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Prehypertension A Meta-Analysis of the Epidemiology, Risk Factors, and Predictors of Progression

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Prehypertension

A Meta-Analysis of the Epidemiology, Risk Factors, and Predictors of Progression

We investigated the prevalence and risk factors of prehypertension, as well as the predictors of progression from prehypertension to hypertension. To do this, we performed a systematic review and meta-analysis of cross-sectional and longitudinal studies, after unrestricted searches of PubMed and The Cochrane Library through September 2010. In addition, we reviewed references, major textbooks, and review articles. Pooled prevalence, standardized mean differences, and odds ratios were estimated by using a random-effects model.

Twenty-six articles met our inclusion criteria; these included 20 cross-sectional and 6 longitudinal studies, with a total sample of 250,741 individuals. The overall pooled prevalence of prehypertension was 36%. The pooled prevalence among males was higher than that among females (40% vs 33%). The pooled standardized mean difference for body mass index was 1.37 (95% confidence interval [CI], 1.20–1.55); for total cholesterol, 8.08 (95% CI, 6.71–9.46); for low-density-lipoprotein cholesterol, 5.14 (95% CI, 3.09–7.18); and for fasting plasma glucose, 4.23 (95% CI, 3.28–5.18); all of which showed more significant results in females. The pooled odds ratio was 1.13 (95% CI, 0.93–1.37) for smoking and 0.98 (95% CI, 0.69–1.39) for drinking. In addition, factors such as older age at baseline, male sex, Mongolian race, and being overweight or obese were predictors of progression to hypertension, according to descriptive analysis.

The prevalence of prehypertension was relatively high, especially for males. There were many modifiable risk factors associated with prehypertension, to which healthcare providers should pay more attention. (*Tex Heart Inst J* 2011;38(6):643-52)

In 2003, the Seventh Report of the Joint National Committee (JNC 7) defined prehypertension as a systolic blood pressure (BP) of 120–139 mmHg or a diastolic BP of 80–89 mmHg in adults 18 years and older.¹ Such intentional identification of patients as “prehypertensive” calls needed attention to the excess risk associated with BP in this range and reminds healthcare providers to pay more attention to prevention. Prehypertension seems indeed to be a precursor of hypertension, associated with many adverse outcomes. Vasan and colleagues² found that the conversion rate of prehypertension to hypertension over 4 years was 30%. Prehypertension is also associated with an increased risk of major cardiovascular-disease events.³ Also, Mullican and associates, in the San Antonio Heart Study,⁴ showed that a BP of 130–139/85–89 mmHg was associated with diabetes mellitus. The prevalence of prehypertension and its associated risk factors has been investigated worldwide since 2003. Many studies have focused also on the predictors of progression from prehypertension to hypertension. However, the results were controversial, and there was no systematic review and meta-analysis to investigate these issues. Therefore, we performed this study in order to systematically review the findings of all available articles. We then combined the findings that met our criteria, in an effort to examine the prevalence and risk factors of prehypertension and (in longitudinal studies) the predictors of progression to hypertension.

Methods

Literature Search Strategy

All relevant studies were identified by searching PubMed and The Cochrane Library through September 2010. These were supplemented by articles cited in these studies, by major textbooks, and by review articles. The key words used in searching were prehypertension, hypertension, prevalence, risk factors, and predictors. The full texts of studies were retained after evaluation. If these did not contain all of the informa-

tion necessary for meta-analysis, we obtained the missing information directly from the authors. Finally, we divided the studies into 2 groups: cross-sectional studies that reported the epidemiology and risk factors of prehypertension; and longitudinal studies that concerned the predictors of progression from prehypertension to hypertension.

Criteria for Inclusion and Exclusion

We included cross-sectional studies that reported the prevalence and risk factors of prehypertension, together with longitudinal studies that investigated the predictors of progression from prehypertension to hypertension. The research had to be original, and the results had to be written in English or Chinese. We required sufficient information to conduct pooled analysis (that is, pooled prevalence); and we required that hypertension and prehypertension be defined in accordance with the criteria set forth in the 2003 JNC 7 report (that is, hypertension is systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg; and prehypertension is systolic BP of 120–139 mmHg or diastolic BP of 80–89 mmHg).

We excluded studies whose participants were drawn from a particular occupation or population, whose results were already in our compendium, or whose samples were too small (<300). In order to avoid inconsistent outcomes, we excluded studies that used non-JNC 7 standards (for example, those inclusive of “high-normal” BP).

Data Extraction and Quality Assessment

Information such as the year of publication and the length of follow-up was coded in a standard format. Two investigators selected the studies, extracted the data independently, and cross-checked them. Discrepancies were resolved by an additional reviewer and through discussion. The quality of all selected studies was evaluated by 2 reviewers, in accordance with the following criteria: the study sample was representative of the general population; recruitment of the study sample was conducted in an appropriate manner; the response rate was adequate to enable conclusions; and the inclusion and exclusion criteria were appropriate and clear. Unqualified studies were omitted.

