

Prehypertension and the Risk of Coronary Heart Disease in Asian and Western Populations: A Meta-analysis

Yuli Huang, MD, PhD; Xiaoyan Cai, MD; Changhua Liu, MD; Dingji Zhu, MD; Jinghai Hua, MD; Yunzhao Hu, MD, PhD; Jian Peng, MD; Dingli Xu, MD

Background—The results of studies on the association between prehypertension (blood pressure 120 to 139/80 to 89 mm Hg) and coronary heart disease (CHD) remain controversial. Furthermore, it is unclear whether prehypertension affects the risk of CHD in Asian and Western populations differently. This meta-analysis evaluated the risk of CHD associated with prehypertension and its different subgroups.

Methods and Results—The PubMed and Embase databases were searched for prospective cohort studies with data on prehypertension and the risk of CHD. Studies were included if they reported multivariate-adjusted relative risks (RRs) with 95% CIs of CHD from prehypertension. A total of 591 664 participants from 17 prospective cohort studies were included. Prehypertension increased the risk of CHD (RR 1.43, 95% CI 1.26 to 1.63, *P*<0.001) compared with optimal blood pressure (<120/80 mm Hg). The risk of CHD was higher in Western than in Asian participants (Western: RR 1.70, 95% CI 1.49 to 1.94; Asian: RR 1.25, 95% CI 1.12 to 1.38; ratio of RRs 1.36, 95% CI 1.15 to 1.61). The population-attributable risk indicated that 8.4% of CHD in Asian participants was attributed to prehypertension, whereas this proportion was 24.1% in Western participants.

Conclusions—Prehypertension, even at the low range, is associated with an increased risk of CHD. This risk is more pronounced in Western than in Asian populations. These results supported the heterogeneity of target-organ damage caused by prehypertension and hypertension among different ethnicities and underscore the importance of prevention of CHD in Western patients with prehypertension. (*J Am Heart Assoc.* 2015;4:e001519 doi: 10.1161/JAHA.114.001519)

Key Words: cardiovascular disease • coronary heart disease • prehypertension • risk

H ypertension is a major cause of cardiovascular disease (CVD). The excess risk of CVD may extend to those with prehypertension (blood pressure [BP] 120–139/80–89 mm Hg).¹ Our prior studies showed that prehypertension was associated with increased risks of composite CVD and stroke.^{2,3} The risks were increased if BP was low, as in low-range prehypertension (120 to 129/ 80 to 84 mm Hg), and were further increased with

Received October 14, 2014; accepted December 30, 2014.

(130 high-range prehypertension to 139/85 89 mm Hg).^{2,3} The effects of abnormal BP on coronary and cerebral arteries are not identical, and the risk of coronary heart disease (CHD) associated with prehypertension is still controversial.4-6 Furthermore, the risks of damage to target organs through hypertension vary significantly among different ethnic groups. Stroke, for example, is more common in Asian patients with hypertension, whereas CHD is more prevalent in American and European patients (traditionally defined as Western) with hypertension.⁷ This difference may be influenced by the environment and by dietary and lifestyle habits⁷; however, it remains unclear whether prehypertension affects the risk of CHD for Asian and Western patients differently.

In view of the substantial implications for public health of ethnic differences in the association between prehypertension and CHD risk, we performed a systematic review and metaanalysis of all available prospective data to examine the association between prehypertension and CHD and to estimate the relative effect of prehypertension on CHD risk in Western and Asian populations.

From the Department of Cardiology, Nanfang Hospital, Southern Medical University, Guangzhou, China (Y. Huang, C.L., D.Z., J.H., J.P., D.X.); Department of Cardiology, the First People's Hospital of Shunde, Foshan, China (X.C., Y. Hu).

Correspondence to: Dingli Xu, MD, or Jian Peng, MD, Department of Cardiology, Nanfang Hospital, Southern Medical University, 1838 North Guangzhou Avenue, Guangzhou 510515, China. E-mails: dinglixu@fimmu.com, jianpeng2003@126.com

^{© 2015} The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Methods

Search Strategy and Selection Criteria

The study was approved by the institutional review committees of the participating hospitals. Following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group,⁸ we systematically searched PubMed and Embase for reports published between January 1, 1966, and June 30, 2014, using a combined text and MeSH heading search strategy with the following terms: prehypertension, prehypertensive, pre-hypertension, pre-hypertensive, blood pressure, arterial pressure, borderline hypertension, and cardiovascular disease, cardiovascular events, coronary artery disease, coronary heart disease, ischemic heart disease, myocardial ischemia, myocardial infarction, angina. We restricted the search to human studies. There were no restrictions on language or publication form. We also reviewed the reference lists of identified reports for other potentially relevant studies. The detailed search strategy for PubMed is presented in Table 1. The strategies for other databases were similar but were adapted as necessary.

Prospective studies were included if they met the following criteria: (1) All participants were aged \geq 18 years, (2) BP and other cardiovascular risk factors were assessed at baseline, (3) multivariate-adjusted relative risks (RRs) or hazard ratios for the events (ie, CHD) associated with prehypertension versus the reference category (optimal BP of <120/ 80 mm Hg) were reported.

Studies were excluded (1) if the RRs were unadjusted or adjusted only for age and sex, (2) if enrollment depended on having specific pathologic disorders (eg, diabetes mellitus or other baseline chronic diseases), or (3) if data were derived from the same cohort or meta-analysis of other cohort studies.

When duplicate publications from the same cohort were identified, only the most recent data were included for analysis.

Data Extraction and Quality Assessment

Two investigators (Y. H. and X. C.) independently used the search strategy to identify potentially relevant reports. Complete articles of potentially relevant reports were obtained and reviewed according to predefined criteria. Information on study and participant characteristics, follow-up duration, and outcome assessment was abstracted and transferred to specially designed, pretested forms. When the primary outcome data were unpublished, we contacted the principal author for additional information.

The quality of each study was evaluated following the guidelines developed by the US Preventive Services Task Force and a modified checklist.^{9,10} This checklist assessed (1) prospective study design, (2) maintenance of comparable

Table 1. Literature Search Strategy for PubMed

1	("Blood Pressure" [Mesh] OR "Arterial Pressure" [Mesh]) OR "Prehypertension" [Mesh]
2	(((((prehypertension[Text Word]) OR pre-hypertension[Text Word]) OR prehypertensive[Text Word]) OR pre-hypertensive[Text Word]) OR "borderline hypertension"[Text Word]) OR "blood pressure" [Text Word]) OR "Arterial Pressure"[Text Word]
3	1 OR 2
4	((((("Cardiovascular Diseases"[Mesh]) OR "Coronary Artery Disease"[Mesh]) OR "Myocardial Ischemia"[Mesh]) OR "Myocardial Infarction"[Mesh]) OR "Angina Pectoris"[Mesh]
5	(((((cardiovascular disease[Text Word]) OR cardiovascular events [Text Word]) OR coronary artery disease[Text Word]) OR coronary heart disease[Text Word]) OR ischemic heart disease [Text Word]) OR myocardial ischemia[Text Word]) OR myocardial infarction[Text Word]) OR angina[Text Word]
6	4 OR 5
7	3 AND 6
8	("Epidemiologic Studies" [Mesh]) OR ((((((("epidemiologic study" [Text Word]) OR epidemiology [Text Word]) OR "cohort study" [Text Word]) OR "longitudinal study" [Text Word]) OR "follow up" [Text Word]) OR "followed up" [Text Word]) OR "observational study" [Text Word]) OR prospective)
9	7 AND 8
10	("Cross-Sectional Studies" [Mesh] OR "Cross-Sectional" [Text Word]
11	9 NOT 10
12	((((Clinical Trial[Publication Type]) OR Case Reports[Publication Type]) OR Comment[Publication Type]) OR Editorial[Publication Type]) OR Review[Publication Type]
13	11 NOT 12
14	animals[MeSH Terms]
15	humans[MeSH Terms]
16	14 NOT 15
17	13 NOT 16

groups, (3) adequate adjustment of potential confounders (at least 5 of 6 factors: age, sex, diabetes mellitus, body mass index or other measure of overweight or obesity, cholesterol, and smoking), (4) documented rate of loss to follow-up, (5) outcome assessed blind to baseline status, (6) clear definition of exposures (prehypertension) and outcomes (CHD), (7) temporality (BP measured at baseline, not at the time of outcome assessment), and (8) follow-up of at least 2 years. Study quality was graded as good if the study met 7 or 8 criteria, as fair for 4 to 6 criteria, and as poor for <4 criteria.

Data Synthesis and Analysis

The primary outcome was the RR of CHD in participants with prehypertension. The secondary outcomes were the RRs of

CHD in American and European participants (defined as *Western*) in comparison with Asian participants. Subgroup analyses of the primary outcome were conducted according to BP (low-range versus high-range prehypertension), specific end points (fatal versus fatal plus nonfatal CHD), sex (men versus women), participant age (average <55 versus \geq 55 years), follow-up duration (<10 versus \geq 10 years), participant number (<10 000 versus \geq 10 000), exclusion of participants with CVD at baseline (yes versus no), and study quality (good versus fair).

For each study, we extracted the multivariate-adjusted risk ratios or hazard ratios (with 95% Cls) for participants with prehypertension versus those with optimal BP. After log transformation of study-specific estimates, the inverse variance approach was used for analysis.² The I² statistic was used to estimate the percentage of variability across studies attributable to between-study heterogeneity (25%, 50%, and 75%, representing low, moderate, and high heterogeneity, respectively).¹¹ We detected between-study heterogeneity for several outcomes; therefore, we generated pooled estimates across studies using random-effects meta-analysis. The Western/Asian ratio of RR (and its 95% Cl) was calculated according to the method described previously.¹²

We assessed the presence of publication bias by inspecting funnel plots for each outcome in which the natural log of RR was plotted against its SE. In addition, we conducted sensitivity analyses in which the pooled RR was recalculated by omitting 1 study at a time. *P* values were 2-tailed, and the statistical significance was set at 0.05. All analyses were performed with RevMan software (version 5.2 for Windows; Cochrane Collaboration).

We also determined the population-attributable risk (PAR) for prehypertension on the basis of the pooled RR. *PAR%* expresses the proportion of disease in the study population that is attributable to the exposure (prehypertension) and that could be eliminated if the exposure were eliminated. The PAR% was calculated as PAR%=(Pe)(RR-1)/([Pe][RR-1]+1) × 100, in which Pe is the proportion of the population exposed to the risk factor (prehypertension) and RR is multivariate adjusted.²

Results

Selected Studies and Characteristics

We determined 27 845 manuscripts at initial retrieval. After screening of the titles and abstracts, 81 were found to qualify for full review (Figure 1). Finally, we included 17 prospective cohort studies, with a total of 591 664 participants derived from the general population, for analysis.^{4–6,13–26}





Table 2 summarizes the key features of the included studies. Of the 17 studies, 10 reported incidence of CHD,^{4–} $^{6,13-15,21-23,26}$ 5 reported mortality from CHD,^{16,18,19,24,25} and 2 reported both CHD morbidity and mortality associated with prehypertension.^{17,20} Ten studies were from Asia,^{14,15,17–21,23,25,26} and 7 were from the United States and Europe.^{4–6,13,16,22,24} The proportion of Asian participants was 73.5%. The mean age at enrollment was 54.6 years, and the mean duration of follow-up was 8.53 years. The mean prevalence of prehypertension was 38.8%. Three studies enrolled only women,^{13,19,23} whereas the others included both sexes, with the proportion of women amounting to 59.2%. Four studies did not exclude participants with CVD at baseline,^{16–19} and all others included participants without CVD.

