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PREVENTION OF HYPERTENSION: PUBLIC HEALTH CHALLENGES (NK HOLLENBERG, SECTION EDITOR)

Association Between Pre-hypertension and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Prospective Studies

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Abstract
Background The quantitative associations between prehypertension or its separate blood pressure (BP) ranges and the risk of main cardiovascular diseases (CVDs) have not been reliably documented.
Methods We performed a comprehensive search of PubMed (1966 to June 2012) and the Cochrane Library (1988 to June 2012) without language restrictions. Prospective studies were included if they reported multivariate-adjusted risk ratios (RRs) and corresponding 95 % confidence intervals (CIs) of desirable outcomes, including fatal or non-fatal incident stroke, coronary heart disease, myocardial infarction (MI) or total CVD events, with respect to prehypertension or its separate BP ranges (low range: 120–129/80–84 mmHg; high range: 130–139/85–89 mmHg) at baseline with normal BP (<120/80 mmHg) as reference. Pooled RRs were estimated using a random-effects model or a fixed-effects model.
Results Twenty-nine articles met our inclusion criteria, with 1,010,858 participants. Both low-range and high-range prehypertension were associated with a greater risk of developing or dying of total CVD (low-range: RR: 1.24; 95 % CI: 1.10 to 1.39; high range: RR: 1.56; 95 % CI: 1.36 to 1.78), stroke (low-range: RR: 1.35; 95 % CI: 1.10 to 1.66; high-range: RR: 1.95; 95 % CI: 1.69 to 2.24) and myocardial infarction (MI) (low range: RR: 1.43; 95 % CI: 1.10 to 1.86; high range: RR: 1.99; 95 % CI: 1.59 to 2.50). The whole range prehypertension had a 1.44-fold (95 % CI: 1.35 to 1.53), 1.73-fold (95 % CI: 1.61 to 1.85), and 1.79-fold (95 % CI: 1.45 to 2.22) risk of total CVD, stroke, and MI, respectively. There was no evidence of publication bias.
Conclusions Prehypertensive patients have a greater risk of incident stroke, MI and total CVD events. The impact was markedly different between the low and high prehypertension ranges.

Keywords Prehypertension · Cardiovascular diseases · Meta-analysis

All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented, and for their discussed interpretation.

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Introduction

Cardiovascular disease (CVD) is the leading cause of premature morbidity and mortality [1]. High blood pressure (BP) constitutes a major cardiovascular risk factor [2, 3]. More than 7 million deaths worldwide and 1.27 million premature cardiovascular deaths in China were attributable to high BP

[3, 4]. The number of hypertensive adults was predicted to increase by about 60 % to a total of 1.56 billion in 2025 all over the world [5], leading to an extremely huge global disease burden.

The relationship between BP and CVD risk is continuous. No definable threshold has been identified, down to a BP of at least 115/75 mmHg [6]. This might be one of the reasons that the concept of prehypertension was brought up in guidelines for the management of BP by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [7]. The disease burden caused by prehypertension is impressive [4, 8]. Also considering the high prevalence and underdiagnosis rate of prehypertension [9, 10] and the high progression rate from prehypertension to hypertension [11, 12], effective strategies on prevention for this segment of the population would be of great value.

To identify persons at high risk of CVDs and to provide evidence for the prevention and treatment strategies of prehypertension, recognition of how risky prehypertension is for developing or dying of CVDs becomes the first step to take. There exist considerable studies showing that prehypertension is associated with stroke, myocardial infarction (MI), or coronary heart disease (CHD), but the results are inconsistent. For example, Qureshi et al. found that prehypertension was not associated with stroke [13], while a few other studies found the opposite relationship [14, 15]. It is difficult to confirm this issue in a single study, due to limited events. Therefore, we performed this meta-analysis to assess the associations between baseline prehypertension and incident stroke, CHD, MI and total CVD events at a prospective level.

Methods

Literature Search

We performed a systematic review of the published literature according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group [16]. We conducted a comprehensive search of PubMed (1966 to June 2012) and the Cochrane Library (1988 to June 2012) without language restrictions. Search terms including MeSH words and text words were related to exposure ("prehypertensi*" or "high normal blood pressure") and to outcomes ("cardiovascular disease", "coronary disease", "myocardial ischemia", "myocardial infarction", "coronary stenosis", "acute coronary syndrome", "atherosclerosis", "ischemic heart disease", "angina", "stroke", "cerebral infarction", "intracranial hemorrhage", "cerebrovascular disease", "cerebrovascular attack", "cardiovascular mortality", "cardiovascular event"). The literature search was undertaken by two authors (Guo X and Zhang XY) independently. Articles published in non-English language were reviewed and translated. We also manually searched the references of original and relevant reviews to ascertain additional studies. If the articles did not contain all of the necessary information, we contacted the authors for any possible additional published or unpublished data.

Inclusion and Exclusion Criteria

As described in our previous study [17], studies had to meet the following criteria for inclusion: (1) original article with prospective cohort design; (2) they assessed prehypertension or high normal BP as baseline exposure; (3) they assessed fatal or non-fatal incident stroke, CHD, MI, or total CVD events as outcome; (4) median follow-up of at least 3 years; and (5) they reported multivariate-adjusted risk ratio (RR) or hazard ratio (HR) and 95 % confidence interval (95 % CI) between exposure and outcomes with normal BP as reference. Multiple samples with different gender, age or ethnic groups from the same population were also included. If we identified multiple reports from the same study, the one with the most detailed information was adopted.

Studies were excluded if they met one of the following criteria: (1) no original data, such as reviews or comments; (2) only age-adjusted and gender-adjusted or unadjusted RR or HR was reported; (3) duplicated studies; (4) not conducted in human; and (5) data were derived from secondary analyses of clinical trials.

Data Extraction

Two investigators (Guo L and Li Z) extracted the data independently, with discrepancies resolved by an additional reviewer (Zheng) and through discussion. A standardized data extraction form was used. Information extracted included first author's name, publication year, country, sample characteristics, prevalence of prehypertension, follow-up, definition of high BP, adjusted variables, outcome assessment, and multivariate-adjusted RRs or HRs and corresponding 95 % CIs. An electronic abstraction database was created in Microsoft Excel.

