

# Association of “Elevated Blood Pressure” and “Stage 1 Hypertension” With Cardiovascular Mortality Among an Asian Population

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**Background**—The new American College of Cardiology/American Heart Association high blood pressure (BP) guidelines in the United States have lowered definition of hypertension by defining normal as systolic/diastolic BP <120/80 mm Hg; elevated BP as systolic between 120 and 129 mm Hg and diastolic <80 mm Hg; and stage 1 hypertension as systolic between 130 and 139 mm Hg or diastolic between 80 and 89 mm Hg.

**Methods and Results**—We investigated the association between the new hypertension definition and cardiovascular disease mortality among Chinese in Singapore. We used data from 30 636 participants of a population-based cohort, the SCHS (Singapore Chinese Health Study), who had BPs measured using a standard protocol at ages 46 to 85 years between 1994 and 2005. Information on lifestyle factors was collected at recruitment (1993–1998) and follow-up 1 interviews (1999 and 2004). Mortality was identified via nationwide registry linkage up to December 31, 2016. Neither elevated BP (hazard ratio, 0.89; 95% confidence interval, 0.74–1.07) nor stage 1 hypertension (hazard ratio, 0.94; 95% confidence interval, 0.81–1.11) was associated with increased risk of cardiovascular mortality compared with normal BP in the whole cohort. Stage 1 hypertension was associated with increased cardiovascular risk only in those <65 years of age and without a history of cardiovascular disease (hazard ratio, 1.40; 95% confidence interval, 1.01–1.94), but not in those ≥65 years of age or with a history of cardiovascular disease.

**Conclusions**—Our data suggest that the newly defined stage 1 hypertension may not be associated with increased cardiovascular mortality across all ages among Chinese in Singapore, but that the at-risk subpopulation is limited to those <65 years of age and without a prior cardiovascular disease. (*J Am Heart Assoc.* 2018;7:e008911. DOI: 10.1161/JAHA.118.008911.)

**Key Words:** cardiovascular disease • Chinese • high blood pressure • mortality • prehypertension

Clinical guidelines are powerful tools to translate research into rationale for clinical actions, with the ultimate aim of improving patient outcome. The “2017 High Blood Pressure Clinical Practice Guideline” drawn up by American College of Cardiology and American Heart Association in the United

States has set a new goal in treatment of high blood pressure (BP) and recommended that “BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP.”<sup>1</sup> This set of new high BP guidelines has lowered definition of hypertension by defining normal as <120/80 mm Hg; elevated BP as systolic 120 to 129 mm Hg and diastolic <80 mm Hg; and stage 1 hypertension as systolic 130 to 139 mm Hg or diastolic 80 to 89 mm Hg.<sup>1</sup> Whether this new definition should be globally applied across geographical regions and ethnicities remains unclear, and outside the United States, these guidelines have yet to be adopted by countries in Europe or Asia.

The findings of studies in Chinese population with regard to cardiovascular disease (CVD) risk associated with BP levels defined as elevated or stage 1 hypertension in the new guidelines are controversial.<sup>2–5</sup> We used data from the SCHS (Singapore Chinese Health Study) to investigate the association between different BP categories and the risk of mortality from CVD among middle-aged and elderly adults of Chinese ethnicity in Singapore.

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## Clinical Perspective

### What Is New?

- Our data from this population-based cohort of middle-aged and older Chinese in Singapore showed that increased risk of cardiovascular disease mortality associated with the newly defined stage 1 hypertension (130–139/80–89 mm Hg) was only observed in participants who were both <65 years of age and without history of cardiovascular disease, but not in older participants or those with such prior history.

### What Are the Clinical Implications?

- We urge for more research on the issues of blood pressure targets for elderly people and those at high risk of cardiovascular disease across geographical regions and ethnicities to fill in knowledge gaps about possible heterogeneity by these factors; thus, clinicians can make evidence-based decisions tailored to different populations in the clinical management of hypertension.
- Until more studies have been done, we suggest that clinicians adopt a cautionary approach, on a case-by-case basis, to setting blood pressure targets in older patients or those with cardiovascular history, particularly in those with Chinese ethnicity.

## Methods

The data that support the findings of this study as well as analytic methods and study materials are available from the corresponding author on reasonable request and are in compliance with National Institutes of Health guidelines.

## Study Population

A total of 35 303 Chinese women and 27 954 Chinese men, aged 45 to 74 years, were enrolled in the population-based cohort, the SCHS, between April 1993 and December 1998. The design of the SCHS was described in detail previously.<sup>6</sup> Briefly, the study participants belonged to 2 major dialect groups in Singapore, the Hokkien and the Cantonese, originating from Fujian and Guangdong provinces in southern China, respectively. All the study participants resided in government housing estates, where 86% of the Singapore population lived at the time of enrollment. Structured questionnaires were used to obtain information on demographics, lifestyle factors (physical activity, sleep duration, tobacco use, and alcohol intake), usual diet, and medical history through in-person interviews at recruitment. Between 1999 and 2004, during follow-up 1 interviews, 52 322 participants were recontacted via telephone calls, and

information on lifestyle factors and medical history was updated.<sup>7</sup>

From April 1994 to December 1999, a random 3% of the study participants were contacted to donate blood and single-void urine specimens. Between January 2000 and April 2005, this biospecimen collection was extended to 32 543 participants, constituting a consent rate of ≈60% of surviving cohort participants at that time. BP was measured before biospecimen collection. A total of 30 636 participants with BP measurements and who also participated in the follow-up 1 interviews were included in the current analysis. This study was approved by the Institutional Review Board at the National University of Singapore, and all enrolled participants provided informed consent.