Statistical Analysis

Crude prevalence and its standard errors were calculated. Pooled prevalence was estimated by means of the Stata[®] statistical software package, version 11.0 (Stata-Corp LP; College Station, Texas), using the “metan” command. Data related to risk factors were entered into RevMan 5.0 software (The Cochrane Collaboration; Oxford, UK) for the meta-analysis, with combined results displayed using SPSS version 17.0 software (IBM Corporation; Somers, NY). Pooled standardized mean differences (SMDs) and odds ratios (ORs)

were estimated by using a random-effects model, with 95% confidence intervals (CIs) calculated. Cochrane’s χ^2 test and the I^2 index for heterogeneity were used to evaluate between-study heterogeneity. Statistically significant heterogeneity was considered present at $P < 0.1$ and $I^2 > 50\%$.⁵ Subgroup analyses were carried out to investigate between-study heterogeneity, with a focus on sex differences between studies. As a consequence of insufficient data, we performed descriptive analysis on the predictors of progression from prehypertension to hypertension.

Results

The initial database search generated 1,123 papers, 179 of which were retained for further review. After more detailed evaluation, 26 articles^{6–31} met our inclusion criteria, including 20 cross-sectional^{6–25} and 6 longitudinal studies.^{26–31} We included a total sample of 250,741 individuals, consisting of 120,605 men and 130,136 women from 13 countries. Figure 1 provides a diagram of the selection process and reasons for excluding studies. The characteristics of the 26 included studies are summarized in Tables I and II.

Epidemiology of Prehypertension

In most of the 20 cross-sectional studies, the age of the sample group ranged between 35 and 60 years. Only 2 studies had a mean age ≥ 60 years.^{13,20} Except for 2 studies,^{14,18} the sexual distributions of the groups were in general balanced, with the male portion at around 40%

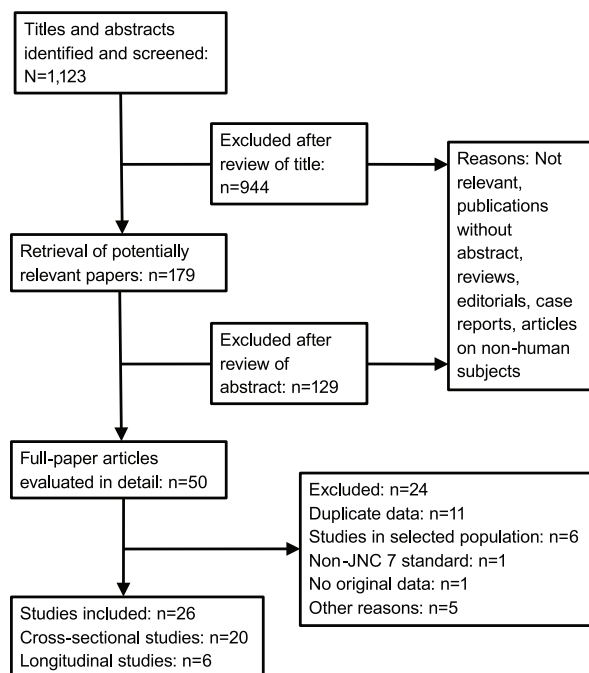


Fig. 1 Flow chart of the study-selection process.

JNC = Joint National Committee

TABLE I. Characteristics of 20 Cross-Sectional Studies, Reporting Prevalence and Risk Factors of Prehypertension

