

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. CARDIA Study

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

The CARDIA Study began in 1985-1986, enrolling 5,115 black and white adults ages 18 to 30 years who were recruited in Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The cohort is balanced with respect to race (52% of the participants are black), sex (55% are women), and educational level (40% have ≤ 12 years of education). Serial follow-up exams were conducted 2, 5, 7, 10, 15, 20, 25, and 30 years after baseline (Year 0).

BP measurement

Systolic blood pressure (SBP) and diastolic BP (DBP) were measured at each CARDIA examination following standardized protocols; the details are described in *National Heart Lung and Blood Institute, Coronary Artery Risk Development in Young Adults (CARDIA) Study Manual of Operation, 1985*. <https://www.nhlbi.nih.gov/research/resources/obesity/population/cardia.htm>. Briefly mentioned,

1. Research staff were carefully and centrally trained prior to participating. Prior to certification, each technician had their vision and hearing tested by reading and auditory (Korotkoff sound tape) tests, respectively. Recertification occurred every six months according to the instructions in the Manual of Operations.
2. Staff chose the correct cuff size and wrapped the cuff around the arm with the center of the bladder over the brachial artery. Close attention was paid to the equipment to ensure that BP measurements had a standardized high level of accuracy and precision; equipment includes stethoscope, random-zero and standard sphygmomanometers, and cuff and bulb. The appropriate BP cuff size was determined by measuring the participant's arm circumference at the mid-point between the acromion and olecranon; the pediatric cuff was used for an arm circumferences (AC) less than 24.5 cm, the standard adult cuff for ACs of 24.5-33 cm, the large adult cuff for ACs of 33-41 cm, and the thigh cuff for ACs above 41 cm.
3. Research staff measured right-arm brachial artery BP 3 times after the participant had been sitting in a quiet room for 5 minutes. The inner aspect of the bend at the elbow (cubital fossa) was maintained at heart level and the legs were uncrossed.
4. Measurement: staff inflated the cuff to the R-Z peak inflation level, holding the pressure constant with the bulb (wait 5 seconds), placed the bell of stethoscope on the brachial artery, and slowly deflated the cuff (2 mmHg per second). Staff recorded the 1st and 5th Korotkoff sounds, reading the pressure in mmHg to the nearest even number and

recording it.

5. Caffeine, eating, heavy physical activity, smoking, and alcohol intake were proscribed for two hours prior to BP recording.

6. BP measures were made before the physical examination, blood drawing, treadmill test, or any stressful interview.

7. BP measures were made in a separate room, or at minimum, in an area properly screened from all other activity and other participants.

From the Year 0 to Year 10 exams, research staff measured right-arm brachial artery BP 3 times after the participant had been sitting in a quiet room for 5 minutes. Three measurements were taken at 1-minute interval, and the mean of the 2nd and 3rd measurements was used for the analysis of office BP.¹ Members of the CARDIA research staff took measurements by using a Hawksley random-zero sphygmomanometer (Hawksley, Sussex, United Kingdom).

Data collection

Race was determined from responses to closed-ended questions about the race of each participant's natural mother and father. Education level, height, weight, medication use, and history of diabetes and CVD were collected using standardized protocols and quality control procedures across study centers at each visit, as described previously.^{1,2} Smoking status was defined as current, former, or never by self-report.³ Leisure-time physical activity was assessed with the CARDIA Physical Activity History Questionnaire,⁴ an interviewer-administered self-report of frequency of participation in each of 13 categories of sports and exercise during the previous 12 months.⁵ The 13 categories included 8 vigorous-intensity activities (running or jogging; racquet sports; biking; swimming; exercise or dance class; job lifting, carrying, or digging; shoveling or lifting during leisure; and strenuous sports) and 5 moderate-intensity activities (nonstrenuous sports, walking and hiking, golfing and bowling, home exercises or calisthenics, and home maintenance or gardening). For each activity, interviewers asked participants the following questions to assess frequency of participation:

1. Did you (do this activity) in the past 12 months for at least 1 hour total time per month?

2. How many months did you do this activity?

3. How many months did you do this activity for at least 'X' hours per week?

X" varied from 2 through 5. An intensity score was assigned to each activity.⁶ The exercise score was computed by multiplying the sum of months of infrequent activity plus 3 times the months of frequent activity by intensity of the activity, and summing over all activities; the score was expressed in "exercise units" (EU).

Blood was drawn by venipuncture according to a standard protocol.² Total cholesterol and high-density lipoprotein cholesterol were measured enzymatically. Fasting glucose was measured using the hexokinase method. Information on smoking status and education was collected via standardized protocols and quality control across study centers.