## Assessment of BP and Other Covariates

For each of the 30 636 participants, BP was measured in a seated position in the home by trained staff using Omron automatic digital BP monitor HEM-705CP. Three measurements were obtained at 3-minute intervals for each participant, and the average of the readings was rounded to the next integer and used as the final BP measurement. During the visit for BP measurements, information on history of hypertension and use of antihypertensive medications was updated.

At recruitment and follow-up 1 interviews, information on smoking, alcohol intake, and self-reported history of medical conditions diagnosed by physicians, including diabetes mellitus, hypertension, coronary heart disease (CHD), and stroke, was collected. Body mass index (BMI; in kg/m<sup>2</sup>) was calculated as body weight in kilograms divided by square of height in meters. The enquiry about history of these diseases was made by asking if the participant has been told by a physician that he/she had any of these diseases in separate questions. Using standard protocols, separate studies validated the accuracy of the self-reported diabetes mellitus<sup>8</sup> and hypertension<sup>9</sup> in this cohort. The robustness and accuracy of the self-reported diabetes mellitus data were validated in a separate study analyzing 1651 cohort participants who reported history of diabetes mellitus at either baseline or follow-up 1 interview, and 98.9% were confirmed by medical records or telephone interview.<sup>8</sup>

## Assessment of Mortality

Information on date and cause of death was obtained through linkage analysis with the nationwide registry of birth and death in Singapore, and primary cause of death (ie, leading disease or condition) was used for analysis. As of December 31, 2016, when vital status for cohort participants was updated, only 41 participants from this cohort were known to be unavailable for follow-up because of migration out of

Singapore or for other reasons. This suggests that, in this cohort, unavailability for follow-up is negligible and vital statistics are virtually complete. Underlying causes of death were coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*; codes 390 to 459 were used for CVD deaths, codes 410 to 414 were used for CHD deaths, and codes 430 to 438 were used for stroke deaths.

## Statistical Analysis

For each participant, we calculated person-years as the duration between the date of BP measurement and the date of death, unavailability for follow-up, or December 31, 2016, whichever came first. Cox proportional hazards were used to examine associations between BP categories and CVD mortality risk. The 5 BP categories for the present analysis were created as follows: normal BP (ie, systolic BP <120 mm Hg and diastolic BP <80 mm Hg), elevated BP (systolic BP=120–129 mm Hg and diastolic BP <80 mm Hg), stage 1 hypertension (systolic BP=130–139 mm Hg or diastolic BP=80–89 mm Hg), low stage 2 hypertension (systolic BP=140–149 mm Hg or diastolic BP=90–99 mm Hg), and high stage 2 hypertension (systolic BP  $\geq$ 150 mm Hg or diastolic BP  $\geq$ 100 mm Hg). In the multivariate models, we adjusted for age (continuous), sex, dialect group (Hokkien or Cantonese; as an indicator of origin), level of education (none, primary school, secondary school, or more), cigarette smoking at follow-up 1 (none, ex-smoker, or current smoker), alcohol intake at follow-up 1 (never, monthly, weekly, or daily), physical activity level at baseline (<0.5, 0.5–<4, or  $\geq$ 4 h/wk), sleep duration at baseline ( $\leq$ 5, 6–8, or  $\geq$ 9 h/d), BMI at follow-up 1 (<20.0, 20.0–23.9, 24.0–27.9, or  $\geq$ 28.0 kg/m<sup>2</sup>), history of comorbidities at recruitment or follow-up 1 (diabetes mellitus, CHD, and stroke), and use of antihypertensive medications.

We also conducted stratified analysis to examine the association between BP categories and CVD mortality in different subgroups of our participants by age groups (those who were <65 versus  $\geq$ 65 years of age at BP measurement); sex (men versus women); self-reported history of physician-diagnosed heart attack, angina, or stroke (CVD history; no versus yes); and BMI groups (<23 versus  $\geq$ 23 kg/m<sup>2</sup>). The stratification by BMI was done using 23.0 kg/m<sup>2</sup> as the cutoff because this is the World Health Organization's recommendation of BMI trigger point for public health action in Asians<sup>10</sup> and also the median value of BMI in this study population. The statistical significance in the heterogeneity of the associations between different strata was tested by including the product between BP categories and stratification variable as an interaction term in the Cox model. All the statistical analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC), with a 2-sided *P* value <5% as statistically

significant. *P* value for trend was computed by introducing BP categories to the models as a continuous variable

## Results

The mean $\pm$ SD age of our participants at time of BP measurement was 63.0 $\pm$ 7.8 years. More than half of the participants in our study (55.7%) were women. Approximately 55.5% of the population were <65 years of age and without CVD history, 4.1% were <65 years of age and with CVD history, and 40.4% were  $\geq$ 65 years of age. Table 1 shows the characteristics of study participants according to BP categories created for this study. In our study population, 21.3% of participants had normal BP, 11.5% had elevated BP, 23.5% had stage 1 hypertension, 17.3% had low stage 2 hypertension, and 26.3% had high stage 2 hypertension. Participants at higher BP categories were older, were more likely to be men, had lower educational level, and were more likely to be ever smokers or daily drinkers of alcohol. They were also more likely to have higher BMI and to have history of diabetes mellitus, hypertension, or CVD compared with those in the lower BP categories.

