

ORIGINAL RESEARCH

Link Between Elevated Long-Term Resting Heart Rate Variability and Pulse Pressure Variability for All-Cause Mortality

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BACKGROUND: Elevated long-term systolic blood pressure and resting heart rate (RHR) variability are suggested to amplify the risk of all-cause mortality (ACM). However, the link between increased RHR and pulse pressure for ACM remained unclear.

METHODS AND RESULTS: This study analyzed 46 751 individuals from Kailuan Cohort Study for the end outcome of ACM. A Cox regression model was used to estimate hazard ratios for death events. Kaplan-Meier analysis was performed to study the differences in survival as stratified by the SD, coefficient of variation, and average real variability of RHR and pulse pressure quartiles. A total of 1667 deaths (<65 years of age=866/40351, ≥65 years of age=801/6400) were recorded over 4.97±0.69 years follow-up. Participants under the age of 65 years in the third and fourth quartiles of pulse pressure SD had an independent increase in risk for ACM (hazard ratio [95% CI], 1.16 [1.06–1.28]; and 1.19 [1.05–1.35], respectively). Additionally, participants >65 years of age had a higher risk for ACM across quartiles of RHR-SD. The hazard ratio (95% CI) for the subjects in quartiles 2, 3, and 4 were 1.81 (1.10–2.97), 2.31 (1.37–3.90), and 2.64 (1.63–4.29), respectively.

CONCLUSIONS: An elevated long-term RHR variability combined with an increased pulse pressure variability or vice versa amplifies the risk of ACM.

Key Words: all-cause death ■ blood pressure ■ heart rate ■ pulse pressure

Variations of pulse pressure (PP) have not been included among the main cardiovascular and mortality risk factors, probably attributable to the potential of interdependence with other risk factors and/or of its dynamic nature, as systemic blood pressure (BP) can vary spontaneously from beat to beat and from visit to visit.¹ However, the importance of resting heart rate (RHR) variability is gaining momentum as important risk markers for cardiovascular disease events and all-cause mortality (ACM) in the general population.^{2–5} In the past few years, scientific studies have largely investigated the independent association between visit-to-visit RHR and systolic

blood pressure (SBP) variations in the risk of all causes of death in the general population.^{6,7} Considering the direct effect of SBP in the range of PP readings, it is of interest for the scientific community to understand the link between increased RHR and PP for all causes of death.

Provided that age associated with RHR and blood pressure (BP) negatively and positively, respectively, age-based analysis of long-term RHR and PP may clearly distinguish the effect of PP and its link with RHR in predicting all causes of death. Recently, our study that investigated the link between an increased visit-to-visit variation (VVV) of RHR and SBP for risk

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Supplementary material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014122>

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For Sources of Funding and Disclosures, see page 15.

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CLINICAL PERSPECTIVE

What Is New?

- Combined long-term changes in resting heart rate (RHR) variability and pulse pressure (PP) variability predicts all-cause mortality in general population.
- With an increase in 1 SD of RHR variability, participants less than the age of 65 years in the higher quartiles of PP-SD had an independent increase in risk for all-cause mortality.
- However, with an increase in 1 SD of pulse pressure variability, participants greater than 65 years of age had a higher risk for all-cause mortality across quartiles of RHR-SD.

What Are the Clinical Implications?

- Strict RHR and PP variability control among the general population may identify a high-risk population, thereby offsetting the impact of combined long-term visit-to-visit PP and RHR variability on death events.
- Considering PP along other indexes of blood pressure variability besides visit-to-visit RHR variability may increase the importance of vital sign variations in predicting increased risk for all-cause mortality.
- Thus, follow-up clinics that consider blood pressure records should consider standardized blood pressure measurement protocols that include PP readings.

Nonstandard Abbreviations and Acronyms

ACM	all-cause mortality
BP	blood pressure
CV	coefficient of variation
DBP	diastolic blood pressure
PP	pulse pressure
RHR	resting heart rate
SBP	systolic blood pressure

of ACM in the general population demonstrated that participants with the highest quartiles of RHR-SD and SBP-SD had the highest risk of death compared with the participants in the lowest quartiles of RHR-SD and SBP-SD.⁸ After reviewing the finding of our series regarding the long-term RHR variation, we noticed the persistent effect of age.⁸ For instance, our previous study highlighted that older age together with higher SBP was independently linked with greater variation of RHR, and an increase in 4 beats per minute in RHR was found to be significant at the top of PP quartiles

in younger ages. Also, the reverse was true when PP increased by 5 mm Hg at the top quartiles of RHR-SD in older patients. However, the threshold that could estimate the risk for ACM because of the interaction of these parameters (RHR and PP) still requires age-based investigation. So far, to the extent of our knowledge, whether the long-term changes in a combined RHR variability and PP variability might predict ACM has never been investigated in-depth, which is of particular interest in a general population. Also, it is of crucial importance to consider the potential variations that could result from age-related physiological changes, especially in the light of current debate regarding the effect of age in the combined effect of RHR variability and BP readings variability in ACM. Therefore, we investigated the link between an increased RHR variability and PP visit-to-visit variation for ACM based on an increase in 1 SD of heart rate variability or PP variability in the Chinese population registered in the KCS (Kailuan Cohort Study) (ChiCTR-TNRC-11001489).

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This study was based on the KCS, a large contemporary population-based prospective cohort study, conducted between 2006 and 2016 at the health examination center of the Kailuan General Hospital, Tangshan City, Hebei Province of China. We analyzed the KCS data to assess the link between long-term RHR variability and PP variability variation for the risk of ACM in the general population.

Population

Subjects for this study were recruited from KCS. All coal workers regardless of their sex status were invited to participate in the study. We included 101 510 ethnic Chinese participants who had been followed up for 6 years in the KCS. Participants who were above the age of 18 years; had received at least 3 consecutive examinations with complete electrocardiography and BP recordings; and had no history of coronary heart disease, stroke, and/or transient ischemic attack at baseline were eligible for this study.

A total of 46 751 participants were included in the data analysis after excluding subjects with a difference of >5 mm Hg following triplicate BP measurement. The following study participants were also excluded from this study: those with cardiovascular

events (prior history of myocardial infarction/stroke or coronary artery disease, unstable angina and any coronary revascularization procedure, congestive heart failure) and those who had atrial fibrillation or flutter on their ECG readings at examination 1, 2, or 3; had received a pacemaker before examination 3; were lost or died during the first 6 years; and were under the use of β -blockers and nondihydropyridine medication through the entire period of BP and RHR assessment. A detailed description of the assessment follow-up is given in Figure 1. The study was approved by the institutional review board of Kailuan General Hospital. The study protocol was approved

by the First Affiliated Hospital of Dalian Medical University, and the participants provided written informed consent.

Assessment of Long-Term Variation in RHR and PP

RHR and PP variability were assessed for 6 years between 2006 and 2011, and outcomes were analyzed from the end of the third examination to the end of the follow-up period (December 2016). We assessed clinical characteristics at the end of the third ECG and BP examination (2010–2011) and adjusted to RHR-SD

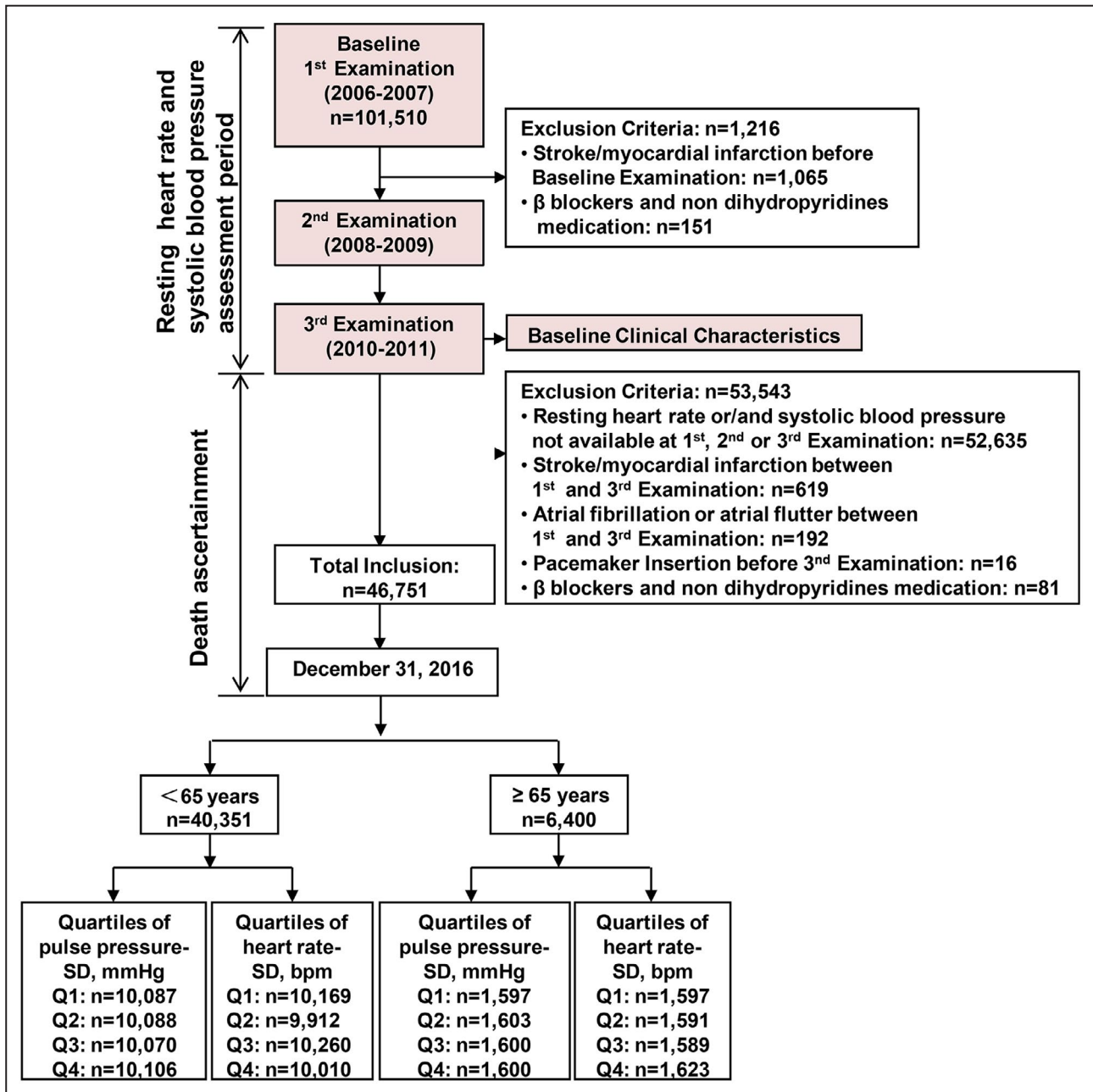


Figure 1. Flowchart of the follow-up period and participants included in the Kailuan Cohort Study.

and PP-SD to prove that RHR variability and PP variability assessed over a long period of time were not consequences of diseases and/or deteriorating health, as these extrinsic factors can themselves influence RHR variability and BP variability. In addition, the coefficient of variation (CV) and average real variability (ARV) were also calculated in individuals with all visits.

