

ORIGINAL RESEARCH ARTICLE



# Heart Stress and Blood Pressure Management in Older Adults: Post Hoc Analysis of the ASPREE Trial

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**BACKGROUND:** Blood pressure (BP) management in older adults is complex because of age-related physiological changes and uncertainty around ideal systolic BP (SBP) targets. Heart stress (HS), defined by age-adjusted elevation in NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, may improve cardiovascular disease (CVD) risk stratification and support more individualized BP management.

**METHODS:** We conducted a post hoc analysis of ASPREE (Aspirin in Reducing Events in the Elderly) involving 11 941 community-dwelling older adults without CVD at enrollment (mean age, 75.1 years; 53.5% women). HS was defined by NT-proBNP  $\geq 150$  pg/mL for participants 65 to 74 years of age and  $\geq 300$  pg/mL for participants  $\geq 75$  years of age. Participants were categorized into 4 groups by hypertension and HS status. The primary outcome was total CVD events (a composite of nonfatal myocardial infarction, fatal or nonfatal stroke, coronary heart disease death, or hospitalization for heart failure). Associations between hypertension and SBP with total CVD events were examined by HS status using Cox proportional-hazards models and restricted cubic spline. SBP was evaluated categorically ( $<120$ , 120–129, 130–139, 140–159, or  $\geq 160$  mm Hg) and continuously. A landmark sensitivity analysis excluded participants with CVD events or censoring in the first 2 years, with follow-up starting at year 3.

**RESULTS:** HS was present in 25.8% of participants. Compared with the reference group (no hypertension or HS), adjusted hazard ratios (95% CI) for total CVD events were 1.41 (1.18–1.70) for hypertension+no HS, 1.79 (1.34–2.39) for no hypertension+HS, and 2.32 (1.89–2.84) for hypertension+HS ( $P_{\text{trend}} < 0.001$ ). Among participants without HS, the lowest incidence of total CVD events occurred at SBP 130 to 139 mm Hg, showing a U-shaped association across SBP levels ( $P_{\text{nonlinearity}} = 0.011$ ). Among participants with HS, risk increased linearly with SBP ( $P_{\text{linear trend}} = 0.85$ ) and was lowest at SBP  $< 120$  mm Hg. Landmark analyses yielded generally consistent findings.

**CONCLUSIONS:** HS is common in older adults and jointly associated with hypertension and increased CVD risk. The SBP–CVD relationship differs by HS status, suggesting a potential value of HS for guiding individualized BP management. Prospective studies are warranted to determine whether HS-guided strategies improve BP control and reduce CVD risk in older adults.

**Key Words:** biomarkers ■ blood pressure ■ cardiovascular diseases ■ risk

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## Clinical Perspective

### What Is New?

- This is the first large-scale study to show the potential value of heart stress (HS), defined by age-adjusted elevation in NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations, in enhancing cardiovascular disease risk stratification in older adults in the context of primary prevention.
- Systolic blood pressure was differentially associated with risk of total cardiovascular disease events based on HS status: a U-shaped relationship was observed in participants without HS, and a linear, progressively increasing risk with rising systolic blood pressure was seen among those with HS.

### What Are the Clinical Implications?

- Assessment of HS, using age-adjusted NT-proBNP cutoffs, allows the identification of individuals with a high cardiovascular disease risk that would be implied by their systolic blood pressure alone.
- An HS-guided approach may offer a more individualized strategy for blood pressure management and primary prevention of cardiovascular disease in older adults; however, prospective studies are needed to confirm its clinical utility.

**H**ypertension is a major modifiable risk factor for cardiovascular disease (CVD) worldwide,<sup>1</sup> and its prevalence and severity increase with age.<sup>2</sup> Data from nationally representative studies and clinical trials indicate that >70% of adults >65 years of age have hypertension.<sup>3–5</sup> Given the high burden of CVD in this population, optimizing blood pressure (BP) management is a public health priority.<sup>6</sup> Nevertheless, the ideal systolic BP (SBP) targets in older adults remain debated, with major guidelines offering differing recommendations.<sup>7–10</sup> In clinical practice, aggressive BP-lowering in older adults can be challenging because of heterogeneous comorbidity profiles and increased susceptibility to adverse events.<sup>7,11</sup> These complexities underscore the need for more individualized approaches to BP management in this population.<sup>7,11</sup>

NT-proBNP (N-terminal pro-B-type natriuretic peptide), a cardiac biomarker reflecting myocardial wall stress and neurohormonal activation, has emerged as a valuable tool for CVD risk stratification in the general and hypertensive populations.<sup>12–14</sup> NT-proBNP also holds promise for guiding BP treatment intensity.<sup>13–17</sup> However, these studies did not specifically focus on older adults, a group characterized by high CVD risk and age-related physiological changes.<sup>7,11</sup> NT-proBNP increases with age,<sup>18,19</sup> and applying age-specific NT-proBNP cutoffs has been shown to improve the specificity of identifying individuals at high CVD risk.<sup>20,21</sup>

## Nonstandard Abbreviations and Acronyms

<b>ARIC</b>	Atherosclerosis Risk In Communities
<b>ASCOT</b>	Anglo-Scandinavian Cardiac Outcomes Trial
<b>ASPREE</b>	Aspirin in Reducing Events in the Elderly
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>CKD</b>	chronic kidney disease
<b>CVD</b>	cardiovascular disease
<b>HDL</b>	high-density lipoprotein
<b>HF</b>	heart failure
<b>HHF</b>	hospitalization for heart failure
<b>HR</b>	hazard ratio
<b>HS</b>	heart stress
<b>INVEST</b>	International Verapamil SR-Trandolapril Study
<b>MACE</b>	major adverse cardiovascular event
<b>MI</b>	myocardial infarction
<b>NT-proBNP</b>	N-terminal pro-B-type natriuretic peptide
<b>PREVENT</b>	Predicting Risk of CVD Events
<b>SBP</b>	systolic blood pressure
<b>SCORE2-OP</b>	Systematic Coronary Risk Evaluation 2-Older Persons
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial

Building on this, the concept of heart stress (HS), defined as age-adjusted elevation in NT-proBNP levels among individuals with cardiac risk factors such as hypertension, has recently been proposed.<sup>22</sup> In our recent study,<sup>23</sup> HS was shown to enhance the prediction of 10-year risk of hospitalization for heart failure (HHF), particularly in older adults. Despite its potential, the HS framework has not yet been integrated into clinical strategies for BP management. Whether HS can refine CVD risk stratification and support individualized BP management in older adults remains an important area of investigation.

ASPREE (Aspirin in Reducing Events in the Elderly) was a randomized clinical trial that enrolled healthy older adults to assess the efficacy of aspirin in primary prevention.<sup>5,24</sup> NT-proBNP levels were measured at baseline in a large subgroup of the trial participants. To address the aforementioned knowledge gaps, this study aimed to assess the joint associations of hypertension and HS with CVD events; evaluate whether the relationship between baseline SBP and CVD events is modified by HS status; and explore the optimal SBP range for primary prevention of CVD events in older adults stratified by HS status.