After a mean $\pm$ SD 12.9 $\pm$ 3.7 years of follow-up, we identified 2412 participants who died of CVD, including 1379 of CHD and 637 of stroke. In fully adjusted models, compared with normal BP, elevated BP (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.74–1.07) and stage 1 hypertension (HR, 0.94; 95% CI, 0.81–1.11) were associated with nonstatistically significant reduced risk for total CVD mortality (Table 2). As for CHD mortality, compared with normal BP, null associations were observed for elevated BP (HR, 1.00; 95% CI, 0.78–1.28) and stage 1 hypertension (HR, 1.01; 95% CI, 0.82–1.25) in fully adjusted model. Conversely, both low and high stage 2 hypertension was associated with increased risk of total CVD and CHD mortality in an incremental manner. As for stroke mortality, the risk was only significantly increased in those with high stage 2 hypertension (HR, 1.72; 95% CI, 1.31–2.26).

In stratified analysis, compared with normal BP, no significantly higher risk was observed for stage 1 hypertension in any subgroup by sex (*P*=0.27 for interaction), BMI subgroup (*P*=0.69 for interaction), or use of antihypertensive medication (*P*=0.23 for interaction). Overall, stronger associations with CVD mortality were observed across all BP categories in participants <65 years of age (*P*=0.01 for interaction) and in those with no history of CVD (*P*=0.001 for interaction). Specifically, for the association between stage 1 hypertension and CVD mortality, the interaction terms were statistically significant for the observed differences by age group (<65 versus  $\geq$ 65 years; *P*=0.008 for interaction) and CVD history (no versus yes; *P*=0.04 for interaction) (Table 3). When participants were stratified by both age and the history

**Table 1.** Participant's Characteristics According to BP Categories Determined at Baseline or BP Measurement

Variable	BP Categories				
	Normal	Elevated	Stage 1 Hypertension	Stage 2 Hypertension	
				Low	High
Systolic BP, mm Hg	<120	120–129	130–139	140–149	≥150
Diastolic BP, mm Hg	<80	<80	80–89	90–99	≥100
N (%)	6519 (21.3)	3537 (11.5)	7196 (23.5)	5314 (17.3)	8070 (26.3)
Age, y	59.9±7.1	63.0±7.6	61.9±7.3	63.4±7.6	66.2±7.7
Women, n (%)	4308 (66.1)	2128 (60.2)	3826 (53.2)	2711 (51.0)	4096 (50.8)
Dialect group, n (%)					
Hokkien	3393 (52.0)	1796 (50.8)	3684 (51.2)	2625 (49.4)	3955 (49.0)
Cantonese	3126 (48.0)	1741 (49.2)	3512 (48.8)	2689 (50.6)	4115 (51.0)
Education, n (%)					
None	1171 (18.0)	772 (21.8)	1414 (19.6)	1198 (22.5)	2328 (28.8)
Primary	2799 (42.9)	1651 (46.7)	3246 (45.1)	2397 (45.1)	3754 (46.5)
Secondary	2549 (39.1)	1114 (31.5)	2536 (35.2)	1719 (32.3)	1988 (24.6)
Smoking, n (%)					
None	4853 (74.4)	2480 (70.1)	4940 (68.6)	3508 (66.0)	5040 (62.5)
Ex-smoker	726 (11.1)	503 (14.2)	1154 (16.0)	920 (17.3)	1619 (20.1)
Current smoker	940 (14.4)	554 (15.7)	1102 (15.3)	886 (16.7)	1411 (17.5)
Alcohol intake, n (%)					
None	5373 (82.4)	2926 (82.7)	5808 (80.7)	4365 (82.1)	6742 (83.5)
Monthly	487 (7.5)	254 (7.2)	586 (8.1)	360 (6.8)	432 (5.4)
Weekly	515 (7.9)	268 (7.6)	618 (8.6)	412 (7.8)	600 (7.4)
Daily	144 (2.2)	89 (2.5)	184 (2.6)	177 (3.3)	296 (3.7)
Moderate physical activity, n (%)					
<0.5 h/wk	5016 (76.9)	2709 (76.6)	5476 (76.1)	4088 (76.9)	6096 (75.5)
0.5–3 h/wk	1007 (15.4)	518 (14.6)	1082 (15.0)	792 (14.9)	1192 (14.8)
≥4 h/wk	496 (7.6)	310 (8.8)	638 (8.9)	434 (8.2)	782 (9.7)
Sleep, n (%)					
≤5 h/d	579 (8.9)	359 (10.1)	658 (9.1)	500 (9.4)	869 (10.8)
6–8 h/d	5521 (84.7)	2964 (83.8)	6098 (84.7)	4477 (84.2)	6647 (82.4)
≥9 h/d	419 (6.4)	214 (6.1)	440 (6.1)	337 (6.3)	554 (6.9)
Body mass index, kg/m <sup>2</sup>	22.1±3.3	22.9±3.4	23.4±3.5	23.6±3.5	23.8±3.6
Systolic BP, mm Hg	109±7.9	124±2.9	131±6.6	143±4.6	166±14.8
Diastolic BP, mm Hg	68.9±6.2	72.9±4.9	80.1±6.0	84.1±7.8	90.2±10.7
History of hypertension, n (%)	1320 (20.2)	1254 (35.5)	3084 (42.9)	2858 (53.8)	5444 (67.5)
History of diabetes mellitus, n (%)	527 (8.1)	477 (13.5)	901 (12.5)	837 (15.8)	1734 (21.5)
History of cardiovascular disease, n (%)	481 (7.4)	371 (10.5)	710 (9.9)	611 (11.5)	1139 (14.1)
Current use of antihypertensive medications, n (%)	1040 (16.0)	1037 (29.3)	2461 (34.2)	2287 (43.0)	4149 (51.4)