Assessment of Study Quality

As described previously [17], we assessed quality of all articles that met the selection criteria with the following eight items according to the guidelines developed by the US Preventive Task Force and the modified checklist [18–20]: (1) prospective study design; (2) maintenance of comparable groups; (3) adjustment of potential confounders; (4) documented loss of follow-up rate; (5) outcome assessed blind to exposure status; (6) clear and proper definition of exposures (prehypertension) and outcomes (stroke, CHD, MI and total

CVD events); (7) temporality (BP measured at baseline, not at time of outcomes assessment) and (8) follow-up of at least 1 year. Studies were graded as good quality if they met seven to eight criteria; fair if they met four to six; and poor if they met less than four criteria.

Statistical Analysis

We obtained pooled estimates basing on the multivariate-adjusted RRs or HRs with 95 % CIs from included studies in order to estimate the quantitative association between prehypertension and the CVD outcomes. Between-study heterogeneity was tested by Q-statistic and quantified by the I^2 statistic. I^2 statistic of 0–40 % indicates unimportant heterogeneity, 30–60 % indicates moderate heterogeneity, 50–90 % indicates substantial heterogeneity, and 75–100 % indicates considerable heterogeneity [21]. If there existed statistically significant heterogeneity ($P<0.1$ and $I^2>50$ %), we chose a random-effects model, otherwise, a fixed-effects model was used.

Prehypertension was defined as systolic blood pressure (SBP) at 120–139 mmHg or diastolic blood pressure (DBP) at 80–89 mmHg. We further divided prehypertension into two BP ranges (i.e. low range: SBP of 120–129 mmHg or DBP of 80–84 mmHg; and high range: SBP of 130–139 mmHg or DBP of 85–89 mmHg), with normal BP (SBP<120 mmHg and DBP<80 mmHg) the reference category. The outcome assessment was the relative risk of fatal or non-fatal incident stroke, CHD, MI and total CVD in the whole prehypertensive range or in low-range and high-range prehypertension,

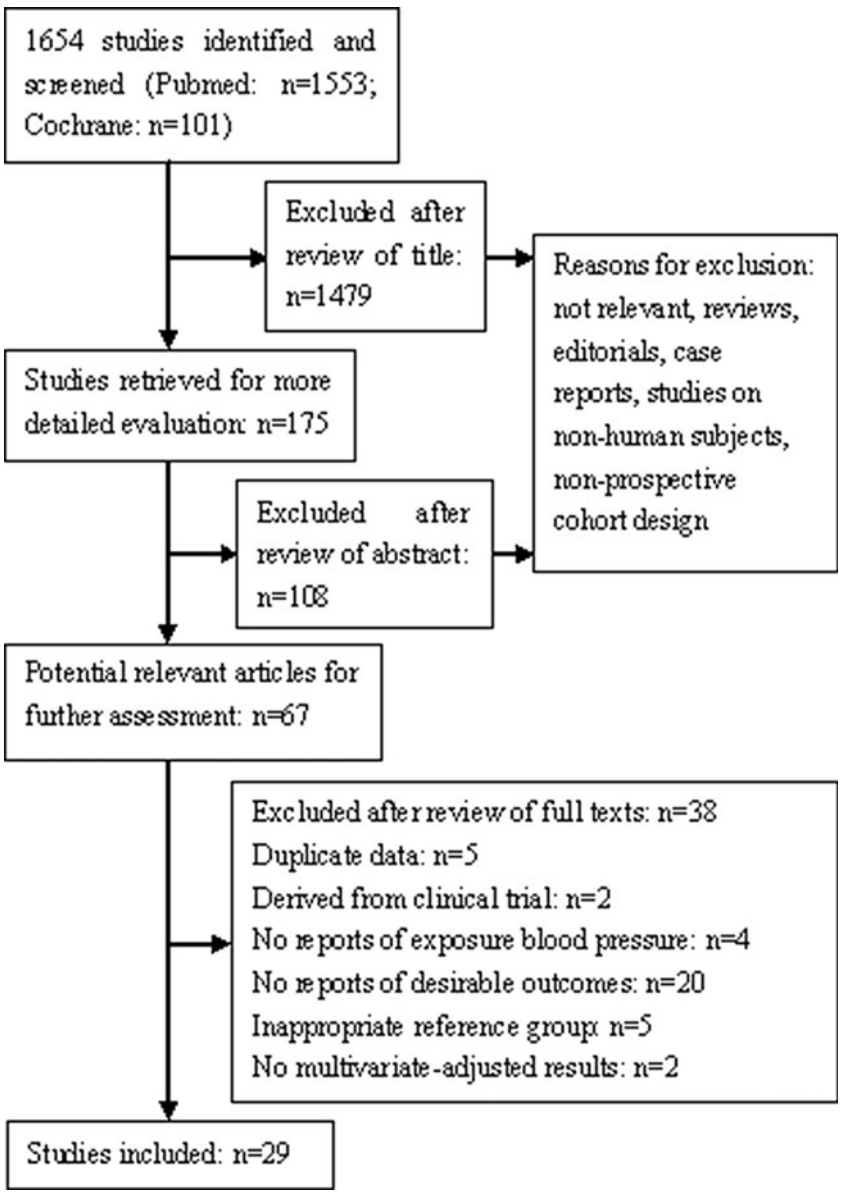

Fig. 1 Flow chart of the study selection process

Table 1 Characteristics of prospective studies included in the systematic review and meta-analysis