## METHODS

Anonymized data not published within this article will be made available by request from any qualified investigator. Requests for data access can be addressed to the ASPREE principal investigators with details for applications provided through <https://aspree.org/aus/for-researchers> or <https://aspree.org/usa/for-researchers>.

### Study Design and Participants

This is a post hoc analysis of ASPREE and ASPREE-XT.<sup>5,24</sup> Detailed trial protocols have been published previously.<sup>25</sup> ASPREE was a randomized, double-blind, placebo-controlled trial designed to assess the effect of low-dose aspirin on primary prevention in older adults. The study enrolled 19 114 community-dwelling participants  $\geq 70$  years of age in Australia or the United States (or  $\geq 65$  years of age for US individuals from underrepresented racial or ethnic groups), all of whom were free of CVD events, including heart failure (HF), myocardial infarction (MI), stroke, or atrial fibrillation, at the time of enrollment. Participants were randomly assigned to receive either 100 mg of enteric-coated aspirin or placebo once daily. After trial completion and cessation of study medication, the ASPREE-XT observational study was conducted to examine the long-term effects of aspirin therapy, and  $>80\%$  of ASPREE participants consented to extended follow-up.<sup>26</sup> In parallel, the ASPREE Healthy Ageing Biobank (ASPREE Biobank) collected and stored blood and urine samples from a voluntary subset of Australian ASPREE participants, using standardized protocols with storage at  $-80^{\circ}\text{C}$  or under nitrogen vapor conditions.<sup>27</sup> Between 2021 and 2023, these biospecimens were shipped from the Monash Biorepository to Hamburg for cardiac biomarker assays, including NT-proBNP. For the current analysis, we excluded 7170 participants without baseline NT-proBNP measurements and 3 participants with missing diastolic BP data. The final analytic cohort comprised 11 941 participants (Figure S1). The median follow-up of this study was 8.3 years (interquartile range, 7.1–9.5). This post hoc analysis is covered under existing ethics approvals for secondary analysis of the ASPREE and ASPREE-XT studies approved by the Monash University human research ethics committee (ID 25829). Written informed consent was obtained from all participants.

### Study Measures

The following measures were captured during the baseline visit. Based on the guidelines,<sup>8,9</sup> which recognize individuals age  $\geq 80$  years as a distinct group, we divided participants into 2 age categories: 65 to 79 years or  $\geq 80$  years. Participants were classified as White or other race or ethnicity. To capture the nuance of CVD risk across SBP levels, baseline SBP was divided into 5 categories ( $<120$ , 120–129, 130–139, 140–159, or  $\geq 160$  mmHg) based on the guidelines and previous study.<sup>8,9,13</sup> Body mass index (BMI) was categorized as  $<18.5$  kg/m<sup>2</sup> (underweight), 18.5 through 24.9 kg/m<sup>2</sup> (normal weight), 25.0 through 29.9 kg/m<sup>2</sup> (overweight), or  $\geq 30.0$  kg/m<sup>2</sup> (obese). Smoking and alcohol consumption were based on self-report and classified as never, former, or current. Family history of MI was determined by self-report.

Diabetes was defined as fasting plasma glucose level  $\geq 7.0$  mmol/L, self-reported diabetes, or use of glucose-lowering medication. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate  $<60$  mL·min<sup>-1</sup>·1.73 m<sup>2</sup> or urinary albumin to creatinine ratio  $\geq 3$  mg/mmol. Medication used at baseline was captured through participants' medical records or self-reported.

### BP Measurements

BP was measured at the baseline visit by trained study personnel according to standardized operating procedures. Measurements were performed with participants seated at rest for at least 5 minutes, using an automated oscillometric device and an appropriately sized cuff based on upper arm circumference. Three consecutive BP measures were taken at 1-minute intervals, and the average of the 3 readings was used to define each participant's baseline BP. Hypertension was defined as either an average SBP  $\geq 140$  mmHg or diastolic BP  $\geq 90$  mmHg at baseline measurements, or taking at least 1 antihypertensive medication.<sup>28</sup>

### Baseline NT-proBNP Measurement and HS Definition

NT-proBNP levels were measured using an ARCHITECT i2000SR immunoassay analyzer. The age-specific NT-proBNP cutoffs used to define HS were informed by a recent consensus statement from the Heart Failure Association of the European Society of Cardiology.<sup>22</sup> These cutoffs,  $\geq 150$  pg/mL for individuals 65 to 74 years of age and  $\geq 300$  pg/mL for those  $\geq 75$  years of age, were designed to reflect age-related increases in NT-proBNP levels, which have been shown to improve specificity in older adults.<sup>23</sup>

### Study Outcomes

The primary outcome of this study was incident total CVD events, a prespecified secondary outcome in the ASPREE trial.<sup>24</sup> Total CVD events was a composite of nonfatal MI, fatal or nonfatal stroke, coronary heart disease death, or HHF, of which only the first event was counted. The secondary outcome was major adverse cardiovascular events (MACEs), defined as a composite of nonfatal MI, fatal or nonfatal ischemic stroke, or coronary heart disease death.<sup>24</sup> The tertiary outcome included HHF, CVD mortality, MI, and stroke. Incident CVD events were identified through medical records, phone calls every 6 months, and annual in-person visits during follow-up. All events were adjudicated by international committees of experts who were blinded to treatment group assignments as part of the main trial protocol.<sup>5,24</sup>

### Statistical Analysis

Participants were divided into 4 groups on the basis of baseline hypertension and HS status as follows: no hypertension or HS, hypertension + no HS, no hypertension + HS, and hypertension + HS. For baseline descriptive data, continuous variables were presented as mean (SD) or median (interquartile range) and categorical variables as frequency (percentage). Group differences were assessed using ANOVA for continuous variables and  $\chi^2$  test for categorical variables.

Cox proportional-hazard models were used to assess the joint associations of hypertension and HS with CVD events in the overall participants as well as separately by sex, BMI, and CKD status, with participants with no hypertension or HS serving as the reference group. The proportional-hazards assumption was assessed using scaled Schoenfeld residuals, and no violation was detected. Models were adjusted for baseline covariates, including age, sex, race, ethnicity, educational level, BMI category, smoking, alcohol consumption, family history of MI, diabetes, CKD, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, use of statin, and randomized trial treatment (aspirin or placebo). To investigate whether HS would modify the relationship between SBP and CVD events, we assessed risks across SBP categories stratified by HS status and evaluated effect modification by including SBP  $\times$  HS interaction terms in the models. SBP  $<120$  mm Hg served as the reference group. To explore the optimal SBP range for primary prevention in older adults with and without HS and allow for a nonlinear relationship, we analyzed the association between SBP (as a continuous variable) and risk of total CVD events using restricted cubic spline models with 3 knots, adjusting for the same covariates described previously. Stratified analysis by baseline antihypertensive treatment status was also performed. Two subgroup analyses were performed. We compared cumulative incidence of total CVD events between participants with and without HS, stratified by hypertension status, across the 2 age categories (65 to 79 years of age and  $\geq 80$  years of age) and by sex. To address potential reverse causality, we conducted a sensitivity landmark analysis excluding participants who experienced a CVD event or were censored within the first 2 years of follow-up, with follow-up starting at year 3. All analyses were performed using Stata 17.0 (StataCorp). All  $P$  values were 2-sided; a value  $<0.05$  was considered statistically significant.

