Supplemental Material

Table S1. Correlations among four SBP variabilities and mean SBP.

Variables	Mean SBP	SD_{SBP}	CV_{SBP}	ARV_{SBP}	VIM_{SBP}
Mean SBP	1	—	—	—	—
SD_{SBP}	0.114*	1	—	—	—
CV_{SBP}	-0.012	0.990*	1	—	—
ARV_{SBP}	0.114*	0.885*	0.873*	1	—
VIM_{SBP}	0.021	0.994*	0.999*	0.878*	1

Pearson's correlation coefficients are shown. * indicates the correlation between different variables. SBP variabilities were determined based on 3 clinic blood pressure measurements from visit 1 to visit 3. SBP: systolic blood pressure; SD: standard deviation; CV: coefficient of variation; ARV: average real variability; VIM: variability independent of the mean.

Table S2. Risk of secondary outcomes associated with SBP variability measured by VIM in participants with optimal SBP levels.

SBP Variability	No. of Events /Total No.	Cumulative Incidence % (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
All-cause mortality					
VIM Q1	437/1766	29.7 (26.3-33.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
VIM Q2	477/1767	33.0 (28.9-37.6)	1.12 (0.98-1.27)	1.10 (0.97-1.26)	1.11 (0.98-1.27)
VIM Q3	511/1766	32.0 (29.5-34.7)	1.19 (1.05-1.35)	1.18 (1.04-1.33)	1.19 (1.05-1.35)
VIM Q4	548/1766	35.5 (32.6-38.6)	1.30 (1.15-1.48)	1.24 (1.09-1.41)	1.26 (1.11-1.44)
P for trend	—	< 0.001	< 0.001	0.001	0.001
Coronary heart disease					
VIM Q1	178/1766	12.6 (10.1-15.6)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
VIM Q2	148/1767	9.8 (8.3-11.5)	0.86 (0.69-1.07)	0.84 (0.68-1.05)	0.84 (0.68-1.05)
VIM Q3	158/1766	10.6 (9.1-12.4)	0.93 (0.75-1.16)	0.92 (0.74-1.14)	0.93 (0.75-1.15)
VIM Q4	186/1766	13.8 (11.8-16.1)	1.14 (0.93-1.40)	1.13 (0.92-1.39)	1.11 (0.90-1.37)
P for trend	—	0.340	0.178	0.214	0.287
Stroke					
VIM Q1	97/1766	7.2 (5.8-8.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
VIM Q2	99/1767	6.6 (5.4-8.0)	1.05 (0.79-1.38)	1.05 (0.79-1.40)	1.07 (0.80-1.42)
VIM Q3	99/1766	6.8 (5.5-8.3)	1.04 (0.79-1.38)	1.05 (0.79-1.39)	1.07 (0.81-1.43)
VIM Q4	93/1766	6.7 (5.4-8.2)	0.98 (0.74-1.31)	0.97 (0.73-1.30)	1.00 (0.75-1.34)
P for trend	—	0.956	0.908	0.865	0.966
Heart failure					
VIM Q1	204/1766	14.6 (12.5-16.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
VIM Q2	208/1767	14.5 (12.6-16.7)	1.02 (0.84-1.24)	1.02 (0.84-1.24)	1.04 (0.86-1.27)
VIM Q3	215/1766	15.0 (13.0-17.3)	1.05 (0.86-1.27)	1.07 (0.88-1.30)	1.10 (0.90-1.33)
VIM Q4	261/1766	19.1 (16.8-21.7)	1.30 (1.08-1.56)	1.26 (1.05-1.52)	1.28 (1.06-1.55)
P for trend	—	0.001	0.006	0.011	0.009

VIM: variability independent of the mean; SBP: systolic blood pressure; HR: hazard ratio; CI: confidence interval.

Model 1: adjusted for age, sex, race at visit 3;

Model 2: adjusted for model 1 + education level, body mass index; smoking status, drinking status, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes, use of aspirin and statin at visit 3;

Model 3: adjusted for model 2 + prevalent hypertension; use of antihypertensive drugs; diastolic blood pressure at visit 3, trend and mean of SBP from visit 1 to visit 3.