First author, Publication year	Study	Country	Prevalence of prehypertension	Sample size (% men)	Follow-up (y)	Age, y (mean, range or SD)	Definition of prehypertension	Adjusted variables	Main outcomes	Study quality
Ramachandran S. Vasan, 2001 [22]	Framingham Heart Study	United States	58.0 %	6,859 (43)	11.1	35–64	JNC 6 and WHO-ISH	Baseline age and BMI, total cholesterol level, presence or absence of DM, smoking and blood pressure category	Major cardiovascular events (CVD death, recognized MI, stroke, or congestive heart failure)	Good
Guixian Wu, 2002 [23]	Cohort study from 11 provinces	China	35.3 %	27,739 (54)	7	35–64	JNC 6 and WHO-ISH	Age, sex, BMI, DM, smoking and cholesterol Age, BMI, serum cholesterol level,	CVD	Fair
Hisatomi Arima, 2003 [24]	Hisayama study	Japan	25.1 %	566 (41)	32	69 (> 60)	JNC 6	smoking, alcohol intake, glucose intolerance, ECG abnormalities and proteinuria	CVD, CHD and stroke	Fair
Kei Asayama, 2004 [25]	Ohasama study	Japan	46.0 %	1,702 (39)	10.6	60 (> 40)	JNC 7	Age, sex, CVD risks (DM,	Stroke	Good
Arch G. Mainous III, 2004 [26]	NHANES II, merged with the NH2 MS	United States	28.7 %	9,087 (NA)	12	30–74	JNC 7	Age, race, sex, smoking, BMI, exercise, total cholesterol, DM, heart failure, heart attack and stroke	All-cause mortality and CVD mortality	Fair
Adnan I. Qureshi, 2005 [13]	Framingham Study	United States	41.2 %	5,181 (45)	31	44 (8.6)	JNC 7	Age, sex, smoking, obesity, DM, hypercholesterolemia and study period	Atherothrombotic brain infarction, all strokes, MI, and coronary artery disease, death from CHD	Good
Heather A. Liszka, 2005 [27]	NHEFS I	United States	33.0 %	8,986 (46)	18	25–74	JNC 7	Age, race, sex, smoking, BMI, exercise, total cholesterol level, DM, history of congestive heart failure, MI and stroke at baseline	Major cardiovascular events (MI, stroke or congestive heart failure)	Good
Abhijit V. Kshirsagar, 2006 [28]	ARIC study	United States	37.3 %	8,960 (45)	11.6	53 (45–64)	JNC 6	Center, age, race, sex, BMI, DM, smoking, LDL, HDL, education level, sport index, cholesterol lowering medication use, fibrinogen, von Willebrand factor, white blood cell count	CVD, CHD or ischemic stroke	Good
Paul D. Terry, 2006 [29]	MRFIT	United States	NA	347,978 (100)	25	35–57	JNC 7	Age, race/ethnicity, income, serum cholesterol level, smoking and use of medication for DM	CVD death	Fair
Wenyu Wang, 2006 [30]	Strong Heart Study	United States	NA	4,549 (NA)	12	56 (45–74)	JNC 7	Age, sex, center, obesity, hypertension, DM, albuminuria, current alcohol drinking and smoking, HDL and LDL	CVD	Good
Judith Hsia, 2007 [14]	WHI	United States	38.8 %	60,785 (0)	7.7	62.8 (7)	JNC 7 or JNC 6	Age, BMI, DM, high cholesterol and smoking	CVD death, MI, stroke, hospitalized heart failure and any cardiovascular event	Good
Kuo Liong Chien, 2007 [31]	CCCC study	Taiwan, China	32.5 %	3,602 (47)	15	> 35	JNC 7	Age, sex, BMI, DM, hypercholesterolemia, left ventricular hypertrophy, smoking and alcohol drinking habits	CVD	Good
Altan Onat, 2008 [32]	Turkish Adult Risk Factor Study	Turkey	32.8 %	3,034 (50)	6.6	48 (12)	Prehypertension (120–139/80–89 mmHg)	Age, sex, heart rate, smoking and obesity	CHD, DM and new MetS	Fair

Table 1 (continued)

First author, Publication year	Study	Country	Prevalence of prehypertension	Sample size (% men)	Follow-up (y)	Age, y (mean, range or SD)	Definition of prehypertension	Adjusted variables	Main outcomes	Study quality
Qiuping Gu, 2008 [33]	NHANES III mortality study	United States	30.8 %	16,917 (42)	8.5	≥18	JNC 7	Age, sex, race/ethnicity, leisure time physical activity, smoking, obesity, and hypercholesterolemia, CVD mortality DM, chronic kidney disease, and a history of congestive heart failure, heart attack, or stroke		Good
Ying Zhang, 2008 [34]	Strong Heart Study	United States	32.1 %	4,507 (40)	13.4	56 (45–74)	JNC 7	Age, sex, BMI, waist circumference, LDL, HDL, triglycerides, physical activity, smoking, alcohol use, microalbuminuria and macroalbuminuria	Stroke	Good
Yoshihiro Kokubo, 2008 [35]	Suita Study	Japan	35.2 %	5,494 (47)	11.7	55 (30–79)	2007 European guidelines	Age, BMI, hyperlipidemia, DM, smoking and drinking status	CVD, MI and stroke	Good
Jeannette Lee, 2008 [36]	Singapore Cardiovascular Cohort Study	Singapore	28.5 %	5,830 (49)	12	39.8 (12.9) for pre group	JNC 7	Age, sex, BMI, total-cholesterol/HDL-cholesterol, ethnic group, study, DM, CVD, smoking and alcohol intake	CVD death and all cause death	Good
Dongfeng Gu, 2009 [15]	China National Hypertension Survey	China	34.5 %	158,666 (49)	7.8	56 (≥40)	JNC 7	Age, sex, high school education, smoking, alcohol consumption, physical activity, BMI, antihypertensive medication, history of CVD or DM, geographic region and urbanization	CVD, CHD and stroke; CVD, CHD and stroke mortality Stroke, intraparenchymal	Good
Ai Ikeda, 2009 [37]	JPHC Study	Japan	43.0 %	33,372 (35)	11	54 (40–69)	2003 European guidelines	Age, BMI, smoking, ethanol intake, antihypertensive medication use, history of DM, serum total cholesterol levels and public health center areas	Hemorrhage, subarachnoid hemorrhage, ischemic stroke, CHD; mortality of stroke, CHD, total CVD, cancer, other causes and all causes	Good
Carlos Lorenzo, 2009 [38]	San Antonio Heart Study	United States	31.6 %	3,580 (NA)	15.2	25–64	JNC 7 or JNC 6	Age, sex, ethnicity, education, BMI, smoking, and total cholesterol concentration	All-cause mortality and CVD mortality	Good
Atsushi Hozawa, 2009 [39]	Ohsaki Cohort Study	Japan	41.8 %	12,928 (43)	11.7	61.2 (9.4)	JNC 7	Age, sex, smoking, hyperglycemia, total cholesterol and BMI	CVD death and all cause death	Good
Mangesh S. Pednekar, 2009 [40]	Mumbai cohort	India	38.8 %	148,173 (59)	5.5	50 (≥35)	JNC 7	Age, education, religion, mother tongue, tobacco habit and BMI	Death from all cause, circulatory system, hypertensive diseases, ischemic heart disease, cerebrovascular diseases, other circulatory system, causes other than circulatory system	Fair
Tsogzolmaa Dorjgochoo, 2009 [41]	Shanghai Women's Health Study	China	39.0 %	68,438 (0)	5	55 (40–70)	2007 European guidelines or JNC7	Education, waist-to-hip ratio, smoking, history of CVD and DM	Stroke, CHD and all-cause mortality	Fair