## RESULTS

### Baseline Characteristics

The mean age of the 11 941 included participants was 75.1 years (SD 4.2), with 14.2% ( $n=1696$ )  $>80$  years of age. Women comprised 53.5% ( $n=6391$ ) of the cohort, and the majority were White (97.9% [ $n=11\ 692$ ]). Overall, 74.5% ( $n=8893$ ) of participants had hypertension at baseline, and among them, 69% ( $n=6176$ ) reported use of antihypertensive therapy. In addition, 1 in 4 (25.8% [ $n=3083$ ]) participants had HS, with a higher prevalence observed among those with versus without hypertension (19.6% versus 6.2%). Baseline characteristics are presented in Table 1. Compared with the other 3 groups, participants with both hypertension and HS had the highest NT-proBNP level, the highest proportion of individuals  $\geq 80$  years of age, the lowest level of educational attainment, the highest mean SBP, and the highest prevalence of obesity, family history of MI, and CKD (all  $P<0.001$ ). The age-specific centile of NT-proBNP per study participant is presented in Figure S2.

### Joint Associations of Hypertension and HS With CVD Events

In the fully adjusted Cox models, compared with the no hypertension or HS group (Table 2), the hazard ratio (HR [95% CI]) for total CVD events was 1.41 (1.18–1.70) for the hypertension + no HS group, 1.79 (1.34–2.39) for the no hypertension + HS group, and 2.32 (1.89–2.84) for the hypertension + HS group ( $P_{\text{trend}} < 0.001$ ). For MACEs, the corresponding HRs (95% CI) were 1.52 (1.23–1.87), 1.75 (1.25–2.45), and 2.15 (1.70–2.72;  $P_{\text{trend}} < 0.001$ ). Similar association patterns were noted for tertiary outcomes, with the hypertension + HS group showing the highest HRs (all  $P_{\text{trend}} < 0.001$ ). These findings were consistent when stratified by sex, BMI, and CKD status (Table S1; all  $P_{\text{interaction}} > 0.05$ ). In addition, as shown in Table S2, among participants with hypertension, those with HS had significantly higher risks for CVD events compared with those without HS. Among participants with HS, although those with hypertension had higher risks than those without hypertension, the differences were not statistically significant.

### Association Between SBP and CVD Events by Baseline HS Status

Among participants with HS (Figure 1), there was a stepwise increase in the risk of total CVD events with rising SBP categories (HRs [95% CI] for 120–129, 130–139, 140–159, and  $\geq 160$  mm Hg versus  $<120$  mm Hg: 1.25 [0.79–1.97], 1.34 [0.87–2.06], 1.38 [0.92–2.08], and 1.68 [1.08–2.59], respectively;  $P_{\text{linear trend}} = 0.018$ ). No significant trend was noted in participants without HS ( $P_{\text{linear trend}} = 0.90$ ), and the lowest incidence of total CVD events was noted at the SBP range of 130–139 mm Hg. No significant interaction was found for total CVD events ( $P=0.21$ ). When SBP was analyzed as a continuous variable (Figure 2A), a U-shaped relationship with risk of total CVD events emerged among participants without HS ( $P_{\text{nonlinearity}} = 0.011$ ), with the lowest risk observed at SBP levels of 130 through 150 mm Hg, and a nadir at 140 mm Hg. Conversely, a linear association was noted among participants with HS ( $P_{\text{nonlinearity}} = 0.85$ ), with higher SBP consistently associated with greater risk of total CVD events. A similar pattern was found for MACEs. There was a significant trend toward increased MACE risk with higher SBP categories in the HS group ( $P_{\text{linear trend}} = 0.049$ ) but not in the no HS group ( $P_{\text{linear trend}} = 0.93$ ). The interaction between SBP and HS was significant for MACEs ( $P=0.04$ ). Among tertiary outcomes, only stroke demonstrated a significant positive association with higher SBP in the HS group ( $P_{\text{linear trend}} = 0.003$ ). Stratified analyses by antihypertensive treatment status also revealed similar patterns (Figure 2B): among participants without HS, a nonlinear relationship between SBP and risk of total CVD events

**Table 1. Baseline Characteristics According to Baseline Hypertension and Heart Stress Status**

Characteristics	Overall (N=11 941)	No hypertension or HS (n=2301)	Hypertension, no HS (n=6557)	No hypertension, HS (n=747)	Hypertension and HS (n=2336)	P value
NT-proBNP, ng/L	120.2 (74.3–202.2)	94.7 (65.8–129.2)	95.2 (63.6–134.2)	249.2 (183.9–361.4)	302.6 (199.6–431.26)	<0.001
Age, y	75.1±4.2	74.5±3.9	75.3±4.2	74.2±4.1	75.1±4.7	<0.001
Age categories, y						<0.001
65–79	10 245 (85.8)	2060 (89.5)	5562 (84.8)	667 (89.3)	1956 (83.7)	
≥80	1696 (14.2)	241 (10.5)	995 (15.2)	80 (10.7)	380 (16.3)	
Women	6391 (53.5)	1175 (51.1)	3131 (47.8)	521 (69.8)	1564 (67.0)	<0.001
Race or ethnicity						0.016
White	11 692 (97.9)	2252 (97.9)	6400 (97.6)	736 (98.5)	2304 (98.6)	
Other race or ethnicity	249 (2.1)	49 (2.1)	157 (2.4)	11 (1.5)	32 (1.4)	
Education ≥12 y	6095 (51.0)	1259 (54.7)	3339 (50.9)	393 (52.6)	1104 (47.3)	<0.001
SBP, mmHg	139.8±16.2	126.2±9.0	144.3±15.0	125.6±9.1	145.0±16.2	<0.001
SBP categories, mmHg						<0.001
<120	1257 (10.5)	536 (23.3)	377 (5.8)	180 (24.1)	164 (7.0)	
120–129	2073 (17.4)	798 (34.7)	738 (11.3)	278 (37.2)	259 (11.1)	
130–139	2677 (22.4)	967 (42.0)	1058 (16.1)	289 (38.7)	363 (15.5)	
140–159	4458 (37.3)	0	3370 (51.4)	0	1088 (46.6)	
≥160	1476 (12.4)	0	1014 (15.5)	0	462 (19.8)	
DBP, mmHg	77.2±9.9	72.8±7.6	78.9±9.9	72.4±7.8	78.4±10.7	<0.001
BMI, kg/m²	28.0±4.5	26.9±3.9	28.5±4.5	26.1±3.9	28.2±5.0	<0.001
BMI categories						<0.001
Underweight	203 (1.7)	50 (2.2)	67 (1.0)	35 (4.7)	51 (2.2)	
Normal weight	2852 (23.9)	717 (31.2)	1271 (19.4)	270 (36.1)	594 (25.4)	
Overweight	5440 (45.6)	1100 (47.8)	3089 (47.1)	322 (43.1)	929 (39.8)	
Obese	3446 (28.9)	434 (18.9)	2130 (32.5)	120 (16.1)	762 (32.6)	
Smoking status						<0.001
Never	6620 (55.4)	1287 (55.9)	3556 (54.2)	452 (60.5)	1325 (56.7)	
Former	4943 (41.4)	925 (40.2)	2825 (43.1)	266 (35.6)	927 (39.7)	
Current	378 (3.2)	89 (3.9)	176 (2.7)	29 (3.9)	84 (3.6)	
Alcohol consumption						<0.001
Never	1862 (15.6)	308 (13.4)	1015 (15.5)	132 (17.7)	407 (17.4)	
Former	557 (4.7)	116 (5.0)	301 (4.6)	20 (2.7)	120 (5.1)	
Current	9522 (79.7)	1877 (81.6)	5241 (79.9)	595 (79.7)	1809 (77.4)	
Family history of MI	5197 (43.5)	940 (40.9)	2864 (43.7)	325 (43.5)	1068 (45.7)	0.010
Diabetes	1154 (9.7)	112 (4.9)	797 (12.2)	26 (3.5)	219 (9.4)	<0.001
CKD	2829 (25.6)	333 (15.6)	1615 (26.5)	143 (20.9)	738 (34.3)	<0.001
Non-HDL cholesterol, mmol/L	3.68 (0.93)	3.77 (0.94)	3.67 (0.93)	3.70 (0.89)	3.62 (0.95)	0.17
HDL cholesterol, mmol/L	1.58 (0.46)	1.60 (0.45)	1.54 (0.45)	1.72 (0.44)	1.63 (0.47)	0.06
Statin	3676 (30.8)	545 (23.7)	2254 (34.4)	125 (16.7)	752 (32.2)	<0.001
Aspirin	5971 (50.0)	1150 (50.0)	3231 (49.3)	414 (55.4)	1176 (50.3)	0.016
Antihypertensives	6176 (51.7)	0	4494 (68.5)	0	1682 (72.0)	<0.001