Three studies did not meet our criteria for adequate adjustment of potential confounders, ^{14,18,19} and these were

also graded as fair according to the predefined qualityassessment criteria. All other studies were adequately adjusted and graded as good. The details of the quality assessment and adjustment for confounders are presented in Table 3. The baseline characteristics in prehypertension and optimal BP groups of the included studies are presented in Table 4.

Association Between Prehypertension and Risk of CHD

Because there was substantial heterogeneity in all studies $(l^2=65\%)$, a random-effects model was used in the analysis. After multivariate adjustment, prehypertension was associated with increased risk of CHD (RR 1.43, 95% CI 1.26 to 1.63) compared with optimal BP (Figure 2). The risk of CHD was higher in Western than in Asian participants (Western: RR

Study	Country	Prevalence of Prehypertension (%)	Sample Size (% Women)	Age (y), Average (Range or SD)	Follow-up (v)	Participants With CVD at Baseline Excluded	Events for Analysis
Qureshi et al ⁴	United States	41.1	5181 (55.3)	44.0 (8.6)	31	Yes	CHD incidence
Lee et al ⁵	United States	32.6	4372 (60.6)	56.2(45 to 74)	12	Yes	CHD incidence
Kshirsagar et al ⁶	United States	37.3	8960 (55)	53(45 to 64)	11.6	Yes	CHD incidence
Hsia et al ¹³	United States	39	60 785 (100)	62.8 (7.0)	7.7	Yes	CHD incidence
Onat et al ¹⁴	Turk	32.8	3034 (50.4)	48 (12)	6.6	Yes	CHD incidence
Kokubo et al ¹⁵	Japan	35	5494 (53)	55 (30 to 79)	11.7	Yes	CHD incidence
Thomas et al ¹⁶	France	54.2	69 989 (40.7)	56.5 (>50)	15.3	No	CHD mortality
Gu et al ¹⁷	China	34.5	158 666 (51)	56 (≥40)	7.7	No	CHD incidence CHD mortality
Pednekar et al ¹⁸	India	38.8	148 173 (40.2)	50 (≥35)	5.5	No	CHD mortality
Dorjgochoo et al ¹⁹	China	33.2	68 438 (100)	55.1±9.1	5.1	No	CHD mortality
lkeda et al ²⁰	Japan	43	33 372 (65)	54 (40 to 69)	11.0	Yes	CHD incidence CHD mortality
Fukuhara et al ²¹	Japan	37.7	2634 (58)	59.1 (≥40)	19	Yes	CHD incidence
Erbel et al ²²	Germany	26.2	4181 (53)	59.3 (40 to 75)	7.18	Yes	CHD incidence
Sadeghi et al ²³	Iran	36	3255 (100)	49.7 (≥35)	6.7	Yes	CHD incidence
Stojanov et al ²⁴	Serbia	40.8	265 (48.7)	43.6 (30 to 60)	36	Yes	CHD mortality
Takashima et al ²⁵	Japan	41.2	8592(56.0)	49.4 (30 to 92)	21.3	Yes	CHD mortality
Hadaegh et al ²⁶	Iran	34.5	6273(57)	47.1 (≥30)	9.3	Yes	CHD incidence

Table 2. Study Characteristics

CHD indicates coronary heart disease; CVD, cardiovascular disease.

 Table 3. Quality Assessment and Confounders Adjusted in the Included Studies

Study	Risk Factors Adjusted				
Qureshi ³	Age, sex, smoking, obesity, DM, hypercholesterolemia, and study period				
Lee ⁴	Age, sex, DM, smoking, LDL-C, HDL-C and albuminuria				
Kshirsagar ⁵	Age, race, sex, BMI, DM, smoking, LDL-C, HDL-C, education level, sport index, CHOL lowering medication, fibrinogen, vWF and WBC	Good			
Hsia ¹²	Age, BMI, DM, CHOL, and smoking	Good			
Onat ¹³	Age, sex, heart rate, smoking, obesity	Fair			
Kokubo ¹⁴	Age, BMI, hyperlipidemia, DM, smoking and drinking status	Good			
Thomas ¹⁵	Age, sex, CHOL, DM, physical activity, smoking, drinking, and antihypertensive drug	Good			
Gu, 2009 ¹⁶	Age, sex, education level, smoking and drinking status, BMI, physical activity, antihypertensive medication, history of CVD or DM, geographic region and urbanization	Good			
Pednekar ¹⁷	Age, education, religion, mother tongue, smoking, and BMI	Fair			
Dorjgochoo ¹⁸ Age, education, waist/hip ratio, smokir history of CVD and DM		Good			
lkeda ¹⁹	Age, sex, BMI, smoking and drinking status, antihypertensive medication, history of DM, CHOL, and public health center areas	Good			
Fukuhara ²⁰	Age, sex, BMI, CHOL, HDL-C, DM, chronic kidney disease, electrocardiogram abnormalities, smoking, drinking, and regular exercise	Good			
Erbel ²¹	Age, sex, cholesterol, DM, and smoking	Good			
Aghababaei ²²	Age, DM, CHOL, BMI, smoking and menopause	Good			
Stojanov ²³	Age, sex, BMI	Fair			
Takashima ²⁴	Age, sex, BMI, CHOL, hyperglycemia, smoking, and drinking habit	Good			
Hadaegh ²⁵	Age, sex, CHOL, BMI, smoking, DM, lipid- lowering medication and family history of premature CVD	Good			

BMI indicates body mass index; CHOL, cholesterol level; CVD: cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; vWF, von Willebrand factor; WBC, white blood cell count.

1.70, 95% CI 1.49 to 1.94; Asian: RR 1.25, 95% CI 1.12 to 1.38; ratio of RRs 1.36, 95% CI 1.15 to 1.61).

There was no evidence of publication bias on visual inspection of the funnel plot (Figure 3). On the basis of the pooled RR, the PARs of CHD for prehypertension were 14.3% in the all-studies population, 24.1% in the Western cohort, and 8.4% in the Asian cohort.

In the subgroup analyses, low-range prehypertension increased the risk of CHD compared with optimal BP (RR 1.27, 95% CI 1.07 to 1.57), and the RR of CHD in high-range prehypertension was 1.58 (95% CI 1.24 to 2.24); however, the difference between low-range and high-range prehypertension was not significant (ratio of RRs 1.24, 95% Cl 0.92 to 1.67). Furthermore, the risk of CHD was higher in studies with a follow-up duration \geq 10 years (RR 1.68, 95% CI 1.50 to 1.90) than in those with <10 years of follow-up (RR 1.27, 95% CI 1.10 to 1.48; ratio of RRs 1.32, 95% CI 1.09 to 1.60), in studies in which participants with CVD at baseline were excluded (RR 1.54, 95% CI 1.34 to 1.77) than in those in which such participants were not excluded (RR 1.21, 95% CI 1.03 to 1.43; ratio of RRs 1.27, 95% CI 1.03 to 1.58), and in studies with adequate adjustment of other risk factors (RR 1.48, 95% Cl 1.30 to 1.49) than in those with inadequate adjustment (RR 1.13, 95% CI 0.99 to 1.28; ratio of RRs 1.31, 95% CI 1.13 to 1.51). There were no significant differences in the comparisons of other subgroups (Table 5).

Sensitivity Analyses

We used multiple methods to test sensitivity and found that the association of prehypertension and risk of CHD was not influenced by the use of fixed-effect models compared with random-effect models, odds ratios compared with RRs, or recalculation by omitting 1 study at a time.

Discussion

In this meta-analysis comprising 591 664 participants, we found that after controlling for multiple cardiovascular risk factors, people with baseline prehypertension—even at low range—had an increased risk of CHD. The results were more significant in studies with a follow-up duration >10 years, with adequate adjustment of other risk factors, and with exclusion of participants with CVD at baseline. More important, the risk of CHD associated with prehypertension was higher in Western than in Asian participants. The PAR calculation indicated that 8.4% of CHD cases could be prevented if prehypertension were eliminated in Asian patients, and this proportion increased to up to 24.1% in Western patients.

The term *prehypertension* has been controversial. An argument against this term is that the range of BP is too broad and that those with prehypertension at the high range (BP 130–139/85–89 mm Hg) and at the low range (BP 120 to 129/80 to 84 mm Hg) may have varying risks of developing CVD.^{27,28} In this study, we obtained robust data to show that persons with baseline prehypertension, even at

Table 4. Baseline Characteristics in Prehypertension and Optimal Blood Pressure Groups