The formulae for SD, CV, and ARV of the RHR and the detailed approach of BP measurement and recordings were described previously.^{2,8} Briefly, RHR was obtained using a 10-second 12-lead ECG from every participant, resting in the supine position, whereas BP was measured from the upper right arm after 5 minutes of rest in the seated position using a calibrated mercury sphygmomanometer. The BP measurement was performed by physicians. For this reason, the BP readings were measured twice to avoid white coat hypertension, and the mean of the 2 BP readings was obtained and recorded as the diastolic blood pressure (DBP) and SBP values. Additional measurements were made if there was a difference of >5 mm Hg following the first 2 readings. The PP readings were calculated by subtracting DBP from SBP. The SD, CV, and ARV of the PP over the first 3 examinations was calculated by the following formulae: $SD = \sqrt{\frac{\sum (PP_i - \overline{PP})^2}{n-1}}$, $CV = \left(\frac{SD}{\overline{PP}}\right) \times 100\%$, $ARV = \frac{1}{n-1} \sum_{i=1}^{n-1} |PP_{i+1} - PP_i|$ where, PP_i is the PP of the participant at the examination, and \overline{PP} is the average PP of the participant across examinations.

Measurements

A standardized interview was conducted during each examination to collect data on demographic and clinical characteristics including health-related lifestyle, family history, and use of any drugs. Fasting (>8 hours) blood specimens were collected and were biochemically examined for the concentration of fasting plasma glucose (FPG) and CRP (C-reactive protein). High-density lipoprotein and serum total cholesterol were measured using standard enzymatic methods. Smoking status was categorized into 3 categories: current smoker, former smoker, and never smoker; whereas physical exercise was grouped into 2 categories: high/intense activity for ≥ 4 hours per week and sedentary/moderate activity for <4 hours per week. Hypertension was defined as SBP ≥ 140 mm Hg and/or diastolic BP (DBP) ≥ 90 mm Hg or a self-reported hypertension history with the current use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose ≥ 7.0 mmol/L or a self-reported history of diabetes mellitus and currently undergoing treatment with antidiabetic medication.

Outcome Assessment

The primary outcome was ACM occurring beyond the first 3 examinations following registration in the KCS.

Death occurrence was investigated through hospital records. To improve the quality of the data on death event, we regularly screened death certificates from the state vital statistics offices annually.

Statistical Analysis

All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). Participants were categorized on the basis of age into 2 groups, including <65 years of age and >65 years of age, and were stratified into quartiles based on the RHR-SD and PP-SD. All categorical variables were expressed as counts and percentiles, and continuous variables were expressed as mean \pm SD. Quartiles were checked for differences using ANOVA and χ^2 test for continuous and categorical data, respectively. The log-rank test for trend and Kaplan-Meier methods were used to compare the survival distributions and study the differences in survival as stratified by RHR and PP quartiles, respectively.

We first calculated the hazards ratios for death associated with quartiles of SD of RHR and PP to establish the association between the long-term RHR/PP variation and ACM. We further calculated hazard ratio (HR) and corresponding 95% CIs for the occurrence of ACM associated with 1 SD increase in RHR and PP. For the outcome ACM, 2 distinct Cox models were employed to look for possible associations with RHR and PP quartiles independently and their associations following the interactions with continuous SD of RHR and PP. The first Cox proportional hazard model for our study was employed to investigate the association of RHR-SD quartiles with an increase in 1 SD in PP, modeled as a continuous variable, for the occurrence of death. Whereas the second Cox model was established to explore the relationship of PP-SD quartiles with an increase in 1 SD in RHR, modeled as a continuous variable, for the occurrence of death. To confirm the consistency of the findings, we again run Cox regression to examine the prognostic value of PP-CV/ARV quartiles with an increase in 1 CV/ARV in RHR. The multivariate Cox models were adjusted for age, sex, body mass index, mean heart rate, mean SBP, fasting plasma glucose, elevated CRP, high/intensive activity, high-density lipoprotein, total cholesterol, and antihypertensive medication. The Schoenfeld residuals test was used to test the proportional hazard assumption in the Cox model. We performed a sensitivity analysis with the aim to control the effect of BP. The analysis was repeated using a fully adjusted model to test for the robustness of estimates in those who had no history of hypertension and those individuals who were free of hypertension or whose BP was controlled during the third examination. The linear

Table 1. Age-Specific Baseline Clinical Characteristics of Participants by Quartiles of SD in PP Variability

	Quartile of SD in PP, mm Hg									
	<65 Y					≥65 Y				
	Quartile 1 <4.7	Quartile 2 4.7–6.4	Quartile 3 6.4–10.0	Quartile 4 ≥10.0	P Value	Quartile 1 <5.8	Quartile 2 5.8–9.6	Quartile 3 9.6–13.7	Quartile 4 ≥13.7	P Value
Participants, n	10 087	10 088	10 070	10 106	...	1597	1603	1600	1600	...
Age (±SD), years	48.0±9.3	48.6±9.4	49.6±9.0	51.9±8.5	<0.001	71.5±4.7	71.6±4.9	71.8±4.9	72.7±5.3	<0.001
Men, %	76.8	76.7	78.0	77.2	0.102	84.2	84.5	83.3	82.3	0.335
BMI (±SD), kg/m ²	25.0±3.3	25.0±3.3	25.1±3.4	25.4±3.4	<0.001	24.9±3.5	25.0±3.4	25.2±3.4	25.3±3.5	0.006
Current smoker, %	38.3	37.9	37.5	35.6	<0.001	19.9	18.3	16.4	15.5	0.005
High/intensive activity, %	11.2	11.3	12.4	12.7	0.001	20.8	20.1	20.6	16.4	0.004
Mean SBP (±SD), mm Hg	123.7±13.9	124.6±14.4	127.5±15.0	135.3±17.3	<0.001	136.2±16.7	138.7±16.2	141.5±16.3	148.5±16.4	<0.001
Mean DBP (±SD), mm Hg	81.9±8.7	82.3±8.7	83.7±9.0	86.6±9.8	<0.001	83.1±8.3	84.1±8.5	84.3±8.5	85.6±8.5	<0.001
Mean heart rate (±SD), beats/min	73.6±7.6	73.5±7.6	73.8±7.7	74.5±8.2	<0.001	72.8±8.5	72.8±8.3	73.1±8.2	73.0±8.6	0.671
TC (±SD), mmol/L	4.9±1.0	5.0±1.4	5.0±1.3	5.0±1.2	<0.001	5.1±1.0	5.1±1.4	5.0±1.0	5.2±2.0	0.020
HDL (±SD), mmol/L	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5	0.337	1.6±0.6	1.5±0.4	1.5±0.5	1.5±0.4	0.116
FPG (±SD), mmol/L	5.5±1.6	5.6±1.6	5.6±1.6	5.8±2.0	<0.001	5.8±1.6	5.8±1.6	6.0±1.8	6.0±1.7	0.002
CRP>2 mg/L, %	29.1	28.8	29.5	32.4	<0.001	40.4	40.6	42.8	45.4	0.014
Diabetes mellitus, %	7.6	7.9	8.6	12.4	<0.001	12.3	12.4	14.4	15.6	0.013
Hypertension, %	31.7	35.5	41.3	58.9	<0.001	53.1	60.9	69.6	79.4	<0.001
Antihypertensive medication drug class, %										
ACE inhibitor	0.7	0.5	0.9	1.2	<0.001	1.0	1.0	1.7	2.1	0.017
ARB	0.1	0.2	0.2	0.4	0.001	0.3	0.4	0.7	1.1	0.025
Calcium channel blocker	0.7	0.6	0.7	1.2	<0.001	2.3	2.8	3.3	2.9	0.340
Diuretic	0.6	0.5	0.8	1.3	<0.001	0.8	0.6	1.4	1.8	0.010
α-Blocker	0.0	0.0	0.0	0.1	0.576	0.0	0.1	0.0	0.2	0.112
Combination tablets	0.7	0.7	1.1	1.7	<0.001	1.7	2.0	3.5	3.4	0.001

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HR, heart rate; PP, pulse pressure; SBP, systolic blood pressure; and TC, total cholesterol.

Table 2. Age-Specific Baseline Clinical Characteristics of Participants by Quartiles of SD in RHR Variability