Values are median (interquartile range), mean±SD, or n (%). BMI indicates body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HS, heart stress; MI, myocardial infarction; and SBP, systolic blood pressure.

persisted in those receiving antihypertensive treatment ( $P_{\text{nonlinearity}}=0.042$ ) and was borderline significant in untreated patients ( $P_{\text{nonlinearity}}=0.09$ ); among participants with HS, the association remained linear regardless of treatment status ( $P_{\text{nonlinearity}}=0.41$  for treated patients and  $P_{\text{nonlinearity}}=0.69$  for untreated patients).

**Table 2. Joint Associations of Hypertension and Heart Stress With Cardiovascular Disease Events**

Characteristics	No hypertension or HS (n=2301)	Hypertension, no HS (n=6557)	No hypertension, HS (n=747)	Hypertension and HS (n=2336)	P value
<b>Total CVD</b>					
No. of events	147	660	72	330	
Incidence rate (95% CI), per 1000 person-y	7.8 (6.7–9.2)	12.5 (11.6–13.5)	12.0 (9.5–15.1)	18.4 (16.5–20.5)	
Unadjusted HR (95% CI)	Ref	1.60 (1.34–1.91)	1.52 (1.14–2.01)	2.37 (1.95–2.87)	<0.001
Fully adjusted HR (95% CI)	Ref	1.41 (1.18–1.70)	1.79 (1.34–2.39)	2.32 (1.89–2.84)	<0.001
<b>MACEs</b>					
No. of events	113	531	53	229	
Incidence rate (95% CI), per 1000 person-y	6.0 (5.0–7.2)	10.0 (9.2–10.9)	8.7 (6.7–11.4)	12.6 (11.1–14.4)	
Unadjusted HR (95% CI)	Ref	1.67 (1.36–2.04)	1.44 (1.04–2.00)	2.11 (1.68–2.64)	<0.001
Fully adjusted HR (95% CI)	Ref	1.52 (1.23–1.87)	1.75 (1.25–2.45)	2.15 (1.70–2.72)	<0.001
<b>HHF</b>					
No. of events	22	92	21	93	
Incidence rate (95% CI), per 1000 person-y	1.2 (0.8–1.8)	1.7 (1.4–2.1)	3.4 (2.2–5.2)	5.0 (4.1–6.2)	
Unadjusted HR (95% CI)	Ref	1.46 (0.92–2.33)	2.93 (1.61–5.33)	4.37 (2.75–6.96)	<0.001
Fully adjusted HR (95% CI)	Ref	1.10 (0.68–1.76)	3.40 (1.86–6.22)	3.63 (2.25–5.85)	<0.001
<b>CVD mortality</b>					
No. of events	53	193	27	141	
Incidence rate (95% CI), per 1000 person-y	2.7 (2.0–3.5)	3.4 (3.0–3.9)	4.2 (2.9–6.1)	7.2 (6.1–8.5)	
Unadjusted HR (95% CI)	Ref	1.27 (0.94–1.72)	1.56 (0.98–2.48)	2.69 (1.96–3.69)	<0.001
Fully adjusted HR (95% CI)	Ref	1.06 (0.77–1.45)	1.79 (1.11–2.88)	2.50 (1.80–3.49)	<0.001
<b>MI</b>					
No. of events	50	271	18	102	
Incidence rate (95% CI), per 1000 person-y	2.6 (2.0–3.5)	5.1 (4.5–5.7)	2.9 (1.8–4.7)	5.5 (4.6–6.7)	
Unadjusted HR (95% CI)	Ref	1.92 (1.42–2.59)	1.11 (0.65–1.90)	2.10 (1.50–2.95)	0.002
Fully adjusted HR (95% CI)	Ref	1.74 (1.27–2.37)	1.42 (0.82–2.44)	2.19 (1.54–3.11)	<0.001
<b>Stroke</b>					
No. of events	68	279	35	123	
Incidence rate (95% CI), per 1000 person-y	3.6 (2.8–4.6)	5.2 (4.6–5.8)	5.7 (4.1–7.9)	6.7 (5.6–8.0)	
Unadjusted HR (95% CI)	Ref	1.44 (1.10–1.88)	1.56 (1.04–2.35)	1.86 (1.39–2.50)	<0.001
Fully adjusted HR (95% CI)	Ref	1.34 (1.02–1.77)	1.69 (1.11–2.57)	1.78 (1.31–2.43)	<0.001

Values fully adjusted for age, sex, race, ethnicity, education, body mass index category, smoking, alcohol consumption, family history of myocardial infarction (MI), diabetes, chronic kidney disease, non-high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, statin, and aspirin. CVD indicates cardiovascular disease; HHF, hospitalization for heart failure; HR, hazard ratio; HS, heart stress; and MACE, major adverse cardiovascular event.