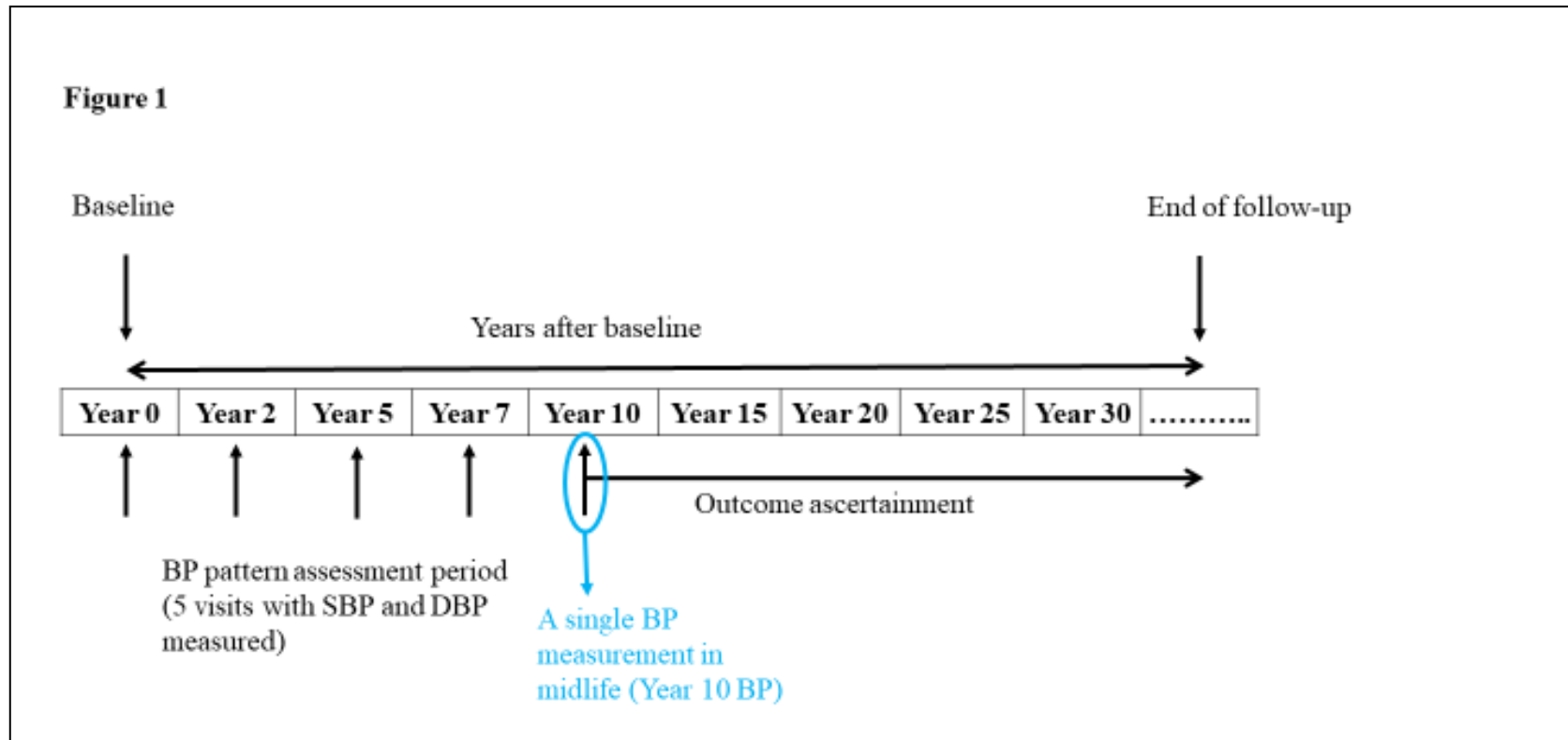
Cardiovascular outcomes

Research staff collected information on hospitalizations and outpatient medical procedures with standardized questionnaires administered during exams and annual contacts. Medical records were requested for potential cardiovascular hospitalizations and outpatient procedures based on participant reported symptoms or reasons for hospitalizations or procedures. Semi-annual contacts provided an opportunity to assess vital status. Vital status was also ascertained through periodic searches of the National Death Index. Medical records, death certificates, informant interviews (for outpatient deaths), and autopsy reports, when available, were used to adjudicate clinical cardiovascular disease (CVD) events.

We recorded incident CVD events through August, 2015. During their scheduled study examinations and yearly telephone interviews, each participant or designated proxy was asked about interim hospital admissions, outpatient procedures, and deaths. Medical records were requested for participants who had been hospitalized or received an outpatient revascularization procedure.

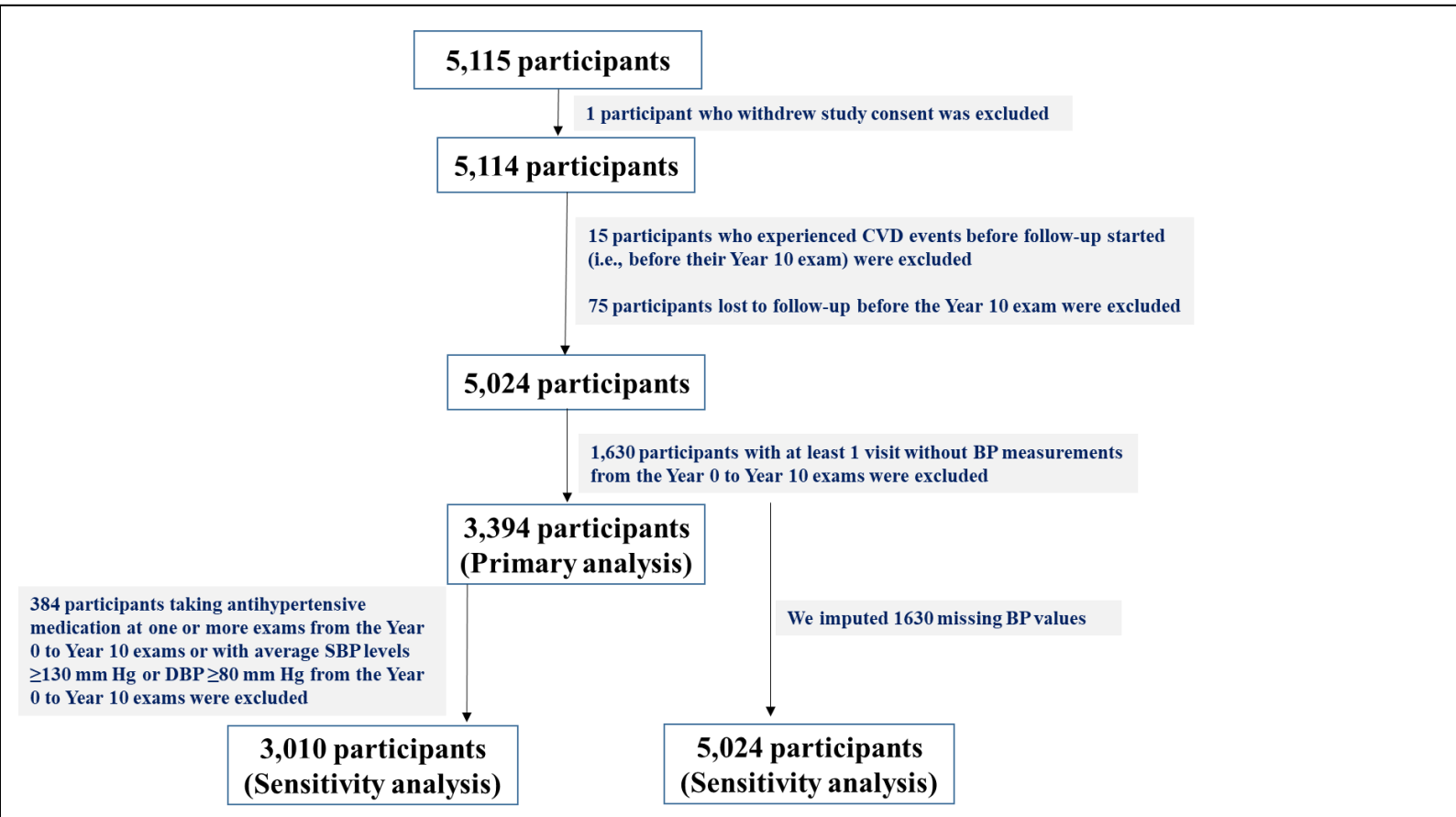
Vital status was assessed every 6 months; medical/death records were requested after consent had been obtained from the participants or next of kin. Two physician members of the Endpoints Committee independently reviewed medical records to adjudicate each possible CVD event or underlying cause of death using specific definitions and a detailed manual of operations (<http://www.cardia.dopm.uab.edu>). If disagreement occurred between the primary reviewers, the case was reviewed by the full committee. Coronary heart disease (CHD) included hospitalization for myocardial infarction, acute coronary syndrome with or without evidence of myocardial necrosis, coronary artery revascularization, or CHD death (including fatal myocardial infarction). CVD included CHD, and hospitalization for heart failure, stroke, transient ischemic attack, intervention for peripheral artery disease, or death from cardiovascular causes. Definitions of each outcome have been previously described.⁷⁻⁹ Participants who did not have events and who did not drop out of the study were censored at the end of the observation period.