Study	Country	Sample Size	Male Sex, %	Age, yr	Prevalence of Prehypertension, %	Method of BP Measurement
Sun ZQ, et al. (2007) ⁶	China	29,970	50.5	35–99	47	Electric sphygmomanometer
Ling LL, et al. (2008) ⁷	China	5,272	48.2	NA	36.34	Mercury sphygmomanometer
Yadav S, et al. (2008) ⁸	India	1,112	50.1	49.8 ± 11.5	32.3	Mercury sphygmomanometer
Agyemang C, et al. (2007) ⁹	Netherlands	1,432	41.1	35–60	32.8	Automated digital BP device
Ishikawa Y, et al. (2008) ¹⁰	Japan	12,048	39.1	18–90	33	Automated digital BP device
Tsai PS, et al. (2005) ¹¹	China	2,225	46.7	18–96	34	Standard sphygmomanometer
Yu D, et al. (2008) ¹²	China	10,748	47	35–74	21.9	Mercury sphygmomanometer
Lin SJ, et al. (2010) ¹³	China	6,204	42.7	61.65 ± 11.85	30.2	Mercury sphygmomanometer
Ferguson TS, et al. (2008) ¹⁴	Jamaica	1,972	33.5	15–74	30	NA
Isezuo SA, et al. (2011) ¹⁵	Nigeria	782	52.3	15–65	58.7	Automated sphygmomanometer
Agyemang C and Owusu-Dabo E (2008) ¹⁶	Ghana	1,431	45	≥18	40	Automated digital BP device
Gupta AK, et al. (2010) ¹⁷	U.S.	10,380	52.3	NA	36.3	Mercury sphygmomanometer
Chockalingam A, et al. (2005) ¹⁸	India	2,007	75	18–86	47.4	Mercury sphygmomanometer
Janghorbani M, et al. (2008) ¹⁹	Iran	69,722	50.3	25–65	52.1	Mercury sphygmomanometer
Kawamoto R, et al. (2008) ²⁰	Japan	2,841	42.5	19–90	25.3	Automated digital BP device
Li H, et al. (2008) ²¹	China	2,589	41.1	20–84	38.39	Mercury sphygmomanometer
Aekplakorn W, et al. (2008) ²²	China	39,290	48.2	≥15	32.8	Mercury sphygmomanometer
Erem C, et al. (2009) ²³	Turkey	4,809	45.9	NA	14.5	Aneroid sphygmomanometer
Yang J, et al. (2010) ²⁴	China	20,167	38.5	35–74	54.6	Mercury sphygmomanometer
Choi KM, et al. (2006) ²⁵	Korea	6,074	43.1	≥20	31.6	Mercury sphygmomanometer

BP = blood pressure; NA = not available; U.S. = United States

Data are expressed as mean ± SD or as number. Criteria for hypertension were in accordance with the Seventh Report of the Joint National Committee (JNC 7).¹

TABLE II. Characteristics of 6 Longitudinal Studies, Reporting Predictors of Progression from Prehypertension to Hypertension

Study	Country	Sample Size with Prehypertension at Baseline	Male Sex, %	Length of Follow-Up	Age, yr	Cases Developing to Hypertension
Pitsavos C, et al. (2008) ²⁶	Greece	782	54.5	5 yr	NA	160
De Marco M, et al. (2009) ²⁷	U.S.	625	37	4 yr	59 ± 7	235
Zheng L, et al. (2010) ²⁸	China	15,061	57.5	28 mo	48.85 ± 10.48	4,917
Liu LK, et al. (2010) ²⁹	China	316	44.6	5 yr	68.4 ± 11.4	99
Player MS, et al. (2007) ³⁰	U.S.	2,334	48.3	4–8 yr	45–64	1,356
Jimenez-Corona A, et al. (2007) ³¹	Mexico	548	49.8	Median 5.8 yr	NA	180

NA = not available; U.S. = United States

Data are expressed as mean ± SD or as number.

to 55%. There were extreme differences in the male-to-female ratio across the groups in the studies by Ferguson¹⁴ and Chockalingam¹⁸ and their respective associates (around 1-to-2 and 3-to-1 male-to-female, respectively).

Most of the studies were conducted in East Asia. Maximum (58.7%) and minimum (14.5%) prevalence of prehypertension appeared in the studies by Isezuo and colleagues¹⁵ and Erem and associates,²³ respectively. The