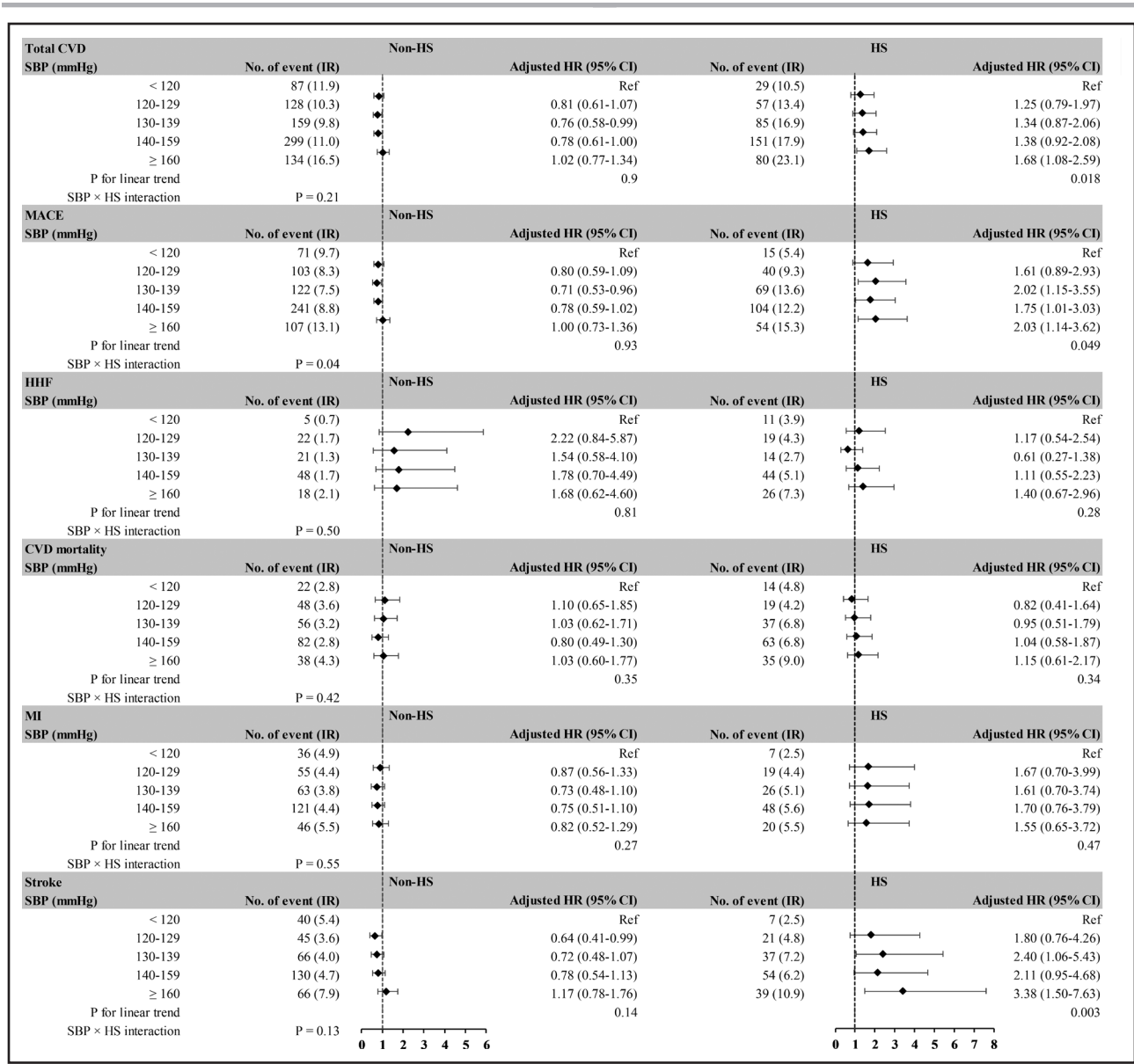
### Cumulative Incidence of Total CVD Events in Participants With or Without HS, Stratified by Age and Sex

In the 65- to 79-year-old subgroup (Figure 3A), among participants without hypertension, those with HS had a nonsignificantly higher cumulative incidence of total CVD events compared with those without HS (log-rank  $P=0.07$ ). Among participants with hypertension, HS was associated with a significantly higher incidence (log-rank  $P<0.001$ ). In the  $\geq 80$ -year subgroup, participants with HS had a significantly higher cumulative incidence of total CVD events than their counterparts without HS, regardless of hypertension status (log-rank  $P=0.004$  and  $<0.001$ , respectively). Among men (Fig-

ure 3B), HS was associated with a higher incidence of total CVD events across both hypertension strata (log-rank  $P<0.001$  for both). Among women, the difference between participants with or without HS was not significant in those without hypertension (log-rank  $P=0.09$ ) but was significant in those with hypertension (log-rank  $P<0.001$ ).

### Sensitivity Landmark Analysis

In the sensitivity landmark analysis, the joint associations of hypertension and HS with CVD events (Table S3) and risk of CVD events across SBP categories stratified by HS status (Figure S3) were generally consistent with the main analyses in both direction and magnitude, although



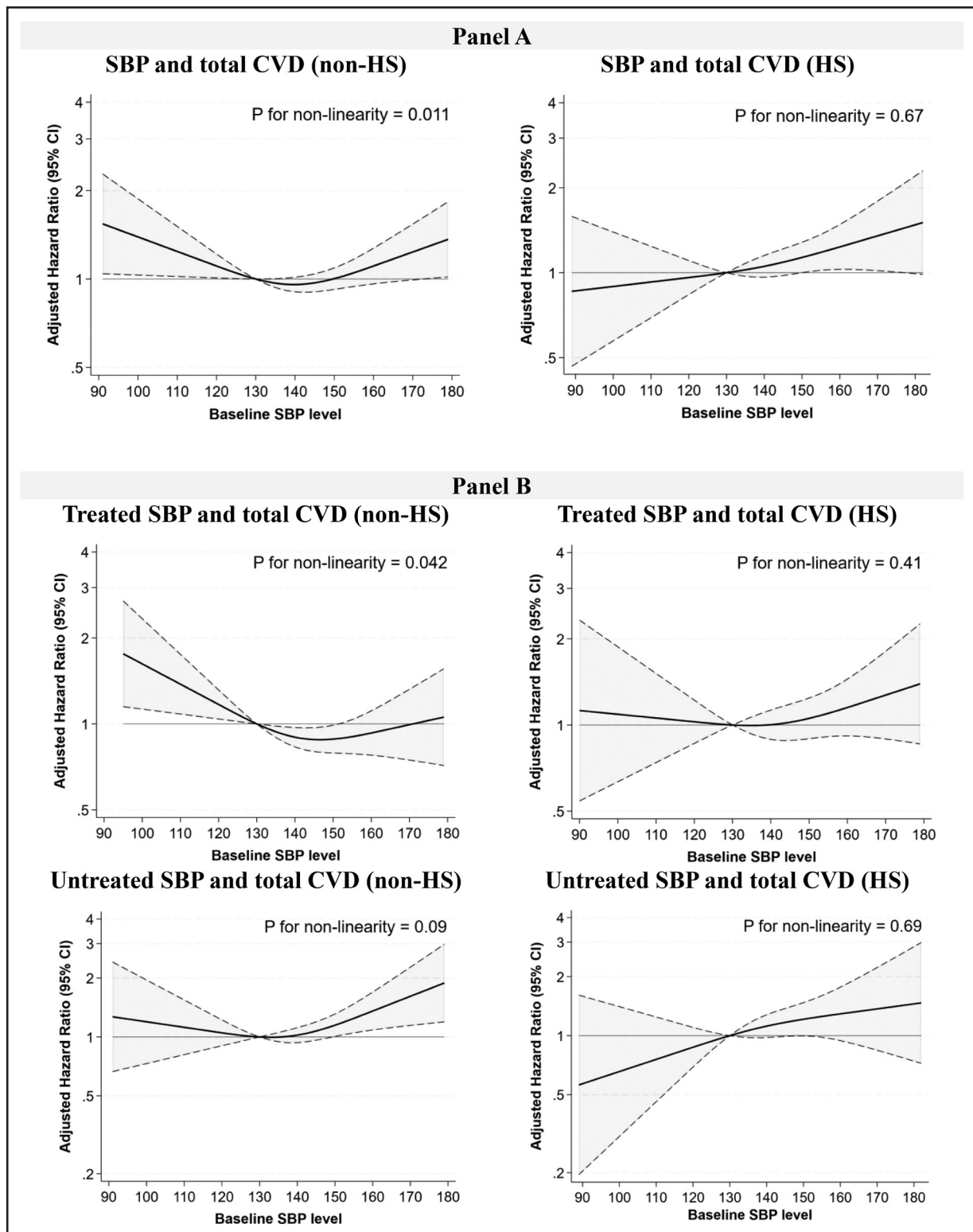
**Figure 1. Risk of cardiovascular disease events across systolic blood pressure categories, stratified by baseline heart stress status.** In participants with heart stress (HS), higher systolic blood pressure (SBP) was associated with a stepwise increase in adjusted risk of total cardiovascular disease (CVD) events; no such trend was found in participants without HS. No significant SBP–HS interaction was found for total CVD events. For major adverse cardiovascular events (MACEs), SBP showed a significant trend in the HS group but not in the group without HS, with a significant interaction. For tertiary outcomes, only stroke showed a positive trend in the HS group, and no significant interactions were found. HHF indicates hospitalization for heart failure; HR, hazard ratio; IR, incidence rate (presented as per 1000 person-years); and MI, myocardial infarction.