Operation of a state of a	Study/BP Group (Participant Number)	Age (y)	SBP (mm Hg)	DBP (mm Hg)	BMI (kg/m²)	DM (%)	TC (mg/dL)	LDL-C (mg/dL)	Smoking (%)
Induma Indum	Qureshi et al ⁴	-	-			-			
IPre-fl Rotinger et all42.9.8.2°128.6.6°80.1.5°25.7.3.6°17.21.7.4.3°ICI.61Kaivarger et all55.4.6106.4.867.720.6.4.25	Optimal BP (1012)	39.6±7.4	112±6	72±5	24.0±3.	1	205±41	_	61
Kshivagar et allOptimal BP (5622)53.60.61.867.1725.01.45010131.4824Low-range preAtr (2059)54.64°132.45°79.4°25.15.4°10-137.38°24'High-range pre-HT (2059)65.46°132.45°79.4°28.14.5.3°10"-10137.38°24'Pre-HT (2356)60.74.6.7109.4769.4626.94.521.81.87.4'Robaco at 1°7.4'7.8'29.15.8'3.0"<	Pre-HT (2017)	42.9±8.2*	128±6*	80±5*	25.7±3.6*	1	217±43*	_	61
Optimal BP (6822)53±6105±806±867±726.0±25F13±3*<	Kshirsagar et al ⁶								
Inder-energy54.4°123.4°75.1°75.1°7.4.6.17.3°.137.3°.25'High-range pre-HT (1279)132.4°132.4°79-8°23.1-53°10°.10°.137.3°24'Bisa et a''130.1°19.1°69.162.8.1.52°1.8°17.4.3°.17.4.3°Optimal BP (16002)60.7.6.710.9.1°74.7°2.8.9.5.8°	Optimal BP (5622)	53±6	106±8	67±7	26.0±4.2	5	_	134±38	28
High-range pre-HT (1279)55±6**132±5**79±8*28.1±5.3**10**—137±38*24*Hsia et13*Uptimal BP (16002)60.7±6.7109±776±626.9±5.21.8———10Pre-HT (2566)62.6±6.8*130±11*78±728.9±5.8*1.8———7.4*Kokubo et 1*Potimal BP (603)50.8±1.32*107.8±7.5*86.2±6.7*22.0±2.7*5.8*201.15*—48.6*High-range pre-HT (602)54.0±1.29*13.1±5.8**81.2±6.9**23.2±2.7*5.6*206±35*—46.3*Optimal BP (603)50.8±1.35*13.1±5.8**81.2±6.9**23.2±2.7*5.6*20.5±5.7*46.3*Optimal BP (1240)50.4±1.5*12.2±4.4*75.5±7.1*22.5±3.0*3.3*1.6±3.9*—1.17*High-range pre-HT (604)54.9±1.5*132.4±.9**79.7±6.9**22.8±3.2*4.0*21.43*—1.17*High-range pre-HT (615)58.9±1.1*132.4±.9**79.7±6.9**22.8±3.2*4.0*23.8±6*—1.9*Uptimal BP (2683)55.9±5.4*131.40.05*80.40.3**24.8±0.05*8.4*23.8±6*.11.2*Uptimal BP (61643)55.9±5.4*131.40.05*80.40.2**8.4*23.8±6*.2.11.2*Uptimal BP (61643)55.9±5.4*131.40.05*21.6±3.5*1.0**23.8±2**.1.11.0**1.0**Uptimal BP (6263)5.9±1.0*10	Low-range pre-HT (2059)	54±6*	123±4*	75±7*	27.5±5.0*	7*	_	137±38*	25*
Hsin et al"3Optime BP (6002)60.7±6.7109±769±6.026.9±5.81.810Pn-HT (25896)62.6±6.8'130±11*76±7*26.9±5.8'3.0*7.4*Kacko et al"	High-range pre-HT (1279)	55±6* [†]	132±5* [†]	79±8*	28.1±5.3* [†]	10* [†]	_	137±38*	24*
İnduma BP (16002)60.7±.67109±.769±.6120.9±.581.81.74Pre-HT (25396)62.6±.68109±.1778±.7728.9±.583.0*7.4*Kakuse at 15WerOptimal BP (803)50.8±12.4117.8±.7568.2±.6722.0±.275.8197±.319.67I dynamage ne-HT (602)50.8±12.41107.8±.7568.2±.6722.0±.275.8201±.359.67I dynamage ne-HT (604)50.8±12.41107.8±.7568.2±.6722.0±.275.8201±.359.67Optimal BP (240)57.8±17.41105.8±.7568.4±.6821.1±.271.5201±.359.15Optimal PP (1240)47.8±11.9105.5±.7468.4±.6821.1±.271.5201±.3521.8±.359.1511.7Optimal PP (240)54.9±.15122.4±.4875.5±.7±22.5±.303.2*21.8±.3512.8±12.8±.7512.8	Hsia et al ¹³								
Pre-HT (28399)62.6 ± .6.8°130 ± .11*78.4 °28.9 ± .5.8°.0.9°	Optimal BP (16002)	60.7±6.7	109±7	69±6	26.9±5.2	1.8	—	_	10
Network of a state of a st	Pre-HT (23596)	62.6±6.8*	130±11*	78±7*	28.9±5.8*	3.0*	_	_	7.4*
ImmOptimal BP (600)54.0:12.0°102.1:5.4°62.6:7.0°22.0:2.1°5.891.91.3°9.7.049.7Low-range pre-HT (603)57.5:12.2°13.14.5.4°81.26.9°32.32.2.7°5.8°20.13.53°9.7.046.3°High-range pre-HT (604)57.5:12.2°13.14.5.4°81.26.9°32.32.2.7°5.8°20.43.53°9.7.0°46.3°Owmen70.5:1.2°12.44.8°75.5:1.7°22.5:1.0°3.0°21.9:3.9°12.1:4°17.1°High-range pre-HT (604)50.9:1.1°12.44.4°75.5:1.7°22.5:1.0°3.0°21.9:3.9°10.117.1°High-range pre-HT (2823)50.9:5.4°131.40.0°80.40.0°4.6.10°21.9:1.0°17.1°17.1°High-range pre-HT (5103)55.9:5.4°131.40.0°81.40.0°8.4.10°18.1°11.1°16.1°17.1°17.1°High-range pre-HT (5103)55.9:5.4°131.40.0°81.40.0°8.4.10°18.1°17.1°17.1°17.1°High-range pre-HT (5103)55.9:5.1°132.01.0°81.40.0°8.4.10°18.1°17.1°	Kokubo et al ¹⁵								
Optimal BP (803) 50.8±13.2* 107.8±7.5* 82.9±6.7* 22.0±2.7* 3.8* 197±31 9.94 9.97 Low-range pre-HT (602) 54.0±1.29* 121.7±5.4* 76.6±6.3* 22.7±6.8* 5.0* 2013.35* -0.04 49.6* High-range pre-HT (463) 57.5±12.4* 131.4±5.4* 75.5±7.1* 21.1±2.7* 1.5* 201±3.5* -0.0* 15.6* Low-range pre-HT (504) 47.8±11.9* 105.5±7.9* 66.4±6.6* 21.1±2.7* 1.5* 201±3.5* -0.0* 15.6* Low-range pre-HT (504) 45.4±1.5* 12.4±4.4* 75.5±7.1* 22.8±3.0* 3.0* 21.8±7.8* -0.0* 11.7* High-range pre-HT (605) 54.8±1.5* 131±0.5* 80±0.3* 24.8±0.0* 8.4* 23.8±0* -0.0* 16.1* Low-range pre-HT (5026) 55.9±5.4* 131±0.5* 80±0.3* 24.8±0.5* 1.0* -0.0* 32.8±5.* 1.8± 32.8±5.* 23.8±5.* 1.0* -0.0* 32.8±5.* 32.8±5.* 1.0** -0.0* 32.8±5.*	Men								
Low-range pre-HT (502)54.0 ± 12.0*12.1 ± 5.4*76.6 ± 6.3*22.7 ± 0.5*201 ± 35*9.0*49.6*High-range pre-HT (463)57.5 ± 12.2**13.1 ± 5.8**81.2 ± 6.9**23.2 ± 2.7**5.6*201 ± 350.0*45.3*Worme10.5 ± 7.966.4 ± 6.621.1 ± 7.1.5201 ± 350.0*1.51.5Low-range pre-HT (504)54.9 ± 1.15*12.2 ± 4.4*75.5 ± 7.1*22.5 ± 3.0*3.3*218.39*0.01.71.5High-range pre-HT (605)54.9 ± 1.15*13.2 ± 4.4*79.7 ± 6.9**22.8 ± 2.*4.0*201 ± 35*0.01.71.7High-range pre-HT (2605)54.9 ± 1.15*13.2 ± 4.4*79.7 ± 6.9**22.8 ± 2.*4.0*21.4 ± 3*0.2*1.71.7Jour-ange pre-HT (2602)54.9 ± 1.15*11.1 ± 0.2*68.1 ± 0.3**23.4 ± 0.4* <t< td=""><td>Optimal BP (803)</td><td>50.8±13.2*</td><td>107.8±7.5*</td><td>68.2±6.7*</td><td>22.0±2.7</td><td>3.8</td><td>197±31</td><td>_</td><td>59.7</td></t<>	Optimal BP (803)	50.8±13.2*	107.8±7.5*	68.2±6.7*	22.0±2.7	3.8	197±31	_	59.7
Hgh-range pre-HT (463)57.5 ± 12.2"13.1 ± 15.8"13.2 ± 2.4"5.420.5 ± 3010.4 ± 6.4*WormenOptima BP (1240)45.8 ± 11.910.5 ± 7.466.4 ± 6.621.1 ± 2.71.5201 ± 3515.6Low-range pre-HT (660)58.9 ± 1.0*12.2 ± 4.4.8"75.5 ± 7.1*2.2 ± 3.4.0*2.1 ± 3.5* <td>Low-range pre-HT (502)</td> <td>54.0±12.9*</td> <td>121.7±5.4*</td> <td>76.6±6.3*</td> <td>22.7±2.6*</td> <td>5.3*</td> <td>201±35*</td> <td>_</td> <td>49.6*</td>	Low-range pre-HT (502)	54.0±12.9*	121.7±5.4*	76.6±6.3*	22.7±2.6*	5.3*	201±35*	_	49.6*
NomenOptimal PP (1240)47.8 ± 1.1.9105.5 ± 7.966.4 ± 6.621.1 ± 2.71.5.5201.4 5.515.6Lowrange pre-HT (640)58.9 ± 1.1.5"132.4 ± 4.8"75.5 ± 7.1"22.5 ± 3.0"3.2"21.8 ± 9"17.1"High-range pre-HT (640)58.9 ± 1.1.5"132.4 ± 4.8"79.7 ± 6.9"22.8 ± 3.2"4.0"22.1 ± 5.5"9.2"Dymal BP (2963)54.8 ± 4.5111 ± 0.268.± 0.123.2 ± 0.066.422.4 ± 717.2"Low-range pre-HT (32823)55.9 ± 5.4"131 ± 0.05"80 ± 0.03"24.6 ± 0.02"8.5"23.3 ± 0"16.1Gu et al ¹⁷ 132 ± 0.1"83 ± 0.04"24.8 ± 0.05"8.4"23.4 ± 0"37.0Pre-HT (58569)55.6 ± 5.1"132 ± 0.1"8.6 ± 0.2"8.4"23.4 ± 0"37.037.0Pre-HT (58569)55.7 ± 0.1106.8 ± 2.0"78.0 ± 7.0"28.4 ± 5.1"1.0"37.0Pre-HT (58569)51.9106.8 ± 2.0"78.0 ± 7.0"28.4 ± 5.1"1.0"37.0Optimal BP (2058)51.921.3 ± 7.0"3.1"Optimal BP (2058)50.921.4 ± 71.0"Inder-ange pre-HT (2463)50.921.4	High-range pre-HT (463)	57.5±12.2* [†]	131.4±5.8* [†]	81.2±6.9* [†]	23.2±2.7* [†]	5.6*	205±35*	_	46.3*
Optimal BP (1240)47.8±1.19105.5±7.9164.4±6.6421.1±2.711.5201±351	Women								
Low-range pre-HT (604) 54.0 ± 11.5* 122.4 ± 4.8* 75.5 ± 7.1* 22.5 ± 3.0* 3.3* 218 ± 39*	Optimal BP (1240)	47.8±11.9	105.5±7.9	66.4±6.6	21.1±2.7	1.5	201±35	_	15.6
High-range pre-HT (465) 58.9±11.5* ¹ 132.4±4.9* ⁸ 79.7±6.9* ¹ 22.8±3.2* 4.0* 221±35*	Low-range pre-HT (504)	54.0±11.5*	122.4±4.8*	75.5±7.1*	22.5±3.0*	3.3*	218±39*	_	11.7*
Thomas et al ¹⁶ Optimal BP (2963) 54.8±4.5 111±0.2 68±0.1 23.2±0.06 6.4 224±7 Low-range pre-HT (32823) 55.9±5.4* 131±0.05* 80±0.03* 24.6±0.02* 8.5* 23.3±2* High-range pre-HT (5103) 55.6±5.1* 132±0.1* 8.3±0.08* 24.8±0.05* 8.4* 23.3±6* Gut al ¹⁷ <td>High-range pre-HT (465)</td> <td>58.9±11.5*[†]</td> <td>132.4±4.9*[†]</td> <td>79.7±6.9*[†]</td> <td>22.8±3.2*</td> <td>4.0*</td> <td>221±35*</td> <td>_</td> <td>9.2*</td>	High-range pre-HT (465)	58.9±11.5* [†]	132.4±4.9* [†]	79.7±6.9* [†]	22.8±3.2*	4.0*	221±35*	_	9.2*
Optimal BP (2963) 54.8±4.5 111±0.2 68±0.1 23.2±0.06 6.4 224±7 17.9 Low-range pre-HT (52823) 55.9±5.4* 131±0.05* 80±0.03* 24.6±0.02* 8.5* 233±2* 17 High-range pre-HT (5103) 55.6±5.1* 132±0.1* 83±0.08* 24.8±0.05* 8.4* 233±6* 16.1 Gu et al ¹⁷ 70 8.4*0.05* 8.4* 233±6* 16.1 Gu et al ¹⁷	Thomas et al ¹⁶								
Low-range pre-HT (3282) 55.9±5.4* 131±0.05* 80±0.03* 24.6±0.02* 8.5* 233±2* 17 High-range pre-HT (5103) 55.6±5.1* 132±0.1* 83±0.08* 24.8±0.05* 8.4* 233±6* 16.1 Gu et al ¹⁷ 52.6±9.5 106.8±8.2 67.8±6.7 21.6±3.2 1.0 37.0 Pre-HT (58569) 55.7±10.6* 126.1±7.2* 78.0±7.0* 22.8±3.5* 1.9* 40.1* Ikeda et al ²⁰	Optimal BP (2963)	54.8±4.5	111±0.2	68±0.1	23.2±0.06	6.4	224±7	—	17.9