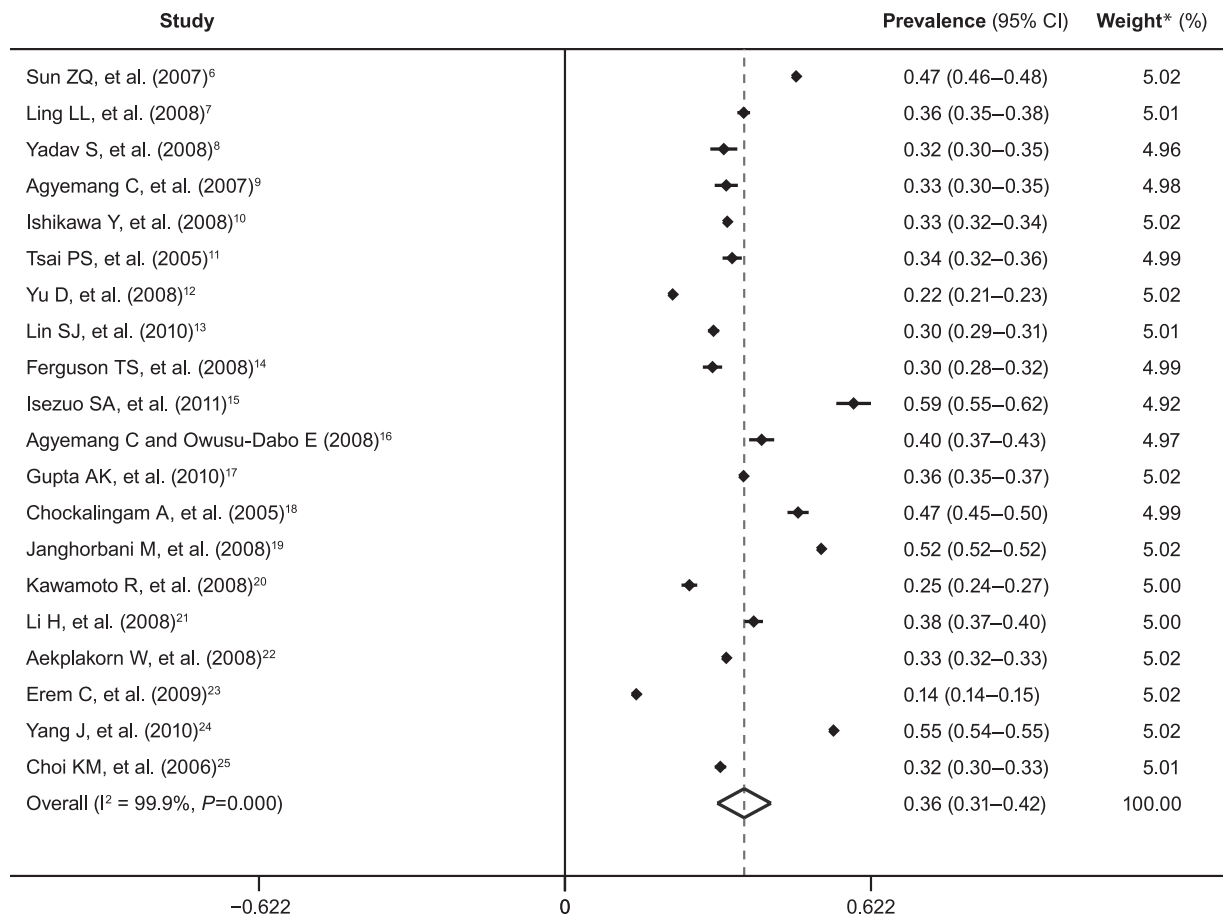


Fig. 2 Pooled prevalence of prehypertension, according to 20 cross-sectional studies.

*Weights are from random-effects analysis.

CI = confidence interval

overall pooled prevalence was 36% (Fig. 2). The pooled prevalence for males was higher than that for females (40% vs 33%; data not shown). After removing non-East Asian countries, we found that the pooled prevalence of prehypertension in 11 studies from East Asian countries (China, Japan, and Korea) was 35% (Fig. 3), which was similar to the overall pooled prevalence. However, the findings had substantial heterogeneity ($P < 0.001$), possibly due to confounding effects of differences in age, distribution of subjects, and so on.

Risk Factors for Prehypertension

Body Mass Index and Waist Circumference. Ten papers,^{9,13,19,20,23,25,31} involving 49,532 people with prehypertension and 37,919 with normotension, reported body mass index (kg/m^2) values sorted by sex. The overall pooled SMD was 1.37 (95% CI, 1.20–1.55) (Fig. 4). The heterogeneity was significant ($\chi^2 = 135.74$, $I^2 = 86\%$). Seven of the included studies^{11,12,17,19,23,25,31} compared waist circumference between individuals with prehypertension and normotension. For males the pooled SMD was 4.06 (95% CI, 3.30–4.82), while for females

it was 4.85 (95% CI, 3.98–5.72) (Fig. 4). The subgroup difference was not significant, with $\chi^2 = 1.07$ and $I^2 = 6.2\%$.

Dyslipidemia. Ten studies^{9,10,12,13,17,19,20,23,25,31} reported a variety of lipid outcomes that included levels of total cholesterol, triglycerides, high-density-lipoprotein cholesterol (HDL-C), and low-density-lipoprotein cholesterol (LDL-C). A pooled analysis of triglycerides (mg/dL) was not performed, because the number of studies was insufficient. Total cholesterol values (mg/dL) were available for 48,784 individuals with prehypertension and 56,936 individuals with normotension in 9 different studies.^{9,10,12,13,19,20,23,25,31} The pooled SMD was 7.17 (95% CI, 5.27–9.06) for males, 9.04 (95% CI, 6.86–11.22) for females, and 8.08 (95% CI, 6.71–9.46) for both (Fig. 4). There was significant heterogeneity ($\chi^2 = 34.13$, $I^2 = 77\%$). Seven studies^{10,12,17,20,23,25,31} reported HDL-C values (mg/dL) and 5 studies^{12,20,23,25,31} reported LDL-C values (mg/dL), separated by sex. The results of meta-analysis are displayed in Figure 4.