Data are given as mean±SD unless otherwise indicated. BP indicates blood pressure.

of CVD, compared with their counterparts with normal BP, stage 1 hypertension was associated with a statistically significant 40% higher risk of CVD mortality in individuals who

were both free of CVD history and <65 years of age at BP measurement (HR, 1.40; 95% CI, 1.01–1.94). We did not find increased risk of CVD mortality associated with stage 1

**Table 2.** HRs (95% CIs) for CVD Mortality According to Categories of BP

Variable	BP Categories				
	Normal	Elevated	Stage 1 Hypertension	Stage 2 Hypertension	
				Low	High
<b>CVD mortality</b>					
Cases/person-years	262/86 267	200/46 259	390/95 099	438/68 919	1122/97 013
Model 1	1.00	0.96 (0.80–1.16)	1.01 (0.86–1.18)	1.32 (1.13–1.53)	1.87 (1.63–2.15)
Model 2	1.00	0.98 (0.81–1.18)	1.02 (0.87–1.19)	1.33 (1.14–1.56)	1.89 (1.64–2.17)
Model 3	1.00	0.91 (0.76–1.09)	0.98 (0.83–1.14)	1.24 (1.06–1.45)	1.75 (1.52–2.01)
Model 4	1.00	0.89 (0.74–1.07)	0.94 (0.81–1.11)	1.18 (1.01–1.38)	1.64 (1.43–1.89)
<b>CHD mortality</b>					
Cases/person-years	138/86 267	119/46 259	222/95 099	267/68 919	633/97 013
Model 1	1.00	1.10 (0.86–1.41)	1.09 (0.88–1.35)	1.53 (1.24–1.88)	2.04 (1.69–2.46)
Model 2	1.00	1.11 (0.87–1.43)	1.09 (0.88–1.35)	1.53 (1.25–1.89)	2.04 (1.68–2.46)
Model 3	1.00	1.02 (0.79–1.30)	1.04 (0.84–1.29)	1.42 (1.15–1.74)	1.87 (1.54–2.26)
Model 4	1.00	1.00 (0.78–1.28)	1.01 (0.82–1.25)	1.36 (1.11–1.68)	1.78 (1.47–2.16)
<b>Stroke mortality</b>					
Cases/person-years	71/86 267	54/46 259	94/95 099	99/68 919	319/97 013
Model 1	1.00	0.94 (0.66–1.34)	0.91 (0.67–1.24)	1.09 (0.80–1.49)	1.91 (1.46–2.48)
Model 2	1.00	0.96 (0.67–1.37)	0.93 (0.68–1.27)	1.12 (0.83–1.53)	1.96 (1.50–2.56)
Model 3	1.00	0.91 (0.63–1.29)	0.89 (0.65–1.21)	1.04 (0.76–1.41)	1.80 (1.38–2.36)
Model 4	1.00	0.89 (0.62–1.27)	0.87 (0.64–1.19)	1.00 (0.73–1.37)	1.72 (1.31–2.26)

Multivariable model 1: adjusted for age, sex, dialect group, and education level. Multivariable model 2: further adjusted for body mass index, smoking status, alcohol intake, physical activity, and sleep duration. Multivariable model 3: further adjusted for history of CHD, stroke, and diabetes mellitus. Multivariable model 4: further adjusted for antihypertensive medication use. BP indicates blood pressure; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; and HR, hazard ratio.

hypertension among those who were  $\geq 65$  years of age or those with history of CVD at BP measurement (Table 4, Figure). We tested if our findings were sensitive to the measurement date by adding a categorical variable representing year of BP measurement to the statistical models, but our results remained unchanged.

## Discussion

Our data from this large cohort of middle-aged and older Chinese in Singapore suggest that the newly defined stage 1 hypertension, according to the revised American College of Cardiology/American Heart Association high BP guidelines in United States, may not be associated with increased risk of CVD, CHD, or stroke mortality across all ages in the general population. In this study, a higher risk associated with stage 1 hypertension was only observed in participants  $< 65$  years of age and without CVD history, but not in the older participants or those with history of CVD.