some significant trends and differences observed in the main analyses were attenuated, likely because of reduced sample size and event number.

**DISCUSSION**

In this post hoc analysis of 11 941 older adults free of CVD from the ASPREE study, we found that HS was highly prevalent, and the coexistence of hypertension and HS, defined by age-adjusted elevation in NT-proBNP level, was associated with the highest risks of total CVD

events, MACEs, HHF, CVD mortality, MI, and stroke. These findings suggest a joint effect of HS and hypertension on CVD risk and highlight the potential value of HS for refining risk stratification in older adults. HS significantly modified the relationship between SBP and MACE risk. Among individuals with HS, total CVD risk rose steadily with increasing SBP, whereas a U-shaped association was observed in those without HS. These associations remained generally consistent in the sensitivity landmark analysis, suggesting that reverse causality is unlikely to explain the observed results. Taken together,



**Figure 2. Risk of total cardiovascular disease events across systolic blood pressure as a continuous variable, stratified by heart stress status and baseline antihypertensive treatment.**

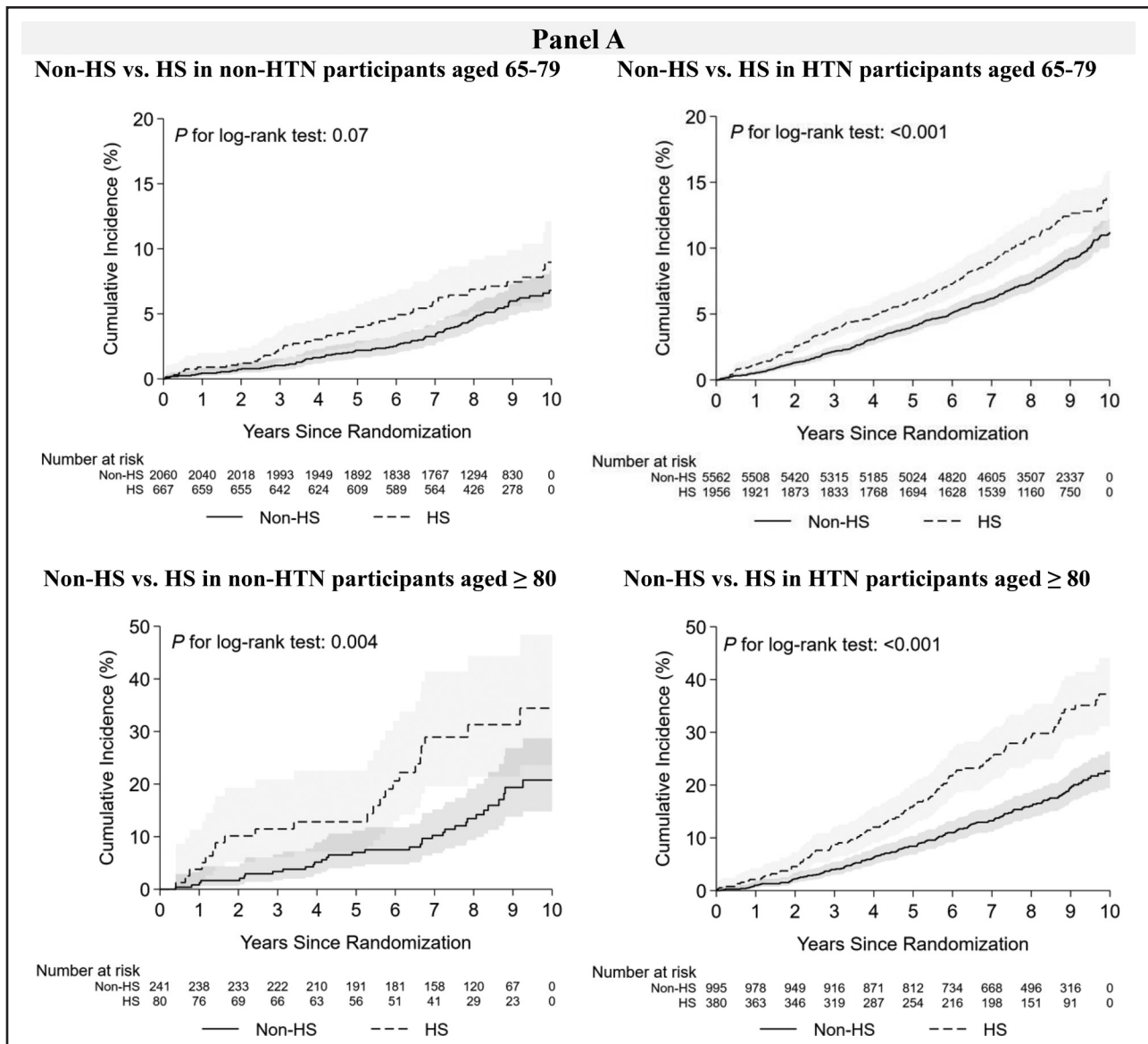
**A**, Among participants without heart stress (HS), the association between systolic blood pressure (SBP) and risk of total cardiovascular disease (CVD) events was nonlinear ( $P_{\text{nonlinearity}}=0.011$ ), showing a U-shaped curve with the lowest risk at SBP levels of 130 to 150 mmHg and a nadir at 140 mmHg. In participants with HS, the association appeared linear ( $P_{\text{nonlinearity}}=0.67$ ), with higher SBP consistently associated with greater risk.