Fasting Plasma Glucose. Eight studies^{9,10,12,13,19,20,23,25} reported fasting plasma glucose (mg/dL) from 48,236 in-

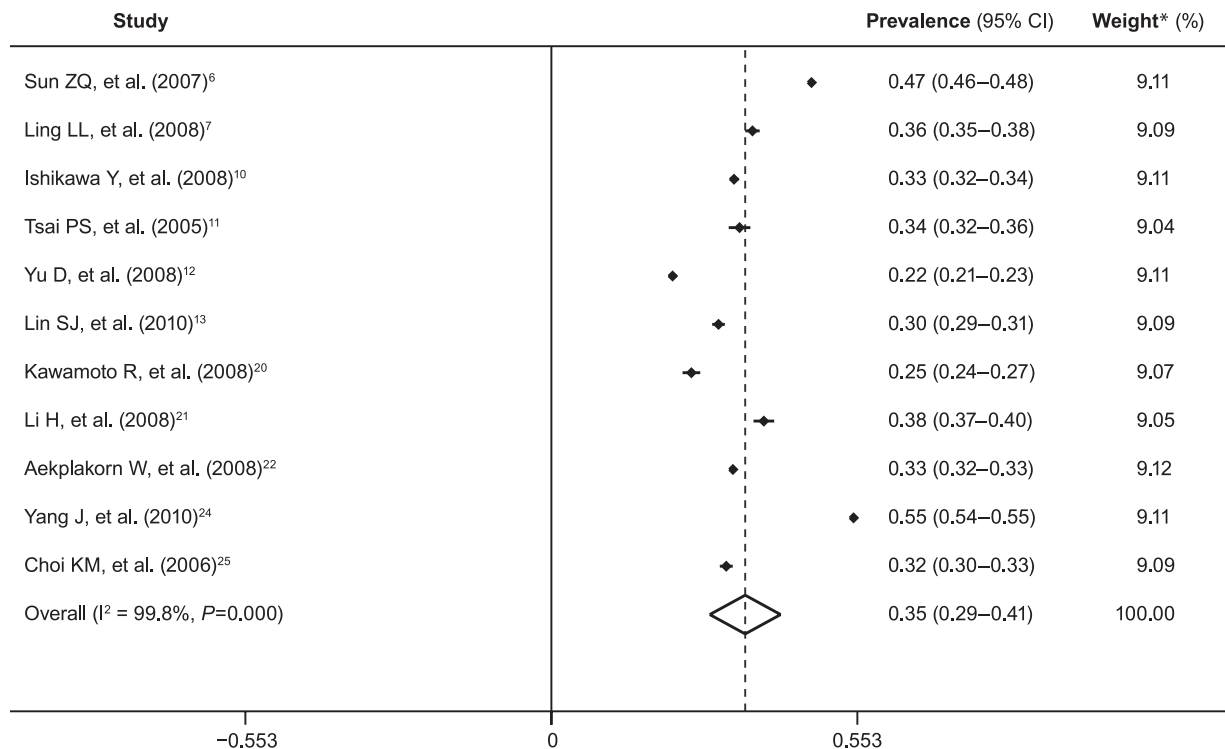


Fig. 3 Pooled prevalence of prehypertension in East Asia.

*Weights are from random-effects analysis.

CI = confidence interval

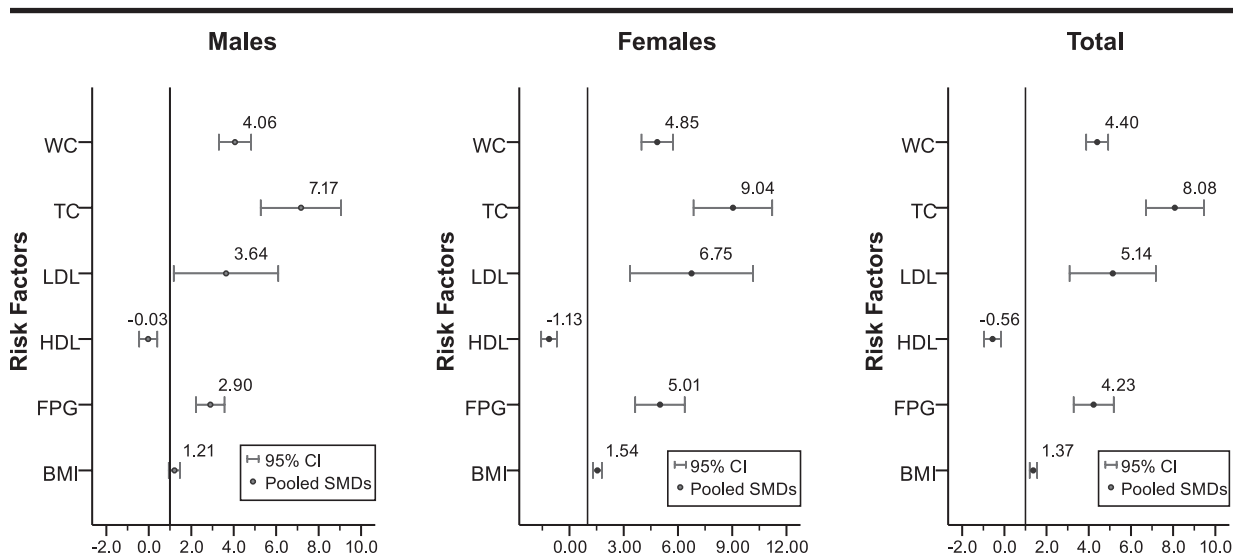


Fig. 4 Pooled standardized mean differences (SMDs) and 95% confidence intervals (CI) of risk factors in males and females.