In a meta-analysis of 16 prospective studies,<sup>11</sup> high-range prehypertension, defined as systolic/diastolic BP 130 to 139/85 to 89 mm Hg, was associated with 56% higher risk of

CVD (relative risk [RR], 1.56; 95% CI, 1.36–1.78), whereas low-range prehypertension, defined as 120 to 129/80 to 84 mm Hg, was associated with 24% higher CVD risk (RR, 1.24; 95% CI, 1.10–1.39). The Asian cohort studies used for these pooled analyses for low/high-range prehypertension composed mostly studies from Japan (5 studies), while China, Korea, Iran, and India contributed 1 study each.<sup>11</sup> The non-Asian studies came mostly from the United States (7 studies). When stratified by geographical location, the summary risk estimate associated with high-range prehypertension was significantly lower for CVD mortality among Asian studies compared with non-Asian studies (RR, 1.49 versus 1.66;  $P=0.007$  for heterogeneity). In fact, the summary risk estimate for the association between high-range hypertension and CHD mortality from Asian studies did not reach statistical significant (RR, 1.19; 95% CI, 0.97–1.47). Similarly, for low-range prehypertension, the adverse association with CVD mortality was significantly lower among the Asian studies compared with the non-Asian studies (RR, 1.17 versus 1.37;  $P=0.01$  for heterogeneity). Moreover, an age-specific association was observed, with evidence of higher CVD mortality risk at younger age ( $< 65$  years) but not at older age: RR, 1.23

**Table 3.** HRs (95% CIs) for CVD Mortality According to Categories of BP Stratified by Sex, Age, History of CVD, and Antihypertensive Medication Use at BP Measurement

Variable	BP Categories				
	Normal	Elevated	Stage 1 Hypertension	Stage 2 Hypertension	
				Low	High
<b>Men</b>					
Cases/person-years	132/27 234	104/17 362	214/42 886	261/32 579	645/45 658
Model 1	1.00	0.89 (0.69–1.16)	0.90 (0.72–1.12)	1.28 (1.04–1.59)	1.83 (1.51–2.22)
Model 2	1.00	0.88 (0.68–1.14)	0.88 (0.71–1.10)	1.25 (1.01–1.55)	1.77 (1.45–2.15)
<b>Women</b>					
Cases/person-years	130/59 033	96/28 897	176/52 212	177/36 340	477/51 355
Model 1	1.00	0.91 (0.70–1.18)	1.03 (0.82–1.30)	1.11 (0.88–1.40)	1.56 (1.27–1.91)
Model 2	1.00	0.88 (0.67–1.15)	0.98 (0.78–1.23)	1.03 (0.82–1.30)	1.41 (1.15–1.74)
<b>Aged &lt;65 y</b>					
Cases/person-years	87/68 248	46/29 414	135/65 301	143/41 924	264/45 241
Model 1	1.00	0.93 (0.65–1.34)	1.23 (0.93–1.62)	1.88 (1.43–2.46)	2.71 (2.10–3.49)
Model 2	1.00	0.91 (0.63–1.30)	1.19 (0.90–1.57)	1.78 (1.35–2.34)	2.54 (1.96–3.29)
<b>Aged ≥65 y</b>					
Cases/person-years	175/18 018	154/16 845	255/29 798	295/26 995	858/51 772
Model 1	1.00	0.82 (0.66–1.02)	0.82 (0.67–0.99)	0.96 (0.79–1.16)	1.36 (1.15–1.60)
Model 2	1.00	0.80 (0.65–1.00)	0.79 (0.65–0.96)	0.92 (0.76–1.11)	1.28 (1.09–1.52)
<b>Without history of CVD</b>					
Cases/person-years	178/80 689	131/41 917	275/86 442	300/61 818	782/85 357
Model 1	1.00	0.93 (0.74–1.16)	1.04 (0.86–1.25)	1.29 (1.07–1.56)	1.85 (1.56–2.19)
Model 2	1.00	0.90 (0.72–1.13)	0.99 (0.82–1.20)	1.22 (1.01–1.47)	1.70 (1.43–2.02)
<b>With history of CVD</b>					
Cases/person-years	84/5578	69/4342	115/8657	138/7101	340/11 656
Model 1	1.00	0.84 (0.61–1.15)	0.79 (0.60–1.05)	1.06 (0.81–1.40)	1.44 (1.13–1.84)
Model 2	1.00	0.84 (0.61–1.16)	0.80 (0.60–1.06)	1.08 (0.82–1.42)	1.46 (1.14–1.88)
<b>Without antihypertensive medication</b>					
Cases/person-years	173/73 044	112/33 036	206/63 082	195/39 737	441/48 181
Model 1	1.00	0.93 (0.73–1.18)	0.99 (0.81–1.22)	1.22 (0.99–1.50)	1.79 (1.49–2.15)
<b>With antihypertensive medication</b>					
Cases/person-years	89/13 222	88/13 223	184/32 017	243/29 182	681/48 832
Model 1	1.00	0.74 (0.55–1.00)	0.78 (0.60–1.00)	0.98 (0.77–1.25)	1.34 (1.07–1.67)
<b>BMI &lt;23 kg/m<sup>2</sup></b>					
Cases/person-years	154/54 491	109/24 438	179/45 303	216/30 392	497/39 161
Model 1	1.00	0.94 (0.74–1.21)	0.96 (0.77–1.19)	1.31 (1.06–1.62)	1.77 (1.47–2.14)
Model 2	1.00	0.92 (0.72–1.17)	0.93 (0.75–1.15)	1.24 (1.00–1.53)	1.64 (1.35–1.99)
<b>BMI ≥23 kg/m<sup>2</sup></b>					
Cases/person-years	108/31 776	91/21 821	211/49 796	222/38 527	625/57 852
Model 1	1.00	0.84 (0.63–1.11)	0.94 (0.75–1.19)	1.11 (0.88–1.40)	1.64 (1.33–2.02)
Model 2	1.00	0.82 (0.62–1.09)	0.91 (0.72–1.15)	1.07 (0.85–1.35)	1.56 (1.27–1.93)