High-range pre-HT (5103) 55.6±5.1* 132±0.1* 83±0.08* 24.8±0.05* 8.4* 233±6* — 16.1 Gu et al ¹⁷ Optimal BP (64043) 52.6±9.5 106.8±8.2 67.8±6.7 21.6±3.2 1.0 — — A 37.0 Pre-HT (58569) 55.7±10.6* 126.1±7.2* 78.0±7.0* 22.8±3.5* 1.9* — — 40.1* Ikeda et al ²⁰ 5.7±10.6* 126.1±7.2* 78.0±7.0* 22.8±3.5* 1.9* — — 40.1* Ikeda et al ²⁰ — — 22.9±3.5* 1.9* — 40.1* Optimal BP (2058) 51.9 — — 23.3 5.1 186. — 45.9* Iubw-range pre-HT (2436) 54.6 — — 23.6 7.1* 194.0 — 44.6* Women — … 24.1 3.2* 205 … 2.9* Iuby-range pre-HT (4487) 52.9 … … <t< td=""><td>Low-range pre-HT (32823)</td><td>55.9±5.4*</td><td>131±0.05*</td><td>80±0.03*</td><td>24.6±0.02*</td><td>8.5*</td><td>233±2*</td><td>_</td><td>17</td></t<>	Low-range pre-HT (32823)	55.9±5.4*	131±0.05*	80±0.03*	24.6±0.02*	8.5*	233±2*	_	17
Gu et al ¹⁷ Optimal BP (64043)52.6 ± 9.5106.8 ± 8.267.8 ± 6.721.6 ± 3.21.037.0Pre-HT (58569)55.7 ± 10.6*126.1 ± 7.2*78.0 ± 7.0*22.8 ± 3.5*1.9*40.1*Ikeda et al ²⁰ MernOptimal BP (2058)51.922.35.118652.1I.ow-range pre-HT (2456)53.123.35.219445.9*Migh-range pre-HT (2456)53.123.67.1*19445.9*Women23.67.1*19445.9*Optimal BP (5536)50.921.7*20.1*19445.9*I.ow-range pre-HT (4867)50.921.7*20.1*19421.9*Optimal BP (5536)50.921.5*20.5*21.9*I.ght-range pre-HT (4867)55.1 ± 10.3110.8 ± 7.7*66.7 ± 7.7*21.4 ± 2.6*51.120.3 ± 320.4*21.4*21.4*21.4*21.4*21.4*21.4*21.4*21.4*	High-range pre-HT (5103)	55.6±5.1*	132±0.1*	83±0.08*	24.8±0.05*	8.4*	233±6*	_	16.1
Optimal BP (64043) 52.6 ± 9.5 106.8 ± 8.2 67.8 ± 6.7 21.6 ± 3.2 1.0 $ 37.0$ Pre-HT (58569) $55.7 \pm 10.6^{\circ}$ $126.1 \pm 7.2^{\circ}$ $78.0 \pm 7.0^{\circ}$ $22.8 \pm 3.5^{\circ}$ 1.9° $ 40.1^{\circ}$ Ikeda et al ²⁰ MenOptimal BP (2058) 51.9 $ 22.3$ 5.1 186 $ 52.1$ Low-range pre-HT (2456) 53.1 $ 23.3$ 5.2 194 $ 45.9^{\circ}$ High-range pre-HT (2433) 54.6 $ 23.6$ 7.1° 194 $ 45.9^{\circ}$ WomenUow-range pre-HT (2463) 50.9 $ 22.7$ 2.0 201 $ 45.9^{\circ}$ Ibigh-range pre-HT (4467) 52.9 $ 23.5$ 2.2 205 $ 2.9^{\circ}$ High-range pre-HT (4467) 52.9 $ 21.1^{\circ}$ 3.2° 209 $ 3.1^{\circ}$ Fukuhara et al ²¹ Uotimal BP (657) 55.1 ± 10.3 110.8 ± 7.7 66.7 ± 7.7 21.4 ± 2.6 5.1 20.3 ± 4.9 $ 29.7$ Low-range pre-HT (545) $56.4 \pm 11.7^{\circ}$ $133.8 \pm 8.5^{\circ^{\dagger}}$ $78.6 \pm 8.5^{\circ^{\dagger}}$ $23.4 \pm 2.1^{\circ^{\dagger}}$ 14.7° $21.2 \pm 3.5^{\circ^{\dagger}}$ $ 25.2^{\circ}$ Erbel et al ²² Dytimal BP (200) 56.7 111.46 71.45 26.3 ± 3.7 5.0 21.4 ± 3.4 33.5	Gu et al ¹⁷								
Pre-HT (58569) 55.7±10.6* 126.1±7.2* 78.0±7.0* 22.8±3.5* 1.9* — — 40.1* Ikeda et al ²⁰ Men Optimal BP (2058) 51.9 — — 22.3 5.1 186 — 52.1 Low-range pre-HT (2456) 53.1 — — 23.3 5.2 194 — 45.9* High-range pre-HT (2430) 54.6 — — 23.6 7.1* 194 — 44.6* Women	Optimal BP (64043)	52.6±9.5	106.8±8.2	67.8±6.7	21.6±3.2	1.0	—	_	37.0
Ikeda et al ²⁰ Men Optimal BP (2058) 51.9 22.3 5.1 186 52.1 Low-range pre-HT (2456) 53.1 23.3 5.2 194 45.9* High-range pre-HT (2483) 54.6 - 23.6 7.1* 194 - 44.6* Women - 22.7 2.0 201 - 4.5 Low-range pre-HT (4867) 52.9 - 23.5 2.2 205 - 2.9* High-range pre-HT (4467) 52.9 - - 24.1 3.2* 209 - 2.9* High-range pre-HT (4467) 54.5 - - 24.1 3.2* 209 - 3.1* Fukuhara et al ²¹ - - 26.12.1* 3.2* 209 - 29.7 Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 - 25.2* High-	Pre-HT (58569)	55.7±10.6*	126.1±7.2*	78.0±7.0*	22.8±3.5*	1.9*	—	_	40.1*
Men Optimal BP (2058) 51.9 22.3 5.1 186 52.1 Low-range pre-HT (2456) 53.1 23.3 5.2 194 45.9* High-range pre-HT (2483) 54.6 23.6 7.1* 194 44.6* Women 23.6 7.1* 194 45.9* Optimal BP (5536) 50.9 22.7 2.0 201 4.5 Low-range pre-HT (4867) 52.9 23.5 2.2 205 2.9* High-range pre-HT (4867) 54.5 24.1 3.2* 209 3.1* Fukuhara et al ²¹ 24.1 3.2* 209 29.7 Low-range pre-HT (545) 55.1±10.3 110.8±7.7 66.7±7.7 21.4±2.6 5.1 203±40 24.4* High-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0*	lkeda et al ²⁰								
Optimal BP (2058) 51.9 22.3 5.1 186 52.1 Low-range pre-HT (2456) 53.1 23.3 5.2 194 45.9* High-range pre-HT (2483) 54.6 23.6 7.1* 194 44.6* Women 23.6 7.1* 194 45.9* Low-range pre-HT (2483) 50.9 23.6 7.1* 194 44.6* Women 23.6 7.1* 2.0 201 4.5 Low-range pre-HT (4867) 52.9 - 23.5 2.2 205 2.9* High-range pre-HT (4471) 54.5 - - 24.1 3.2* 209 - 3.1* Fukuhara et al ²¹ - - 73.7 ±7.0* 21.4±2.6 5.1 203±40 -<	Men								
Low-range pre-HT (2456)53.123.35.219445.9*High-range pre-HT (2433)54.623.67.1*19444.6*Women22.72.02014.5Low-range pre-HT (4867)50.923.52.22052.9*High-range pre-HT (4467)54.524.13.2*2093.1*Fukuhara et al ²¹ 24.13.2*20929.7Low-range pre-HT (545)55.1±10.3110.8±7.766.7±7.721.4±2.65.1203±4024.4*High-range pre-HT (545)56.4±11.7*123.5±7.0*73.7±7.0*22.6±2.3*12.6*205±4524.4*High-range pre-HT (447)58.8±10.6*†133.8±8.5*†78.6±8.5*†23.4±2.1*†14.7*212±33*†25.2*Erbel et al ²² 25.2*25.2*Men55±7111±671±526.3±3.75.0221±36144±3433.5	Optimal BP (2058)	51.9	—	—	22.3	5.1	186	—	52.1
High-range pre-HT (2483)54.623.67.1*19444.6*WomenOptimal BP (5536)50.922.72.02014.5Low-range pre-HT (4867)52.923.52.22052.9*High-range pre-HT (441)54.524.13.2*2093.1*Fukuhara et al ²¹ 66.7±7.721.4±2.65.1203±4029.7Optimal BP (657)55.1±10.3110.8±7.766.7±7.721.4±2.65.1203±4029.7Low-range pre-HT (545)56.4±11.7*123.5±7.0*73.7±7.0*22.6±2.3*12.6*205±4524.4*High-range pre-HT (447)58.8±10.6**133.8±8.5**78.6±8.5**23.4±2.1**14.7*212±33**25.2*Erbel et al ²² MenOptimal BP (200)55±7111±671±526.3±3.75.0221±3614±3433.5	Low-range pre-HT (2456)	53.1	—	—	23.3	5.2	194	—	45.9*
Women Optimal BP (5536) 50.9 22.7 2.0 201 4.5 Low-range pre-HT (4867) 52.9 23.5 2.2 205 2.9* High-range pre-HT (4441) 54.5 24.1 3.2* 209 3.1* Fukuhara et al ²¹ 66.7±7.7 21.4±2.6 5.1 203±40 29.7 Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 24.4* High-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 24.4* High-range pre-HT (447) 58.8±10.6*† 133.8±8.5*† 78.6±8.5*† 23.4±2.1*† 14.7* 212±33*† 25.2* Erbel et al ²²	High-range pre-HT (2483)	54.6	—	—	23.6	7.1*	194	—	44.6*
Optimal BP (5536) 50.9 22.7 2.0 201 4.5 Low-range pre-HT (4867) 52.9 23.5 2.2 205 2.9* High-range pre-HT (4441) 54.5 24.1 3.2* 209 3.1* Fukuhara et al ²¹ 24.1 3.2* 203±40 29.7 Low-range pre-HT (545) 55.1±10.3 110.8±7.7 66.7±7.7 21.4±2.6 5.1 203±40 29.7 Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 24.4* High-range pre-HT (447) 58.8±10.6* [†] 133.8±8.5* [†] 78.6±8.5* [†] 23.4±2.1* [†] 14.7* 212±33* [†] 25.2* Erbel et al ²²	Women								
Low-range pre-HT (4867)52.923.52.22052.9*High-range pre-HT (4441)54.524.13.2*2093.1*Fukuhara et al ²¹ Optimal BP (657)55.1±10.3110.8±7.766.7±7.721.4±2.65.1203±4029.7Low-range pre-HT (545)56.4±11.7*123.5±7.0*73.7±7.0*22.6±2.3*12.6*205±4524.4*High-range pre-HT (447)58.8±10.6* [†] 133.8±8.5* [†] 78.6±8.5* [†] 23.4±2.1* [†] 14.7*212±33* [†] 25.2*Erbel et al ²² MenOptimal BP (200)55±7111±671±526.3±3.75.0221±36144±3433.5	Optimal BP (5536)	50.9	—	—	22.7	2.0	201	—	4.5
High-range pre-HT (4441) 54.5 — — 24.1 3.2* 209 — 3.1* Fukuhara et al ²¹	Low-range pre-HT (4867)	52.9	—	—	23.5	2.2	205	—	2.9*
Fukuhara et al ²¹ Optimal BP (657) 55.1±10.3 110.8±7.7 66.7±7.7 21.4±2.6 5.1 203±40 — 29.7 Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 — 24.4* High-range pre-HT (447) 58.8±10.6*† 133.8±8.5*† 78.6±8.5*† 23.4±2.1*† 14.7* 212±33*† — 25.2* Erbel et al ²²	High-range pre-HT (4441)	54.5	—	—	24.1	3.2*	209	—	3.1*
Optimal BP (657) 55.1±10.3 110.8±7.7 66.7±7.7 21.4±2.6 5.1 203±40 — 29.7 Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 — 24.4* High-range pre-HT (447) 58.8±10.6* [†] 133.8±8.5* [†] 78.6±8.5* [†] 23.4±2.1* [†] 14.7* 212±33* [†] — 25.2* Erbel et al ²²	Fukuhara et al ²¹								
Low-range pre-HT (545) 56.4±11.7* 123.5±7.0* 73.7±7.0* 22.6±2.3* 12.6* 205±45 — 24.4* High-range pre-HT (447) 58.8±10.6* [†] 133.8±8.5* [†] 78.6±8.5* [†] 23.4±2.1* [†] 14.7* 212±33* [†] — 25.2* Erbel et al ²² Men Optimal BP (200) 55±7 111±6 71±5 26.3±3.7 5.0 221±36 144±34 33.5	Optimal BP (657)	55.1±10.3	110.8±7.7	66.7±7.7	21.4±2.6	5.1	203±40	—	29.7
High-range pre-HT (447) 58.8±10.6* [†] 133.8±8.5* [†] 78.6±8.5* [†] 23.4±2.1* [†] 14.7* 212±33* [†] — 25.2* Erbel et al ²² Men Optimal BP (200) 55±7 111±6 71±5 26.3±3.7 5.0 221±36 144±34 33.5	Low-range pre-HT (545)	56.4±11.7*	123.5±7.0*	73.7±7.0*	22.6±2.3*	12.6*	205±45	_	24.4*
Erbel et al ²² Men 55±7 111±6 71±5 26.3±3.7 5.0 221±36 144±34 33.5	High-range pre-HT (447)	58.8±10.6* [†]	133.8±8.5* [†]	78.6±8.5* [†]	23.4±2.1* [†]	14.7*	212±33* [†]	_	25.2*
Men Optimal BP (200) 55±7 111±6 71±5 26.3±3.7 5.0 221±36 144±34 33.5	Erbel et al ²²								
Optimal BP (200) 55±7 111±6 71±5 26.3±3.7 5.0 221±36 144±34 33.5	Men								
	Optimal BP (200)	55±7	111±6	71±5	26.3±3.7	5.0	221±36	144±34	33.5