**B**, Among participants without HS, the nonlinear pattern persisted among those receiving antihypertensive treatment ( $P_{\text{nonlinearity}}=0.042$ ), whereas a borderline nonlinear association was observed among untreated individuals ( $P_{\text{nonlinearity}}=0.09$ ). In participants with HS, both treated ( $P_{\text{nonlinearity}}=0.41$ ) and untreated ( $P_{\text{nonlinearity}}=0.69$ ) groups demonstrated a linear association between higher SBP and increased CVD risk.

this differential risk pattern underscores the potential value of NT-proBNP-based HS assessment to inform individualized BP management in older adults, for whom optimal SBP targets remain a subject of ongoing debate.

Several studies support the use of NT-proBNP for CVD risk stratification. In the ARIC study (Atherosclerosis Risk In Communities), elevated NT-proBNP levels identified individuals at heightened CVD risk, including those with stage 1 hypertension who were not otherwise treatment candidates.<sup>12</sup> Pooled cohort analyses have shown that NT-proBNP elevation predicts adverse

outcomes even in the absence of hypertension, whereas a normal NT-proBNP level is associated with lower risk even among those with elevated BP.<sup>13</sup> Furthermore, in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and SPRINT (Systolic Blood Pressure Intervention Trial), NT-proBNP enhanced CVD risk prediction,<sup>14,17</sup> and helped identify patients who benefited more from intensive SBP lowering.<sup>17</sup> Whereas these studies support the predictive value of NT-proBNP levels, none used the age-adjusted elevation in NT-proBNP levels, nor did they focus on older adults specifically. Our findings expand on



**Figure 3. Cumulative incidence of total cardiovascular disease events in participants with or without heart stress, stratified by age and sex.**

**A**, In participants 65 to 79 years of age, heart stress (HS) was associated with a borderline higher cumulative incidence of total cardiovascular disease (CVD) events among those without hypertension (HTN) and a significantly higher cumulative incidence among those with hypertension. In participants ≥80 years of age, HS was associated with a significantly higher cumulative incidence of total CVD events regardless of hypertension status. **B**, In men, HS was consistently associated with a significantly higher cumulative incidence of total CVD events across groups with or without hypertension. In women, HS was associated with a nonsignificantly higher cumulative incidence among those without hypertension and a significantly higher cumulative incidence among those with hypertension. (*Continued*)

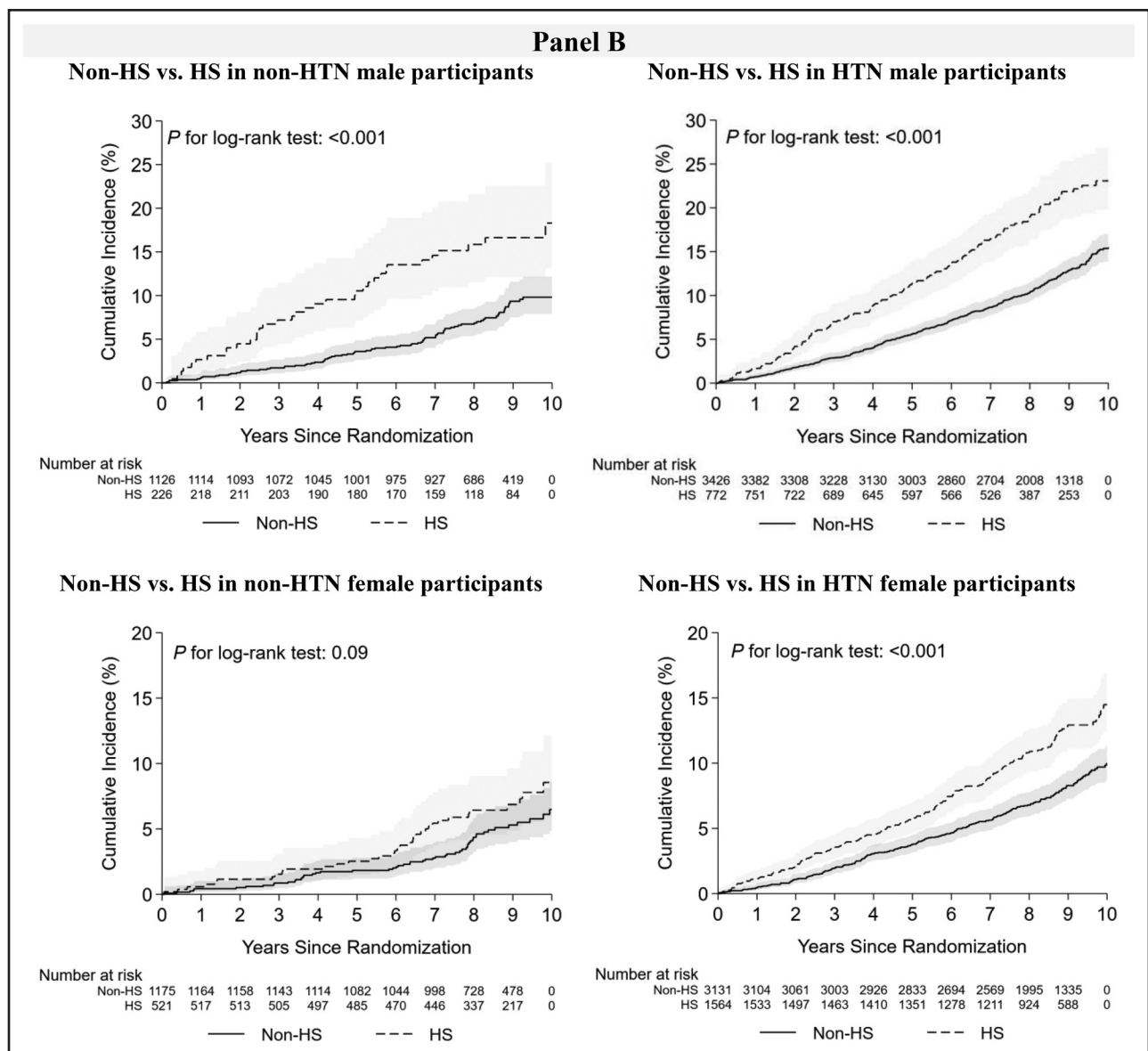


Figure 3 Continued.

this evidence, providing novel support for the incorporation of age-specific NT-proBNP cutoffs to identify high-risk individuals among otherwise healthy older adults with elevated BP or hypertension.

