Effects of Prehypertension and Hypertension Subtype on Cardiovascular Disease in the Asia-Pacific Region

Hisatomi Arima, Yoshitaka Murakami, Tai Hing Lam, Hyeon Chang Kim, Hirotsugu Ueshima, Jean Woo, Il Suh, Xianghua Fang and Mark Woodward

Hypertension. 2012;59:1118-1123; originally published online April 30, 2012;
doi: 10.1161/HYPERTENSIONAHA.111.187252
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Effects of Prehypertension and Hypertension Subtype on Cardiovascular Disease in the Asia-Pacific Region

Hisatomi Arima, Yoshitaka Murakami, Tai Hing Lam, Hyeon Chang Kim, Hirotsugu Ueshima, Jean Woo, Il Suh, Xianghua Fang, Mark Woodward, on behalf of the Asia Pacific Cohort Studies Collaboration

Abstract—The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure defined blood pressure (BP) levels of 120 to 139/80 to 89 mm Hg as prehypertension and those of ≥140/90 mm Hg as hypertension. Hypertension can be divided into 3 categories, isolated diastolic (IDH; systolic BP <140 mm Hg and diastolic BP ≥90 mm Hg), isolated systolic (systolic BP ≥140 mm Hg and diastolic BP <90 mm Hg), and systolic-diastolic hypertension (systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg). Although there is clear evidence that isolated systolic hypertension and systolic-diastolic hypertension increase the risks of future vascular events, there remains uncertainty about the effects of IDH. The objective was to determine the effects of prehypertension and hypertension subtypes (IDH, isolated systolic hypertension, and systolic-diastolic hypertension) on the risks of cardiovascular disease (CVD) in the Asia-Pacific Region. The Asia Pacific Cohort Studies Collaboration is an individual participant data overview of cohort studies in the region. This analysis included a total of 346 570 participants from 36 cohort studies. Outcomes were fatal and nonfatal CVD. The relationship between BP categories and CVD was explored using a Cox proportional hazards model adjusted for age, cholesterol, and smoking and stratified by sex and study. Compared with normal BP (<120/80 mm Hg), hazard ratios (95% CIs) for CVD were 1.41 (1.31–1.53) for prehypertension, 1.81 (1.61–2.04) for IDH, 2.18 (2.00–2.37) for isolated systolic hypertension, and 3.42 (3.17–3.70) for systolic-diastolic hypertension. Separately significant effects of prehypertension and hypertension subtypes were also observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke. In the Asia-Pacific region, prehypertension and all hypertension subtypes, including IDH, thus clearly predicted increased risks of CVD. **(*Hypertension*. 2012; 59:1118-1123.)** ● **Online Data Supplement**

Key Words: prehypertension ■ hypertension ■ hypertension subtype ■ isolated diastolic hypertension ■ cardiovascular disease ■ coronary heart disease ■ stroke

Cardiovascular disease (CVD) is a leading cause of premature death and disability globally.[1,2] Elevation of blood pressure (BP) is one of the most important preventable causes of CVD: ≈54% of stroke and 47% of coronary heart disease worldwide have been attributed to it.[3] The relationship of BP with the risk of CVD is continuous down to systolic (SBP) and diastolic BP (DBP) levels of ≈110 to 115 and 70 to 75 mm Hg, respectively.[4,5] There is also continuous association between pulse pressure and CVD.[6] However, current guidelines for management of hypertension[7–9] recommend classification of BP levels based on cutoff values to simplify diagnostic and treatment approaches in clinical practice.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defined BP levels of 120 to 139/80 to 89 mm Hg as prehypertension based on the evidence of a modest increase in cardiovascular risk among individuals with such levels.[7] Because of its high prevalence,[10,11] a substantial part of the burden of CVD occurs among people with prehypertension.[12–14]

Hypertension is usually defined as BP levels of ≥140/90 mm Hg[7–9] and can be divided into 3 categories, isolated diastolic hypertension (IDH), isolated systolic hypertension (ISH), and diastolic with systolic hypertension (systolic-diastolic hypertension [SDH]).[15] A number of observational

Received November 4, 2011; first decision November 21, 2011; revision accepted April 9, 2012.