Multivariable model 1: adjusted for age, sex, dialect group, education level, BMI, smoking status, alcohol intake, physical activity, sleep duration, and history of coronary heart disease, stroke, and diabetes mellitus. Multivariable model 2: further adjusted for antihypertensive medications use. BMI indicates body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; and HR, hazard ratio.

**Table 4.** HRs (95% CIs) for CVD Mortality According to Categories of BP Stratified by Age and History of CVD at BP Measurement

Variable	BP Categories				
	Normal	Elevated	Stage 1 Hypertension	Stage 2 Hypertension	
				Low	High
<b>Aged &lt;65 y and without history of CVD</b>					
Cases/person-years	60/65 332	28/27 612	100/60 941	106/38 689	186/41 565
Model	1.00	0.91 (0.58–1.42)	1.40 (1.01–1.94)	2.05 (1.48–2.85)	2.81 (2.07–3.83)
<i>P</i> value for interaction*		Reference	Reference	Reference	Reference
<b>Aged &lt;65 y and with history of CVD</b>					
Cases/person-years	27/2916	18/1802	35/4360	37/3235	78/3676
Model	1.00	0.85 (0.46–1.58)	0.74 (0.44–1.25)	1.07 (0.64–1.80)	1.86 (1.16–2.98)
<i>P</i> value for interaction*		0.67	0.02	0.02	0.02
<b>Aged ≥65 y and without history of CVD</b>					
Cases/person-years	118/15 357	103/14 305	175/25 501	194/23 129	596/43 791
Model	1.00	0.81 (0.62–1.05)	0.79 (0.63–1.00)	0.89 (0.71–1.12)	1.28 (1.04–1.56)
<i>P</i> value for interaction*		0.74	0.005	<0.001	<0.001
<b>Aged ≥65 y and with history of CVD</b>					
Cases/person-years	57/2661	51/2540	80/4297	101/3866	262/7981
Model	1.00	0.83 (0.57–1.22)	0.80 (0.56–1.12)	1.04 (0.74–1.45)	1.33 (0.99–1.79)
<i>P</i> value for interaction*		0.49	0.006	<0.001	<0.001

Multivariable model: adjusted for age; sex; dialect group; education level; body mass index; smoking status; alcohol intake; physical activity; sleep duration; history of coronary heart disease, stroke, and diabetes mellitus; and antihypertensive medication use. BP indicates blood pressure; CI, confidence interval; CVD, cardiovascular disease; and HR, hazard ratio. \**P* value for interaction was calculated by product of age–CVD history groups (4 levels) and BP categories in a Cox regression model (12 interaction terms).

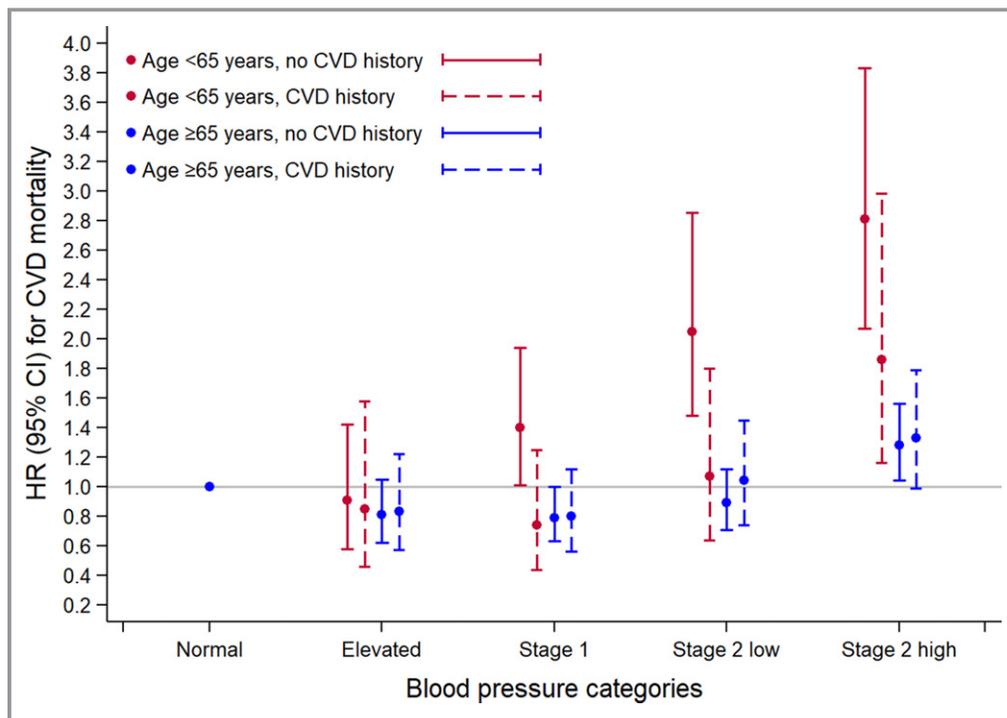
versus 0.85 at low-range prehypertension and 1.60 versus 1.07 at high-range prehypertension ( $P=0.09$  for heterogeneity). This concurs with our finding among those without history of CVD, because we also observed significantly higher risk of CVD mortality associated with stage 1 hypertension in participants <65 years of age.