	Quartile of SD in RHR, beats/min									
	<65 Y					≥65 Y				
	Quartile 1 <3.5	Quartile 2 3.5–5.8	Quartile 3 5.8–8.5	Quartile 4 ≥8.5	P Value	Quartile 1 <4.0	Quartile 2 4.0–6.1	Quartile 3 6.1–9.0	Quartile 4 ≥9.0	P Value
Participants, n	10 169	9912	10 260	10 010	-	1597	1591	1589	1623	...
Age (±SD), years	49.6±9.2	50.0±9.1	49.4±9.3	49.5±9.3	0.794	71.8±4.9	71.7±4.8	72.0±5.0	72.1±5.1	0.092
Men, %	74.8	76.0	77.7	80.3	<0.001	81.3	83.0	84.2	85.6	0.009
BMI (±SD), kg/m ²	25.2±3.3	25.1±3.3	25.1±3.3	25.1±3.4	0.472	25.1±3.5	25.2±3.3	25.1±3.4	25.1±3.5	0.796
Current smoker, %	36.3	36.8	38.1	38.1	0.015	17.2	17.1	18.3	17.6	0.792
High/intensive activity, %	12.1	11.6	11.8	12.0	0.679	19.5	19.6	19.6	19.1	0.986
Mean SBP (±SD), mm Hg	126.4±15.6	126.9±15.3	127.6±15.6	130.2±16.8	<0.001	140.0±16.5	140.6±17.1	141.5±17.1	142.7±17.4	<0.001
Mean DBP (±SD), mm Hg	82.9±9.0	83.2±9.1	83.4±9.1	84.9±9.6	<0.001	83.7±8.3	83.9±8.3	84.3±8.5	85.1±8.9	<0.001
Mean heart rate (±SD), beats/min	71.8±6.8	72.5±6.9	73.7±7.5	77.3±8.7	<0.001	70.6±7.3	71.9±7.6	72.8±7.8	76.3±9.5	<0.001
TC (±SD), mmol/L	5.0±1.4	5.0±1.2	5.0±1.0	5.0±1.3	0.051	5.1±1.5	5.1±1.0	5.1±2.0	5.1±1.1	0.910
HDL (±SD), mmol/L	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5	0.320	1.6±0.5	1.5±0.4	1.5±0.6	1.6±0.5	0.382
FPG (±SD), mmol/L	5.6±1.9	5.6±1.7	5.6±1.5	5.7±1.7	<0.001	5.8±1.6	5.8±1.5	5.9±1.7	6.1±1.9	<0.001
CRP>2 mg/L, %	28.6	28.9	30.4	31.8	<0.001	39.9	43.7	40.9	44.5	0.020
Diabetes mellitus, %	8.3	8.9	8.7	10.6	<0.001	12.6	11.7	12.5	17.9	<0.001
Hypertension, %	39.9	41.2	40.9	45.5	<0.001	65.2	64.9	66.6	66.2	0.696
Antihypertensive medication drug class, %										
ACE inhibitor	0.7	0.6	0.8	1.1	0.004	1.3	0.9	1.8	1.8	0.146
ARB	0.2	0.3	0.2	0.2	0.410	0.8	0.4	0.7	0.6	0.548
Calcium channel blocker	0.8	0.9	0.7	0.9	0.320	2.8	2.1	3.2	3.3	0.156
Diuretic	0.8	0.8	0.8	0.9	0.873	0.9	1.2	1.1	1.4	0.719
α-Blocker	0.0	0.1	0.0	0.1	0.009	0.1	0.1	0.1	0.1	1.000
Combination tablets	1.0	0.9	0.9	1.3	0.028	2.8	2.1	2.7	2.8	0.571

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; RHR, resting heart rate; SBP, systolic blood pressure; and TC, total cholesterol.

trend line was included to show whether heart rate is increasing at a steady rate. A $P \leq 0.01$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Participants

Among the 101 510 subjects who registered for KCS during the study period, 46 751 participants had

sufficient data to evaluate the RHR and PP visit-to-visit variation at all 3 time points. The baseline clinical characteristics were evaluated in the third examination. Participants in higher quartiles of SD of RHR and PP had higher mean SBP and DBP than in lower quartiles. Despite the age category, participants in higher quartiles of SD of RHR were more likely to have hypertension and a higher proportion of elevated CRP, and less likely to be current smokers, unlike the participants in higher quartiles of SD of PP. Similarly, participants in higher quartiles of SD of PP

Table 3. Cumulative Mortality and HRs (95% CIs) for All-Cause Mortality Associated With Quartile of SD of RHR Variability and PP Variability in Participants <65 Years of Age

	Quartile of RHR-SD Variability, beats/min				P for Trends
	Quartile 1 (<3.5)	Quartile 2 (3.5–5.8)	Quartile 3 (5.8–8.5)	Quartile 4 (≥8.5)	
Total, n	10 169	9912	10 260	10 010	-
Deaths, n (%)	148 (1.5)	183 (1.8)	256 (2.5)	279 (2.8)	<0.001
Model 1 [*]	1.00 (Ref)	1.28 (1.03, 1.58)	1.72 (1.41, 2.11)	1.93 (1.58, 2.35)	<0.001
Model 2 [†]	1.00 (Ref)	1.28 (1.03, 1.59)	1.71 (1.39, 2.09)	1.86 (1.52, 2.27)	<0.001
Model 3 [‡]	1.00 (Ref)	1.28 (1.03, 1.60)	1.48 (1.20, 1.83)	1.59 (1.29, 1.96)	<0.001
	Quartile of RHR-CV Variability, beats/min				P for Trends
	Quartile 1 (<5.0)	Quartile 2 (5.0–7.9)	Quartile 3 (7.9–11.5)	Quartile 4 (≥11.5)	
Total, n	10 241	10 153	10 073	9884	
Model 3 [‡]	1.00 (Ref)	1.26 (1.01, 1.56)	1.48 (1.20, 1.82)	1.61 (1.31, 1.98)	<0.001
	Quartile of RHR-ARV Variability, beats/min				P for Trends
	Quartile 1 (<4.0)	Quartile 2 (4.0–7.0)	Quartile 3 (7.0–11.0)	Quartile 4 (≥11.0)	
Total, n	10 576	8876	10 552	10 347	
Model 3 [‡]	1.00 (Ref)	1.32 (1.05, 1.65)	1.45 (1.20, 1.72)	1.57 (1.27, 1.93)	<0.001
	Quartile of PP-SD Variability, mm Hg				P for Trends
	Quartile 1 (<4.7)	Quartile 2 (4.7–6.4)	Quartile 3 (6.4–10.0)	Quartile 4 (≥10.0)	
Total, n	10 087	10 088	10 070	10 106	-
Deaths, n (%)	155 (1.5)	163 (1.6)	218 (2.2)	330 (3.3)	<0.001
Model 1 [*]	1.00 (Ref)	1.05 (0.85, 1.31)	1.42 (1.16, 1.74)	2.15 (1.78, 2.61)	<0.001
Model 2 [†]	1.00 (Ref)	1.01 (0.81, 1.25)	1.28 (1.04, 1.57)	1.71 (1.41, 2.07)	<0.001
Model 3 [‡]	1.00 (Ref)	0.95 (0.76, 1.20)	1.17 (0.95, 1.44)	1.34 (1.09, 1.63)	0.001
	Quartile of PP-CV Variability, mm Hg				P for Trends
	Quartile 1 (<10.5)	Quartile 2 (10.5–15.7)	Quartile 3 (15.7–22.5)	Quartile 4 (≥22.5)	
Total, n	10 141	10 083	10 294	9833	
Model 3 [‡]	1.00 (Ref)	1.03 (0.84, 1.27)	1.11 (0.91, 1.35)	1.33 (1.10, 1.61)	<0.001
	Quartile of PP-ARV Variability, mm Hg				P for Trends
	Quartile 1 (<4.9)	Quartile 2 (4.9–8.0)	Quartile 3 (8.0–12.2)	Quartile 4 (≥12.2)	
Total, n	10 737	10 431	10 136	9047	
Model 3 [‡]	1.00 (Ref)	1.17 (0.95, 1.45)	1.17 (0.95, 1.44)	1.38 (1.13, 1.69)	<0.001

ACE indicates angiotensin-converting enzyme; ARV, average real variability; CV, coefficient of variation; HR, hazard ratio; PP, pulse pressure; and RHR, resting heart rate.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean PP, mean RHR, fasting plasma glucose, total cholesterol, high-density lipoprotein, elevated C-reactive protein, and ACE inhibitor.

had a higher mean age, body mass index, and fasting plasma glucose than in lower quartiles. Also, participants who were <65 years of age in higher quartiles of SD of RHR were more likely to be smokers and more likely to have hypertension and a higher proportion of elevated CRP. Demographic data for the study participants and for each of the 2 groups separately are shown for RHR and PP in Tables 1 and 2, respectively. Simultaneously, we remodeled the quartiles by CV or ARV of RHR and PP so as to test the repetition of the following results.

Relationship Between Visit-to-Visit PP Variability/RHR Variability and ACM in Participants ≤65 Years of Age

Table 3 presents the HRs of death among participants (≤65 years of age) grouped by quartile of RHR-SD/CV/ARV variability and PP-SD/CV/ARV variability. The participants in the highest variability of RHR-SD quartile had a significantly increased risk of death. This association persisted even after adjusting for potential confounding factors, including

Table 4. Cumulative Mortality and HRs (95% CI) for All-Cause Mortality Associated With Quartile of SD of RHR Variability and PP Variability in Participants >65 Years of Age

	Quartile of RHR-SD Variability, beats/min				P for Trends
	Quartile 1 (<4.0)	Quartile 2 (4.0–6.1)	Quartile 3 (6.1–9.0)	Quartile 4 (≥9.0)	
Total, n	1597	1591	1589	1623	...
Deaths, n (%)	147 (9.2)	205 (12.9)	212 (13.3)	237 (14.6)	<0.001
Model 1 [*]	1.00 (Ref)	1.42 (1.15, 1.76)	1.48 (1.20, 1.83)	1.64 (1.33, 2.01)	<0.001
Model 2 [†]	1.00 (Ref)	1.44 (1.17, 1.78)	1.44 (1.16, 1.77)	1.57 (1.28, 1.93)	<0.001
Model 3 [‡]	1.00 (Ref)	1.33 (1.07, 1.65)	1.35 (1.09, 1.68)	1.41 (1.13, 1.75)	0.035
	Quartile of RHR-CV Variability, bpm				P for Trends
	Quartile 1 (<5.3)	Quartile 2 (5.3–8.3)	Quartile 3 (8.3–12.3)	Quartile 4 (≥12.3)	
Total, n	1446	1533	1619	1802	
Model [†]	1.00 (Ref)	1.27 (1.03, 1.57)	1.35 (1.08, 1.68)	1.36 (1.09, 1.69)	<0.001
	Quartile of RHR-ARV Variability, bpm				P for Trends
	Quartile 1 (<4.5)	Quartile 2 (4.5–7.5)	Quartile 3 (7.5–11.0)	Quartile 4 (≥11.0)	
Total, n	1517	1393	1728	1762	
Model [†]	1.00 (Ref)	1.13 (0.90, 1.42)	1.20 (0.97, 1.48)	1.28 (1.03, 1.58)	<0.001
	Quartile of PP-SD Variability, mm Hg				P for Trends
	Quartile 1 (<5.8)	Quartile 2 (5.8–9.6)	Quartile 3 (9.6–13.7)	Quartile 4 (≥13.7)	
Total, n	1597	1603	1600	1600	-
Deaths, n (%)	147 (9.2)	196 (12.2)	215 (13.4)	243 (15.2)	<0.001
Model 1 [*]	1.00 (Ref)	1.34 (1.08, 1.66)	1.49 (1.21, 1.84)	1.70 (1.39, 2.09)	<0.001
Model 2 [†]	1.00 (Ref)	1.32 (1.07, 1.63)	1.45 (1.17, 1.79)	1.52 (1.24, 1.86)	<0.001
Model 3 [‡]	1.00 (Ref)	1.39 (1.12, 1.74)	1.49 (1.20, 1.86)	1.51 (1.22, 1.88)	<0.001
	Quartile of PP-CV Variability, mm Hg				P for Trends
	Quartile 1 (<10.8)	Quartile 2 (10.8–16.7)	Quartile 3 (16.7–24.1)	Quartile 4 (≥24.1)	
Total, n	1546	1385	1614	1855	
Model [†]	1.00 (Ref)	1.27 (1.01, 1.60)	1.52 (1.23, 1.88)	1.54 (1.25, 1.90)	<0.001
	Quartile of PP-ARV Variability, mm Hg				P for Trends
	Quartile 1 (<6.6)	Quartile 2 (6.6–10.9)	Quartile 3 (10.9–17.1)	Quartile 4 (≥17.1)	
Total, n	1054	1153	1552	2641	
Model [†]	1.00 (Ref)	1.32 (1.00, 1.75)	1.46 (1.12, 1.89)	1.66 (1.31, 2.12)	<0.001