From the George Institute for Global Health (H.A., Y.M., M.W.), University of Sydney, Sydney, New South Wales, Australia; School of Public Health/Department of Community Medicine (T.H.L.), University of Hong Kong, Hong Kong, China; Department of Preventive Medicine (H.C.K., I.S.), Yonsei University College of Medicine, Seoul, Korea; Department of Preventive Medicine (H.C.K.), Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Health Science (H.U.), Shiga University of Medical Science, Shiga, Japan; Division of Geriatrics (J.W.), Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China; Department of Epidemiology and Social Medicine (X.F.), Xuanwu Hospital, Capital Medical University, Beijing, China; Department of Epidemiology (M.W.), Johns Hopkins University, Baltimore, MD.

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.111.187252/-/DC1.

Correspondence to Mark Woodward, George Institute for Global Health, University of Sydney, PO Box M201, Missenden Road, New South Wales 2050, Australia. E-mail markw@georgeinstitute.org.au

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.111.187252**

studies have demonstrated clear associations of ISH and SDH with future cardiovascular events.[16–21] In contrast, there has been uncertainty surrounding the effects of IDH on the risks of CVD.[16–23] As a result, patients with IDH, which constitutes 14% to 24% of the total hypertensive population,[18,20,24] are less likely to receive clinical attention and BP-lowering treatment than those with ISH or SDH.[18–20]

The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual participant data overview of cohort studies in the region.[25,26] Previous studies from the APCSC have focused on the continuous effects of BP on the risk of CVD.[5,6] In the present analysis, we provide detailed information about the associations between prehypertension and hypertension subtypes (IDH, ISH, and SDH) and the risk of CVD.

Methods

All of the APCSC cohort studies recorded date of birth (or age), sex, and BP at baseline and date of death (or age at death) during follow-up. Studies were excluded if enrollment depended on having a particular condition of a risk factor. For this report, only participants aged from 30 to 90 years at baseline with information on smoking status and total cholesterol were included. Studies were classified as Asian if participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan, and Thailand, and as ANZ (predominantly White) if participants were recruited from Australia or New Zealand. In most studies, BP was measured at rest in the seated position using a standard mercury sphygmomanometer.[5,6] Smoking status was self-reported as never smoker, ex-smoker, or current smoker. Because the APCSC is based on existing data, no ethics approval was needed for the present study.

All of the studies reported deaths attributed to CVD; some studies also reported nonfatal CVD events, defined as events that did not result in death within 28 days. All of the analyses use pooled fatal and nonfatal outcomes, taking the first recorded event as the index event. Outcomes were classified according to the Ninth Revision of International Classification of Disease. The outcomes considered in this analysis were coronary heart disease (Ninth Revision of International Classification of Disease 410–414), hemorrhagic stroke (431.0–432.9), ischemic stroke (433.0–434.9), and total CVD (390–459). Because most studies identified events using record linkage, verification of stroke was not routinely reported. All of the data provided were checked for completeness and consistency and recoded, when necessary, to ensure maximize comparability across cohorts. Summary reports were referred back to the principal investigators of each collaborating study for review and confirmation.

Cox proportional hazard models were used to examine the effects of BP category on CVD. Baseline hazards were allowed to differ by sex and cohort by using these variables as strata in the Cox models. Age, total serum cholesterol, and smoking status were included as confounders in all of the models. BP categories were classified as normal BP (SBP <120 mm Hg and DBP <80 mm Hg), prehypertension (SBP 120–139 mm Hg and/or DBP 80–89 mm Hg), IDH (SBP <140 mm Hg and DBP ≥90 mm Hg), ISH (SBP ≥140 mm Hg and DBP <90 mm Hg), and SDH (SBP ≥140 mm Hg and DBP ≥90 mm Hg). Normal BP was taken as the reference category for hazard ratios (HRs). Subgroup analyses by sex, age (<65 years and ≥65 years), and region (Asia/ANZ) were performed for total CVD. Comparison of the effects of BP categories between subgroups was done by adding interaction terms to the statistical models. All of the statistical analyses were performed using SAS release 9.20 (SAS Institute Inc, Cary, NC).

Results

Baseline and Follow-Up Data

Data from 36 cohort studies, which included 346 570 participants, were included in the present analyses (Table S1, available in the online-only Data Supplement). The mean age of participants at baseline was 48 years, 41% were women, and 78% were from Asia. Percentage of BP categories was 38%, 38%, 6%, 8%, and 11% for normal BP, prehypertension, IDH, ISH, and SDH, respectively. During a mean follow-up of 7 years, 8598 people (2.5%) experienced a CVD event, 3270 (0.9%) experienced coronary heart disease, 1503 (0.4%) experienced ischemic stroke, and 1015 (0.3%) experienced hemorrhagic stroke.