eFigure 1. Study Design



Visit-to-visit BP variability and cumulative exposure to BP are dependent on the number and interval of visits with BP measurements. In one prior study, the association of visit-to-visit BP variability with CVD outcomes was statistically significant when participants' BP variability was estimated using ≥ 5 visits, but not statistically significant when participants' BP variability was using < 4 visits (Shimbo D, et al. *Hypertension*. 2012;60:625-630). To maximize the number of visits available to calculate visit-to-visit BP variability in the current study, we determined BP patterns using measurements collected over 5 visits (i.e., at the Year 0, 2, 5, 7, and 10 exams). Each BP pattern measurement was calculated using 5 clinic BP measurements from the Year 0 to Year 10 exams. A single BP measurement in midlife was defined using the BP measurement obtained at the Year 10 exam. The Year 10 exam date was defined as the time origin for time-to-event analysis. Follow-up time was censored on the date the event occurred. Participants who did not have events were censored at the last contact with the participant.

eFigure 2. Flow Chart: Sample for the Analyses, CARDIA



eTable 1. Correlations Among Blood Pressure Pattern Measurements (n = 3394)												
Variables	Mean SBP	Mean DBP	Cumulative exposure to SBP	Cumulative exposure to DBP	SD_{SBP}	SD_{DBP}	CV_{SBP}	CV_{DBP}	MRV_{SBP}	MRV_{DBP}	VIM_{SBP}	VIM_{DBP}
Mean SBP, mm Hg	-	-	-	-	-	-	-	-	-	-	-	-
Mean DBP, mm Hg	0.76‡	-	-	-	-	-	-	-	-	-	-	-
Cumulative exposure to SBP, mm Hg×years	0.94‡	0.72‡	-	-	-	-	-	-	-	-	-	-
Cumulative exposure to DBP, mm Hg×years	0.71‡	0.96‡	0.77‡	-	-	-	-	-	-	-	-	-
SD _{SBP} , mm Hg	0.36‡	0.31‡	0.32‡	0.28‡	-	-	-	-	-	-	-	-
SD _{DBP} , mm Hg	0.27‡	0.10‡	0.25‡	0.09‡	0.43‡	-	-	-	-	-	-	-
CV _{SBP} , %	0.16‡	0.16‡	0.13‡	0.14‡	0.97†	0.39‡	-	-	-	-	-	-
CV _{DBP} , %	0.07‡	-0.15‡	0.06‡	-0.16‡	0.32†	0.96‡	0.32‡	-	-	-	-	-
MRV _{SBP} , mm Hg	0.27‡	0.24‡	0.23‡	0.21‡	0.84‡	0.34‡	0.83‡	0.26‡	-	-	-	-
MRV _{DBP} , mm Hg	0.19‡	0.04*	0.17‡	0.02	0.33‡	0.83‡	0.31‡	0.81‡	0.34‡	-	-	-
VIM _{SBP} , unit	0.03	0.06‡	0.005	0.05†	0.93‡	0.36‡	0.99‡	0.31‡	0.80‡	0.29‡	-	-
VIM _{DBP} , unit	0.19‡	-0.004	0.17‡	-0.02	0.39‡	0.99‡	0.37‡	0.99‡	0.31‡	0.83‡	0.34‡	-
Annual change in SBP, mm Hg/year	0.20‡	0.23‡	0.20‡	0.23‡	0.24‡	0.27‡	0.18‡	0.19‡	0.13‡	0.11‡	0.14‡	0.24‡
Annual change in DBP, mm Hg/year	0.22‡	0.13‡	0.20‡	0.14‡	0.18‡	0.41‡	0.13‡	0.36‡	0.10‡	0.18‡	0.10‡	0.40‡