ACE indicates angiotensin-converting enzyme; ARV, average real variability; CV, coefficient of variation; HR, hazard ratio; PP, pulse pressure; and RHR, resting heart rate.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean PP, mean RHR, fasting plasma glucose, total cholesterol, high-density lipoprotein, elevated C-reactive protein, and ACE inhibitor.

age, sex, body mass index, current smoker, mean PP, mean RHR, fasting plasma glucose, total cholesterol, high-density lipoprotein, elevated CRP, and angiotensin-converting enzyme inhibitor. The HR of death for the fourth versus the first quartile of RHR-SD variability was 1.59 (1.29–1.96), whereas for the fourth versus the first quartile of PP-SD was 1.34 (1.09–1.63). The HRs (95% CI) for ACM was further evaluated using quartile of CV and ARV of RHR variability and PP variability. Importantly, the participants in the highest variability of RHR-CV and RHR-ARV quartiles had a significantly increased risk of death (Tables S1 and S2).

Relationship Between Visit-to-Visit PP Variability/RHR Variability and ACM in Participants ≥65 Years of Age

The association between the variability of PP-SD and the risk of death among participants >65 years of age is presented in Table 4. The participants in the highest variability of RHR SD and PP SD quartiles had a significantly increased risk of death. Compared with participants in the first quartile of RHR SD variability, the HRs (95% CIs) for the subjects in quartiles 2, 3, and 4 were 1.33 (1.07–1.65), 1.35 (1.09–1.68), and 1.41 (1.13–1.75), respectively (*P* for trend=0.035). Compared with participants

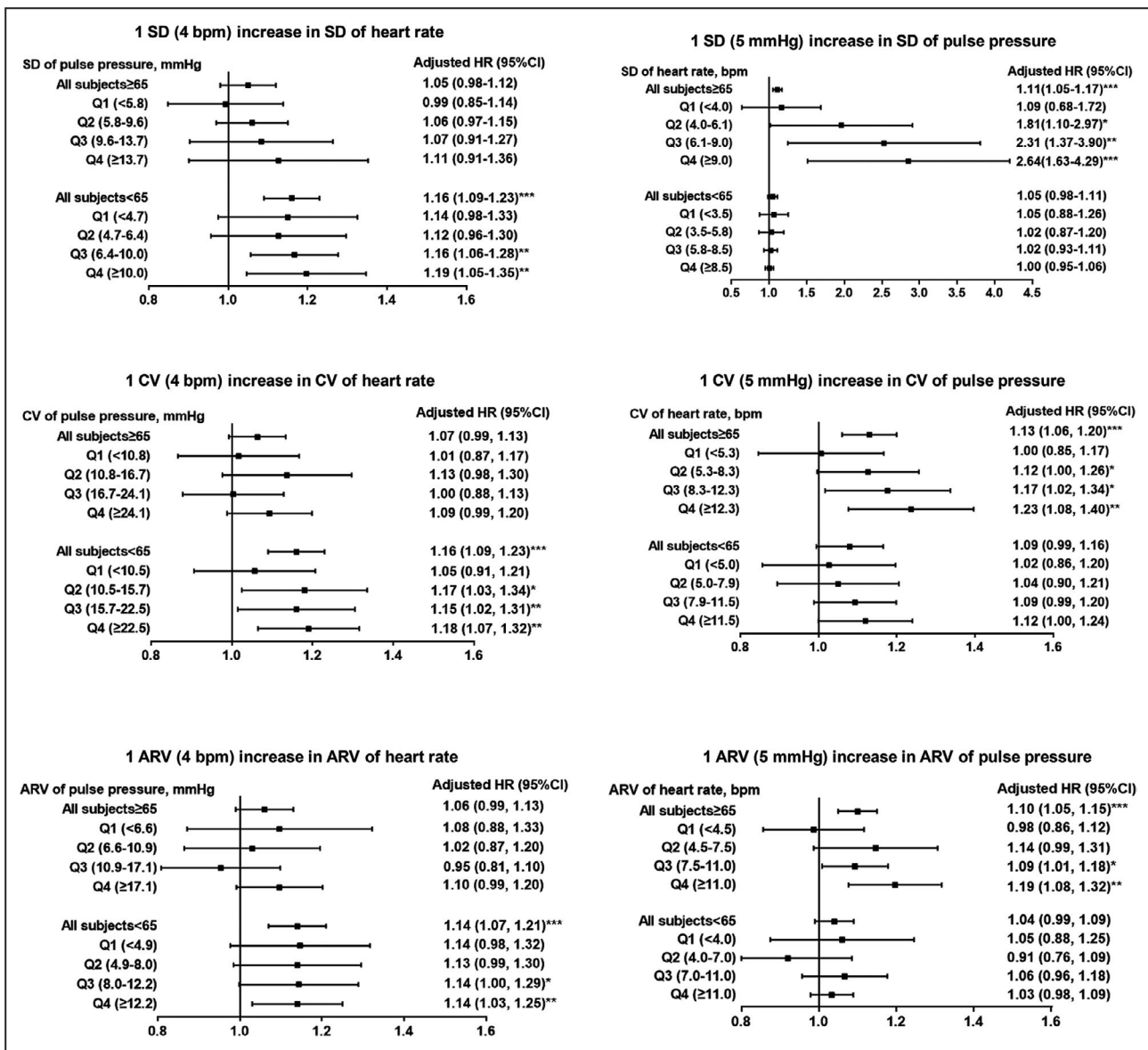


Figure 2. Adjusted hazard ratios with 95% CIs for 1 SD/CV/ARV increase in SD/CV/ARV resting heart rate variability and pulse pressure variability of all-cause mortality. ARV indicates average real variability; CV, coefficient of variation; and SD, standard deviation.

of the first quartile of PP-SD variability, the multivariate-adjusted HRs and 95% CIs of all causes of death were 1.39 (1.12–1.74), 1.49 (1.20–1.86), and 1.51 (1.22–1.88) for the second, third, and fourth quartiles, respectively. Also, the visit-to-visit variability of PP, assessed by CV and ARV, were strongly associated with all causes of death in participants >65 years of age (Tables S3 and S4).

Effect of RHR Variability and Pulse Pressure Variability Interaction in All-Cause of Death

The forest plot illustrates the HRs associated with an increase in 1 SD (4 beats/min) in RHR variability among participants grouped by quartiles of PP-SD variability and the HR associated with an increase in 1 SD (5 mm Hg) in PP variability among participants grouped by quartiles of RHR SD variability (Figure 2). With an increase in 1 SD of RHR variability, the Cox regression confirmed that participants under the age of 65 years in the third and fourth quartiles of PP-SD variability had an independent increase in risk for ACM (HR [95% CI]=1.16 [1.06–1.28]; and 1.19 [1.05–1.35], respectively). Also, in the population <65 years of age, an increase in 1 RHR-CV/ARV variability was markedly associated with increased risk for ACM among those of the highest quartiles of PP-CV/ARV variability.

With an increase in 1 SD of PP variability, participants >65 years of age had a higher risk for ACM across quartiles of RHR SD variability. The HR (95% CI) for the subjects in quartiles 2, 3, and 4 were 1.81 (1.10–2.97),

2.31 (1.37–1.3.90), and 2.64 (1.63–4.29), respectively. In this general population >65 years of age, an increase in PP-CV variability was markedly associated with increased risk of ACM, with adjusted HRs and 95% CIs for lowest versus highest quartiles of RHR-CV variability 1.23 (1.08–1.40) (Table S5). Similar findings were replicated when the combined RHR variability and PP variability effects were assessed by ARV (Table S6).

Absolute Risk of Mortality

We calculated 6 years' absolute risk of mortality using the Cox proportional hazard model (Figure 3). After a mean follow-up of 4.97±0.69 years, 1667 of 46 751 participants died; 866 of 40 351 deaths occurred in participants who were <65 years of age, whereas 801 of 6400 deaths occurred in participants >65 years of age. The cumulative incidence of ACM shows a progressively higher risk of death across quartiles of RHR-SD variability and quartiles of PP-SD variability in Figure 4A through 4D (log-rank test; all *P*<0.001). The Schoenfeld residuals test showed that the corresponding *P* value of Pearson correlation had no linear correlation between Schoenfeld residuals and time rank (Figure 5).

Comparison of Hemodynamic Parameters Measured at the 3 Examinations

As the present study is focusing on the variability of the most critical hemodynamic parameters along a certain period of time, it is important to see how these hemodynamic parameters change along the 3 examinations

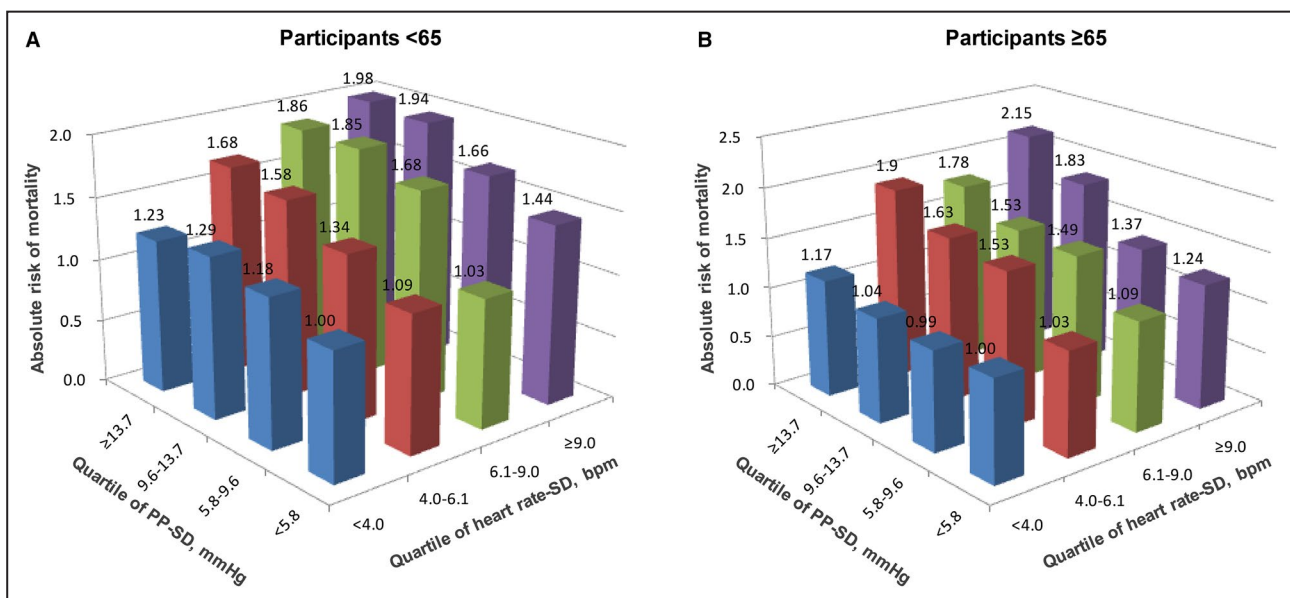


Figure 3. Absolute risk of mortality by quartiles of the SD of long-term variability in pulse pressure and resting heart rate variability for participants younger and older than 65 years of age.

