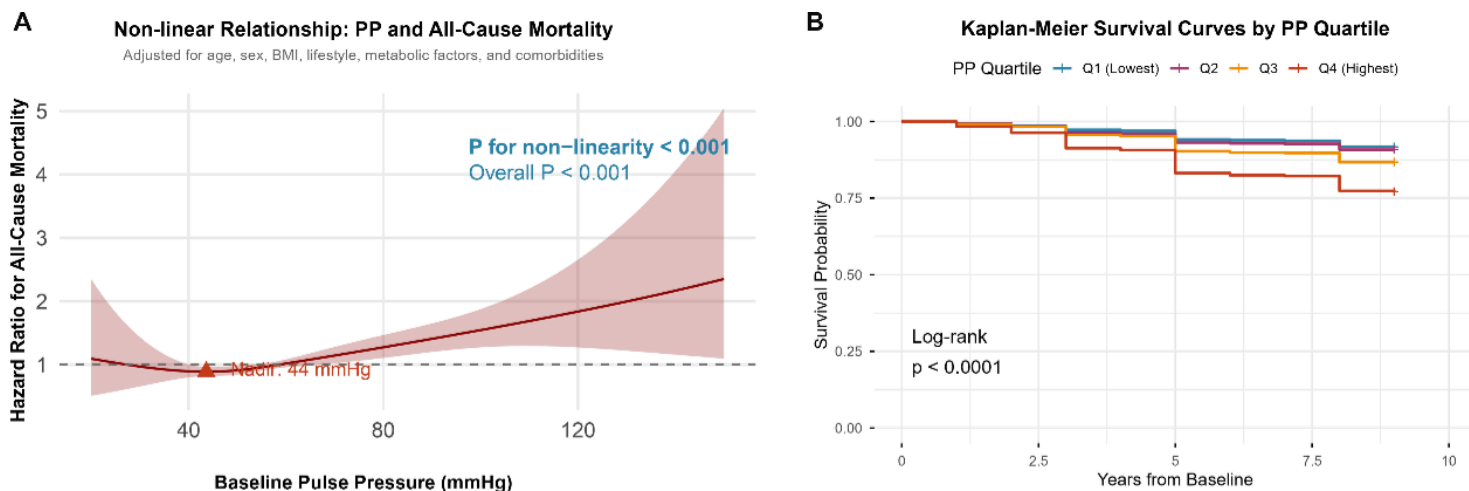


Figure 5

Associations between baseline pulse pressure and all-cause mortality. (A) Restricted cubic spline curve showing a U-shaped relationship between PP and mortality, with the nadir at approximately 44 mmHg (P for non-linearity < 0.001). The shaded area represents the 95% confidence interval. **(B)** Kaplan-Meier survival curves stratified by PP quartiles, showing significantly lower survival in the highest quartile (log-rank P < 0.0001). PP, pulse pressure; HR, hazard ratio; CI, confidence interval; Q1–Q4, quartiles 1 to 4.

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