BMI = body mass index; FPG = fasting plasma glucose; HDL = high-density-lipoprotein cholesterol; LDL = low-density-lipoprotein cholesterol; TC = total cholesterol; WC = waist circumference

dividuals with prehypertension and 36,190 individuals without. The pooled SMD was 2.90 (95% CI, 2.22–3.57) for males, 5.01 (95% CI, 3.64–6.37) for females, and 4.23 (95% CI, 3.28–5.18) for both (Fig. 4). The between-study heterogeneity was significant ($\chi^2 = 17.13$, $I^2 = 94.2\%$).

Smoking and Drinking. Ten studies^{6-9,11,13,15,17,18,23} investigated the association between smoking and prehypertension. The pooled OR was 1.13 (95% CI, 0.93–1.37) (Fig. 5). Eight studies^{6,7,9,11,13,17,18,23} reported drinking status in 16,557 individuals with prehypertension and 11,823 without, but provided conflicting results. The

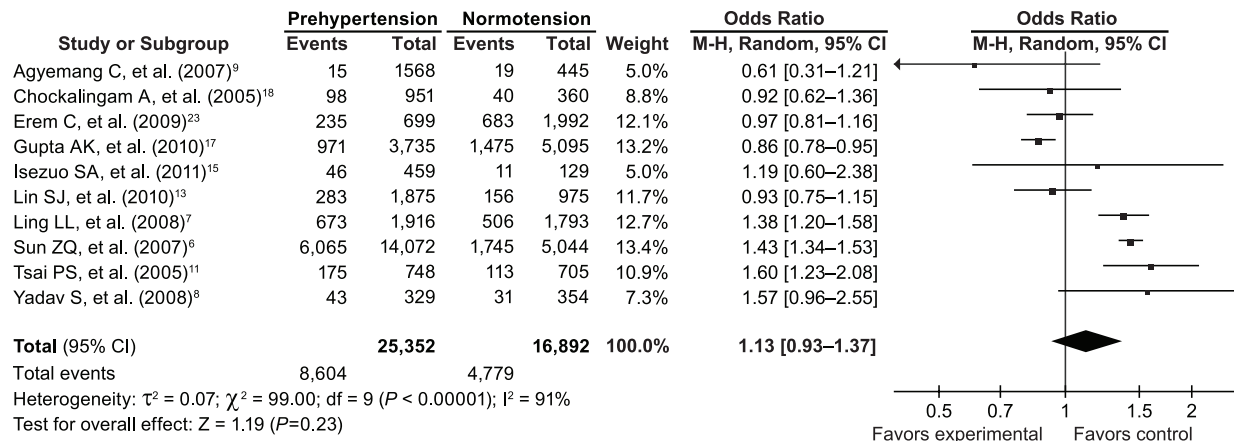


Fig. 5 Pooled odds ratios and 95% confidence intervals (CI) of smokers.

M-H = Mantel-Haenszel test; df = degrees of freedom

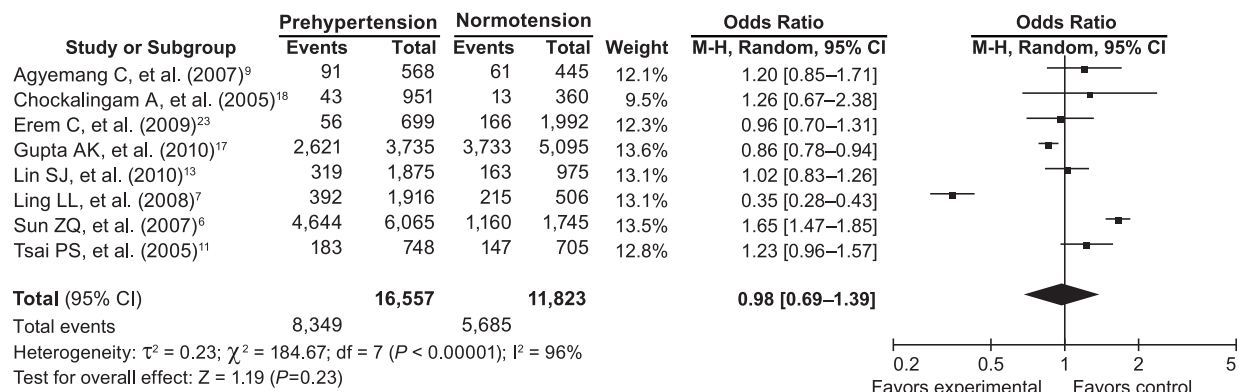


Fig. 6 Pooled odds ratios and 95% confidence intervals (CI) of alcohol drinkers.