A, Adjusted hazard ratios for all-cause mortality in each group by quartiles of the SD of long-term variability in PP and heart rate variability in participants <65. **B**, Adjusted hazard ratios for all-cause mortality in each group by quartiles of the SD of long-term variability in PP and resting heart rate variability in participants ≥65. PP indicates pulse pressure.

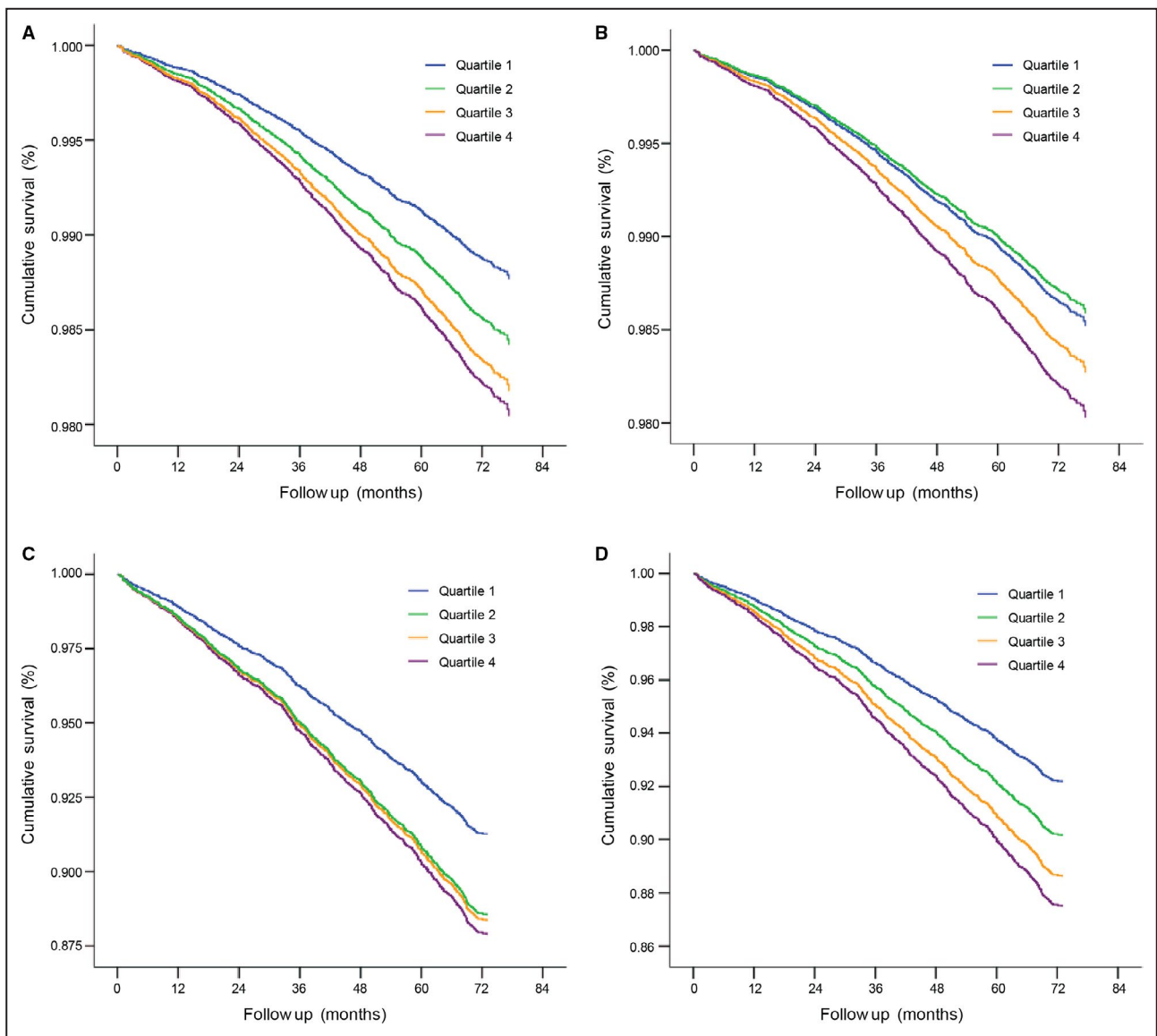


Figure 4. The Kaplan–Meier survival curves for all-cause mortality.

The Kaplan–Meier survival curves of participants <65 by quartiles of RHR-SD (A) and PP-SD (B). The Kaplan–Meier survival curves of participants ≥65 by quartiles of RHR-SD (C) and PP-SD (D). PP indicates pulse pressure; and RHR, resting heart rate.

and what trends these parameters show in time. The changes in hemodynamic parameters from the first visit to the last visit are demonstrated in Figures 6 and 7. The actual average values of RHR and PP across the quartiles of the 3 visits are presented in Table S7. The descriptive statistics of hemodynamic parameters measured at the 3 examinations (from the first examination to the last examination) showed that the average RHR and PP was significantly higher in quartile 4 compared with quartiles 1, 2, and 3 across the 3 visits.

Sensitivity Analyses

To control the BP influence on mortality, we initially categorized the participants into 2 groups: (1) those with

no history of hypertension (as per self-reported history of hypertension; n=40 098) and (2) those normotensive participants (individuals who were free of hypertension or whose BP was controlled during the third examination within the normal range defined as DBP <90 mm Hg and SBP <140 mm Hg; n=32 061). We further investigated the HRs and 95% CIs for 1 SD rise in RHR-SD and PP-SD for the 2 groups of participants. Figure 8 shows a linear trend line, which clearly describes that the HR has consistently risen through quartiles of RHR-SD and PP-SD in both groups. Also, the fourth quartile of RHR-SD and PP-SD were associated with the highest risk of ACM, suggesting that hypertension status did not influence the outcome of the data.

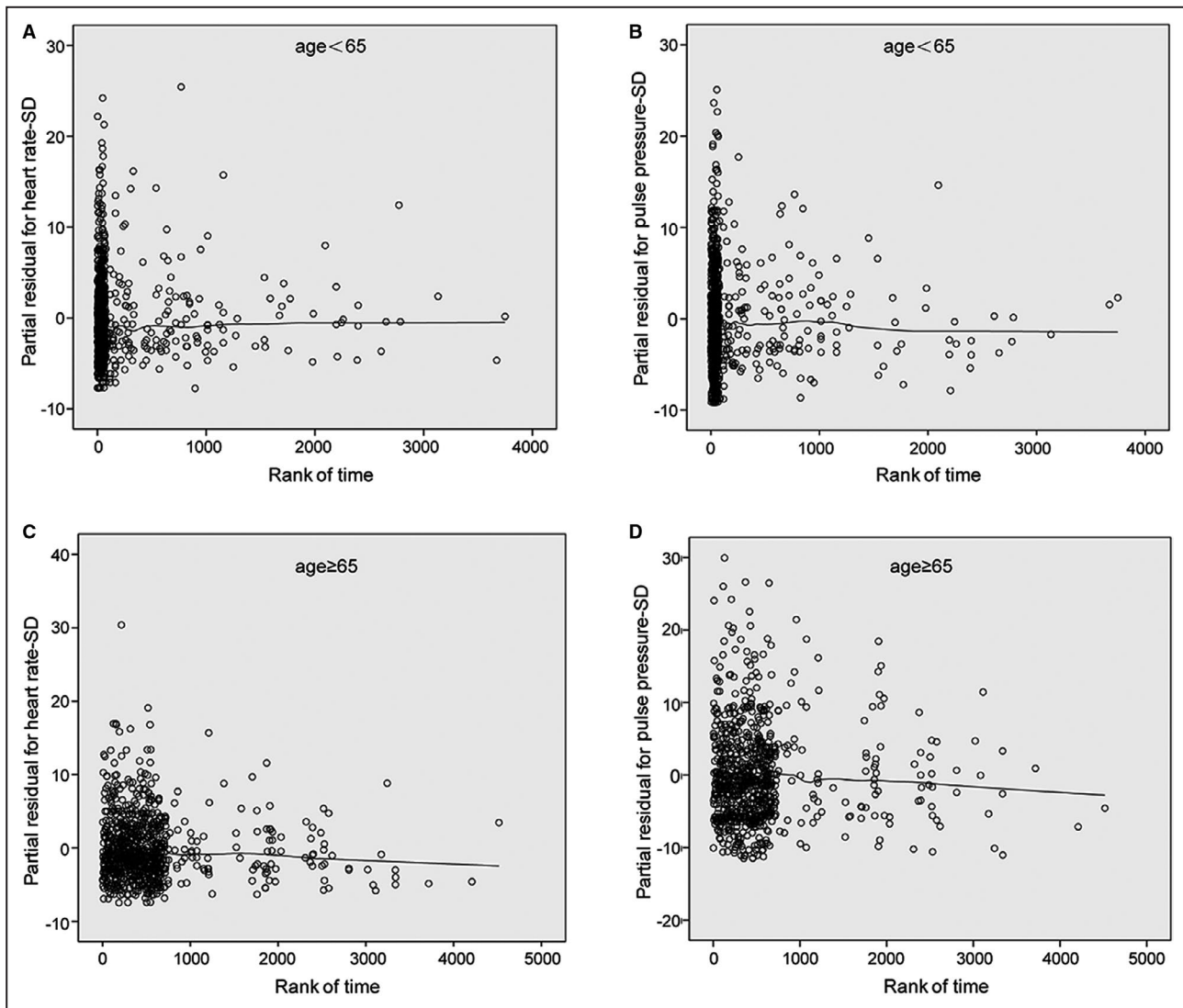


Figure 5. The smoothing curve of Schoenfeld partial residuals against time rank.