Effects of BP Category on the Risk of CVD

Compared with normal BP, prehypertension and all of the hypertension subtypes were clearly associated with increased risks of CVD even after controlling for age, sex, cholesterol, and smoking (Figure 1). The risks of CVD increase in the order of prehypertension, IDH, ISH, and SDH ($P<0.0001$ for normal BP versus prehypertension; <0.0001 for prehypertension versus IDH; 0.0013 for IDH versus ISH; and <0.0001 for ISH versus SDH). When prehypertension was divided into isolated diastolic prehypertension (SBP <120 mm Hg and DBP 80–89 mm Hg), isolated systolic prehypertension (SBP 120–139 mm Hg and DBP <80 mm Hg), and systolic-diastolic prehypertension (SBP 120–139 mm Hg and DBP 80–89 mm Hg), HRs were 1.08 (95% CI, 0.91–1.29), 1.42 (1.30–1.56), and 1.47 (1.34–1.61), respectively. Effects of prehypertension and hypertension subtypes were comparable between fatal CVD (HR, 1.33 [95% CI, 1.20–1.46] for prehypertension, 1.77 [1.51–2.06] for IDH, 2.07 [1.87–2.29] for ISH, and 3.16 [2.87–3.49] for SDH) and nonfatal CVD (1.57 [1.39–1.76] for prehypertension, 2.04 [1.72–2.42] for IDH, 2.38 [2.09–2.72] for ISH, and 3.93 [3.48–4.43] for SDH). Separately, significant effects of prehypertension and hypertension subtypes were also observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke (Figure 1), and the risks of each outcome increased in the order of prehypertension, IDH, ISH, and SDH (normal BP versus prehypertension, $P<0.0001$ for all; prehypertension versus IDH, $P<0.0001$ for all; IDH versus ISH, $P=0.95$, 0.0008, and 0.09 for coronary heart disease, ischemic stroke, and hemorrhagic stroke, respectively; and ISH versus SDH, $P<0.0001$ for all). The relationship of each BP category with coronary heart disease was weaker than for ischemic or hemorrhagic stroke. Between 2 stroke subtypes, the association with hemorrhagic stroke was stronger than for ischemic stroke.

Among subjects of the present analysis, a total of 121 051 participants had information on BP-lowering treatment. Compared with normal BP without treatment, number of events per subject and multivariable-adjusted HR (95% CI) for development of CVD were 1041/39 479 and 1.25 (95% CI, 1.10–1.42) for prehypertension without treatment, 106/3028 and 1.53 (95% CI, 1.19–1.95) for IDH without treatment, 1365/19 644 and 1.62 (95% CI, 1.43–1.85) for ISH without treatment, 1042/12 887 and 2.41 (95% CI, 2.10–2.75) for SDH without treatment, and 1407/18 231 and 2.77 (95% CI, 2.43–3.16) for treated hypertension.

Effects of BP Category on the Risk of Total CVD by Subgroups

There were similar effects of prehypertension and hypertension subtypes on the risks of CVD between male and female