Table 1 (continued)

First author, Publication year	Study	Country	Prevalence of prehypertension	Sample size (% men)	Follow-up (y)	Age, y (mean, range or SD)	Definition of prehypertension	Adjusted variables	Main outcomes	Study quality
Fumitaka Tanaka, 2010[42]	Iwate-KENCO study	Japan	25.2 %	22,676 (34)	2.7	62 (40–80)	SBP ≥120 but < 140 mmHg or DBP ≥80 but < 90 mmHg	Age, sex, total cholesterol, HDL cholesterol, renal dysfunction, BMI, DM, smoking, alcohol intake and atrial fibrillation	Ischemic stroke	Good
Yukiko Ishikawa, 2010 [43]	The Jichi Medical School Cohort Study	Japan	32.3 %	11,000 (39)	10.7	55.1 (11.5)	JNC 7 or 2009 JSH	Age, sex, BMI, DM, hyperlipidemia, alcohol habits and smoking	CVD	Good
Nan Hee Kim, 2011 [44]	South-West Seoul (SWS) Study	Korea	28.7 %	2,376 (22)	7.6	> 60	JNC 7 or 2007 European guidelines	Age, sex, BMI, fasting glucose, total cholesterol, HDL cholesterol and smoking	CVD death and all cause death	Good
F Hadaegh, 2012 [45]	Middle Eastern community-based cohort of TLGS	Iran	34.5 %	6,273 (43)	9.3	Middle age: 42.5; elderly: 66.3	2007 European guidelines	Age, sex, total chlesterol, BMI, lipid drug, DM, smoking and family history of premature CVD	CVD, CHD	Good
Masayo Fukuhara, 2012 [46]	His ayama Study	Japan	37.7 %	2,634 (42)	19	≥40	JNC 7	Age, sex, BMI, total cholesterol, HDL cholesterol, DM, chronic kidney disease, ECG abnormalities, smoking, drinking and regular exercise	CVD, stroke and CHD	Good
Raimund Erbel, 2012 [47]	Heinz Nixdorf Recall Study	Germany	26.2 %	4,181 (47)	7.18	45–75	JNC 7	Age, cholesterol, DM and smoking	MI, stroke and coronary revascularization	Good

NA not available; *SD* standard deviation; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *BMI* body mass index; *DM* diabetes mellitus; *CVD* cardiovascular disease; *CHD* coronary heart disease; *MI* myocardial infarction; *ECG* electrocardiograph; *LDL* low density lipoprotein; *HDL* high density lipoprotein; *MetS* metabolic syndrome

JNC 6/WHO-ISH/2007 European guidelines/2003 European guidelines/2009 JSH [57–61]: high normal blood pressure (130–139/85–89 mmHg) and normal blood pressure (120–129/80–84 mmHg); JNC 7 [7]: prehypertension (120–139/80–89 mmHg)

respectively. Subgroup analyses were performed according to average age (<65 years vs. ≥65 years), gender (men vs. women), location (Asian vs. non-Asian), sample size (<10000 vs. ≥10000), follow-up (<10 years vs. ≥10 years) and study quality (good vs. fair).

Possible publication bias was evaluated visually by funnel plots and statistically by Begg's and Egger's tests. We also evaluated the influence of individual studies by sensitivity analysis to see the extent to which inferences depend on a particular study or group of studies. All analyses were performed using statistical package Stata version 11.0 and values of $P<0.05$ were considered to be statistical significant.

Results

Literature Search and Study Characteristics

The initial database search generated 1,654 papers, of which 1,587 were excluded after review of title and abstract. Among the retrieved 67 articles, 29 articles met our inclusion criteria,