The smoothing curve of RHR-SD (A) and PP-SD (B) in participants <65 years. The smoothing curve of RHR-SD (C) and PP-SD (D) in participants ≥ 65 years. PP indicates pulse pressure; and RHR, resting heart rate.

DISCUSSION

In this cohort followed for 6 years, RHR variability and PP variability were independently associated with an increased risk of ACM. This association of the RHR-SD and PP-SD with all causes of death remains consistent even after adjusting for potential confounders, which confirmed that RHR and PP variability predicts the subsequent occurrence of ACM. Participants with the highest quartile of RHR-SD, and PP-SD (RHR-SD ≥ 8.5 beats/min and PP-SD ≥ 10.34 mm Hg) had the highest risk of death compared with the participants in the lowest quartiles of RHR-SD and PP-SD variability. Interestingly, other variability measures, including CV and ARV replicated similar findings to the visit-to-visit variability measured by SD, independent of mean.

In the past, various studies reported that hour-to-hour and day-to-day variability in BP and heart rate associated with cardiovascular morbidity and mortality, as well as with several cardiovascular risk factors.^{9–12} The RHR variability has also been thoroughly examined, and an elevated RHR variability has been identified as a marker of cardiovascular events and ACM.^{5,13–15} In this study, the SDs of RHR and PP were significantly associated with risk of death in the general population. The findings regarding RHR and PP associations with ACM remain consistent after multivariate adjustment for the potential confounding factors, suggesting that a rate control strategy is not inferior to a cardiovascular disease control strategy in preventing the risk of ACM. Thus, our results provide insights into the importance of a comprehensive public health strategy to enhance

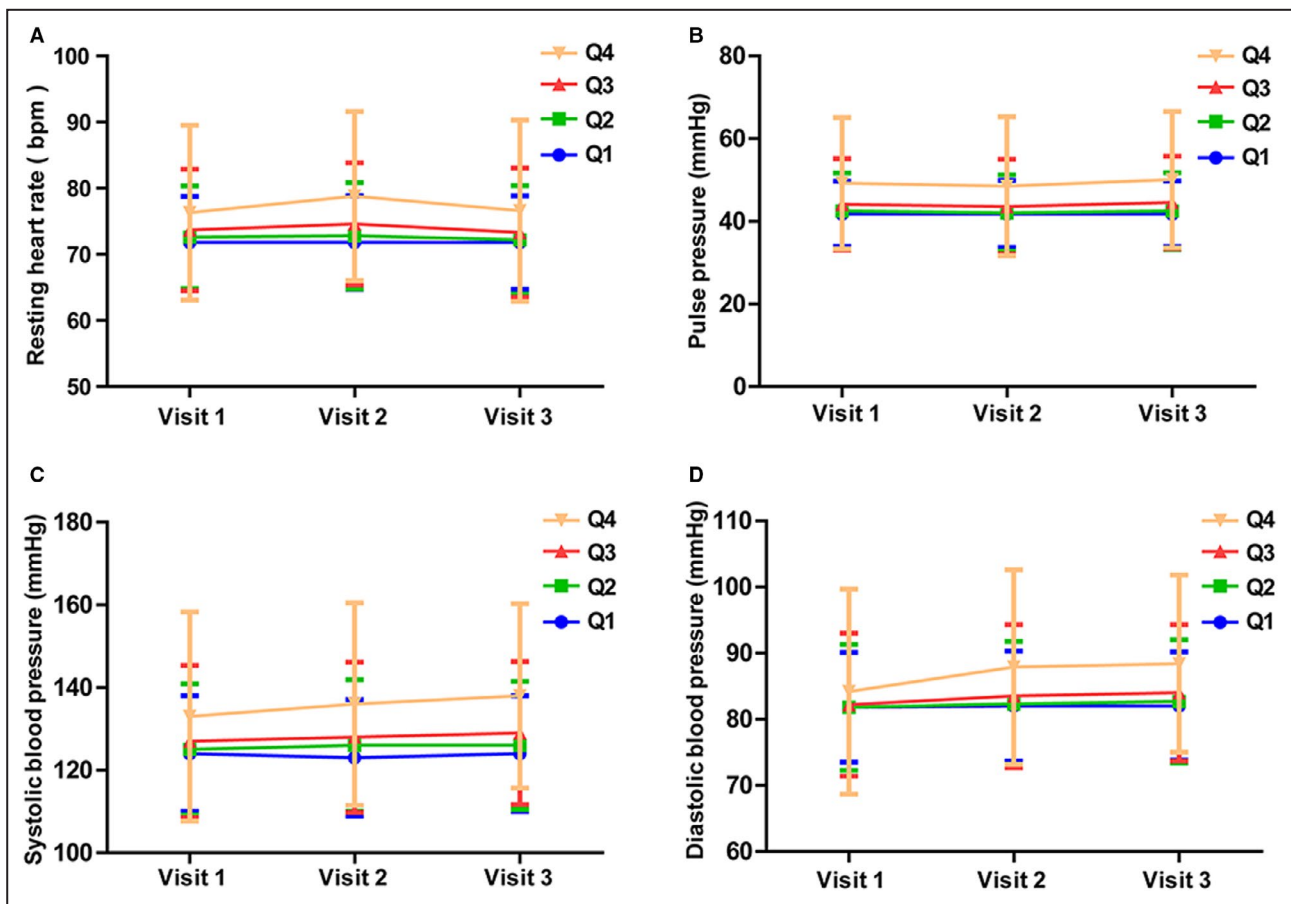


Figure 6. The actual changes in hemodynamic parameters from the first visit to the last visit among participants <65 years of age.

A, Resting heart rate. **B,** Pulse pressure. **C,** Systolic blood pressure. **D,** Diastolic blood pressure.

the quality of healthy life and increase the life expectancy of the population.

Our previous study from KCS reported that elevated RHR variability is a potential predictor of long-term mortality among the aged population without an established cardiovascular disease.² We published an article that explored the link between elevated long-term RHR variability and SBP variability for ACM recently, also using data from KCS,⁸ and reported a significant association of RHR variability with death. Similarly, the present findings support that RHR variability is predictive of ACM, even after multiple adjustments for potential confounders. Thus, the main conclusions of our 3 articles appear to be consistent and suggest that there is a positive association between a visit-to-visit RHR variability and ACM. These persistent findings generated using KCS data can be interpreted as being of scientific interest. Hence, considering the consistent findings from KCS data and the previous studies that have shown similar findings, we are not only left to assume but also to confirm that the RHR variability predicts ACM.

In the present study, the interaction analysis shows that participants in the highest variability of RHR-SD

and PP-SD quartiles had a significantly increased risk of death. With an increase in 1 SD of RHR, participants <65 years of age in the higher quartiles of PP SD had an independent increase in risk for ACM. However, with an increase in 1 SD of PP, participants >65 years of age had a higher risk for ACM across quartiles of RHR-SD. These findings demonstrate that an elevated long-term RHR variability combined with an increased PP variability or vice versa may amplify the risk of ACM. Nevertheless, the impact of an increase in 1 SD of RHR (4 beats/min) and 1 SD of PP (5 mm Hg) was largely affected by age. This could be explained because of the negative association between heart rate variability and age,¹⁶ which could mitigate the effect of RHR variability for ACM in the group aged ≥ 65 . It should be noted that an increase in resting heart rate put a greater impact for ACM in young ages compared with the old-aged population, whereas the observation of an increase in ACM in the old-aged population following an increase in 1 SD of PP could still be attributed to aging-associated arterial stiffness. Documented evidence reported that an impaired baroreflex sensitivity is linked with the

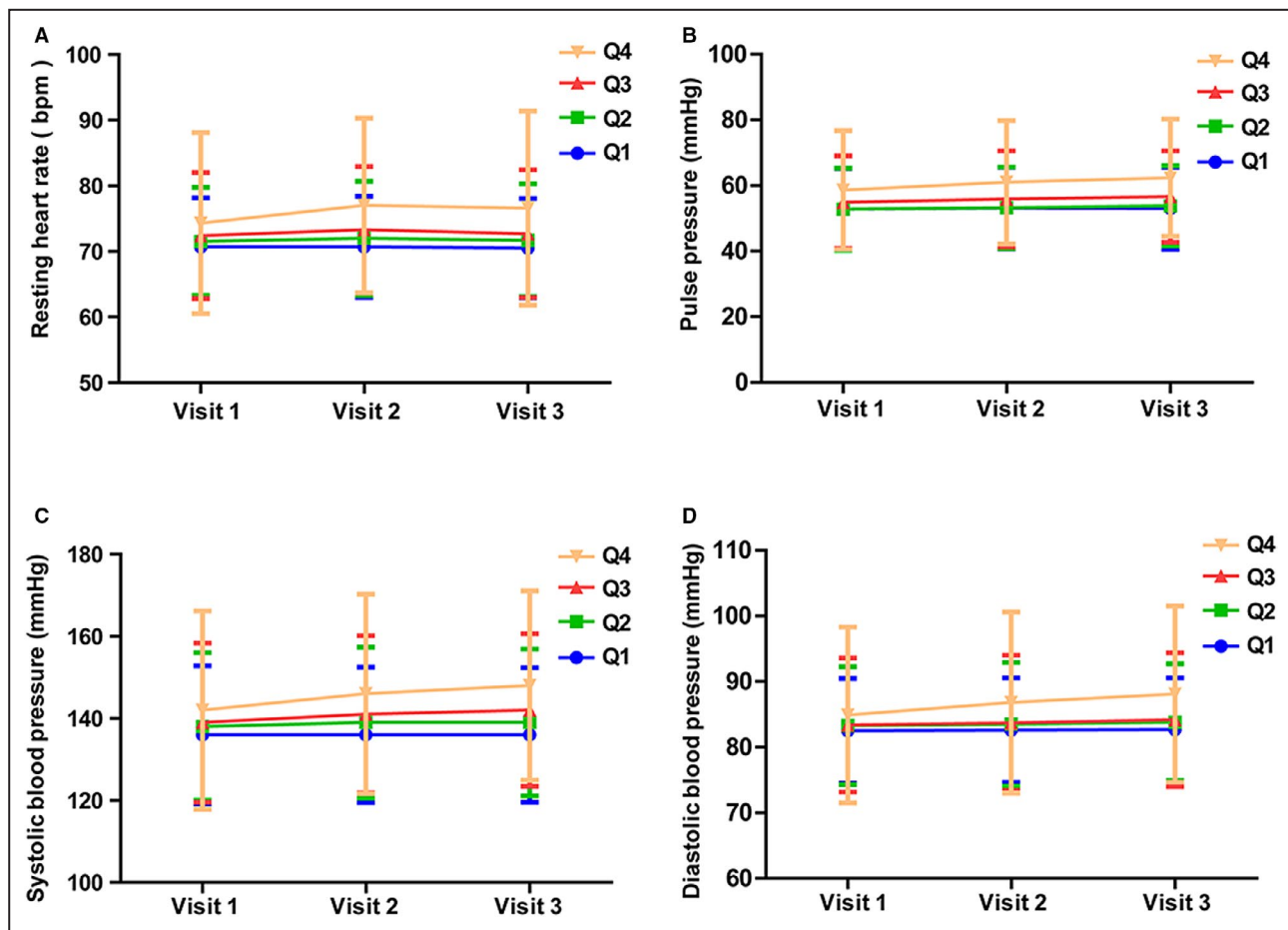


Figure 7. The actual changes in hemodynamic parameters from the first visit to the last visit among participants >65 years of age.