Continued

Table 4. Continued

Study/BP Group (Participant Number)	Age (y)	SBP (mm Hg)	DBP (mm Hg)	BMI (kg/m²)	DM (%)	TC (mg/dL)	LDL-C (mg/dL)	Smoking (%)
Pre-HT (596)	57±7*	129±6*	81±5*	27.2±3.3	4.5	227±39	148±36	30.1
Women					-		-	
Optimal BP (618)	56±7	107±8	70±6	25.3±4.1	1.0	226±38	139±36	28.0
Pre-HT (500)	59±8*	127±7*	79±6*	27±4*	3.4*	236±41*	148±38*	22.0*
Sadeghi et al ²³	-		<u>.</u>	-				
Optimal BP (1073)	43.3±9.07	_		26.6±4.5	6	_	_	2
Pre-HT (1185)	49.6±10.7*	_		27.9±4.6*	10*	_	_	2
Stojanov et al ²⁴								
Optimal BP (24)	40.46±5.12	_		26.49±2.50	_	_	_	54.2
Pre-HT (108)	43.27±7.55	_	_	26.90±3.17	_	_	_	56.5
Takashima et al ²⁵	-		<u>.</u>	-	-	-		
Optimal BP (1622)	43.4±10.9	109.6±6.4	67.6±6.6	21.7±2.8	3.5	181±32	_	26.7
Pre-HT (3538)	46.7±11.9*	126.7±6.6*	77.4±6.9*	22.4±3.0*	5.3*	186±32*	_	34.1*
Hadaegh et al ²⁶								
Middle aged (30 to 60 years)								
Optimal BP (2298)	40.2±7.7	105.9±7.8	70.5±5.7	26.1±4.1	3.4	205±43	_	21.3
Low-range pre-HT (1125)	42.0±8.2*	118.4±6.9*	79.6±4.2*	28.0±4.3*	6.0*	213±43*	_	13.5*
High-range pre-HT (666)	44.4±8.4* [†]	126.2±8.2* [†]	84.8±4.2* [†]	28.3±4.3*	10.7* [†]	221±43* [†]	_	11.0*
Elderly (aged ≥60 years)								
Optimal BP (196)	65.8±5.2	109.6±7.4	67.7±6.6	24.7±4.1	13.3	221±43	—	21.9
Low-range pre-HT (195)	65.6±4.5	122.3±4.8*	75.8±6.7*	26.6±3.9*	13.8	224±46	—	8.7*
High-range pre-HT (181)	66.5±5.1	132.4±5.6*	78.5±7.4* [†]	27.0±3.6*	18.2	221±43	_	11.0*

The baseline characteristics in pre-HT and optimal BP groups were not reported in the studies by Lee et al,⁵ Onat et al,¹⁴ Pednekar et al,¹⁸ and Dorjgochoo et al.¹⁹ BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; pre-HT, prehypertension; SBP, systolic blood pressure; TC, total cholesterol.

*vs optimal BP.

[†]vs low-range pre-HT.

the low range, were at increased risk of CHD. These results were supported by our prior studies, which showed that even low-range prehypertension increased the risk of stroke² and end-stage renal disease²⁹ compared with optimal BP. Unlike the present study, Shen et al reported in another recently published meta-analysis that the association between lowrange prehypertension and CHD was not significant.³⁰ The possible interpretation for these inconsistent findings may owe to the different inclusion criteria of the meta-analyses. The analysis by Shen et al included some studies with teenaged participants (aged <18 years) and included data from meta-analyses. In contrast, we included only prospective cohort studies with adults, with the RR of CHD reported in a multivariate-adjusted model. This feature decreases the possibility of other known confounders influencing the association between prehypertension and CHD. To avoid duplicate inclusion, we excluded data derived from the same cohort or from meta-analysis of other cohort studies.

Furthermore, we used a wider search strategy, including the terms *prehypertension, prehypertensive, borderline hypertension, blood pressure*, and *arterial pressure*, to detect potential related studies. Our study finally included 17 studies, 3 of which were not included in the prior study.^{5,16,21} We believe that the wider search strategy is important to help capture potentially relevant studies. Meta-analyses may be biased if they fail to identify all relevant studies.

In clinical trials of hypertension treatment, the ratio of stroke to myocardial infarction has been reported as 5 to 8:1 in Chinese patients and 1:1 in Western patients.⁷ In this study, we found that the PAR of prehypertension for CHD was 8.4% in Asians, a proportion approximately one third that of Westerners (24.1%). Our prior study also showed that the risk of CVD mortality in prehypertensive persons tended to be higher in black participants than in other ethnic groups.³¹ These differences may be affected by the environment and by dietary and lifestyle habits. These results further supported