Pearson's correlation coefficients are shown. BP patterns were determined based upon 5 clinic BP measurements from the Year 0 to Year 10 exams. SBP=systolic blood pressure; DBP=diastolic blood pressure; SD=standard deviation; CV=coefficient of variation; MRV=mean real variability; VIM=BP variability independent of the mean. Statistical significance was defined as $P < 0.05$. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

eTable 2. Associations of Each Systolic Blood Pressure Pattern Measurement With Characteristics at the Year 0 or 10 Examinations (n = 3394)							
Variables	Mean SBP, mm Hg	Cumulative exposure to SBP, mm Hg×years	SD_{SBP}, mm Hg	CV_{SBP}, %	MRV_{SBP}, mm Hg	VIM_{SBP}, unit	Annual change in SBP, mm Hg/year
Year 0 exam							
Age years	0.02	0.01	0.07‡	0.06†	0.03	0.05†	0.06†
Body mass index, kg/m ²	0.31‡	0.29‡	0.16‡	0.10‡	0.12‡	0.06‡	0.13‡
Physical activity, exercise unit	0.05†	0.06†	-0.05†	-0.06‡	-0.02	-0.06‡	-0.10‡
Total cholesterol, mg/dL	0.09‡	0.07‡	0.02	0.01	0.01	-0.01	0.01
High-density lipoprotein, mg/dL	-0.16‡	-0.16‡	-0.06†	-0.03	-0.06‡	-0.01	-0.04*
Year 10 exam							
Age years	0.004	0.001	0.02	0.02	-0.003	0.02	0.01
Body mass index, kg/m ²	0.28‡	0.27‡	0.13‡	0.07‡	0.08‡	0.001	0.18‡
Physical activity, exercise unit	0.07‡	0.05†	-0.05†	-0.06†	-0.01	-0.07‡	-0.07‡
Total cholesterol, mg/dL	0.14‡	0.12‡	0.03	-0.001	0.01	-0.03	0.05†
High-density lipoprotein, mg/dL	-0.18‡	-0.18‡	-0.03	0.01	-0.03	0.05 †	0.03
SBP, mm Hg	0.84‡	0.78‡	0.41‡	0.24‡	0.28‡	0.12‡	0.58‡
DBP, mm Hg	0.65‡	0.61‡	0.33‡	0.20‡	0.23‡	0.12‡	0.46‡
Pearson's correlation coefficients are shown. BP patterns were determined based upon 5 clinic BP measurements from the Year 0 to Year 10 exams. SBP=systolic blood pressure; SD=standard deviation; CV=coefficient of variation; MRV=mean real variability; VIM=BP variability independent of the mean. Statistical significance was defined as <i>P</i> < 0.05. * <i>P</i> < 0.05; † <i>P</i> < 0.01; ‡ <i>P</i> < 0.001.							

eTable 3. Differences in Each Systolic Blood Pressure Pattern Measurement by Characteristics at the Year 0 or 10 Examinations (n = 3394)							
Characteristics	Mean SBP levels, mm Hg	Cumulative exposure to SBP, mm Hg×years	SD_{SBP}, mm Hg	CV_{SBP}, %	MRV_{SBP}, mm Hg	VIM_{SBP}, unit	Annual change in SBP, mm Hg/year
Sex							
Men, n=1,502	113.04±9.02‡	1123.78±95.43‡	6.44±2.95*	5.67±2.42	7.35±3.56†	6.03±2.53‡	-0.12±1.02‡
Women, n=1,892	105.28±9.01	1048.79±93.19	6.17±3.25	5.81±2.75	6.97±3.70	6.43±2.94	0.10±1.03
Race							
Whites, n=1,837	106.96±9.21‡	1065.46±96.59‡	5.88±2.64‡	5.49±2.38‡	6.73±3.36‡	6.04±2.63‡	-0.17±0.89‡
African Americans, n=1,557	110.78±10.07	1101.46±103.23	6.78±3.54	6.06±2.83	7.62±3.88	6.50±2.92	0.21±1.14
Current smoker at Year 0							
Yes, n=921	109.02±9.90	1085.43±101.96	6.69±3.54‡	6.08±2.89‡	7.51±3.89‡	6.59±3.03‡	0.12±1.14‡
No, n=2,452	108.6±9.7	1080.26±100.84	6.13±2.92	5.62±2.48	6.99±3.50	6.12±3.03	-0.04±0.98
Current smoker at Year 10							
Yes, n=829	109.74±10.22‡	1091.50±103.55†	6.75±3.66‡	6.09±2.92‡	7.60±3.99‡	6.57±3.00‡	0.11±1.16‡
No, n=2,565	108.38±9.64	1078.90±100.36	6.14±2.91	5.64±2.49	6.99±3.51	6.15±2.69	-0.03±0.98
Antihypertensive medication use at Year 0							
Yes, n=27	124.12±13.34‡	1240.86±136.87‡	10.89±6.83‡	8.54±4.74‡	12.32±7.00‡	8.48±4.43‡	0.31±1.97
No, n=3,367	108.59±9.67	1080.70±99.95	6.25±3.05	5.73±2.57	7.10±3.57	6.24±2.75	0.001±1.02
Antihypertensive medication use at the Year 10							
Yes, n=103	125.09±12.58‡	1242.45±127.10‡	10.13±5.73‡	7.96±3.95‡	10.68±5.47‡	7.91±3.72‡	0.47±1.90‡
No, n=3,291	108.20±9.25	1076.96±96.15	6.17±2.92	5.68±2.53	7.03±3.51	6.20±2.73	-0.01±0.99
Diabetes at Year 0							
Yes, n=21	113.60±10.78*	1128.77±108.47*	8.85±3.24‡	7.73±2.55‡	9.32±4.28†	8.17±2.62†	0.27±1.43
No, n=3,373	108.68±9.79	1081.69±101.18	6.28±3.11	5.74±2.60	7.13±3.63	6.24±2.78	0.002±1.03
Diabetes at Year 10							
Yes, n=120	114.21±11.40‡	1135.18±115.26‡	7.74±4.18‡	6.66±3.08‡	8.65±4.74‡	7.00±3.05†	0.26±1.23†
No, n=3,274	108.51±9.68	1080.03±100.21	6.24±3.06	5.72±2.58	7.08±3.58	6.23±2.76	-0.01±1.02

P values were obtained by un-paired t test. SBP patterns were determined based upon 5 clinic BP measurements from the Year 0 to Year 10 exams. SBP=systolic blood pressure; SD=standard deviation; CV=coefficient of variation; MRV=mean real variability; VIM=BP variability independent of the mean. Statistical significance was defined as *P* <0.05. * *P*<0.05; † *P*<0.01; ‡ *P*<0.001.