A, Resting heart rate. B, Pulse pressure. C, Systolic blood pressure. D, Diastolic blood pressure.

stiffness of the arterial wall and is predictive of cardiovascular mortality.^{17,18} Also, the reason why in our study an increase in 1 SD of PP had a larger prognostic effect in participants >65 years of age compared with young age could partially be explained by the fact that individuals with elevated BP display greater low-frequency BP variability, which may indicate an altered sympathetic nervous system functionality compared with that in normotensive individuals.^{19,20} A previous study documented that PP was a better predictor of cardiovascular risk than diastolic, systolic, or mean arterial pressure,²¹ as PP readings might be more closely related to autonomic function than those based on SBP or DBP readings.²⁰

Apart from a large number of participants, our study has several other strengths. To our knowledge, this is the first large study that addresses the prognostic implications of long-term RHR variability and PP variability and all causes of death in participants grouped by age, with the aim to control the influence of age in older participants. However, this study has several limitations. There is still no consensus on the

best way to define visit-to-visit RHR variability and PP variability; therefore, we have no reference value for the visit-to-visit variation. For this reason, our study may not fully control the influence of physiological variations. Though we recorded RHR and PP in the same season annually, autonomic dysfunction can cause swings in hemodynamic variables, which could contribute to variations in the interval between visits for each time point. The definitions of variability for our study were based on annual examinations of RHR and PP. As such, more frequent RHR and PP assessments could have improved the variations that could result from age-related physiological changes, as these parameters show variations over more prolonged periods. Arterial stiffness caused by aging and hypertension may still represent a source of hemodynamic variability, which may magnify random BP changes for the participants in the subgroup >65 years of age.

In conclusion, elevated long-term RHR and PP variations are independent risk markers for ACM in the general population. An elevated long-term PP variability combined with an increased RHR variability or vice versa

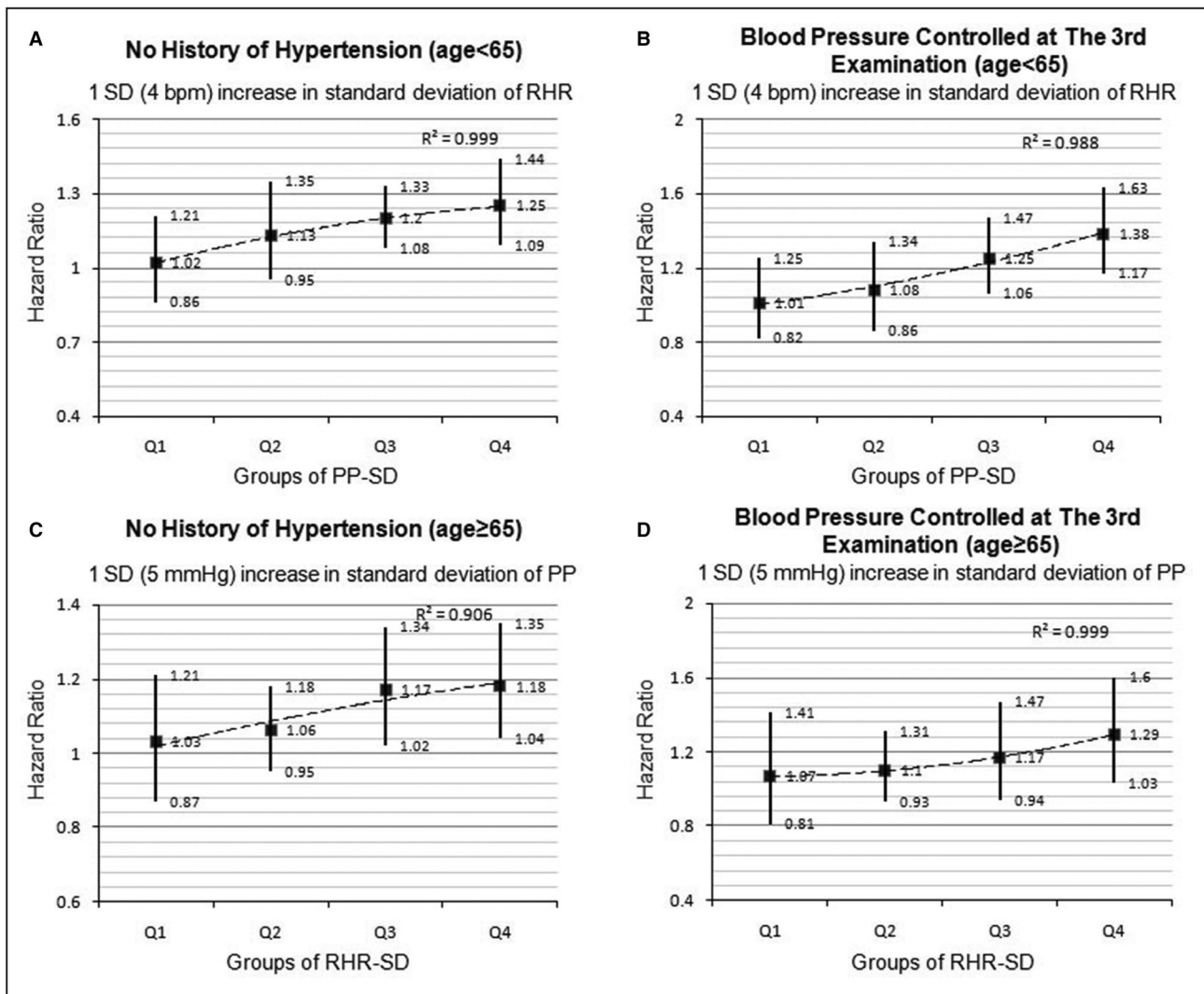


Figure 8. Sensitivity analyses.

A, Hazard ratio and 95% CI for 1 SD rise in RHR-SD for participants <65 years of age grouped by quartiles of PP-SD for those without history of hypertension. **B**, Hazard ratio and 95% CI for 1 SD rise in RHR-SD for participants <65 years of age grouped by quartiles of PP-SD with controlled blood pressure at the third exam. **C**, Hazard ratio and 95% CI for 1 SD rise in PP-SD for participants ≥65 years of age grouped by quartiles of RHR-SD for those without history of hypertension. **D**, Hazard ratio and 95% CI for 1 SD rise in PP-SD for participants ≥65 years of age grouped by quartiles of RHR-SD with controlled blood pressure at the third exam. PP indicates pulse pressure; and RHR, resting heart rate.

may amplify the risk of death but is highly influenced by age. The standardized implementation and monitoring methods to improve home pulse and BP monitoring should consider the importance of PP variability, and the practice guidelines should recommend a strict pulse and BP monitoring for the middle- and old-aged population.

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Sources of Funding

This research was funded by National Natural Science Foundation of China, grant number 81570313.

Disclosures

None.

Supplementary Materials

Tables S1–S7

ARTICLE INFORMATION

Received August 1, 2019; accepted February 14, 2020.

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Supplemental Material

Table S1. Cumulative mortality and hazards ratios (95% confidence interval) for all-cause mortality associated with quartile of CV of resting heart rate variability and pulse pressure variability in participants younger than 65 years old.

	Quartile of RHR-CV variability, bpm				P for trends
	Quartile 1 (<5.0)	Quartile 2 (5.0-7.9)	Quartile 3 (7.9-11.5)	Quartile 4 (≥11.5)	
Total, n	10241	10153	10073	9884	-
Deaths, n (%)	154 (1.5)	191 (1.9)	257 (2.6)	264 (2.7)	<0.001
Model 1*	1.00 (Ref)	1.26 (1.02, 1.56)	1.71 (1.40, 2.09)	1.97 (1.46, 2.18)	<0.001
Model 2†	1.00 (Ref)	1.25 (1.01, 1.54)	1.67 (1.36, 2.04)	1.70 (1.39, 2.07)	<0.001
Model 3‡	1.00 (Ref)	1.26 (1.01, 1.56)	1.48 (1.20, 1.82)	1.61 (1.31, 1.98)	<0.001
	Quartile of PP-CV variability, mmHg				P for trends
	Quartile 1 (<10.5)	Quartile 2 (10.5-15.7)	Quartile 3 (15.7-22.5)	Quartile 4 (≥22.5)	

Total, n	10141	10083	10294	9833	
Deaths, n (%)	189 (1.9)	199 (2.0)	218 (2.1)	260 (2.6)	0.001
Model 1*	1.00 (Ref)	1.06 (0.87, 1.29)	1.14 (0.94, 1.39)	1.43 (1.18, 1.72)	<0.001
Model 2†	1.00 (Ref)	1.03 (0.84, 1.25)	1.13 (0.93, 1.38)	1.35 (1.12, 1.63)	<0.001
Model 3‡	1.00 (Ref)	1.03 (0.84, 1.27)	1.11 (0.91, 1.35)	1.33 (1.10, 1.61)	<0.001

CV=coefficient of variation.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean pulse pressure, mean resting heart rate, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein and ACE inhibitor.

Table S2. Cumulative mortality and hazards ratios (95% confidence interval) for all-cause mortality associated with quartile of ARV of resting heart rate variability and pulse pressure variability in participants younger than 65 years old.