M-H = Mantel-Haenszel test; df = degrees of freedom

pooled OR was 0.98 (95% CI, 0.69–1.39) (Fig. 6). Pooled analysis showed that the heterogeneity of both smoking and drinking were significant.

Predictors of Progression from Prehypertension to Hypertension. Six articles^{26–31} provided information on predictors of progression from prehypertension to hypertension. The length of follow-up ranged from around 28 months to 5 years. Meta-analysis could not be performed due to insufficient data. Metabolic factors (for example, lipids) and life habits (for example, smoking) received more attention. Some of the main predictors from these studies are displayed in Table III.

Discussion

Epidemiology of Prehypertension

We found that the prevalence of prehypertension varied in a very wide range across studies. Therefore, a simple meta-analysis to combine the findings of studies would be informative, even using random-effects models. Our

study found, on the basis of 20 included studies, that the overall prevalence of prehypertension was 36%. In the analysis of 11 East Asian countries, the pooled prevalence was 35%, indicating the minor influence of geographic distribution in our study. We observed that the pooled prevalence of prehypertension among males (40%) was much higher than that among females (33%), which was similar to the hypertension prevalence observed in a study from Korea (41.5% in men vs 24.5% in women).³² Yet the opposite result was found in the meta-analysis of hypertension in Iran,³³ in which the estimated prevalence in men was 1.3% less than that in women. The same conclusion (that more women are hypertensive than men) was reached in other studies as well.^{34–37} Sexual differences in the distribution of prehypertension and hypertension apparently exist, but they seem to vary from culture to culture, which implies an interaction between social and biological mechanisms. Although many reports^{33,35,38} have observed a significant correlation between blood pressure and increasing age,

TABLE III. Main Predictors Analyzed by Multiple Logistic Regression or Cox Regression in 6 Longitudinal Studies

Study	Main Predictors	Odds Ratio (95% CI)	Hazard Ratio (95% CI)
Pitsavos C, et al. (2008) ²⁶	Age (per 1 yr)	1.09 (1.07–1.12)	
	Male versus female sex	0.40 (0.21–0.68)	
	Education status (per 1 yr of school)	0.94 (0.88–0.98)	
	Waist circumference (per 1 cm)	1.04 (1.02–1.06)	
	C-reactive protein (per 1 mg/L)	1.12 (1.05–1.20)	
De Marco M, et al. (2009) ²⁷	Baseline SBP (per 10 mmHg)	1.60 (1.30–2.00)	
	Waist circumference (per 10 cm)	1.10 (1.01–1.30)	
	Diabetes mellitus	2.73 (1.77–4.21)	
	Higher left ventricular mass index (per 5 g/m ^{2.7})	1.15 (1.01–1.25)	
	Stroke volume index (per 5 mL/m ^{2.04})	1.25 (1.10–1.50)	
Player MS, et al. (2007) ³⁰	High levels of trait anger	1.53 (1.05–2.24)	
Zheng L, et al. (2010) ²⁸	Baseline age (per 5 yr)		1.111 (1.095–1.126)
	Mongolian race		1.079 (1.010–1.152)
	Alcohol drinking		1.177 (1.109–1.249)
	Family history of hypertension		1.184 (1.080–1.298)
	Salt intake (g/d)		1.004 (1.002–1.006)
	Overweight and obese		1.349 (1.261–1.444)
Jimenez-Corona A, et al. (2007) ³¹	Baseline SBP (110–119 mmHg)		2.43 (1.50–3.93) (females)
	Baseline DBP (70–79 mmHg)		2.44 (1.05–5.69) (males) 2.33 (1.65–3.31) (females) 1.80 (0.92–3.52) (males)
Liu LK, et al. (2010) ²⁹	NA		

CI = confidence interval; DBP = diastolic blood pressure; NA = not available; SBP = systolic blood pressure

we failed to break down the estimated prevalence of prehypertension by age group because our data were insufficient.

Risk Factors for Prehypertension

We found that individuals with prehypertension had higher body mass indices and waist circumferences than did people with normotension; waist circumferences showed greater relative differences. Excess weight, especially obesity, is an established risk factor for hypertension. A meta-analysis of 24 case-control studies in China reported that being overweight was an important risk factor for hypertension, with pooled OR 1.616 (95% CI, 1.600–1.633).³⁹ The consistent effect of being overweight or obese on both prehypertension and hypertension might indicate that these conditions have the same impact on BP. Although the proposed causes of hypertension have been discussed in many studies,^{40–42} the mechanism remains uncertain. In controlling arterial hypertension, weight reduction has resulted in significant decreases.^{43,44} It is reasonable to conclude that the same benefits apply to prehypertension.