eTable 4. Associations of Each Diastolic Blood Pressure Pattern Measurement With Characteristics at the Year 0 or Year 10 Examinations (n = 3394)							
Variables	Mean DBP, mm Hg	Cumulative exposure to DBP, mm Hg×years	SD_{DBP}, mm Hg	CV_{DBP}, %	MRV_{DBP}, mm Hg	VIM_{DBP}, unit	Annual change in DBP, mm Hg/year
Year 0 exam							
Age years	0.14‡	0.13‡	-0.08‡	-0.12‡	-0.07‡	-0.10‡	-0.04*
Body mass index, kg/m ²	0.28‡	0.26‡	0.10‡	0.02	0.08‡	0.06‡	0.11
Physical activity, exercise unit	-0.02	-0.02	-0.04*	-0.03	-0.02	-0.03*	-0.05†
Total cholesterol, mg/dL	0.12‡	0.10‡	0.02	-0.01	0.02	0.01	0.01
High-density lipoprotein, mg/dL	-0.14‡	-0.14‡	-0.04*	-0.003	-0.01	-0.02	-0.06‡
Year 10 exam							
Age years	0.08‡	0.07‡	-0.05†	-0.07‡	-0.03	-0.06‡	-0.02
Body mass index, kg/m ²	0.25‡	0.24‡	0.10‡	0.03	0.06‡	0.07‡	0.19‡
Physical activity, exercise unit	-0.02	-0.03	-0.05†	0.04*	-0.03	-0.04*	-0.04*
Total cholesterol, mg/dL	0.13‡	0.12‡	0.03*	0.001	0.01	0.02	0.10‡
High-density lipoprotein, mg/dL	-0.16‡	-0.15‡	-0.01*	0.02	0.02	0.003	-0.04*
SBP, mm Hg	0.67‡	0.62‡	0.33‡	0.15‡	0.20‡	0.25‡	0.43‡
DBP, mm Hg	0.79‡	0.74‡	0.32‡	0.11‡	0.18‡	0.23‡	0.57‡
Pearson's correlation coefficients are shown. BP patterns were determined based upon 5 clinic BP measurements from the Year 0 to Year 10 exams. DBP=diastolic blood pressure; SD=standard deviation; CV=coefficient of variation; MRV=mean real variability; VIM= BP variability independent of the mean. Statistical significance was defined as $P < 0.05$. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.							

eTable 5. Differences in Each Diastolic Blood Pressure Pattern Measurement by Demographic Variables and Clinical Characteristics at the Year 0 or 10 Examinations (n = 3394)

Characteristics	Mean DBP, mm Hg	Cumulative exposure to DBP, mm Hg×years	SD _{DBP} , mm Hg	CV _{DBP} , %	MRV _{DBP} , mm Hg	VIM _{DBP} , unit	Annual change in DBP, mm Hg/year
Sex							
Men, n=1,502	71.72±7.63‡	713.65±80.62‡	6.32±2.94	8.89±4.29*	7.10±3.38	6.24±2.91	0.39±0.98
Women, n=1,892	67.36±7.49	671.09±78.40	6.18±2.95	9.24±4.51	7.04±3.60	6.26±2.98	0.36±0.94
Race							
Whites, n=1,837	68.17±7.33‡	679.06±77.40‡	5.70±2.55‡	8.45±3.93‡	6.55±3.17‡	5.75±2.59‡	0.21±0.86‡
African Americans, n=1,557	70.61±8.24	702.74±85.69	6.88±3.24	9.84±4.82	7.67±3.74	6.84±3.23	0.58±1.02
Current smoker at Year 0							
Yes, n=921	68.7±8.2‡	684.21±85.54*	6.74±3.30‡	9.89±4.95‡	7.39±3.79‡	6.77±3.30‡	0.51±1.05‡
No, n=2,452	69.5±7.7	691.84±80.63	6.06±2.78	8.79±4.17	6.94±3.37	6.06±2.79	0.33±0.91
Current smoker at Year 10							
Yes, n=829	68.99±8.40	686.67±85.68	6.80±3.27‡	9.93±4.80‡	7.62±3.84‡	6.82±3.23‡	0.51±1.02‡
No, n=2,565	69.38±7.67	690.97±80.96	6.06±2.81	8.81±4.25	6.88±3.35	6.07±2.83	0.33±0.93
Antihypertensive medication use at Year 0							
Yes, n=27	82.56±9.63‡	828.07±102.13‡	7.64±4.40*	9.18±5.05	8.04±3.89	7.08±3.98	0.30±1.42
No, n=3,367	69.18±7.75	688.81±81.04	6.23±2.93	9.09±4.41	7.06±3.49	6.25±2.94	0.38±0.95
Antihypertensive medication use at Year 10							
Yes, n=103	83.69±8.11‡	831.80±85.12‡	8.36±4.42‡	9.99±5.12*	8.93±4.25‡	7.73±4.01‡	0.50±1.52
No, n=3,291	68.84±7.41	685.48±78.01	6.18±2.86	9.06±4.39	7.01±3.45	6.21±2.90	0.37±0.93
Prevalent diabetes at Year 0							
Yes, n=21	72.76±9.00*	725.70±92.07*	7.04±2.43	9.65±3.19	7.68±3.79	6.88±2.31	0.39±1.14
No, n=3,373	69.27±7.84	689.70±82.05	6.24±2.95	9.08±4.42	7.06±3.49	6.25±2.95	0.38±0.95
Prevalent diabetes at Year 10							
Yes, n=120	74.04±9.54‡	736.90±98.24‡	6.86±3.04*	9.27±3.91	7.59±3.65	6.66±2.86	0.46±1.05
No, n=3,274	69.11±7.73	688.20±81.00	6.22±2.94	9.08±4.43	7.05±3.48	6.24±2.95	0.37±0.95

P values were obtained by the un-paired t test. SBP patterns were determined based upon 5 clinic BP measurements from the Year 0 to Year 10 exams. DBP=diastolic blood pressure; SD=standard deviation; CV=coefficient of variation; MRV=mean real variability; VIM= BP variability independent of the mean. Statistical significance was defined as *P* <0.05.