To our best knowledge, there were 3 prior studies about prehypertension and CVD risk conducted in Chinese populations.<sup>2,4,5</sup> The average age of participants from all the previously described 3 studies in Chinese populations was ≈55 years, which was ≈8 years younger than the average age of 63 years in our study. In Shanghai Women's Health Study,<sup>2</sup> in line with our findings, high normal BP (130–139/85–89 mm Hg) was also not associated with CHD mortality (RR, 0.82; 95% CI, 0.33–1.99). In contrast, it was associated with 2.34 (95% CI, 1.32–4.12) times higher risk of stroke mortality compared with optimal BP (<120/80 mm Hg). Moreover, their findings on BP at 120 to 129/80 to 84 mm Hg corroborate our finding of a null association for elevated BP, because they also did not find significant association with stroke (RR, 1.21; 95% CI, 0.67–2.17) or CHD (RR, 0.68; 95% CI, 0.29–1.61) mortality<sup>2</sup> for this BP category.

In the other 2 studies among Chinese populations,<sup>4,5</sup> prehypertension was defined as systolic BP 120 to

139 mm Hg and diastolic BP 80 to 90 mm Hg, without further categorization into a low or high range. In a follow-up study conducted in Taiwan, prehypertension was associated with a 73% (HR, 1.73; 95% CI, 1.00–2.98) higher risk of cardiovascular events.<sup>4</sup> In a nationwide study in China,<sup>5</sup> the HRs (95% CIs) associated with prehypertension were 1.22 (1.15–1.30) for CVD mortality (8745 events), 1.47 (1.23–1.75) for CHD mortality (1300 events), and 1.67 (1.50–1.86) for stroke mortality (4249 events). In their subgroup analysis, the significant association with CVD mortality was only observed in participants with at least 1 CVD risk factor (RR, 1.19; 95% CI, 1.11–1.28) but not in those without any CVD risk factor (RR, 1.11; 95% CI, 0.91–1.36). This led the authors to conclude that medical treatment of prehypertension may not be as beneficial as treatment of established hypertension in the general population.<sup>5</sup> In accordance with our results, this study also found that, although the association was significant among participants <65 years of age (HR, 1.29; 95% CI, 1.17–1.43), the association was weaker and of borderline significance among participants ≥65 years of age (HR, 1.08; 95% CI, 0.99–1.17).<sup>5</sup>

In line with our findings, another study in Singapore, composed of 77% Chinese, 15% Malays, and 6% Indians, demonstrated that, although prehypertension was associated



**Figure.** Association between categories of blood pressure and cardiovascular disease (CVD) mortality stratified by age and history of CVD. CI indicates confidence interval; HR, hazard ratio.

with CVD mortality, the risk estimate did not reach statistical significance (HR, 1.5; 95% CI, 0.8–2.6). This study was likely underpowered because the finding was based on 30 CVD deaths in the prehypertension group and did not provide information about cause-specific mortality, such as CHD and stroke mortality.<sup>3</sup> Notably, apart from ethnic mix, the participants were much younger than ours (mean age, 39 versus 63 years). Hence, the results supported our finding of an increased risk associated with stage 1 hypertension only among younger participants <65 years of age at BP measurements and without CVD history.

In a meta-analysis of 18 prospective studies, prehypertension, defined as systolic/diastolic BP 120 to 139/80 to 89 mm Hg, was associated with 28% higher risk of CVD mortality (RR, 1.28; 95% CI, 1.16–1.41).<sup>12</sup> Among these 18 studies included, 8 conducted in Asian countries comprised 3 Japanese studies, 2 Chinese studies, and 1 study each of Singaporeans (mixed ethnic groups), Koreans, and Indians. In this meta-analysis, a stronger association was observed in the pooled analysis for stroke mortality (RR, 1.41; 95% CI, 1.28–1.56) than CHD mortality (RR, 1.12; 95% CI, 1.02–1.23).<sup>12</sup>

In a recent meta-analysis<sup>13</sup> of 11 randomized clinical trials, although BP-lowering treatment in individuals with BP <140/90 mm Hg significantly reduced risk of a composite of CHD and stroke (RR, 0.89; 95% CI, 0.82–0.96), the investigators suggested that the benefit in risk reduction might be limited to stroke (RR, 0.77; 95% CI, 0.58–1.01) and not to CHD (RR,

1.04; 95% CI, 0.91–1.18). Their stratified analysis also revealed that the reduced risk was observed only in individuals at risk of CVD. The randomized controlled trials included in this meta-analysis mostly involved Hispanic, black, white, and Indian participants, and there was no mention of participants with Chinese ethnicity.<sup>13</sup> In the SPRINT (Systolic Blood Pressure Intervention Trial) involving 9361 participants in United States, intensive control of BP to <120/80 mm Hg in patients at high risk of CVD but without history of diabetes mellitus significantly lowered the risk of major cardiovascular outcomes and CVD mortality. However, most of the participants in this study belonged to the white, black, or Hispanic race.<sup>14</sup> Hence, although these findings support the American College of Cardiology/American Heart Association BP guidelines in lowering BP threshold for definition of hypertension in United States, they do not provide direct evidence of their benefits in other ethnicities, such as Chinese.