Table S3. Risk of cardiovascular outcomes associated with SBP variability (VIM) as a continuous variable (per 1_SD = 3.73) in participants with optimal SBP levels.

Outcomes	No. of Events (%)	Model 1		Model 2		Model 3	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
MACE	2691 (38.1)	1.08 (1.04-1.12)	< 0.001	1.06 (1.02-1.10)	0.002	1.06 (1.02-1.10)	0.002
Secondary outcomes							
All-cause mortality	1973 (27.9)	1.10 (1.05-1.14)	< 0.001	1.07 (1.03-1.12)	0.001	1.08 (1.03-1.13)	0.001
Coronary heart disease	670 (9.5)	1.06 (0.99-1.14)	0.113	1.06 (0.98-1.14)	0.143	1.05 (0.97-1.13)	0.243
Stroke	388 (5.5)	0.98 (0.88-1.08)	0.675	0.97 (0.88-1.08)	0.585	0.98 (0.89-1.08)	0.693
Heart failure	888 (12.6)	1.10 (1.03-1.18)	0.003	1.09 (1.02-1.16)	0.009	1.09 (1.02-1.16)	0.010

VIM: variability independent of the mean; SBP: systolic blood pressure; SD: standard deviation; HR: hazard ratio; CI: confidence interval; MACE: major adverse cardiovascular event.

MACE was defined as the first occurrence of all-cause mortality, coronary heart disease, stroke, and heart failure.

Model 1: adjusted for age, sex, race at visit 3;

Model 2: adjusted for model 1 + education level, body mass index; smoking status, drinking status, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes, use of aspirin and statin at visit 3;

Model 3: adjusted for model 2 + prevalent hypertension; use of antihypertensive drugs; diastolic blood pressure at visit 3, trend and mean of SBP from visit 1 to visit 3.

Table S4. Risk of MACE associated with SBP variability (SD, CV, or ARV) in participants with optimal SBP levels.

SBP Variability	No. of Events /Total No.	Cumulative Incidence % (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Standard deviation (SD)					
SD Q1	627/1778	39.9 (36.0-44.0)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
SD Q2	633/1794	38.4 (35.8-41.1)	1.01 (0.91-1.13)	1.01 (0.90-1.13)	1.02 (0.91-1.14)
SD Q3	693/1762	43.0 (40.1-45.9)	1.13 (1.02-1.26)	1.11 (1.00-1.24)	1.11 (1.00-1.24)
SD Q4	738/1731	46.1 (43.4-48.9)	1.26 (1.13-1.40)	1.20 (1.08-1.34)	1.19 (1.07-1.33)
P for trend	—	< 0.001	< 0.001	< 0.001	0.001
Coefficient of variation (CV)					
CV Q1	632/1765	39.2 (36.2-42.2)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
CV Q2	646/1763	42.0 (37.6-46.7)	1.04 (0.93-1.16)	1.03 (0.92-1.15)	1.04 (0.94-1.17)
CV Q3	687/1771	41.4 (38.9-44.0)	1.10 (0.99-1.23)	1.09 (0.98-1.21)	1.11 (0.99-1.23)
CV Q4	726/1766	45.2 (42.3-48.2)	1.21 (1.09-1.34)	1.18 (1.06-1.31)	1.21 (1.08-1.35)
P for trend	—	< 0.001	< 0.001	0.002	< 0.001
Average real variability (ARV)					
ARV Q1	559/1527	40.1 (37.0-43.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
ARV Q2	667/1961	38.2 (34.5-42.2)	0.91 (0.81-1.02)	0.92 (0.82-1.03)	0.91 (0.82-1.02)
ARV Q3	695/1781	43.1 (40.2-46.1)	1.08 (0.96-1.20)	1.07 (0.96-1.19)	1.06 (0.94-1.18)
ARV Q4	770/1796	46.1 (43.5-48.8)	1.19 (1.06-1.32)	1.16 (1.04-1.29)	1.14 (1.02-1.27)
P for trend	—	< 0.001	< 0.001	< 0.001	0.001

MACE: major adverse cardiovascular event; SBP: systolic blood pressure; HR: hazard ratio; CI: confidence interval.