Study or Subgroup log[Risk Ratio] SE Weight IV. Random, 95% CI Sample Size IV. Random, 95% CI Asains Kokubo 2008 0.6206 0.2498 4.4% 1.86 [1.14, 3.03] 5494 Onat 2008 0.2927 0.2031 5.6% 1.34 [0.90, 2.00] 3034 Gu 2009 0.2776 0.0659 10.6% 1.32 [1.16, 1.50] 1586666 Ikeda 2009 0.2277 0.0659 10.5% 1.10 [0.96, 1.26] 148173 Dorigochoo 2009 -0.3011 0.382 2.4% 0.74 [0.35, 1.56] 68438 Pednekar 2009 0.0953 0.0695 1.050 [0.88, 2.84] 8592 Takashima 2012 0.4827 0.298 3.5% 1.58 [0.88, 2.84] 8592 Fukuhara 2012 0.3507 0.216 5.2% 1.42 [0.93, 2.17] 2634 Hadaegh 2013 0.0862 0.120 8.5% 1.09 [0.86, 1.38] 6273 Subtotal (95% Cl) 5.76% 1.002 [0.41, 17, 1, 2.39] 8960					Risk Ratio		Risk Ratio
Asains Kokubo 2008 0.6206 0.2498 4.4% 1.86 [1.14, 3.03] 5494 Onat 2008 0.2927 0.2031 5.6% 1.34 [0.90, 2.00] 3034 Gu 2009 0.2776 0.0659 10.6% 1.32 [1.16, 1.50] 158666 Ikeda 2009 0.2927 0.2896 4.0% 1.34 [0.79, 2.27] 33372 Dorigochoc 2009 -0.3011 0.382 2.4% 0.74 [0.35, 1.56] 68438 Pednekar 2009 0.0953 0.0695 10.5% 1.10 [0.96, 1.28] 148173 Aghababaei 2012 0.4824 0.3056 3.3% 1.62 [0.89, 2.95] 3255 Takashima 2012 0.4574 0.2986 3.5% 1.98 [0.88, 2.84] 8592 Fukuhara 2013 0.0862 0.1209 8.5% 1.09 [0.86, 1.38] 6273 Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] 437931 437931 Heterogeneity: Tau² = 0.01; Chi² = 11.48, df = 9 (P = 0.24); I² = 22% 1265 148 [100, 2.19] 69989 Lee 2006 0.3436 0.1727 6.4% 1.70 [1.20, 2.41] 5181 5181	Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Sample Size	IV, Random, 95% Cl
Kokubo 2008 0.6206 0.2498 4.4% 1.66 $[1.41, 3.03]$ 5494 Onal 2008 0.2927 0.2031 5.6% 1.34 $[1.61, 1.50]$ 3034 Gu 2009 0.2927 0.2696 4.0% 1.34 $[1.61, 1.50]$ 158666 Ikeda 2009 0.2927 0.2696 4.0% 1.34 $[1.61, 1.50]$ 158666 Ikeda 2009 0.2927 0.2696 4.0% 1.34 $[1.61, 1.50]$ 1586666 Ikeda 2009 0.0953 0.6695 1.05 1.10 $[0.61, 1.26]$ 148173 Degischer 0.4824 0.3056 3.3% 1.62 $[0.88, 2.95]$ 3255 Takashima 2012 0.4824 0.3056 0.5% 1.42 $[0.39, 2.17]$ 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.95 $0.66, 1.38]$ 6273 Subtotal (95% Cl) 57.9% 1.25 $1.21, 1.38]$ 437931 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22\% Test for overall effect: Z = 4.05 (P	Asains						
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Kokubo 2008	0.6206	0.2498	4.4%	1.86 [1.14, 3.03]	5494	
Gu 2009 0.2776 0.0659 10.6% 1.32 [1.16, 1.50] 1586666 Ikeda 2009 0.2927 0.2696 4.0% 1.34 [0.79, 2.27] 33372 Dorjgochoo 2009 -0.3011 0.382 2.4% 0.74 [0.35, 1.56] 68438 Pednekar 2009 0.0953 0.0695 10.5% 1.10 [0.96, 1.26] 148173 Aghababaei 2012 0.4824 0.3056 3.3% 1.62 [0.89, 2.95] 3255 Takashima 2012 0.4574 0.2966 3.5% 1.58 [0.88, 2.84] 8592 Fukuhara 2012 0.4577 0.216 5.2% 1.42 [0.93, 2.17] 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 [0.86, 1.38] 6273 Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] 437931 4 Westerners 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] 5181 Cureshi 2005 0.5306 0.1777 6.4% 1.70 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Subtotal (95% CI) 42.1%	Onat 2008	0.2927	0.2031	5.6%	1.34 [0.90, 2.00]	3034	+
Ikeda 2009 0.2927 0.2696 4.0% 1.34 $[0.79, 2.27]$ 33372 Dorjgochoo 2009 -0.3011 0.382 2.4% 0.74 $[0.35, 1.56]$ 68438 Pednekar 2009 0.0953 0.0695 10.5% 1.10 $[0.96, 1.26]$ 148173 Aghababaei 2012 0.4824 0.3056 3.5% 1.58 $[0.88, 2.84]$ 8592 Takashima 2012 0.4574 0.2966 3.5% 1.09 $[0.66, 1.38]$ 6273 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 $[0.66, 1.38]$ 6273 Subtotal (95% CI) 57.9% 1.25 $[1.21, 1.38]$ 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: Z = 4.05 (P < 0.0001)	Gu 2009	0.2776	0.0659	10.6%	1.32 [1.16, 1.50]	158666	
Dorjgochoo 2009 -0.3011 0.382 2.4% 0.74 [0.35, 1.56] 68438 Pednekar 2009 0.0953 0.0695 10.5% 1.10 [0.96, 1.26] 148173 Aghababaei 2012 0.4824 0.3056 3.3% 1.62 [0.89, 2.95] 3255 Takashima 2012 0.4874 0.2986 3.5% 1.58 [0.88, 2.84] 8592 Fukuhara 2012 0.3507 0.216 5.2% 1.42 [0.93, 2.17] 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 [0.86, 1.38] 6273 Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: $Z = 4.05$ (P < 0.0001) Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] 5181 Kshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 Theterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: $Z = 7.81$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 7.81$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Total (95% CI) Prehypertension	Ikeda 2009	0.2927	0.2696	4.0%	1.34 [0.79, 2.27]	33372	
Pednekar 2009 0.0953 0.0695 10.5% 1.10 [0.96, 1.26] 148173 Aghababaei 2012 0.4824 0.3056 3.3% 1.62 [0.89, 2.95] 3255 Takashima 2012 0.4574 0.2986 3.5% 1.58 [0.88, 2.84] 8592 Fukuhara 2012 0.3507 0.216 5.2% 1.42 [0.33, 2.17] 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 [0.86, 1.38] 6273 Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: Z = 4.05 (P < 0.0001) Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] Kshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 The 2012 0.157 0.3851 2.4% 1.71 [1.52, 2.49] 4181 Subtotal (95% CI) 42.1% 1.70 [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: Z = 7.81 (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0003); l ² = 65% Test for overall effect: Z = 7.81 (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0003); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001)	Dorjgochoo 2009	-0.3011	0.382	2.4%	0.74 [0.35, 1.56]	68438	
Aghababaei 2012 0.4824 0.3056 3.3% 1.62 $[0.89, 2.95]$ 3255 Takashima 2012 0.4574 0.2986 3.5% 1.58 $[0.88, 2.84]$ 8592 Fukuhara 2012 0.3507 0.216 5.2% 1.42 $[0.93, 2.17]$ 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 $[0.86, 1.38]$ 6273 Subtotal (95% CI)57.9% 1.25 $[1.12, 1.38]$ 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22%Test for overall effect: $Z = 4.05$ (P < 0.0001)WesternersQureshi 2005 0.5306 0.1777 6.4% 1.70 $[1.20, 2.41]$ 5181 Kshirsagar 2006 0.7031 0.085 9.9% 2.02 $[1.71, 2.39]$ 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 $[1.11, 1.79]$ 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 $[1.40, 2.21]$ 60785 Thomas 2008 0.392 0.2 5.7% 1.48 $[1.00, 2.19]$ 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 $0.50, 9.28]$ 265 Erbel 2012 0.0157 0.3851 2.4% 1.70 $[1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.04 ; Chi ² = 45.92 , df = 16 (P = 0.0001); l ² = 65% 591664 0.1 0.2 0.5 1 2 5 Total (95% CI)100.0% 1.43 $[1.26, 1.63]$ 0.1 0.2 <td>Pednekar 2009</td> <td>0.0953</td> <td>0.0695</td> <td>10.5%</td> <td>1.10 [0.96, 1.26]</td> <td>148173</td> <td>1--</td>	Pednekar 2009	0.0953	0.0695	10.5%	1.10 [0.96, 1.26]	148173	1- -
Takashima 2012 0.4574 0.2986 3.5% 1.58 $0.88, 2.84$] 8592 Fukuhara 2012 0.3507 0.216 5.2% 1.42 $0.93, 2.17$] 2634 Hadaegh 2013 0.0862 0.1209 8.5% 1.09 $0.86, 1.38$] 6273 Subtotal (95% CI) 57.9% 1.25 $[1.12, 1.38]$ 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% 437931 437931 Test for overall effect: Z = 4.05 (P < 0.0001)	Aghababaei 2012	0.4824	0.3056	3.3%	1.62 [0.89, 2.95]	3255	
Fukuhara 2012 0.3607 0.216 5.2% $1.42 [0.93, 2.17]$ 2634 Hadaegh 2013 0.0862 0.1209 8.5% $1.09 [0.86, 1.38]$ 6273 Subtotal (95% Cl) 57.9% $1.25 [1.12, 1.38]$ 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% 437931 WesternersQureshi 2005 0.5306 0.1777 6.4% $1.70 [1.20, 2.41]$ 5181 Kshirsagar 2006 0.7031 0.085 9.9% $2.02 [1.71, 2.39]$ 8960 Lee 2006 0.3436 0.1221 8.4% $1.41 [1.11, 1.79]$ 4372 Hsia 2007 0.5653 0.1168 8.6% $1.76 [1.40, 2.21]$ 60785 Thomas 2008 0.392 0.2 5.7% $1.48 [1.00, 2.19]$ 69989 Stojanov 2012 0.7655 0.7463 0.7% $2.15 [0.50, 9.28]$ 265 Erbel 2012 0.157 0.3851 2.4% $1.17 [0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% $1.70 [1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.01 ; Chi ² = 7.81 (P < 0.00001) $12 = 05.\%$ 591664 Test for overall effect: Z = $7.81 (P < 0.00001)$ 100.0% $1.43 [1.26, 1.63]$ 591664 Heterogeneity: Tau ² = 0.04 ; Chi ² = 45.92, df = 16 (P = 0.0003), l ² = 09.2\% 591664 $0.1 0.2 0.5$ $1 2 5 10$ Optimal blood pressurePrehypertension	Takashima 2012	0.4574	0.2986	3.5%	1.58 [0.88, 2.84]	8592	
Hadaegh 2013 0.0862 0.1209 8.5% 1.09 [0.86, 1.38] Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: $Z = 4.05$ (P < 0.0001) Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] Kshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] Erbel 2012 0.157 0.3851 2.4% 1.17 [0.55, 2.49] Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: Z = 7.81 (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Total (95% CI) 102.05 12 2.88 df = 1 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Total (95% CI) 12 2.88 df = 1 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Total (95% CI) 12 2.88 df = 1 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Total (95% CI) 12 2.88 df = 1 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Total (95% CI) 12 2.88 df = 1 (P = 0.0001); l ² = 0.0001); l ² = 0.0001; l ² = 0.0001) Test for subpround differences: Chi ² = 12.88 df = 1 (P = 0.0001); l ² = 0.0001); l ² = 0.0001; l ² = 0.00001; l ² = 0.00000; l ² = 0.00000; l ² = 0.00000; l ² = 0.00000; l ² = 0.0000; l ² = 0.	Fukuhara 2012	0.3507	0.216	5.2%	1.42 [0.93, 2.17]	2634	
Subtotal (95% CI) 57.9% 1.25 [1.12, 1.38] 437931 Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: $Z = 4.05$ (P < 0.0001)	Hadaegh 2013	0.0862	0.1209	8.5%	1.09 [0.86, 1.38]	6273	
Heterogeneity: Tau ² = 0.01; Chi ² = 11.48, df = 9 (P = 0.24); l ² = 22% Test for overall effect: $Z = 4.05$ (P < 0.0001) Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] 5181 Kshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 Erbel 2012 0.157 0.3851 2.4% 1.17 [0.55, 2.49] 4181 Subtotal (95% CI) 42.1% 1.70 [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: $Z = 7.81$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Total (95% CI) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0003), l ² = 92.2%	Subtotal (95% CI)			57.9%	1.25 [1.12, 1.38]	437931	◆
Test for overall effect: $Z = 4.05 (P < 0.0001)$ Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 [1.20, 2.41] 5181 Kshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 Erbel 2012 0.157 0.3851 2.4% 1.17 [0.55, 2.49] 4181 Subtotal (95% Cl) 42.1% 1.70 [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: $Z = 7.81 (P < 0.00001)$ Total (95% Cl) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42 (P < 0.00001)$ Total (95% Cl) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0003) l ² = 92.2%	Heterogeneity: Tau ² =	0.01; Chi² = 11.48	, df = 9 (I	⊃ = 0.24);	l² = 22%		
Westerners Qureshi 2005 0.5306 0.1777 6.4% 1.70 $[1.20, 2.41]$ 5181 Kshirsagar 2006 0.7031 0.085 9.9% 2.02 $[1.71, 2.39]$ 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 $[1.11, 1.79]$ 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 $[1.40, 2.21]$ 60785 Thomas 2008 0.392 0.2 5.7% 1.48 $[1.00, 2.19]$ 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 $[0.50, 9.28]$ 265 Erbel 2012 0.157 0.3851 2.4% 1.17 $[0.55, 2.49]$ 4181 Subtotal (95% CI) 42.1% 1.70 $[1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.01 ; Chi ² = 7.87 , df = 6 (P = 0.25); l ² = 24% 591664 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 5.42 (P < 0.00001) 12 65% 0.1 0.2 0.5 1 2 5	Test for overall effect:	Z = 4.05 (P < 0.00	01)				
Qureshi 2005 $0.5306 \ 0.1777 \ 6.4\% \ 1.70 \ [1.20, 2.41]$ 5181 Kshirsagar 2006 $0.7031 \ 0.085 \ 9.9\% \ 2.02 \ [1.71, 2.39]$ 8960 Lee 2006 $0.3436 \ 0.1221 \ 8.4\% \ 1.41 \ [1.11, 1.79]$ 4372 Hsia 2007 $0.5653 \ 0.1168 \ 8.6\% \ 1.76 \ [1.40, 2.21]$ 60785 Thomas 2008 $0.392 \ 0.2 \ 5.7\% \ 1.48 \ [1.00, 2.19]$ 69989 Stojanov 2012 $0.7655 \ 0.7463 \ 0.7\% \ 2.15 \ [0.50, 9.28]$ 265 Erbel 2012 $0.157 \ 0.3851 \ 2.4\% \ 1.17 \ [0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% \ 1.70 \ [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% 591664 Test for overall effect: Z = 5.42 (P < 0.00001)	Westerners						
ConstrainedConstrainedConstrainedConstrainedConstrainedKshirsagar 2006 0.7031 0.085 9.9% 2.02 [1.71, 2.39] 8960 Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50 , 9.28] 265 Erbel 2012 0.157 0.3851 2.4% 1.17 [0.55 , 2.49] 4181 Subtotal (95% Cl)42.1% 1.70 [1.49 , 1.94] 153733 Heterogeneity: Tau ² = 0.01 ; Chi ² = 7.87 , df = 6 (P = 0.25); l ² = 24% 591664 Test for overall effect: Z = 7.81 (P < 0.00001) 1.43 [1.26 , 1.63] 591664 Heterogeneity: Tau ² = 0.04 ; Chi ² = 45.92 , df = 16 (P = 0.0001); l ² = 65% 591664 Test for overall effect: Z = 5.42 (P < 0.00001) $1.2 = 0.5\%$ $1 = 2 = 5 = 10$ Optimal blood pressurePrehypertension	Oureshi 2005	0.5306	0 1777	64%	1 70 [1 20 2 41]	5181	_
Lee 2006 0.3436 0.1221 8.4% 1.41 [1.11, 1.79] 4372 Hsia 2007 0.5653 0.1168 8.6% 1.76 [1.40, 2.21] 60785 Thomas 2008 0.392 0.2 5.7% 1.48 [1.00, 2.19] 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 [0.50, 9.28] 265 Erbel 2012 0.157 0.3851 2.4% 1.17 [0.55, 2.49] 4181 Subtotal (95% Cl) 42.1% 1.70 [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: Z = 7.81 (P < 0.00001) Total (95% Cl) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: Z = 5.42 (P < 0.00001) Test for overall effect: Z = 5.42 (P < 0.00001) Test for subgroup differences: Chi ² = 12 88 df = 1 (P = 0.0003) l ² = 92.2%	Kshirsagar 2006	0 7031	0.085	9.9%	2 02 [1 71 2 39]	8960	
Hsia 2007 0.5653 0.1168 8.6% 1.76 $[1.40, 2.21]$ 60785 Thomas 2008 0.392 0.2 5.7% 1.48 $[1.00, 2.19]$ 69989 Stojanov 2012 0.7655 0.7463 0.7% 2.15 $[0.50, 9.28]$ 265 Erbel 2012 0.157 0.3851 2.4% 1.17 $[0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% 1.70 $[1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.01 ; Chi ² = 7.87 , df = 6 (P = 0.25); l ² = 24% 153733 4 Test for overall effect: Z = 7.81 (P < 0.00001) 100.0% 1.43 $[1.26, 1.63]$ 591664 Heterogeneity: Tau ² = 0.04 ; Chi ² = 45.92 , df = 16 (P = 0.0001); l ² = 65% 591664 -10.2 0.5 1 2 5 100 00001 ; l ² = 65% 0.1 0.2 0.5 1 2 5 10 00001 ; l ² = 65% 0.1 0.2 0.5 1 2 5 10 0.1 0.2 0.5 1 2 5 10 0.1 <	Lee 2006	0.3436	0 1221	8.4%	1 41 [1 11 1 79]	4372	_ _ _
Thomas 2008 0.392 0.2 5.7% $1.48 [1.00, 2.19]$ 69989 Stojanov 2012 0.7655 0.7463 0.7% $2.15 [0.50, 9.28]$ 265 Erbel 2012 0.157 0.3851 2.4% $1.17 [0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% $1.70 [1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24\% 153733 Total (95% Cl) 100.0% $1.43 [1.26, 1.63]$ 591664 Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65\% 591664 $6.1 0.2 0.5 1 2 5 10$ Total (95% Cl) 100.0% $1.43 [1.26, 1.63]$ 591664 Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65\% 591664 92.2% Test for overall effect: Z = 5.42 (P < 0.00001) $2.5 10$ $0.1 0.2 0.5 1 2 5 10$ $2.5 10$ Optimal blood pressure Prehypertension	Hsia 2007	0.5653	0.1168	8.6%	1 76 [1 40 2 21]	60785	
Stojanov 2012 0.7655 0.7463 0.7% 2.15 $[0.50, 9.28]$ 265 Erbel 2012 0.157 0.3851 2.4% 1.17 $[0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% 1.70 $[1.49, 1.94]$ 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% 153733 591664 Test for overall effect: Z = 7.81 (P < 0.00001) 100.0% 1.43 $[1.26, 1.63]$ 591664 Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65\% 591664 0.1 0.2 0.5 1 2 5 100 100.0% 1.43 10.2 0.5 1 2 5 100 0.1 0.2 0.5 1 2 5 10 0.1 0.2 0.5 1 2 5 10 0.1 0.2 0.5 1 2 5 10 0.1 0.2 0.5 1 2 5 10 0.1 0.2 0.5 1 2 5 10 0.5 <t< td=""><td>Thomas 2008</td><td>0.392</td><td>0.1100</td><td>5.7%</td><td>1 48 [1 00 2 19]</td><td>69989</td><td></td></t<>	Thomas 2008	0.392	0.1100	5.7%	1 48 [1 00 2 19]	69989	
Erbel 2012 $0.157 \ 0.3851 \ 2.4\% \ 1.17 \ [0.55, 2.49]$ 4181 Subtotal (95% Cl) 42.1% \ 1.70 \ [1.49, 1.94] 153733 Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% 153733 Test for overall effect: Z = 7.81 (P < 0.00001)	Stojanov 2012	0 7655	0 7463	0.7%	2 15 [0 50 9 28]	265	
Subtotal (95% Cl) 42.1% 1.70 [1.49, 1.94] Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: Z = 7.81 (P < 0.00001)	Erbel 2012	0 157	0.3851	2.4%	1 17 [0 55 2 49]	4181	
Heterogeneity: Tau ² = 0.01; Chi ² = 7.87, df = 6 (P = 0.25); l ² = 24% Test for overall effect: $Z = 7.81$ (P < 0.00001) Total (95% CI) Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Test for subgroup differences: Chi ² = 12.88 df = 1 (P = 0.0003) l ² = 92.2%	Subtotal (95% CI)	0.101	0.0001	42.1%	1.70 [1.49, 1.94]	153733	•
Test for overall effect: $Z = 7.81$ (P < 0.00001) Total (95% Cl) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% 591664 Test for overall effect: $Z = 5.42$ (P < 0.00001) Prehypertension Test for subgroup differences: Chi ² = 12.88 df = 1 (P = 0.0003) l ² = 92.2% Clical (P < 0.0001)	Heterogeneity: Tau ² =	0.01° Chi ² = 7.87	df = 6 (P)	= 0.25)	² = 24%	100100	
Total (95% Cl) 100.0% 1.43 [1.26, 1.63] Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% 591664 Test for overall effect: Z = 5.42 (P < 0.00001)	Test for overall effect:	Z = 7.81 (P < 0.00)	001)	01207,1	2.70		
Heterogeneity: Tau ² = 0.04; Chi ² = 45.92, df = 16 (P = 0.0001); l ² = 65% Test for overall effect: $Z = 5.42$ (P < 0.00001) Test for subgroup differences: Chi ² = 12.88, df = 1 (P = 0.0003), l ² = 92.2%	Total (95% CI)			100.0%	1.43 [1.26, 1.63]	591664	•
Test for overall effect: $Z = 5.42$ (P < 0.00001) Test for subgroup differences: Chi ² = 12 88 df = 1 (P = 0.0003) l ² = 92.2%	Heterogeneity: Tau ² =	0.04: Chi ² = 45.92	df = 16	(P = 0.000)	$(1): ^2 = 65\%$		
Test for subgroup differences: $Chi^2 = 12.8.8$, $df = 1 (P = 0.0003)$ $l^2 = 92.2\%$ Optimal blood pressure Prehypertension	Test for overall effect	7 = 5.42 (P < 0.00)	001)		,.	0.1 0.2	0.5 1 2 5 10
	Test for subgroup diffe	rences: $Chi^2 = 12$	88 df=1	I(P = 0.00))03) I² = 92.2%	Optimal bloo	d pressure Prehypertension