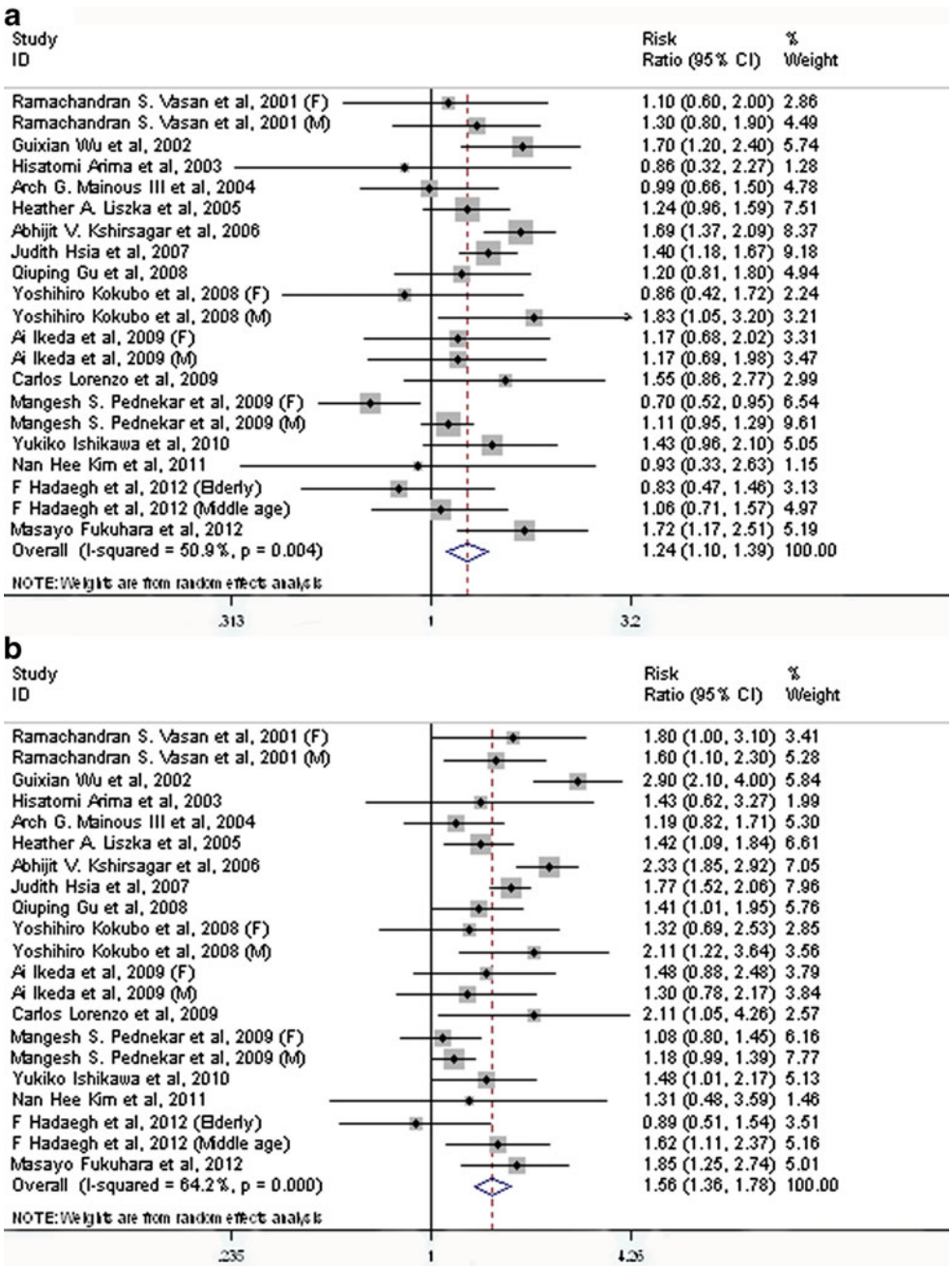

Fig. 2 Association between two ranges of prehypertension, low range (**a**) and high range (**b**), and the risk of developing or dying of total cardiovascular disease. Low range prehypertension: 120–129/80–84 mmHg; high range prehypertension: 130–139/85–89 mmHg. *CI* confidence interval

with 1,010,858 participants [13–15, 22–47]. Figure 1 provides a diagram of the selection process and reasons for exclusion. The included studies varied in sample size from 566 [24] to 347,978 [29]. All but three of the studies [14, 29, 41] included both men and women. Eleven of the studies were conducted in the United States, four in China, eight in Japan, and one each in Germany, India, Iran, Korea, Singapore and Turkey. Follow-up ranged from 6.9 to 25 years. Most of included participants were free of CVDs and were not on use of antihypertensive medication. Table 1 summarizes the characteristics of the included studies.

Prehypertension and Total Cardiovascular Disease

In the pooled analysis from twenty-one populations, both low-range and high-range prehypertension were associated with a greater risk of developing or dying of total CVD (low-range: RR: 1.24; 95 % CI: 1.10 to 1.39, $P<0.001$; high range: RR:

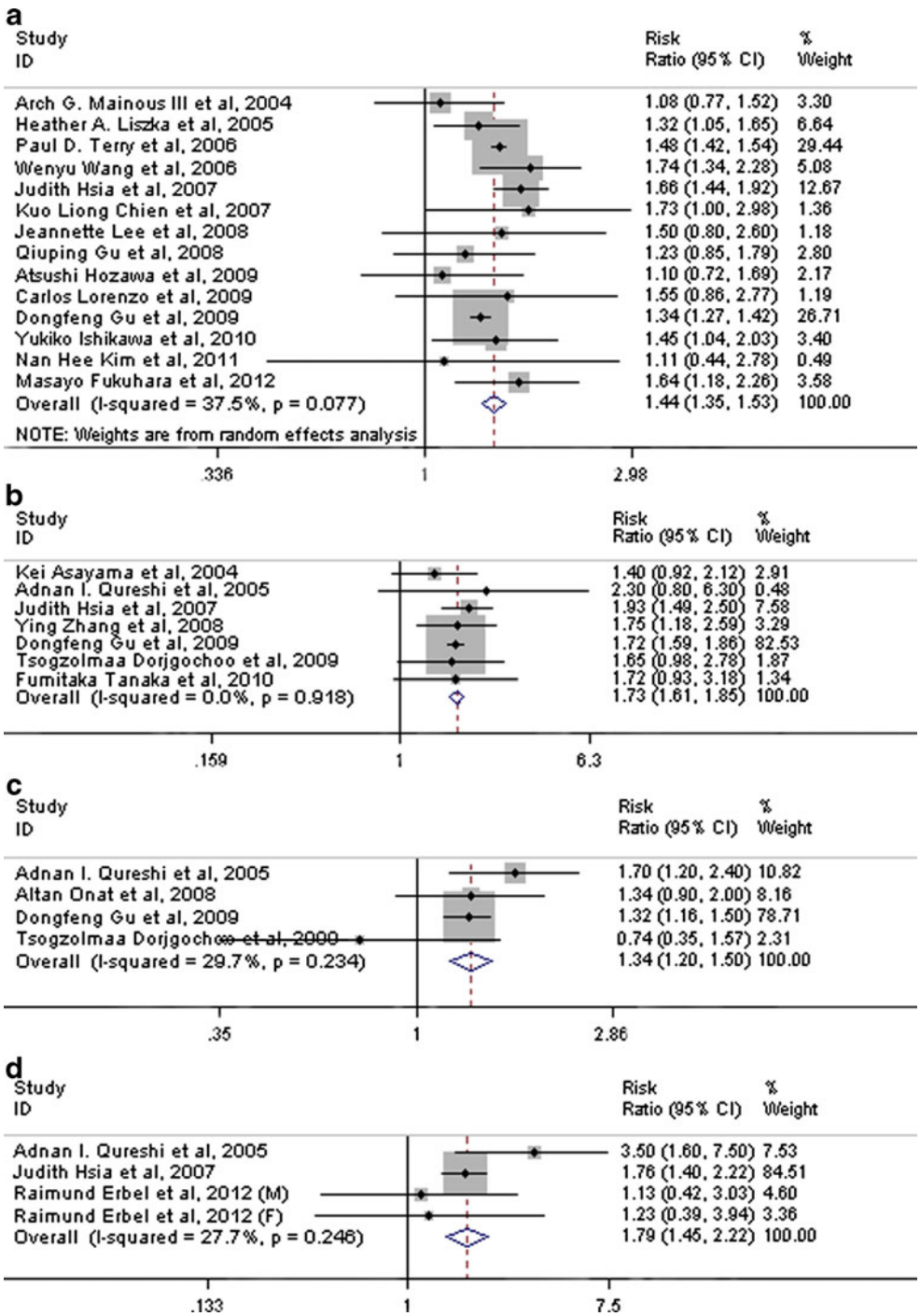

Fig. 3 Association between prehypertension and the risk of developing or dying of total cardiovascular disease (**a**), stroke (**b**), coronary heart disease (**c**), and myocardial infarction (**d**). *CI* confidence interval

1.56; 95 % CI: 1.36 to 1.78, $P<0.001$) (Fig. 2a, b). The risk of total CVD was increased among the whole range of prehypertensive populations (RR: 1.44; 95 % CI: 1.35 to 1.53, $P<0.001$) (Fig. 3a).