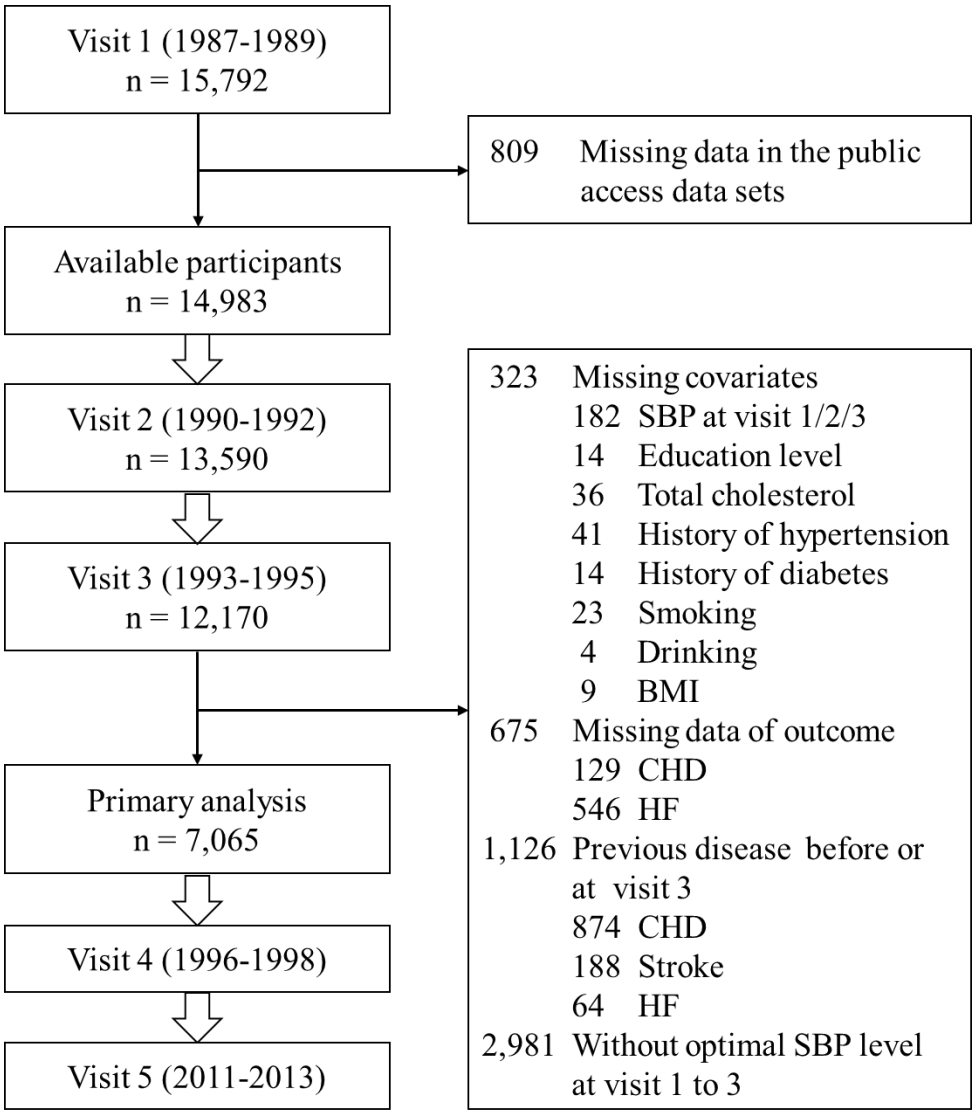
MACE was defined as the first occurrence of all-cause mortality, coronary heart disease, stroke, and heart failure.

