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RESEARCH LETTER

Sex Differences in Blood Pressure Associations With Cardiovascular Outcomes

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For decades, 120 mm Hg has been considered the normal upper limit for adult systolic blood pressure (SBP). Practice guidelines have long referred to this threshold for classifying ranges of blood pressure (BP) elevation and treatment targets, given the consistent epidemiologic finding that cardiovascular disease (CVD) risk is continuously increased from the SBP level of 120 mm Hg and upwards.[1] Amid previous studies using outcomes associations to determine a normal SBP range, there remain limited data on potential sex differences. It is well known that BP levels in adulthood are on average lower in women than men in the healthy state[2]; however, whether or not a lower range of SBP might be considered normal for women versus men is unclear.

We studied 27 542 participants (54% women) without baseline CVD who had standardized SBP measurements performed in 1 of 4 community-based cohort studies: the Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk in Communities Study, and Coronary Artery Risk Development in Young Adults Study.[3] Age and race distributions were similar between sexes (standard mean difference <0.1). Over 28±12 years, 7424 participants (44% women) developed nonfatal or fatal CVD: 3405 myocardial infarction (MI), 4081 heart failure (HF), and 1901 stroke events. We related SBP category (defined by 10 mm Hg increments from <100 mm Hg to ≥160 mm Hg) with incident CVD using cohort-stratified Cox proportional hazards models accounting for competing risks and adjusting for traditional risk factors (Figure); we observed no important violations of the proportional hazards assumptions. We tested for sex interactions and analyzed the MI, HF, and stroke outcomes separately. We also constructed models stratified by age, race, and cohort. We used R version 3.5.1 to perform analyses, with a 2-sided $P<0.05$ considered statistically significant. All participants provided written informed consent, institutional review boards approved all protocols, and National Heart, Lung, and Blood Institute approved data access. All data are available through public access policies of the National Heart, Lung, and Blood Institute BioLINCC repository, which does not contain information that could compromise research participant privacy.

In sex-pooled analyses, the threshold for incident MI and HF was 120 to 129 mm Hg and for stroke was 130 to 139 mm Hg. In sex-specific analyses, we observed increasing CVD risk beginning at lower thresholds of SBP for women than for men (Figure). Incidence of CVD proportionately increased beginning at a lower range of SBP in women compared with men. In multivariable-adjusted analyses, presence of SBP 100 to 109 mm Hg relative to SBP <100 mm Hg was associated with incident CVD in women but not men, in whom risk was seen at SBP 130 to 139 mm Hg. Notably, the magnitude of risk (hazard ratio 1.26) seen in men at the higher SBP threshold was comparable to that seen in women (hazard ratio 1.25) at the lower SBP threshold. We observed similarly consistent sex-specific results

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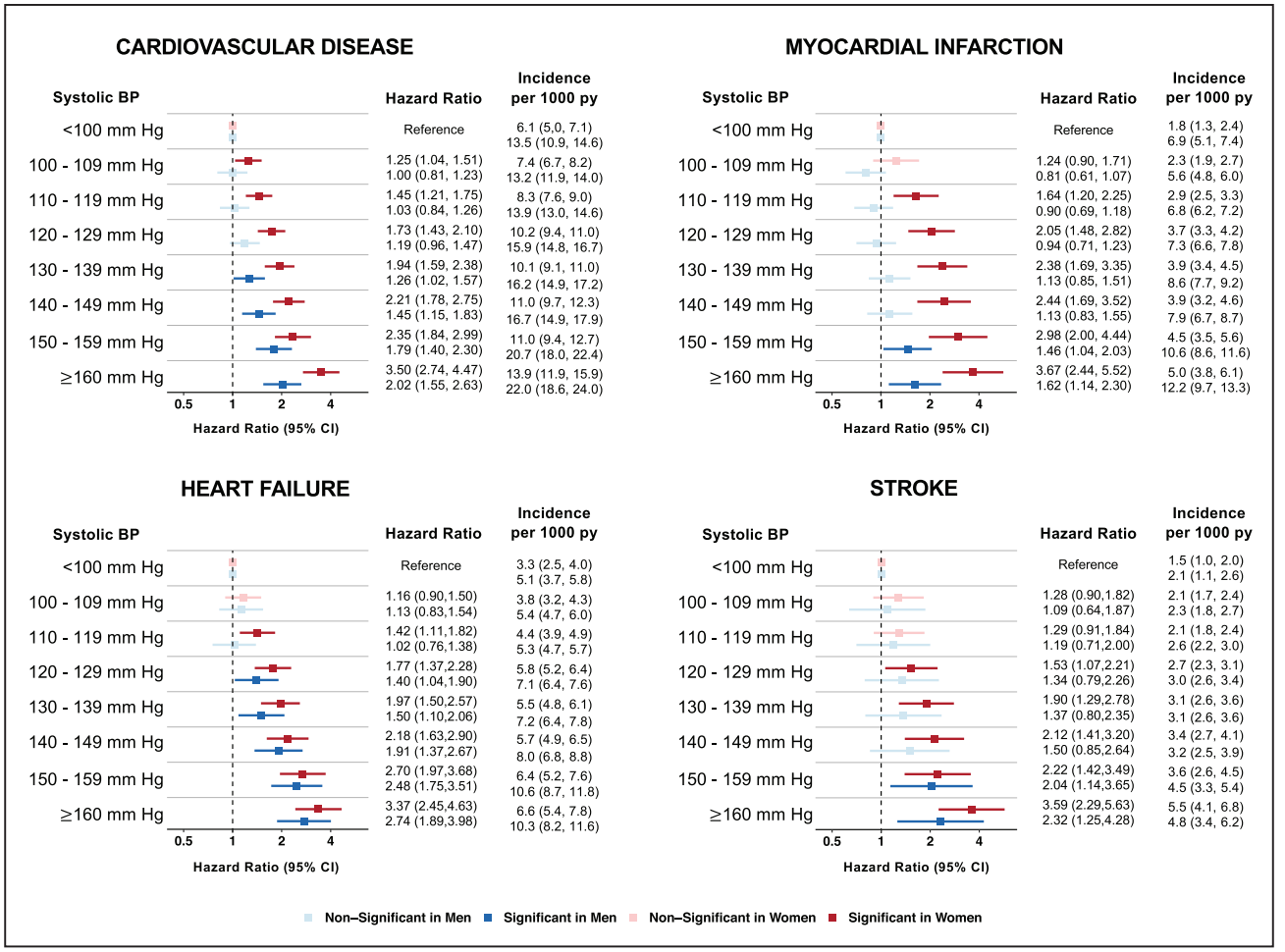