Prehypertension and Stroke

Eight studies with eleven populations and nine studies with twelve populations evaluated the risk of low-range and high-range prehypertension for stroke, respectively. Both two ranges increased the risk of developing or dying of stroke (low-range: RR: 1.35; 95 % CI: 1.10 to 1.66, $P=0.004$; high range: RR: 1.95; 95 % CI: 1.69 to 2.24, $P<0.001$) (Fig. 4a, b). Seven studies investigated the association between the whole range of prehypertension and stroke, the pooled result of which showed that prehypertension was related to a greater risk of developing or dying of stroke (RR: 1.73; 95 % CI: 1.61 to 1.85, $P<0.001$), with no evidence of heterogeneity ($I^2=0$ %, $P=0.918$) (Fig. 3b).

Prehypertension and Coronary Heart Disease

Seven studies with nine populations distinguished the two ranges of prehypertension. The pooled result showed that neither low-range nor high-range prehypertension was significantly associated with an increased risk of developing or dying of CHD (low-range: RR: 1.11; 95 % CI: 0.87 to 1.42, $P=0.39$; high range: RR: 1.33; 95 % CI: 0.96 to 1.83, $P=0.085$) (Fig. 5a, b). However, in the pooled analysis of four studies evaluating the whole range, prehypertension increased the risk of CHD (RR: 1.34; 95 % CI: 1.20 to 1.50, $P<0.001$) (Fig. 3c).

Prehypertension and Myocardial Infarction

In the pooled analysis from three populations, low-range prehypertension increased 1.43-fold risk of developing or dying of MI ($P=0.007$), while high-range prehypertension was associated with a much higher risk (RR: 1.99; 95 % CI: 1.59 to 2.50, $P<0.001$) (Fig. 5c, d). Among the whole range prehypertensive populations, risk of incident MI was also increased (RR: 1.79; 95 % CI: 1.45 to 2.22, $P<0.001$) (Fig. 3d).

Sources of Heterogeneity

Tables 2 and 3 show further analysis stratified by different population groups in each range of prehypertension. Between-study heterogeneity was observed. The heterogeneity of effect was due to differences in gender, age, location, sample size, follow-up or study quality. No publication bias was observed (Begg's test all $P>0.05$; Egger's test all $P>0.05$, figures not

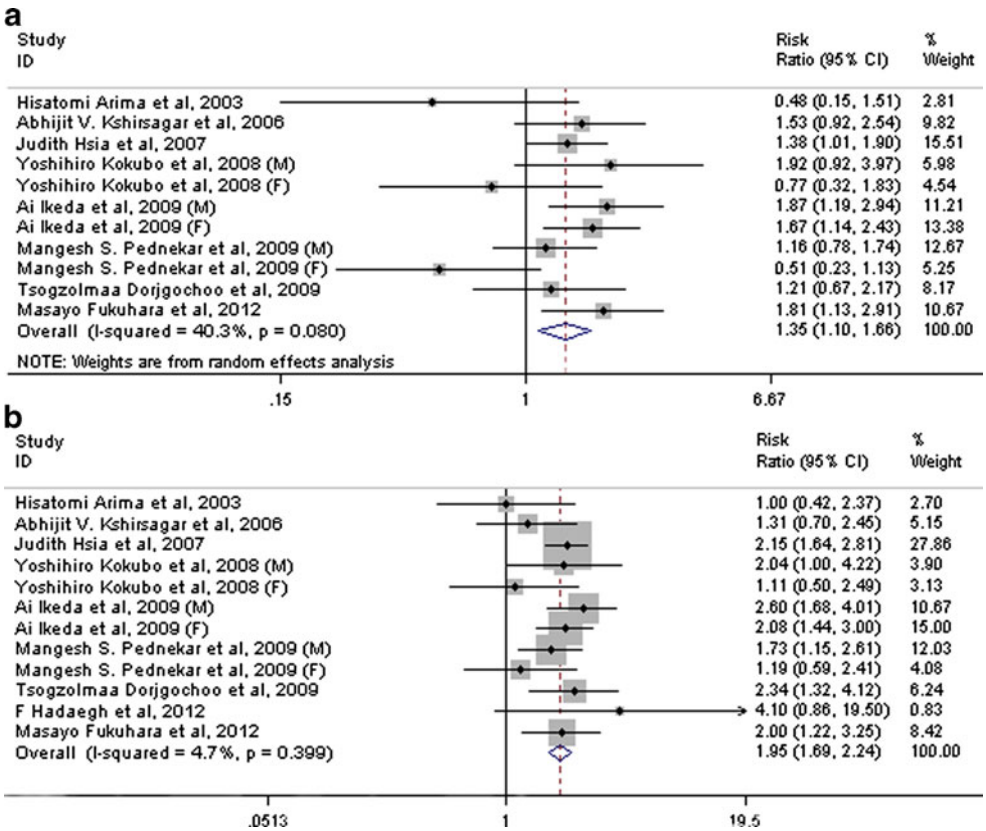

Fig. 4 Association between two ranges of prehypertension, low range (**a**) and high range (**b**), and the risk of developing or dying of stroke. Low range prehypertension: 120–129/80–84 mmHg; high range prehypertension: 130–139/85–89 mmHg. *CI* confidence interval