Ethnic variation in the distribution of risk factors and disease is a function of the frequency of specific genotypes and interaction with environmental factors.<sup>15</sup> Ethnic differences in prevalence of CVD risk factors are well established,<sup>16–18</sup> which, in turn, partially explain the observed differences in burden of CVD.<sup>19,20</sup> Ethnic differences in the relationship between risk factors and CVD explain why the risk scores developed in whites have performed inconsistently across ethnic groups<sup>21</sup> and also why being overweight is associated with greater mortality risk in Asians compared with

whites.<sup>22</sup> Ethnic differences in genetic predisposition to hypertension, even among different subgroups of Asians, are well known,<sup>23</sup> and this might be extended to the impact of BP on CVD risk. Our study participants originated from 2 contiguous provinces in southern China, and variations in genetic, lifestyle, or environmental factors among subethnic groups of Chinese may also account for disparity in results from observational studies involving Chinese originating from different geographical parts of China. Hence, the claim in the new guideline that “this risk gradient was consistent across subgroups defined by sex and race/ethnicity”<sup>1</sup> might root in lack of sufficient data from other ethnicities who are less studied, including Chinese. Moreover, this study shows evidence of effect modification by age and CVD history for the association between stage 1 hypertension and CVD mortality, suggesting that age and preexisting CVD history are factors that need to be considered in determining the group that will benefit from adopting the lower BP cutoff threshold for hypertension definition. Future guidelines may need to consider age groups and preexisting CVD history separately in formulating clinical practice.

Among those <65 years of age in our study population (n=18 267), most (93.1%) had no history of CVD at BP measurement. The finding for a 40% increase in risk of CVD mortality associated with the stage 1 hypertension in this relatively healthy middle-aged population bears public health importance. If our findings are confirmed by independent studies, a preventive program for the stage 1 hypertension screen and lifestyle intervention among people <65 years of age may have significant impact on reducing premature death from CHD and stroke.

The limitations of our study need to be considered when interpreting our findings. First, having BP measured on a single occasion precludes us from accounting for regression dilution bias that may lead to underestimation of the true association. Second, only mortality data were available in this study. Hence, if prehypertension is mostly associated with milder (nonfatal) types of CVD in participants >65 years of age, our study would not be able to show this association. However, the possible grounds or mechanism for such a selective association is not clear yet. Third, data on lipid profile of participants were not available; thus, we were not able to test these associations stratified by overall 10-year CVD risk at 10%, which was used by the guideline for management of hypertension. Fourth, because our participants were middle-aged or older adults of Chinese ancestry, our findings may not be generalizable to younger individuals or other ethnic/racial groups. Fifth, the observational nature of our study does not allow for causal inferences. Sixth, compared with those who were excluded from this study because they did not consent to being visited for the donation of biospecimen (blood or urine) for research and, therefore, did not have BP measurement, those who were included in this

study were, on average, 1.4 years younger, more likely to be Hokkien, and had higher level of education. They were also more likely to be never smokers (3.2%) and had lower prevalence of diabetes mellitus (2.0%) or CVD (0.8%–0.6%). This is expected of longitudinal cohort studies in that participants who continue to participate tend to be healthier, a phenomenon coined the “healthy volunteer effect.”<sup>24</sup> Accordingly, although cohorts tend to be composed of participants who are healthier than the general population, bias is not likely to occur for internal comparisons<sup>24</sup> because it is possible to control this effect by including the differential factors as potential confounders in the statistical models. In our analysis, we have included these lifestyle and health factors that may have confounded the association between BP and mortality risk. Finally, it is still possible that adjustments may not have accounted for unknown confounders, leading to the possibility of residual confounding.

## Perspectives

In conclusion, our study consistently found no higher risk of CVD, CHD, and stroke mortality at elevated BP (systolic/diastolic BP 120–129/<80 mm Hg) or stage 1 hypertension (130–139/80–89 mm Hg), except in individuals <65 years of age and without CVD history. We recommend that more studies should be done in different populations of various ages and ethnicity and by history of preexisting CVD before global adoption of the newly defined hypertension categories, according to American College of Cardiology/American Heart Association guidelines.

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## Author Contributions

Talaei and Hosseini: wrote the first draft. Talaei and W.-P. Koh performed statistical analysis. W.-P. Koh: designed and conducted the whole study. W.-P. Koh, Yuan, A.S. Koh: assisted in interpretation and critically edited the article. All authors read and approved the final article.

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## Disclosures

None.

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