In our study, another consistency with hypertension was observed: fasting plasma glucose, total cholesterol, and LDL-C were significantly associated with prehypertension, while HDL-C was shown as a protective factor. Recent studies have revealed that LDL-C may reduce endothelium-dependent relaxation,⁴⁵ thereby leading to greater vasoconstriction. This may explain why

individuals with either hypertension or prehypertension have higher LDL-C levels. Coca and colleagues⁴⁶ reported that 25% of hypertensive women aged ≥ 55 years had low levels of HDL-C concentration. Akintunde and associates⁴⁷ also found that dyslipidemia was more common among hypertensive subjects, and that fasting plasma glucose increased as the severity of dyslipidemia increased. In consideration of the analogous findings, it seems that other risk factors and mechanisms for hypertension could be applied to prehypertension. In regard to smoking and drinking, we found their effects on prehypertension to be unclear. Some studies concluded that smoking contributes to hypertension,^{48,49} while others did not.⁵⁰ The heterogeneity between studies may result in these uncertain outcomes.

Of interest are our findings that associated risk factors such as body mass index, waist circumference, fasting plasma glucose, total cholesterol, and LDL-C were all more significant in women. This may be related to sex hormones.^{51,52} However, the pooled prevalence of prehypertension among men was much higher than that among women, indicating the potential of a complex interaction or mechanism.

Predictors of Progression from Prehypertension to Hypertension

Different predictors were observed from 6 studies. Pitsavos and colleagues²⁶ reported that increased age, male sex, low education status, and C-reactive pro-

tein were positively associated with the development of hypertension. Waist circumference was found to be an independent predictor in studies both by Pitsavos²⁶ and De Marco and co-authors.²⁷ However, after using a multiple-regression model, Liu and co-investigators²⁹ found that none of the aforementioned factors could independently predict new-onset hypertension during the follow-up period. This discrepancy needs more study for the purpose of clarification. In the Cox stepwise regression analysis by Zheng and colleagues,²⁸ older age at baseline, Mongolian race, alcohol-drinking, being overweight or obese, high salt intake every day, low level of physical activity, and a family history of hypertension were found to be associated with incidence of hypertension. In addition, high levels of anger (as a trait) and high BP levels at baseline were also associated with the development of hypertension.^{30,31} Some of these factors have formed the basis of interventional studies in which comprehensive lifestyle modification has reduced the progression to hypertension.⁵³⁻⁵⁵ However, definite predictors remain unclear. More research on this issue is needed in order to prevent, rather than to treat.

Quality and Variability of Published Studies

To our knowledge, this is the first systematic review and meta-analysis of prehypertension that concerns prevalence and risk factors, as well as the predictors of progression to hypertension. There were few high-quality comparative studies on these issues. Many studies in this review were restricted to small, convenient samples of people with prehypertension, which compromised the investigators' ability to draw broad conclusions from their findings. Some of the included studies failed to mention the survey response rates or their criteria for inclusion and exclusion. The substantial heterogeneity between studies in this review was expected. It can be attributed in part to crude study characteristics (for example, sampling by age, sex, or geographic region—or sampling too few subjects). In addition, the definitions of risk factors were heterogeneous or absent. For example, Tsai and associates¹¹ defined a current smoker as someone who smokes ≥ 1 pack-year, but Sun and colleagues⁶ defined a smoker as a person who smokes at least 10 cigarettes every day. Many other studies failed to define current smoker.

Limitations

Although we attempted to adhere to the guidelines for reporting meta-analyses of observational studies,⁵⁶ there were several limitations that merit discussion.

First, we included only PubMed and The Cochrane Library in our search; although our literature search was extensive, it was limited to articles published in English and Chinese, which raises the possibility of omissions. Unfortunately, there are no agreed-upon criteria for evaluating the quality of cross-sectional studies

(as there are for randomized controlled trials⁵⁷). Our quality-evaluation method might not have captured all methodological aspects of these studies.

Second, there will have been both inter- and intra-study measurement errors in the ascertainment of BP and other indices.

Third, reliable country-specific estimates and analyses of some other risk factors were not produced, due to insufficient data. Although there was substantial heterogeneity among the included studies, meta-regression was not performed, because our main objective was to identify risk factors or predictors that can be useful to identify patients at increased risk.

In addition, a delay between search and publication was inevitable. Therefore, further evidence might have emerged subsequent to our original search, and the results of the meta-analysis must be interpreted cautiously.

Clinical Implications

Prehypertension was highly prevalent in recent years, especially for males. Many risk factors, including weight, dyslipidemia, and impaired glucose metabolism were observed. Factors such as older age at baseline, male sex, low education status, Mongolian race, and alcohol-drinking were reported to be important predictors of progression to hypertension. Healthcare providers should be aware of which segments of the population are at increased risk for cardiovascular disease and of steps that should be taken to treat modifiable risk factors in these people. Further studies are needed to determine which risk factors are independently associated with prehypertension and to determine which are predictors of progression to hypertension.

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