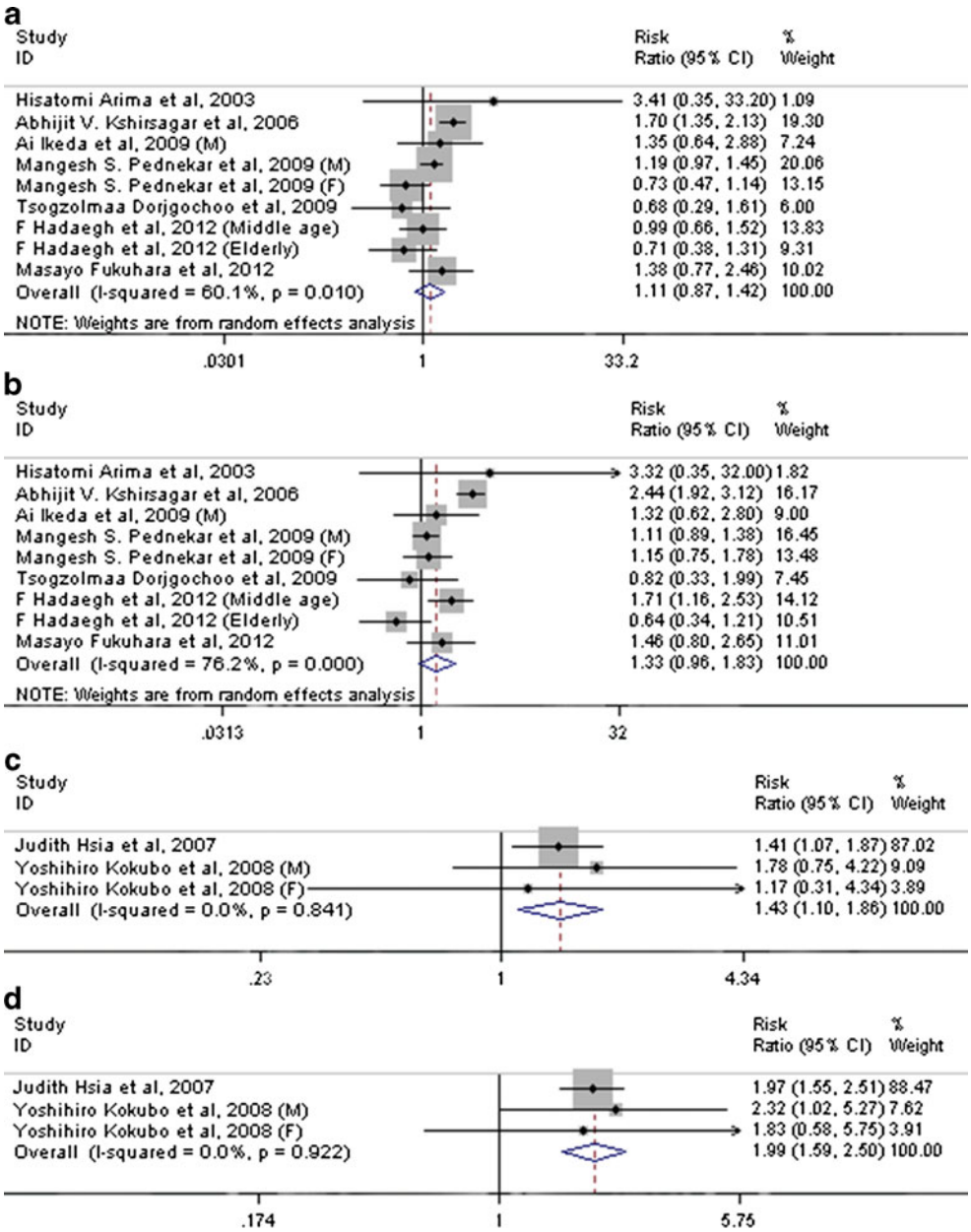

Fig. 5 Association between two ranges of prehypertension, low range (**a** and **c**) and high range (**b** and **d**), and the risk of developing or dying of coronary heart disease (**a** and **b**), and myocardial infarction (**c** and **d**). Low range prehypertension: 120–129/80–84 mmHg; high range prehypertension: 130–139/85–89 mmHg. *CI* confidence interval

shown). The sensitivity analysis showed that the omission of any of the studies from the analysis did not alter the overall finding.

Discussion

The present study provided a comprehensive review of the literature worldwide and quantitative estimates of prospective associations between prehypertension and CVDs among population-based studies. From multivariable adjusted studies, we found that prehypertension was associated with a clearly increased risk of incident stroke, MI and total CVD events, even within the lower range. The effects of prehypertension on CVD outcomes differed by many factors, such as gender, age group and study quality.

The overall prevalence of prehypertension in the US was 31 % according to the Third National Health and Nutrition Examination Survey (NHANES III) [48]. Over 32 million men and 21 million women aged 20 years or older in the US were estimated to be prehypertensive [49]. Given the large population and the robust impact of prehypertension on cardiovascular outcomes, the caused burden is considerable. It was estimated that in China alone, there were 0.22 million cardiovascular deaths in adults attributed to prehypertension in 2005 [4]. In the present study, we found that the baseline prehypertensive population had a 1.44-fold risk of developing

Table 2 Subgroup analyses to explore source of heterogeneity in the low range prehypertension

Subgroups	Stroke				CHD				CVD			
	No.	RR	95 % CI	*P*-value for heterogeneity	No.	RR	95 % CI	*P*-value for heterogeneity	No.	RR	95 % CI	*P*-value for heterogeneity
Gender												
Men	3	1.53	1.01–2.16	0.431	2	1.2	0.99–1.46	0.022	6	1.28	1.07–1.54	0.784
Women	5	1.17	0.83–1.65		2	0.72	0.49–1.07		7	1.08	0.79–1.47	
Age group												
≥65y	1	0.48	0.15–1.52	0.068	2	1.05	0.28–3.93	0.139	3	0.85	0.55–1.33	0.086
<65y	10	1.4	1.15–1.7		7	1.15	0.9–1.48		18	1.226	1.12–1.43	
Location												
Asian	9	1.29	0.98–1.7	0.87	8	1.03	0.84–1.25	0.001	13	1.17	0.98–1.39	0.011
Non-Asian	2	1.42	1.09–1.86		1	1.7	1.35–2.14		8	1.37	1.22–1.53	
Sample size												
<10000	5	1.35	0.9–2.02	0.72	5	1.23	0.84–1.79	0.044	13	1.28	1.10–1.49	0.133
≥10000	6	1.33	1.03—1.71		4	0.99	0.72–1.37		8	1.2	0.99–1.44	
Follow-up												
<10y	4	1.13	0.82–1.55	0.057	5	0.94	0.73–1.2	<0.001	8	1.12	0.92–1.36	0.019
≥10y	7	1.56	1.22–1.99		4	1.64	1.34–2.01		13	1.37	1.22–1.55	
Study quality												
Good	7	1.57	1.32–1.87	0.008	5	1.22	0.87–1.71	0.046	16	1.36	1.24–1.50	0.001
Fair	4	0.9	0.58–1.39		4	0.96	0.65–1.42		5	1.05	0.78–1.41	