HS identified a high-risk subgroup of older adults across both age and sex strata, irrespective of hypertension status. In addition, in those with HS, the absence of a significant difference in CVD events between individuals with or without hypertension suggests that elevated NT-proBNP level confers independent CVD risk beyond traditional BP classifications. Unlike conventional risk factors, NT-proBNP directly reflects subclinical cardiac strain and dysfunction,<sup>22</sup> offering a pathophysiological basis for enhanced CVD risk prediction. Supporting this, findings from the National Health and Nutrition Examination Survey indicate that compared with conventional risk

score-based approaches, a biomarker-guided strategy using NT-proBNP and cardiac troponin may more selectively identify high-risk individuals with stage 1 hypertension, particularly among older adults.<sup>16</sup>

The relationship between SBP and risk of total CVD events differed markedly by HS status, providing important insights for individualized BP management in older adults. Among those without HS, the lowest incidence of CVD events was observed at SBP levels of 130 to 139 mm Hg, aligning with a previous large-scale study,<sup>29</sup> which reported a risk nadir at an SBP of 135.6 mm Hg. Similarly, a secondary analysis of INVEST (International Verapamil SR-Trandolapril Study) showed that among participants age 70 to 79 years and those age ≥80 years, SBP levels of 135 mm Hg and 140 mm Hg were associated with a lower risk of death, MI, or stroke compared

with an SBP <130 mmHg.<sup>30</sup> Although SPRINT showed that in participants >75 years of age intensive SBP treatment (mean 123.4 mmHg) resulted in fewer CVD events compared with standard treatment (mean 134.8 mmHg),<sup>31</sup> SBP was measured using automated office BP measurements, which might read  $\approx$ 14.5 mmHg lower than conventional measurement methods.<sup>32</sup> These data collectively raise concerns about the appropriateness of applying a uniform SBP target of <130 mmHg as recommended by the US guidelines to all older adults.<sup>8</sup> In fact, mildly elevated SBP (eg, 130–140 mmHg) in otherwise healthy older adults may reflect age-related vascular adaptation,<sup>33</sup> and may not warrant initiation of antihypertensive treatment in this population.<sup>34</sup>

In contrast, among participants with HS, there was a linear trend of increasing risk of total CVD events particularly when SBP was >130 mmHg. This association was consistent regardless of antihypertensive treatment status, suggesting that in individuals with elevated NT-proBNP levels, the heart may already be under strain and more vulnerable to BP-related injury.<sup>35</sup> In this context, even modest SBP elevation may accelerate progression to clinically manifested CVD events. These findings raise the hypothesis that SBP targets <130 mmHg may be more appropriate in this subgroup. Supporting this, secondary analyses from SPRINT indicated that the heightened CVD risk associated with elevated NT-proBNP and cardiac troponin levels could be attenuated by achieving a lower SBP target (<120 mmHg, measured by automated office BP).<sup>17</sup> Taken together, our results support a biomarker-guided approach to BP management in older adults, favoring a more conservative SBP target (130–140 mmHg) for those without HS and a lower target (<130 mmHg) for those with HS in the context of primary prevention.

Although no significant interaction between HS and SBP was noted for total CVD events, HS did modify the association between SBP and MACE risk. This suggests that HS may be particularly valuable in refining MACE risk stratification in older adults, a population in whom conventional risk scores often underperform because of age-related attenuation of traditional risk associations and competing risks.<sup>36,37</sup> Recently, the American Heart Association endorsed the PREVENT (Predicting Risk of CVD Events) equation to estimate the 10-year atherosclerotic cardiovascular disease risk and guide primary prevention in people 30 to 79 years of age.<sup>38</sup> In addition, the SCORE2-OP (Systematic Coronary Risk Evaluation 2-Older Persons) risk prediction algorithm was developed to estimate 10-year risk of CVD mortality, MI, or stroke in adults >70 years of age, with externally validated C-statistics ranging from 0.63 to 0.67.<sup>39</sup> A previous study has shown that cardiac biomarkers may provide greater precision than conventional risk scores, such as the pooled cohort equations, for identifying high-risk individuals with stage 1 hypertension, particularly among

those >65 years of age.<sup>16</sup> Building on this evidence, our findings raise the question of whether incorporating HS, defined by age-specific elevation in NT-proBNP concentrations, could enhance the predictive performance of contemporary models like the PREVENT equation and SCORE2-OP risk prediction algorithm in older adults.

Given the known age-related increase in NT-proBNP levels,<sup>18,19</sup> we applied age-specific cutoffs to define HS and demonstrated that this approach retained its discriminatory value in both the 65 to 79-year and  $\geq$ 80-year age groups. These findings for the first time demonstrate the utility of age-specific NT-proBNP cutoffs in identifying older adults who are at high CVD risk, particularly those age  $\geq$ 80 years of age, for whom conventional risk scores, such as the PREVENT equation,<sup>38</sup> are inapplicable. In addition, although NT-proBNP is influenced by additional factors such as sex, BMI, and CKD status, HS remained consistently associated with high CVD risk across these subgroups, reinforcing that age-specific NT-proBNP elevation provides robust risk stratification independent of these key covariates. Whereas we acknowledge the theoretical advantages of incorporating more nuanced cutoffs that account for these factors, our current approach offers an optimal balance between biological relevance and clinical practicality.

## Strengths and Limitations

The key strengths of this study lay within its large sample of well-characterized older adults, long-term follow-up, and rigorously ascertained and adjudicated outcomes. There are also limitations to this study. First, because the trial enrolled healthy older adults without previous CVD, event rates for the tertiary outcomes were relatively low, limiting the statistical power to assess associations between SBP and individual CVD events across HS strata. Moreover, because ASPREE recruited generally healthy older adults, the study population may not fully reflect the broader elderly population, particularly those with frailty, multiple comorbidities, or limited engagement in preventive care, which could introduce selection bias and further restrict generalizability. Second, although we adjusted for a broad range of baseline covariates, residual confounding cannot be excluded. Unmeasured factors such as subclinical disease may have influenced both NT-proBNP concentrations and CVD risk, potentially contributing to the observed associations. Third, the ASPREE cohort was predominantly White (98%), which may limit the generalizability of our findings to other racial and ethnic groups. Given the differences in CVD risk, NT-proBNP concentrations, and treatment responses across populations, validation in more diverse cohorts is needed. Fourth, only baseline BP measures and NT-proBNP data were used in this analysis, precluding assessment of the prognostic relevance of temporal changes in HS status or BP control. Future studies

incorporating serial measurements could help determine whether dynamic changes in these measures provide incremental prognostic information and support more individualized treatment strategies. For example, repeated NT-proBNP testing could identify individuals transitioning into or out of a high-risk “HS” state, prompting intensified monitoring or therapy adjustment, whereas assessment of long-term BP patterns may capture CVD risk more effectively than single measurements. Such data could be obtained through prospective cohort studies or clinical trials with predefined reassessment intervals (eg, annually) or by linkage to electronic health records and laboratory databases. In addition, this was a post hoc analysis of ASPREE, which was not originally designed to evaluate NT-proBNP-guided risk stratification or BP target modification; therefore, the findings should be interpreted as hypothesis-generating. Moreover, participants  $\geq 80$  years of age comprised only 14% of the cohort, limiting the statistical power and generalizability of subgroup results for this oldest age group.

## Conclusions

This study demonstrates that NT-proBNP-based HS assessment can refine CVD risk stratification in older adults and may guide more individualized BP management. Future studies are needed to determine whether such an approach can improve BP management and reduce CVD events in older adults.

## ARTICLE INFORMATION

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## Disclosures

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## Supplemental Material

STROBE Checklist  
Figures S1–S3  
Tables S1–S3

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