	Quartile of RHR-ARV, bpm				P for trends
	Quartile 1 (<4.0)	Quartile 2 (4.0-7.0)	Quartile 3 (7.0-11.0)	Quartile 4 (≥11.0)	
Total, n	10576	8876	10552	10347	
Deaths, n (%)	149 (1.4)	172 (1.9)	249 (2.4)	296 (2.9)	<0.001
Model 1*	1.00 (Ref)	1.39 (1.11, 1.73)	1.68 (1.37, 2.06)	2.04 (1.68, 2.49)	<0.001
Model 2†	1.00 (Ref)	1.38 (1.10, 1.71)	1.65 (1.35, 2.02)	1.97 (1.62, 2.40)	<0.001
Model 3‡	1.00 (Ref)	1.32 (1.05, 1.65)	1.45 (1.20, 1.72)	1.57 (1.27, 1.93)	<0.001
	Quartile of PP-ARV, mmHg				

	Quartile 1 (<4.9)	Quartile 2 (4.9-8.0)	Quartile 3 (8.0-12.2)	Quartile 4 (≥12.2)	P for trends
Total, n	10737	10431	10136	9047	
Deaths, n (%)	158 (1.5)	203 (1.9)	213 (2.1)	292 (3.2)	<0.001
Model 1*	1.00 (Ref)	1.33 (1.08, 1.63)	1.44 (1.17, 1.76)	2.22 (1.83, 2.70)	<0.001
Model 2†	1.00 (Ref)	1.26 (1.02, 1.55)	1.29 (1.05, 1.59)	1.79 (1.47, 2.17)	<0.001
Model 3‡	1.00 (Ref)	1.17 (0.95, 1.45)	1.17 (0.95, 1.44)	1.38 (1.13, 1.69)	<0.001

ARV=average real variability.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean pulse pressure, mean resting heart rate, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein and ACE inhibitor.

Table S3. Cumulative mortality and hazards ratios (95% confidence interval) for all-cause mortality associated with quartile of CV of resting heart rate variability and pulse pressure variability in participants above 65 years old.

	Quartile of RHR-CV, bpm				P for trends
	Quartile 1 (<5.3)	Quartile 2 (5.3-8.3)	Quartile 3 (8.3-12.3)	Quartile 4 (≥12.3)	
Total, n	1446	1533	1619	1802	
Deaths, n (%)	142 (9.8)	196 (12.8)	213 (13.2)	250 (13.9)	0.004
Model 1*	1.00 (Ref)	1.32 (1.07, 1.64)	1.36 (1.10, 1.69)	1.45 (1.18, 1.78)	0.001
Model 2†	1.00 (Ref)	1.32 (1.06, 1.64)	1.34 (1.09, 1.66)	1.35 (1.10, 1.66)	<0.001
Model 3‡	1.00 (Ref)	1.27 (1.03, 1.57)	1.35 (1.08, 1.68)	1.36 (1.09, 1.69)	<0.001
	Quartile of PP-CV, mmHg				

	Quartile 1 (<10.8)	Quartile 2 (10.8-16.7)	Quartile 3 (16.7-24.1)	Quartile 4 (≥24.1)	P for trends
Total, n	1546	1385	1614	1855	
Deaths, n (%)	151 (9.8)	159 (11.5)	227 (14.1)	264 (14.2)	<0.001
Model 1*	1.00 (Ref)	1.19 (0.95, 1.49)	1.46 (1.19, 1.80)	1.50 (1.23, 1.83)	<0.001
Model 2†	1.00 (Ref)	1.18 (0.94, 1.47)	1.43 (1.17, 1.75)	1.45 (1.18, 1.78)	<0.001
Model 3‡	1.00 (Ref)	1.27 (1.01, 1.60)	1.52 (1.23, 1.88)	1.54 (1.25, 1.90)	<0.001

CV=coefficient of variation.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean pulse pressure, mean resting heart rate, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein and ACE inhibitor.

Table S4. Cumulative mortality and hazards ratios (95% confidence interval) for all-cause mortality associated with quartile of ARV of resting heart rate variability and pulse pressure variability in participants younger than 65 years old.

	Quartile of RHR-ARV, bpm				P for trends
	Quartile 1 (<4.5)	Quartile 2 (4.5-7.5)	Quartile 3 (7.5-11.0)	Quartile 4 (≥11.0)	
Total, n	1517	1393	1728	1762	
Deaths, n (%)	151 (10.0)	160 (11.5)	239 (13.8)	251 (14.2)	<0.001
Model 1*	1.00 (Ref)	1.16 (0.93, 1.45)	1.42 (1.16, 1.74)	1.46 (1.19, 1.79)	<0.001
Model 2†	1.00 (Ref)	1.16 (0.93, 1.45)	1.37 (1.12, 1.68)	1.39 (1.14, 1.70)	<0.001
Model 3‡	1.00 (Ref)	1.13 (0.90, 1.42)	1.20 (0.97, 1.48)	1.28 (1.03, 1.58)	<0.001
	Quartile of PP-ARV, mmHg				

	Quartile 1 (<6.6)	Quartile 2 (6.6-10.9)	Quartile 3 (10.9-17.1)	Quartile 4 (≥17.1)	P for trends
Total, n	1054	1153	1552	2641	
Deaths, n (%)	91 (8.6)	125 (10.8)	187 (12.0)	398 (15.0)	<0.001
Model 1*	1.00 (Ref)	1.27 (0.97, 1.66)	1.42 (1.11, 1.83)	1.81 (1.44, 2.27)	<0.001
Model 2†	1.00 (Ref)	1.27 (0.97, 1.67)	1.39 (1.08, 1.79)	1.66 (1.32, 2.09)	<0.001
Model 3‡	1.00 (Ref)	1.32 (1.00, 1.75)	1.46 (1.12, 1.89)	1.66 (1.31, 2.12)	<0.001

ARV=average real variability.

*Unadjusted model.

†Adjusted for age and sex.

‡Adjusted for age and sex, body mass index, current smoker, mean pulse pressure, mean resting heart rate, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein and ACE inhibitor.

Table S5. Adjusted hazards ratios with 95% confidence interval for 1 CV increase in CV of resting heart rate variability and in CV of pulse pressure variability of all-cause mortality.

Categories	1 CV (4 bpm) increase in CV of RHR		Categories	1 CV (5 mmHg) increase in CV of PP	
	variability			variability	
	Age<65	Age≥65		Age<65	Age≥65
All subjects	1.16 (1.09, 1.23)***	1.07 (0.99, 1.13)	All subjects	1.09 (0.99, 1.16)	1.13 (1.06, 1.20)***
CV of PP, mmHg			CV of RHR, bpm		
Q1	1.05 (0.91, 1.21)	1.01 (0.87, 1.17)	Q1	1.02 (0.86, 1.20)	1.00 (0.85, 1.17)
Q2	1.17 (1.03, 1.34)*	1.13 (0.98, 1.30)	Q2	1.04 (0.90, 1.21)	1.12 (1.00, 1.26)*
Q3	1.15 (1.02, 1.31)**	1.00 (0.88, 1.13)	Q3	1.09 (0.99, 1.20)	1.17 (1.02, 1.34)*

Q4	1.18 (1.07, 1.32)**	1.09 (0.99, 1.20)	Q4	1.12 (1.00, 1.24)	1.23 (1.08, 1.40)**
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CV=coefficient of variation.

Adjusted for age, sex, body mass index, high/intensive activity, mean heart rate, mean pulse pressure, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein, and antihypertensive medication.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table S6. Adjusted hazards ratios with 95% confidence interval for 1 ARV increase in ARV of resting heart rate variability and in ARV of pulse pressure variability of all-cause mortality.

Categories	1 ARV (4 bpm) increase in ARV of RHR		Categories	1 ARV (5 mmHg) increase in ARV of PP	
	Age<65	Age≥65		Age<65	Age≥65
All subjects	1.14 (1.07, 1.21)***	1.06 (0.99, 1.13)	All subjects	1.04 (0.99, 1.09)	1.10 (1.05, 1.15)***
ARV of PP, mmHg			ARV of RHR, bpm		
Q1	1.14 (0.98, 1.32)	1.08 (0.88, 1.33)	Q1	1.05 (0.88, 1.25)	0.98 (0.86, 1.12)
Q2	1.13 (0.99, 1.30)	1.02 (0.87, 1.20)	Q2	0.91 (0.76, 1.09)	1.14 (0.99, 1.31)
Q3	1.14 (1.00, 1.29)*	0.95 (0.81, 1.10)	Q3	1.06 (0.96, 1.18)	1.09 (1.01, 1.18)*
Q4	1.14 (1.03, 1.25)**	1.10 (0.99, 1.20)	Q4	1.03 (0.98, 1.09)	1.19 (1.08, 1.32)**

ARV=average real variability. Adjusted for age, sex, body mass index, high/intensive activity, mean heart rate, mean pulse pressure, fasting plasma glucose, total cholesterol, high density lipoprotein, elevated C-reactive protein, and antihypertensive medication. * $P<0.05$; ** $P<0.01$; *** $P<0.001$

Table S7. Mean changes of RHR and PP across the quartiles measured at the three examinations.

	RHR (mean±SD) among Participants <65 years					RHR (mean±SD) among participants ≥65 years				
	Q1	Q2	Q3	Q4	P for trend	Q1	Q2	Q3	Q4	P for trend
Visit 1	71.8±6.98	72.6±7.75	73.7±9.20	76.3±13.2	<0.01	70.7±7.46	71.5±8.25	72.4±9.60	74.3±13.8	<0.01
Visit 2	71.8±7.07	72.8±8.05	74.6±9.25	78.8±12.8	<0.01	70.7±7.70	72.0±8.67	73.3±9.64	77.0±13.3	<0.01
Visit 3	71.8±7.07	72.2±8.21	73.3±9.77	76.6±13.7	<0.01	70.5±7.56	71.7±8.61	72.7±9.74	76.6±14.8	<0.01
	PP (mean±SD) among Participants <65 years					PP (mean±SD) among participants ≥65 years				
	Q1	Q2	Q3	Q4	P for trend	Q1	Q2	Q3	Q4	P for trend
Visit 1	41.8±7.92	42.5±9.17	44.1±11.1	49.2±15.9	<0.01	52.8±12.4	52.8±12.5	54.9±14.1	58.6±18.1	<0.01
Visit 2	41.8±8.10	42.0±9.26	43.6±11.4	48.5±16.8	<0.01	53.1±12.4	53.2±12.4	55.9±14.6	61.0±18.8	<0.01
Visit 3	41.8±7.96	42.5±9.26	44.6±11.2	50.1±16.5	<0.01	53.0±12.5	53.8±12.2	56.6±13.9	62.4±17.9	<0.01