eTable 6. Hazard Ratios for Cardiovascular Disease Associated With 1-SD Increase of blood pressure patterns (n = 3394)			
Systolic blood pressure	Cumulative exposure	VIM	Annual change
One standard deviation change	101.27 mm Hg×years	2.78 units	1.03 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.94 (1.72, 2.19)	1.44 (1.27, 1.63)	1.55 (1.39, 1.73)
Model 2	1.55 (1.33, 1.81)	1.37 (1.20, 1.56)	1.37 (1.22, 1.54)
Model 3	1.03 (0.81, 1.31)	1.20 (1.04, 1.38)	0.97 (0.81, 1.15)
Model 4	1.08 (0.83, 1.38)	1.23 (1.06, 1.42)	0.93 (0.78, 1.12)
Diastolic blood pressure	Cumulative exposure	VIM	Annual change
One standard deviation change	82.15 mm Hg×years	2.95 units	0.95 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.96 (1.72, 2.23)	1.29 (1.15, 1.46)	1.43 (1.25, 1.64)
Model 2	1.50 (1.28, 1.76)	1.20 (1.05, 1.38)	1.28 (1.11, 1.46)
Model 3	1.13 (0.90, 1.41)	1.05 (0.91, 1.22)	0.97 (0.81, 1.15)
Model 4	1.16 (0.93, 1.31)	1.10 (0.93, 1.31)	0.97 (0.78, 1.20)
Adjusted HRs (95% CIs) for cardiovascular disease events for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP pattern measurement (cumulative exposure to SBP, VIM _{SBP} , and annual change in SBP) for analysis of SBP or each DBP pattern measurement (cumulative exposure to DBP, VIM _{DBP} , and annual change in DBP) for analysis of DBP. SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; VIM=BP variability independent of the mean; HDL=high-density lipoprotein.			

eTable 7. Hazard Ratios for Cardiovascular Disease Associated With 1-SD Increase of Blood Pressure Patterns (n = 3394)		
Systolic blood pressure	MRV	SD
One standard deviation change	3.64 mm Hg	3.12, mm Hg
	Hazard ratio (95% confidence interval)	
Model 1	1.48 (1.32, 1.66)	1.57 (1.44, 1.70)
Model 2	1.30 (1.15, 1.48)	1.41 (1.27, 1.56)
Model 3	1.15 (1.00, 1.32)	1.17 (1.02, 1.34)
Model 4	1.15 (0.998, 1.32)	1.18 (1.03, 1.35)
Diastolic blood pressure	MRV	SD
One standard deviation change	3.49 mm Hg	2.94, mm Hg
	Hazard ratio (95% confidence interval)	
Model 1	1.25 (1.09, 1.42)	1.38 (1.23, 1.55)
Model 2	1.13 (0.98, 1.30)	1.24 (1.09, 1.41)
Model 3	1.05 (0.90, 1.22)	1.06 (0.92, 1.23)
Model 4	1.07 (0.91, 1.24)	1.10 (0.93, 1.29)
<p>Adjusted HRs (95% CIs) for cardiovascular disease events for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3, MRV_{SBP} or SD_{SBP}, separately, for analysis of SBP (MRV_{DBP} or SD_{DBP}, separately, for analysis of DBP), mean SBP for analysis of SBP (mean DBP for analysis of DBP), and annual change in SBP for analysis of SBP (annual change in DBP for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; HDL=high-density lipoprotein; MRV=mean real variability; CV= coefficient of variation.</p>		

eTable 8. Hazard Ratios for All-Cause Mortality Associated With 1-SD Increase of Blood Pressure Patterns (n = 3394)			
Systolic blood pressure	Cumulative exposure	VIM	Annual change
One standard deviation change	101.27 mm Hg×years	2.78 units	1.03 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.38 (1.21, 1.58)	1.40 (1.25, 1.58)	1.29 (1.14, 1.47)
Model 2	1.01 (0.85, 1.19)	1.27 (1.13, 1.44)	1.14 (1.00, 1.29)
Model 3	0.75 (0.59, 0.95)	1.24 (1.09, 1.41)	1.03 (0.87, 1.22)
Model 4	0.76 (0.60, 0.98)	1.22 (1.07, 1.39)	0.91 (0.77, 1.09)
Diastolic blood pressure	Cumulative exposure	VIM	Annual change
One standard deviation change	82.15 mm Hg×years	2.95 units	0.95 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.34 (1.17, 1.53)	1.28 (1.15, 1.44)	1.26 (1.10, 1.45)
Model 2	0.95 (0.80, 1.12)	1.20 (1.05, 1.36)	1.18 (1.03, 1.35)
Model 3	0.79 (0.63, 0.98)	1.18(1.03, 1.35)	1.17 (0.99, 1.39)
Model 4	0.85 (0.67, 1.09)	1.13 (0.98, 1.31)	1.04 (0.85, 1.26)
Adjusted HRs (95% CIs) for all-cause mortality for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP patter measurement (cumulative exposure to SBP, VIM _{SBP} , and annual change in SBP) for analysis of SBP or each DBP pattern measurement (cumulative exposure to DBP, VIM _{DBP} , and annual change in DBP) for analysis of DBP. SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; VIM=BP variability independent of the mean; HDL=high-density lipoprotein.			

eTable 9. Hazard Ratios for All-Cause Mortality Associated With 1-SD Increase of Blood Pressure Patterns (n = 3394)		
Systolic blood pressure	MRV	SD
One standard deviation change	3.64 mm Hg	3.12, mm Hg
	Hazard ratio (95% confidence interval)	
Model 1	1.49 (1.34, 1.65)	1.44 (1.32, 1.57)
Model 2	1.29 (1.15, 1.45)	1.24 (1.12, 1.37)
Model 3	1.26 (1.12, 1.42)	1.21 (1.07, 1.37)
Model 4	1.28 (1.13, 1.44)	1.23 (1.09, 1.40)
Diastolic blood pressure	MRV	SD
One standard deviation change	3.49 mm Hg	2.94, mm Hg
	Hazard ratio (95% confidence interval)	
Model 1	1.28 (1.14, 1.45)	1.34 (1.19, 1.49)
Model 2	1.16 (1.02, 1.32)	1.20 (1.06, 1.36)
Model 3	1.15 (1.00, 1.31)	1.18 (1.04, 1.35)
Model 4	1.13 (0.99, 1.30)	1.15 (0.99, 1.33)
<p>Adjusted HRs (95% CIs) for all-cause mortality for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3, MRV_{SBP} or SD_{SBP}, separately, for analysis of SBP (MRV_{DBP} or SD_{DBP}, separately, for analysis of DBP), mean SBP for analysis of SBP (mean DBP for analysis of DBP), and annual change in SBP for analysis of SBP (annual change in DBP for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; HDL=high-density lipoprotein; MRV=mean real variability; CV= coefficient of variation.</p>		

eTable 10. Hazard Ratios for Cardiovascular Disease Associated With 1-SD Increase of Blood Pressure Patterns Among Participants not Taking Antihypertensive Medication and With Mean SBP <130 mm Hg and DBP <80 mm Hg From the Year 0 to Year 10 Examinations (n = 3010)

Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.8 mm Hg	2.78 units	1.03 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	2.05 (1.63, 2.57)	1.26 (1.06, 1.50)	1.41 (1.16, 1.72)
Model 2	1.76 (1.35, 2.30)	1.28 (1.07, 1.54)	1.38 (1.12, 1.70)
Model 3	1.03 (0.68, 1.57)	1.22 (1.01, 1.48)	1.01 (0.79, 1.30)
Model 4	1.25 (0.74, 2.10)	1.25 (1.03, 1.52)	1.06 (0.79, 1.42)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.86 mm Hg	2.95 units	0.95 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.83 (1.41, 2.37)	1.19 (1.01, 1.40)	1.27 (1.05, 1.53)
Model 2	1.55 (1.16, 2.05)	1.14 (0.95, 1.37)	1.16 (0.95, 1.41)
Model 3	1.27 (0.87, 1.85)	1.06 (0.87, 1.29)	0.95 (0.75, 1.21)
Model 4	1.40 (0.88, 2.22)	1.12 (0.90, 1.38)	1.03 (0.77, 1.38)

Adjusted HRs (95% CIs) for cardiovascular disease events for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, prevalent diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP pattern measurement for analysis of SBP (or DBP for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval; VIM=BP variability independent of the mean.

eTable 11. Hazard Ratios for All-Cause Mortality Associated With 1-SD Increase of Blood Pressure Patterns Among Participants not Taking Antihypertensive Medication and With Mean SBP <130 mm Hg and DBP <80 mm Hg From the Year 0 to Year 10 Examinations (n = 3010)

Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.8 mm Hg	2.78 units	1.03 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.32 (1.08, 1.62)	1.32 (1.14, 1.54)	1.25 (1.04, 1.50)
Model 2	1.11 (0.87, 1.41)	1.28 (1.09, 1.49)	1.17 (0.97, 1.40)
Model 3	0.89 (0.61, 1.28)	1.27 (1.08, 1.48)	1.10 (0.88, 1.37)
Model 4	1.09 (0.70, 1.70)	1.27 (1.08, 1.48)	1.03 (0.64, 1.67)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.86 mm Hg	2.95 units	0.95 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.12 (0.90, 1.40)	1.23 (1.07, 1.41)	1.23 (1.04, 1.45)
Model 2	0.95 (0.74, 1.21)	1.19 (1.02, 1.39)	1.15 (0.96, 1.37)
Model 3	0.90 (0.65, 1.26)	1.19 (1.02, 1.40)	1.22 (0.98, 1.51)
Model 4	1.18 (0.99, 1.39)	1.17 (0.99, 1.39)	1.20 (0.93, 1.55)
<p>Adjusted HRs (95% CIs) for all-cause mortality for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, prevalent diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP pattern measurement for analysis of SBP (or each DBP pattern measurement for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval; VIM=BP variability independent of the mean.</p>			

eTable 12. Observation Number of Imputed Blood Pressure and Covariates: a Sensitivity Analysis With Imputation of Missing Blood Pressure and Covariate Measurements	
Total number after imputing missing BP and covariates	n=5114
	Number of imputed observations for each variable
SBP at the Year 0 exam	0
DBP at the Year 0 exam	1
SBP at the Year 2 exam	492
DBP at the Year 2 exam	492
SBP at the Year 5 exam	767
DBP at the Year 5 exam	767
SBP at the Year 7 exam	1031
DBP at the Year 7 exam	1031
SBP at the Year 10 exam	1178
DBP at the Year 10 exam	1178
Age at the Year 10 exam	1171
Sex	0
Race	0
Study site	0
Body mass index at the Year 10 exam	1229
Smoking status at the Year 10 exam	1186
Educational attainment at the Year 10 exam	1187
Total cholesterol at the Year 10 exam	1241
HDL cholesterol at the Year 10 exam	1241
Physical activity at the Year 10 exam	1205
Antihypertensive medication use at the Year 10 exam	1178
Diabetes at the Year 10 exam	1196
SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL=High-density lipoprotein	

eTable 13. Mean (SD) of Each Blood Pressure Pattern Measurement in a Multiple Imputation Sample (n = 5024)	
A single SBP at the Year 10 exam, mm Hg	110.4±12.9
A single DBP at the Year 10 exam, mm Hg	72.6±10.3
BP pattern measurement calculated using 5 clinic BPs measured from the Year 0 to Year 10 exams	
Mean SBP, mm Hg	109.05±9.86
Mean DBP, mm Hg	69.40±7.93
VIM _{SBP} , unit	6.47±2.78
VIM _{DBP} , unit	6.45±2.95
MRV _{SBP} , mm Hg	7.37±3.73
MRV _{DBP} , mm Hg	7.28±3.56
CV _{SBP} , %	5.92±2.62
CV _{DBP} , %	9.36±4.46
Mean annual change in SBP, mm Hg/year	0.046±1.06
Mean annual change in DBP, mm Hg/year	0.42±0.97
SBP=systolic blood pressure; DBP=diastolic blood pressure; VIM=BP variability independent of the mean; MRV=mean real variability; CV=coefficient of variation.	

eTable 14. Hazard Ratios for Cardiovascular Disease Associated With 1-SD Increase in Blood Pressure Patterns in a Multiple Imputation Sample (n = 5024)

Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.9 mm Hg	2.78 units	1.06 mm Hg per year
Hazard ratio (95% confidence interval)			
Model 1	1.89 (1.71, 2.08)	1.39 (1.25, 1.55)	1.50 (1.36, 1.67)
Model 2	1.60 (1.41, 1.83)	1.31 (1.17, 1.46)	1.32 (1.18, 1.48)
Model 3	1.20 (0.95, 1.51)	1.16 (1.02, 1.31)	0.95 (0.81, 1.12)
Model 4	1.26 (0.97, 1.63)	1.19 (1.05, 1.34)	0.99 (0.82, 1.19)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.9 mm Hg	2.95 units	0.97 mm Hg per year
Hazard ratio (95% confidence interval)			
Model 1	1.92 (1.72, 2.15)	1.28 (1.15, 1.41)	1.34 (1.19, 1.51)
Model 2	1.53 (1.33, 1.77)	1.20 (1.06, 1.35)	1.18 (1.04, 1.35)
Model 3	1.31 (1.06, 1.61)	1.09 (0.95, 1.23)	0.92 (0.79, 1.08)
Model 4	1.38 (1.05, 1.81)	1.16 (1.00, 1.33)	0.99 (0.80, 1.23)

Adjusted HRs (95% CIs) for cardiovascular disease events for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP pattern measurement for analysis of SBP (or each DBP pattern measurement for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval; VIM=BP variability independent of the mean.

eTable 15. Hazard Ratios for All-Cause Mortality Associated With 1-SD Increase of Blood Pressure Patterns in a Multiple Imputation Sample (n = 5024)

Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.9 mm Hg	2.78 units	1.06 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.52 (1.37, 1.68)	1.34 (1.21, 1.48)	1.26 (1.12, 1.42)
Model 2	1.17 (1.03, 1.34)	1.23 (1.11, 1.37)	1.12 (1.00, 1.26)
Model 3	1.01 (0.81, 1.26)	1.20 (1.08, 1.34)	1.01 (0.87, 1.18)
Model 4	1.04 (0.80, 1.34)	1.20 (1.08, 1.34)	0.99 (0.82, 1.19)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.9 mm Hg	2.95 units	0.97 mm Hg per year
	Hazard ratio (95% confidence interval)		
Model 1	1.46 (1.31, 1.63)	1.31 (1.19, 1.43)	1.25 (1.10, 1.41)
Model 2	1.10 (0.96, 1.26)	1.24 (1.11, 1.37)	1.16 (1.03, 1.32)
Model 3	0.99 (0.80, 1.21)	1.22 (1.09, 1.36)	1.13 (0.97, 1.31)
Model 4	1.15 (0.90, 1.47)	1.21 (1.07, 1.37)	1.08 (0.89, 1.31)

Adjusted HRs (95% CIs) for all-cause mortality for each standard deviation higher BP measure are shown. Model 1 is unadjusted. Model 2 includes adjustment for age at the Year 10 exam; race; sex; educational level; study site; and clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, prevalent diabetes, and antihypertensive medication use). Model 3 includes the variable in Model 2 and a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP. Model 4 includes the variables in Model 3 and each SBP pattern measurement for analysis of SBP (or each DBP pattern measurement for analysis of DBP). SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval; VIM=BP variability independent of the mean.

eTable 16. Hazard Ratios for Cardiovascular Disease Associated With 1-SD Increase of Blood Pressure Patterns: Fine-Gray Model

Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.80 mm Hg	2.78 units	1.03 mm Hg per year
	Hazard ratio (95% confidence interval)		
Original model	1.25 (0.90, 1.74)	1.23 (1.07, 1.43)	0.99 (0.81, 1.26)
Fine-Gray model	1.28 (0.89, 1.84)	1.21 (1.05, 1.40)	1.00 (0.79, 1.27)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.86 mm Hg	2.95 units	0.95 mm Hg per year
	Hazard ratio (95% confidence interval)		
Original model	1.35 (0.99, 1.84)	1.11 (0.93, 1.31)	1.04 (0.82, 1.32)
Fine-Gray model	1.38 (0.98, 1.95)	1.09 (0.92, 1.30)	1.05 (0.80, 1.36)

Adjusted HRs (95% CIs) for cardiovascular disease events for each standard deviation higher BP measure are shown.

All models include adjustment for age at the Year 10 exam; race; sex; educational level; study site; clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use); a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP; and each SBP pattern measurement (mean SBP, VIM_{SBP}, and annual change in SBP) for analysis of SBP or each DBP pattern measurement (mean DBP, VIM_{DBP}, and annual change in DBP) for analysis of DBP. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; VIM=BP variability independent of the mean; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

eTable 17. Hazard Ratios for All-Cause Mortality Associated With 1-SD Increase of Blood Pressure Patterns: Fine-Gray Model			
Systolic blood pressure	Mean	VIM	Annual change
One standard deviation change	9.80 mm Hg	2.78 units	1.03 mm Hg per year
Hazard ratio (95% confidence interval)			
Original model	0.98 (0.81, 1.19)	1.26 (1.10, 1.43)	0.98 (0.81, 1.19)
Fine-Gray model	0.96 (0.71, 1.29)	1.24 (1.09, 1.40)	0.97 (0.81, 1.17)
Diastolic blood pressure	Mean	VIM	Annual change
One standard deviation change	7.86 mm Hg	2.95 units	0.95 mm Hg per year
Hazard ratio (95% confidence interval)			
Original model	0.97 (0.71, 1.41)	1.24 (1.09, 1.41)	1.18 (0.83, 1.66)
Fine-Gray model	1.04 (0.77, 1.41)	1.14 (0.98, 1.33)	1.12 (0.91, 1.38)
Adjusted HRs (95% CIs) for all-cause mortality for each standard deviation higher BP measure are shown.			
All models include adjustment for age at the Year 10 exam; race; sex; educational level; study site; clinical and behavioral characteristics at the Year 10 exam or the closest prior exam to the Year 10 exam (body mass index, smoking status, physical activity, total cholesterol, HDL cholesterol, diabetes, and antihypertensive medication use); a single SBP measurement at the Year 10 exam for analysis of SBP or a single DBP measurement at the Year 10 exam for analysis of DBP; and each SBP pattern measurement (mean SBP, VIM _{SBP} , and annual change in SBP) for analysis of SBP or each DBP pattern measurement (mean DBP, VIM _{DBP} , and annual change in DBP) for analysis of DBP. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=hazard ratio; VIM=BP variability independent of the mean; HDL=high-density lipoprotein; LDL=low-density lipoprotein.			

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