Model 1: adjusted for age, sex, race at visit 3;

Model 2: adjusted for model 1 + education level, body mass index; smoking status, drinking status, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes, use of aspirin and statin at visit 3;

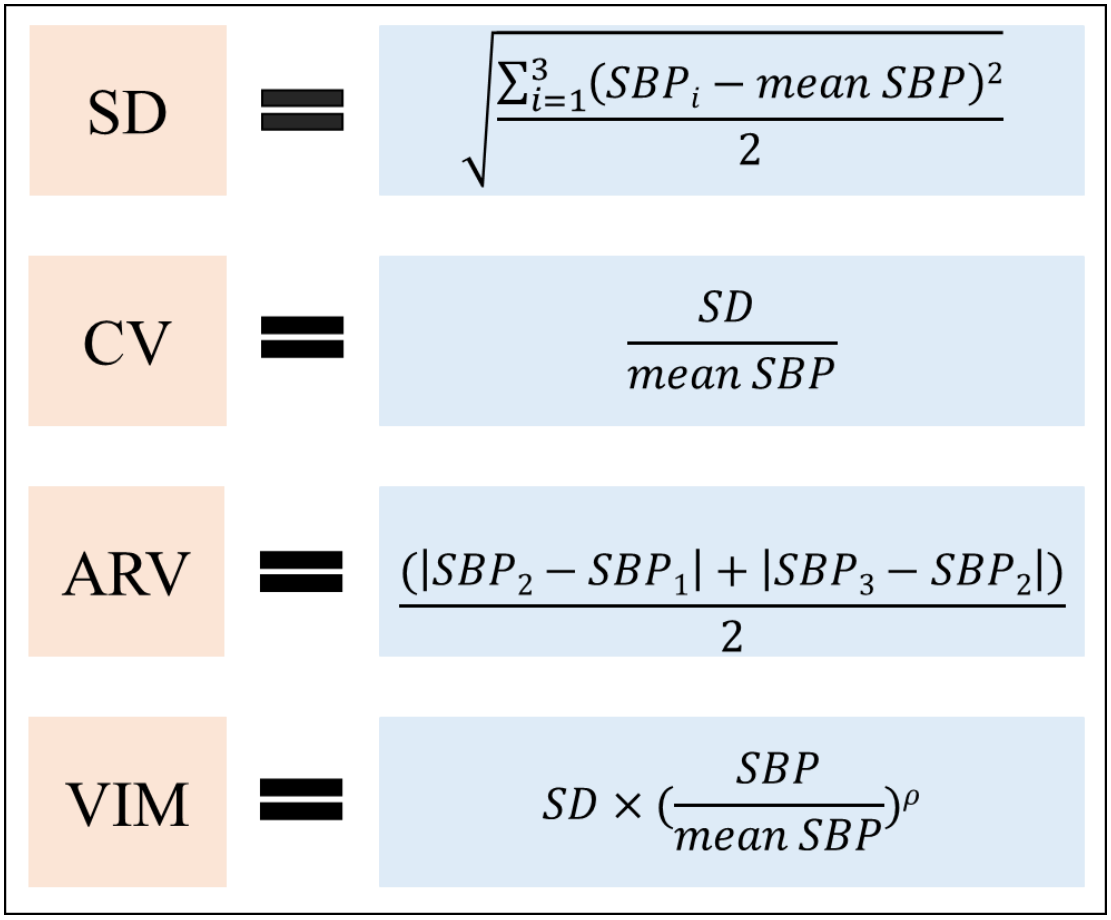
Model 3: adjusted for model 2 + prevalent hypertension; use of antihypertensive drugs; diastolic blood pressure at visit 3, trend and mean of SBP from visit 1 to visit 3.

Figure S1. Study flowchart with detailed exclusion information.