Figure 2. Forest plot of comparison: prehypertension vs optimal blood pressure. Outcome was coronary heart disease in Asian and Western participants.

the heterogeneity of target-organ damage caused by prehypertension and hypertension among different ethnicities and underscore the importance of prevention of CHD in Western patients with prehypertension.

Considering the incidence of prehypertension of 30% to 50%²⁷ in addition to the robust and significant association between prehypertension and CHD, especially in Western participants, successful intervention in this large population could have a major impact on public health. Randomized trials examining the effects of antihypertensive therapy on the primary prevention of cardiovascular events specifically in those with prehypertension are rare, so professional societies do not currently recommend pharmacotherapy for prehypertension.^{32–34} In fact, the definitions of *hypertension* and *prehypertension* were not addressed in the 2014 report from the panel members appointed to the Eighth Joint National Committee (JNC-8),³⁴ but thresholds for pharmacological treatment were defined. It is recommended that in the general

population, pharmacological treatment should be initiated to lower BP, with a target <140/90 mm Hg or <150/90 mm Hg in those aged <60 or ≥60 years, respectively.

For secondary prevention, data on whether antihypertensive therapy in prehypertensive patients with CHD could stem the progression of disease are also inconsistent. The substudy of the Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial showed that in CHD patients treated with amlodipine, enalapril, or placebo, those with hypertensive average BP had a significant increase in atheroma volume and those with prehypertensive BP had no major change, whereas those with optimal BP had a decrease in atheroma volume detected by repeated intravascular ultrasound over 2 years of follow-up.³⁵ In contrast, the recently published Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study (AQUARIUS) did not find the same results.³⁶ In that study, 458 CHD participants with BP in the prehypertension range (systolic



Figure 3. Funnel plot of comparison, prehypertension vs optimal blood pressure. Outcome was coronary heart disease in Asian and Western participants. RR indicates relative risks.