Figure. Sex differences in associations of systolic blood pressure (BP) with incident cardiovascular disease.
Sex-specific associations of systolic BP and hazards for incident cardiovascular disease were estimated using Cox proportional hazards models (systolic BP <100 mm Hg as referent) adjusting for age, race, body mass index, diastolic BP, antihypertensive therapy, high-density lipoprotein cholesterol level, total cholesterol level, cholesterol-lowering medication, diabetes mellitus, and smoking status. Results with significant hazards are depicted in bold color symbols, and results with nonsignificant hazards are depicted in faded color symbols. Values for both adjusted hazard ratios (95% confidence interval [CI]) and unadjusted incidence (95% CI) per 1000 person-years (py) are provided to display both the relative and absolute risks associated with increasing systolic BP range in women and men.

for MI, HF, and stroke. In fact, the MI risk for women with SBP 110 to 119 mm Hg was comparable with the MI risk for men with SBP ≥160 mm Hg; similarly, the HF risk for women with SBP 110 to 119 mm Hg was comparable with HF risk for men with SBP 120 to 129. Stroke risk also manifested at sex-specific, albeit higher, thresholds: Risk for women with SBP 120 to 129 mm Hg was comparable with risk in men with SBP 140 to 149 mm Hg. In restricted splines regression of SBP as a continuous rather than a categorical variable, findings were similar (data not shown). Results were also similar in analyses stratified by age, race, and cohort; excluding participants taking antihypertensive medication; excluding diastolic BP adjustment; and relating diastolic BP with CVD risk. Multiplicative sex interaction terms indicated consistently larger associations in women than men across all outcomes, with the greatest statistical significance seen for MI (P=0.006) and HF (P=0.058). In analyses of age interactions, the association of SBP with CVD risk was more pronounced in younger versus older women (median age <52 versus ≥52 years), whereas no age interaction was seen for men (likelihood ratio test: χ^2=16.00, P<0.001 for women; χ^2=4.64, P=0.098 for men).

Sex differences in cardiovascular risk may arise in part from unrecognized sex specificity regarding the optimal range of SBP. Expanding from previous reports of basal SBP values existing within a lower normal range for women than for men,[2,3] our results indicate that CVD risk is associated with elevations from lower SBP ranges in women compared with men. These findings could be related to differences in vascular anatomy and physiology (eg, smaller arterial diameter in women than men seen after normalizing for body size)[4] such that exposures leading to SBP elevation above sex-specific normal ranges may also elevate CVD risk in a sex-specific manner. Taken together, and on the background of previous work, our outcomes-based results suggest the possible need for a lower sex-specific definition of optimal SBP for women. If the ideal physiologic range

of BP truly is lower for women than for men, current approaches to using sex-agnostic targets for lowering elevated BP could benefit from careful reassessment. Further investigations are needed to validate our findings as well as prospectively determine whether ideal treatment targets for hypertension might indeed be lower for women than for men.

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Disclosures

None.

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