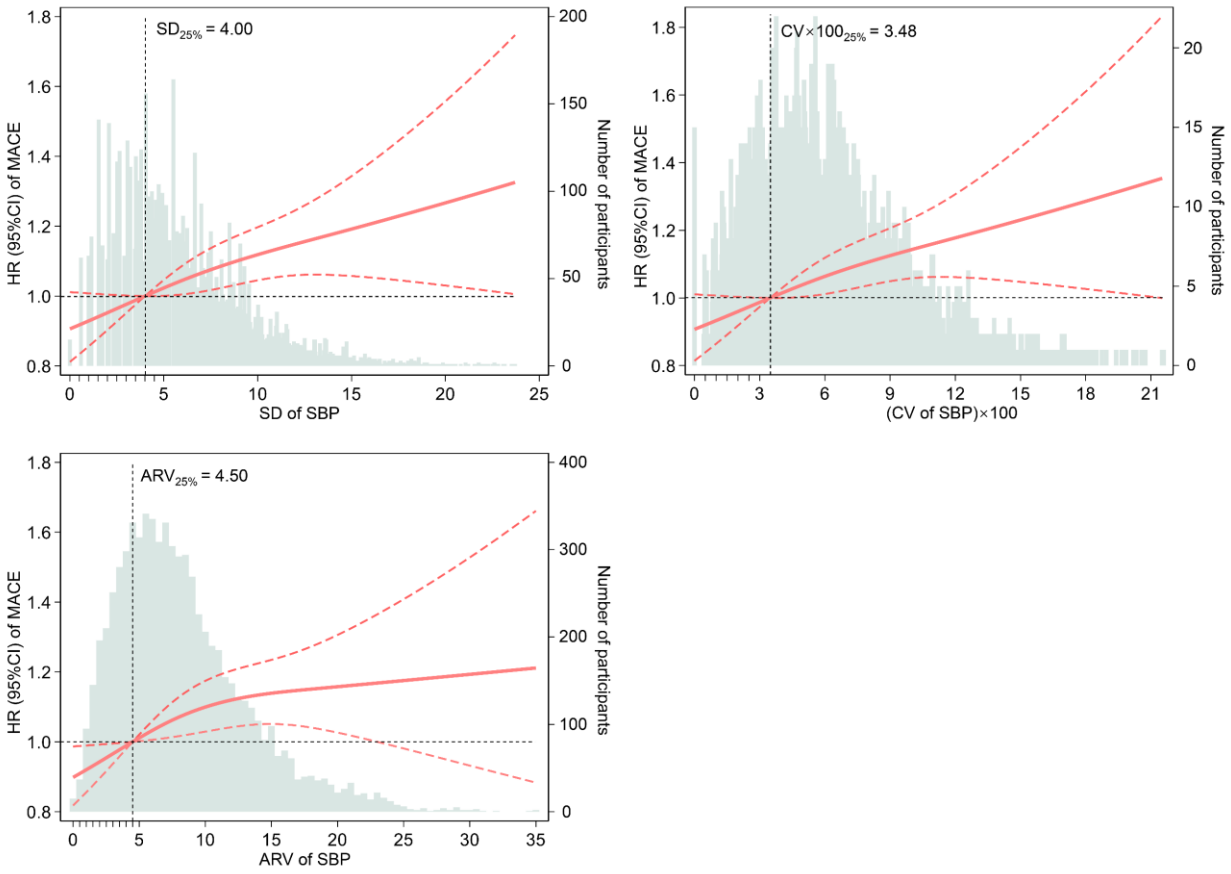
SBP: systolic blood pressure; BMI: body mass index; CHD: coronary heart disease; HF: heart failure.

Figure S2. The calculating formula of SD, CV, ARV and VIM.



SBP: systolic blood pressure; SD: standard deviation; CV: coefficient of variation; ARV: average real variability; VIM: variability independent of the mean; Mean SBP level was calculated across the first 3 visits for each participant; $i = 1$, 2 and 3 denote the measurements of visit 1, 2 and 3; ρ is the regression coefficient on the basis of regressing the natural logarithm of SD on the natural logarithm of the mean SBP.

Figure S3. Multivariable-adjusted HRs of MACE according to visit-to-visit SBP variability measured by SD, CV, and ARV in adults with optimal SBP levels.



The HRs (orange-red solid line) and 95% CIs (orange-red dotted lines) are derived from the Cox Model 3 that adjusted for age, sex, race, education level, body mass index, smoking status, alcohol use status, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes, use of aspirin and statin, prevalent hypertension, use of antihypertensive drugs, diastolic blood pressure at visit 3, trend and mean of SBP from visit 1 to visit 3. SBP variability was centred at the 25th percentile of sample and modelled using a restricted cubic spline with knots at the 5th, 50th, and 95th percentiles. Histograms represent the frequency distribution of SBP variability.

HR: hazard ratio; MACE: major adverse cardiovascular event; SBP: systolic blood

pressure; SD: standard deviation; CV: coefficient of variation; ARV: average real variability; CI: confidence interval.