BP between 125 and 139 mm Hg) underwent intravascular ultrasound imaging and were randomized to receive aliskiren or placebo for 104 weeks. Disease progression was measured by repeated intravascular ultrasound examination after at least 72 weeks of treatment. Although the BP levels in the aliskiren group were 2.09/1.45 mm Hg lower than in the placebo group, there were no significant differences in regression of atheroma volume (P=0.08) in the aliskiren and placebo groups. It should be noted that the negative results may be confounded by the small sample size, the limited follow-up duration, and the extensive use of multiple drugs for secondary prevention of CHD, such as statins and β -blockers. Furthermore, patients enrolled in the AQUARIUS study showed a high prevalence of other cardiovascular risk factors (mean body mass index 30 kg/m², 29.2% with diabetes, 83.9% with history of hypertension, 30.7% with history of smoking). Considering these inconsistent results, we agree that lifestyle modification is the mainstay of treatment for prehypertension in the general population. In our study, however, we also found that the risk of CHD with prehypertension was higher in Western participants and in studies with a follow-up duration ≥ 10 years. Consequently, controlled trials with large samples and long follow-up duration are required to determine the lower BP target in patients with CHD, especially in high-risk subpopulations and different ethnicities.

It is interesting that in comparison to an optimal BP group, prehypertension increased the risk of CHD in the studies that excluded participants with CVD at baseline (RR 1.54, 95% CI

1.34 to 1.77) and in those studies that did not exclude participants with CVD at baseline (RR 1.21, 95% CI 1.03 to 1.43). These results highlight the importance of primary intervention for prehypertension and secondary prevention for CHD. Furthermore, the RR of CHD with prehypertension was much more pronounced in studies that excluded CVD at baseline than in those that did not (P=0.03). This may be because in those studies that did not exclude participants with CVD at baseline, the comparable group (optimal BP group) may also have included participants with CVD, which was associated with a higher risk of CHD events. This feature may have had a diluting effect when the RR of CHD was calculated.

The main strengths of our study are the very large sample size and the consistency of results in subgroup analyses and sensitivity analyses. Furthermore, the included studies were restricted to prospective cohort studies and reported multivariate-adjusted RRs. Alternatively, some limitations of this meta-analysis should be considered. First, the determination of BP in most of the studies was based on single-day measurements, although multiple readings were taken. This approach may misclassify BP levels and lead to dilution bias. Second, we did not have access to patient-level data; however, most of the studies were adequately adjusted for potential confounders and were of high quality, reducing the likelihood that other cardiovascular risk factors influenced the association between prehypertension and CHD. Third, persons with prehypertension are more likely to progress to hypertension than those with optimal BP, but most of the

Table 5. Subgroup Analyses of the Association betweenPrehypertension and Cardiovascular Morbidity

Subgroup	Risk Ratio (95% CI)	P Value Between Subgroups					
Blood pressure range							
Low-range prehypertension	1.27 (1.07 to 1.50)	0.15					
High-range prehypertension	1.58 (1.24 to 2.02)						
Sex							
Men	1.67 (1.17 to 2.38)	0.27					
Women	1.30 (1.01 to 1.69)						
CHD end point							
Fatal	1.50 (1.31 to 1.72)	0.23					
Nonfatal and fatal	1.29 (1.06 to 1.58)						
Participant average age							
<55 years	1.44 (1.14 to 1.81)	0.98					
≥55 years	1.44 (1.27 to 1.62)						
Follow-up duration	2	6					
<10 years	1.27 (1.10 to 1.48)	0.004					
≥10 years	1.68 (1.50 to 1.90)						
Participant number	^	5					
<10 000	1.52 (1.29 to 1.79)	0.26					
≥10 000	1.32 (1.10 to 1.58)						
Participants with baseline CVD excluded							
Yes	1.54 (1.34 to 1.77)	0.03					
No	1.21 (1.03 to 1.43)						
Study quality							
Good (score 7 to 8)	1.48 (1.30 to 1.69)	0.004					
Fair (score 4 to 6)	1.13 (0.99 to 1.28)						

CHD indicates coronary heart disease; CVD, cardiovascular disease.

included studies did not adjust the BP clarification and management afterward.

Conclusions

After adjusting for multiple cardiovascular risk factors, prehypertension—even at the low range—is associated with a high risk of CHD. This risk is more pronounced in Western than in Asian patients. These results supported the heterogeneity of target-organ damage caused by prehypertension and hypertension among different ethnicities and underscore the importance of prevention of CHD in Western patients with prehypertension. Future clinical trials are needed to determine whether interventions for prehypertension have different effects on risk of CHD in different ethnicities.

Huang, Peng, and Xu conceived and designed the review. Huang and Cai identified and acquired reports of trials, abstracted data and assessed risk of bias. Huang, Cai, Hua, and Zhu drafted the manuscript. Xu and Peng provided supervision. Liu and Huang conducted the statistical analyses and contacted authors of included studies to obtain additional information. All of the authors contributed to the interpretation of data and all of the authors critically revised the manuscript. All of the authors approved the final version of the manuscript submitted for publication and are guarantors for the study.

Sources of Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosures

None.

References

- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JJ, Jones DW, Materson BJ, Oparil S, Wright JJ, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560–2572.
- Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, Hu Y, Wu Y, Xu D. Prehypertension and the risk of stroke: a meta-analysis. *Neurology*. 2014;82:1153–1161.
- Huang Y, Wang S, Cai X, Mai W, Hu Y, Tang H, Xu D. Prehypertension and incidence of cardiovascular disease: a meta-analysis. *BMC Med*. 2013;11:177.
- Qureshi Al, Suri MF, Kirmani JF, Divani AA, Mohammad Y. Is prehypertension a risk factor for cardiovascular diseases? *Stroke*. 2005;36:1859–1863.
- Lee ET, Howard BV, Wang W, Welty TK, Galloway JM, Best LG, Fabsitz RR, Zhang Y, Yeh J, Devereux RB. Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. *Circulation*. 2006;113:2897–2905.
- Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. Am J Med. 2006;119:133–141.
- 7. Liu LS. 2010 Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2011;39:579–615.
- Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
- Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21–35.
- Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341:c4249.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326:219.
- Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, LaCroix AZ, Black HR. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation*. 2007;115:855–860.
- Onat A, Yazici M, Can G, Kaya Z, Bulur S, Hergenc G. Predictive value of prehypertension for metabolic syndrome, diabetes, and coronary heart disease among Turks. *Am J Hypertens*. 2008;21:890–895.

- Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension*. 2008;52:652–659.
- Thomas F, Blacher J, Benetos A, Safar ME, Pannier B. Cardiovascular risk as defined in the 2003 European blood pressure classification: the assessment of an additional predictive value of pulse pressure on mortality. *J Hypertens*. 2008;26:1072–1077.
- Gu D, Chen J, Wu X, Duan X, Jones DW, Huang JF, Chen CS, Chen JC, Kelly TN, Whelton PK, He J. Prehypertension and risk of cardiovascular disease in Chinese adults. J Hypertens. 2009;27:721–729.
- Pednekar MS, Gupta R, Gupta PC. Association of blood pressure and cardiovascular mortality in India: Mumbai cohort study. *Am J Hypertens*. 2009;22:1076–1084.
- Dorjgochoo T, Shu XO, Zhang X, Li H, Yang G, Gao L, Cai H, Gao YT, Zheng W. Relation of blood pressure components and categories and all-cause, stroke and coronary heart disease mortality in urban Chinese women: a populationbased prospective study. *J Hypertens*. 2009;27:468–475.
- Ikeda A, Iso H, Yamagishi K, Inoue M, Tsugane S. Blood pressure and the risk of stroke, cardiovascular disease, and all-cause mortality among Japanese: the JPHC Study. *Am J Hypertens*. 2009;22:273–280.
- Fukuhara M, Arima H, Ninomiya T, Hata J, Yonemoto K, Doi Y, Hirakawa Y, Matsumura K, Kitazono T, Kiyohara Y. Impact of lower range of prehypertension on cardiovascular events in a general population: the Hisayama Study. *J Hypertens*. 2012;30:893–900.
- 22. Erbel R, Lehmann N, Mohlenkamp S, Churzidse S, Bauer M, Kalsch H, Schmermund A, Moebus S, Stang A, Roggenbuck U, Brocker-Preuss M, Dragano N, Weimar C, Siegrist J, Jockel KH. Subclinical coronary atherosclerosis predicts cardiovascular risk in different stages of hypertension: result of the Heinz Nixdorf Recall Study. *Hypertension*. 2012;59:44–53.
- Sadeghi M, Aghababaei E, Talaei M, Sarrafzadegan N. Do hypertension and prehypertension count as cardiovascular risk factors among women in an Iranian society? *Int J Cardiol.* 2012;155:S2.
- Stojanov V, Paunovic K, Jakovljevic B, Lovic D, Jurisic V. Blood pressure categories and mortality during a thirty-six-year follow-up. *Cent. Eur. J. Med.*. 2012;1–8.
- 25. Takashima N, Ohkubo T, Miura K, Okamura T, Murakami Y, Fujiyoshi A, Nagasawa SY, Kadota A, Kita Y, Miyagawa N, Hisamatsu T, Hayakawa T, Okayama A, Ueshima H. Long-term risk of BP values above normal for cardiovascular mortality: a 24-year observation of Japanese aged 30 to 92 years. J Hypertens. 2012;30:2299–2306.
- Hadaegh F, Mohebi R, Khalili D, Hasheminia M, Sheikholeslami F, Azizi F. High normal blood pressure is an independent risk factor for cardiovascular disease among middle-aged but not in elderly populations: 9-year results of a population-based study. *J Hum Hypertens*. 2013;27:18–23.
- 27. Elliott WJ, Black HR. Prehypertension. Nat Clin Pract Cardiovasc Med. 2007;4:538–548.
- Gupta P, Nagaraju SP, Gupta A, Mandya CK. Prehypertension—time to act. Saudi J Kidney Dis Transpl. 2012;23:223–233.

- Huang Y, Cai X, Zhang J, Mai W, Wang S, Hu Y, Ren H, Xu D. Prehypertension and incidence of ESRD: a systematic review and meta-analysis. *Am J Kidney Dis.* 2014;63:76–83.
- Shen L, Ma H, Xiang MX, Wang JA. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. *Am J Cardiol.* 2013;112:266–271.
- Huang Y, Su L, Cai X, Mai W, Wang S, Hu Y, Wu Y, Tang H, Xu D. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. *Am Heart J.* 2014;167:160–168.
- 32. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Ryden L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159-2219.
- 33. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, Flack JM, Carter BL, Materson BJ, Ram CV, Cohen DL, Cadet JC, Jean-Charles RR, Taler S, Kountz D, Townsend R, Chalmers J, Ramirez AJ, Bakris GL, Wang J, Schutte AE, Bisognano JD, Touyz RM, Sica D, Harrap SB. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens. 2014;32:3–15.
- 34. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SJ, Svetkey LP, Taler SJ, Townsend RR, Wright JJ, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–520.
- Sipahi I, Tuzcu EM, Schoenhagen P, Wolski KE, Nicholls SJ, Balog C, Crowe TD, Nissen SE. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. J Am Coll Cardiol. 2006;48:833–838.
- Nicholls SJ, Bakris GL, Kastelein JJ, Menon V, Williams B, Armbrecht J, Brunel P, Nicolaides M, Hsu A, Hu B, Fang H, Puri R, Uno K, Kataoka Y, Bash D, Nissen SE. Effect of aliskiren on progression of coronary disease in patients with prehypertension: the AQUARIUS randomized clinical trial. *JAMA*. 2013;310:1135–1144.