CHD coronary heart disease; *CVD* cardiovascular disease; *RR* risk ratio; *CI* confidence interval

or dying of total CVD. Even within the lower range group, the risk was increased, indicating that effective intervention in this early stage might reduce a substantial future burden. A recent meta-analysis including 18 studies reported a higher RR of

Table 3 Subgroup analyses to explore source of heterogeneity in the high range prehypertension

Subgroups	Stroke				CHD				CVD			
	No.	RR	95 % CI	*P*-value for heterogeneity	No.	RR	95 % CI	*P*-value for heterogeneity	No.	RR	95 % CI	*P*-value for heterogeneity
Gender												
Men	3	2.09	1.58–2.75	0.772	2	1.13	0.91–1.39	0.854	6	1.61	1.11–2.32	0.108
Women	5	1.99	1.64–2.4		2	1.08	0.73–1.59		7	1.58	1.25–2.00	
Age group												
≥65y	2	1.39	0.65–2.97	0.378	2	1.01	0.24–4.24	0.021	3	1.07	0.71–1.63	0.086
<65y	10	1.97	1.71–2.28		7	1.43	1.03–1.97		18	1.6	1.39–1.84	
Location												
Asian	10	1.93	1.62–2.29	0.831	8	1.19	1.97–1.47	<0.001	13	1.49	1.22–1.81	0.007
Non-Asian	2	1.99	1.55–2.55		1	2.44	1.91–3.11		8	1.66	1.42–1.95	
Sample size												
<10000	6	1.61	1.21–2.15	0.141	5	1.54	0.96–2.49	<0.001	13	1.61	1.37–1.89	0.133
≥10000	6	2.07	1.76–2.43		4	1.12	0.93–1.34		8	1.51	1.21–1.88	
Follow-up												
<10y	5	1.99	1.63–2.43	0.76	5	1.12	0.85–1.48	<0.001	8	1.47	1.15–1.87	0.116
≥10y	7	1.9	1.55–2.33		4	1.95	1.36–2.79		13	1.64	1.43–1.88	
Study quality												
Good	8	2.06	1.74–2.42	0.194	5	1.47	0.95–2.28	<0.001	16	1.65	1.48–1.84	0.002
Fair	4	1.65	1.25–2.2		4	1.11	0.92–1.34		5	1.44	0.99–2.09	

CHD coronary heart disease; *CVD* cardiovascular disease; *RR* risk ratio; *CI* confidence interval

1.55 for CVD among prehypertensive participants [50]. This higher risk might be explained by the fact that some studies evaluating fatal events as outcomes were not included in that analysis. Although a secondary analysis of a clinical trial, which was not included in the present study, found that prehypertension was not associated with an increased risk of fatal CVD [51], the impact of drug use was not fully eliminated. In line with a former study in the Asia-Pacific region [52], we observed that the effect of prehypertension on total CVD vanished among participants aged 65 years or older.

Stroke is most highly correlated with BP among various vascular diseases [53]. The present study found that prehypertensive participants increased about 1.7-fold in risk of developing or dying of stroke, which was similar to the result from a previous study [54]. The RR for incident stroke was also quite similar in the analysis by Huang et al. [50], indicating a robust association between prehypertension and stroke. A recent meta-analysis of 16 randomized controlled trials indicated that antihypertensive therapy among prehypertensives could significantly reduce the risk of stroke [55], leading to a doubt that whether only lifestyle modification recommended by JNC 7 [7] is adequate. In our further subgroup analyses, we observed that among the low-range prehypertensive population, only men with prehypertension had a significantly increased risk for stroke, while the gender-specific result disappeared in the high-range population. The underlying mechanism is not understood. We also found that prehypertension was not associated with stroke among the elderly, the potential reasons of which were discussed by Lee et al. [54].

Also, we observed a 1.34-fold risk of CHD associated with prehypertension from four studies, which was a little higher than the result in the Asia-Pacific region [52] and lower than the result from Huang et al. [50]. While in the analyses of two separate range groups, the results were not statistically significant, even in the high-range prehypertension. This discrepancy is probably due to different distributions of the included populations. A novel finding is that high range prehypertensive population had a nearly two-fold risk of developing or dying of MI, meriting attentions in the clinical work. However, the number of included studies is relatively small, and more cohorts are expected. Of note, Butler et al. found that among the elderly, prehypertension was related to a 1.63-fold risk of incident heart failure over 10 years follow-up in the US [56]. The positive association was consistent with a previous study [14], indicating a roll of mildly raised BP in the mechanism of heart failure.

The strengths of our study include the comprehensive review of the literature worldwide and the large sample size we collected. There are limitations in the present study that merit discussion. First, the contributing studies varied in the degree of confounders. Although we only included multivariable adjusted studies to minimize the impacts, it remains a possibility that residual confounding and bias across the studies caused overestimation of the associations. Second, due to the limited number of studies, we pooled results from studies involving different definitions of CVD, which might compromise the results. In addition, although our literature search was extensive, there still was a possibility of omissions. Plus, a delay between search and publication was inevitable. Even though our meta-analysis has several limitations, it probably represents the most comprehensive review and the most accurate estimate to critically appraise the evidence surrounding the association between prehypertension and different types of CVD.

Conclusions

From the worldwide data, prehypertension was significantly associated with an increased risk of incident stroke, MI and total CVD. The impact was markedly different between the two BP ranges. Effective BP reduction treatment giving full consideration of the risk stratifications of different BP ranges should be initiated in this early stage to reduce a substantial future burden. Trials investigating the effects of BP reduction on different types of CVD outcomes among prehypertensive subjects are expected.

Compliance with Ethics Guidelines

Conflict of Interest Xiaofan Guo, Xiaoyu Zhang, Liang Guo, Zhao Li, Liqiang Zheng, Shasha Yu, Hongmei Yang, Xinghu Zhou, Xingang Zhang, Zhaoqing Sun, Jue Li, and Yingxian Sun declare that they have no conflict of interest.

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