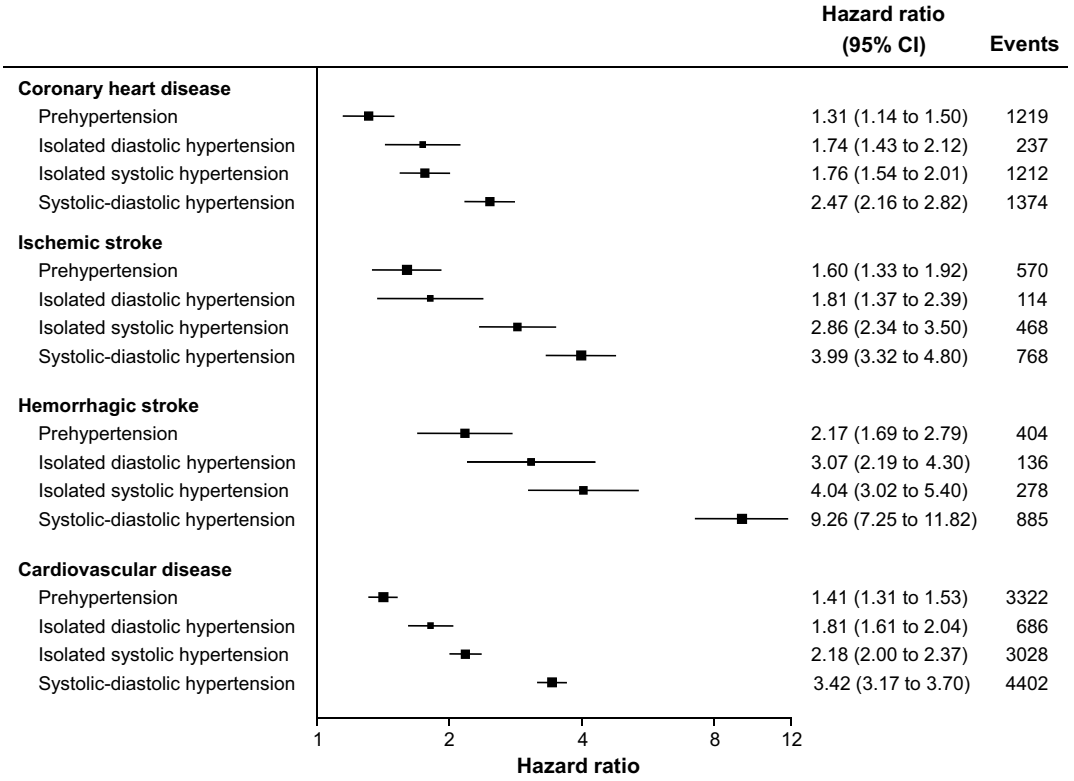

Figure 1. Effects of prehypertension and hypertension subtype on the risk of cardiovascular disease and its major subtypes. Hazard ratios were adjusted for age, total cholesterol, and smoking and stratified by sex and study. Normal blood pressure was used as the reference group. The center of each solid box is plotted against the point estimate, and the horizontal lines are drawn to the 95% confidence limits. Areas of the boxes are proportional to the reciprocal of the variance of the estimates.

participants (P for homogeneity=0.16; Figure 2). On the other hand, effects of each BP category on the risks of CVD were larger among subjects aged <65 years compared with those aged ≥65 years (P for homogeneity <0.001), and there were no clear effects of prehypertension on CVD among older subjects. Likewise, there were stronger associations between each BP category and the risk of CVD among participants recruited from Asia than from ANZ (P for homogeneity <0.001). A higher HR for each BP category, among Asian subjects compared with ANZ subjects, was also observed for coronary heart disease (P for homogeneity=0.02), ischemic stroke (P for homogeneity=0.02), and hemorrhagic stroke (P for homogeneity=0.002; Figure S1, available in the online-only Data Supplement). Although the number of events is limited, particularly in ANZ, similar patterns were observed between BP categories and each subtype of CVD among participants from Asia and ANZ. Heterogeneity in the effects of each BP category across subgroups defined by age was also observed for coronary heart disease (P for homogeneity=0.04), ischemic stroke (P for homogeneity <0.001), and hemorrhagic stroke (P for homogeneity=0.002).

Discussion

Findings from the current study, based on prospective data from ≈350 000 individuals from the Asia-Pacific region, provide good evidence of clear associations of prehypertension and all types of hypertension, including IDH, with future risks of CVD. Separately, significant associations were observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke. These associations remained significant after controlling for the confounding effects of age, sex, cholesterol, and smoking. Furthermore, increased risks of CVD associated with prehypertension and hypertension subtypes were observed across subgroups defined by age, sex, and geographical region, although there was a certain degree of heterogeneity in the strength of the associations by age and region.

Large-scale observational studies have demonstrated that prehypertension is associated with increased risks of premature death and cardiovascular morbidity, particularly at BP levels of 130 to 139/85 to 89 mm Hg.[13,27–33] Likewise, a number of large-scale cohort studies have reported significant effects of prehypertension separately on the risks of stroke[13,29,30,32] and coronary heart disease.[13,29] The present analysis from the APCSC confirmed the results from the previous observational studies and provided more detailed information about the separately significant associations of prehypertension with all of the major types of CVD, including ischemic and hemorrhagic stroke in the Asia-Pacific region.

Despite the clear evidence of ISH and SDH as important predictors of future vascular events,[16–21] a number of observational studies have failed to show significant effects of IDH on the risks of cardiovascular morbidity or mortality, probably because of the smaller number of subjects with IDH.[16–19,22] However, 2 recent large-scale cohort studies conducted in China have demonstrated clear effects of IDH on the risks of coronary heart disease, stroke, and total CVD.[20,21] The analysis reported

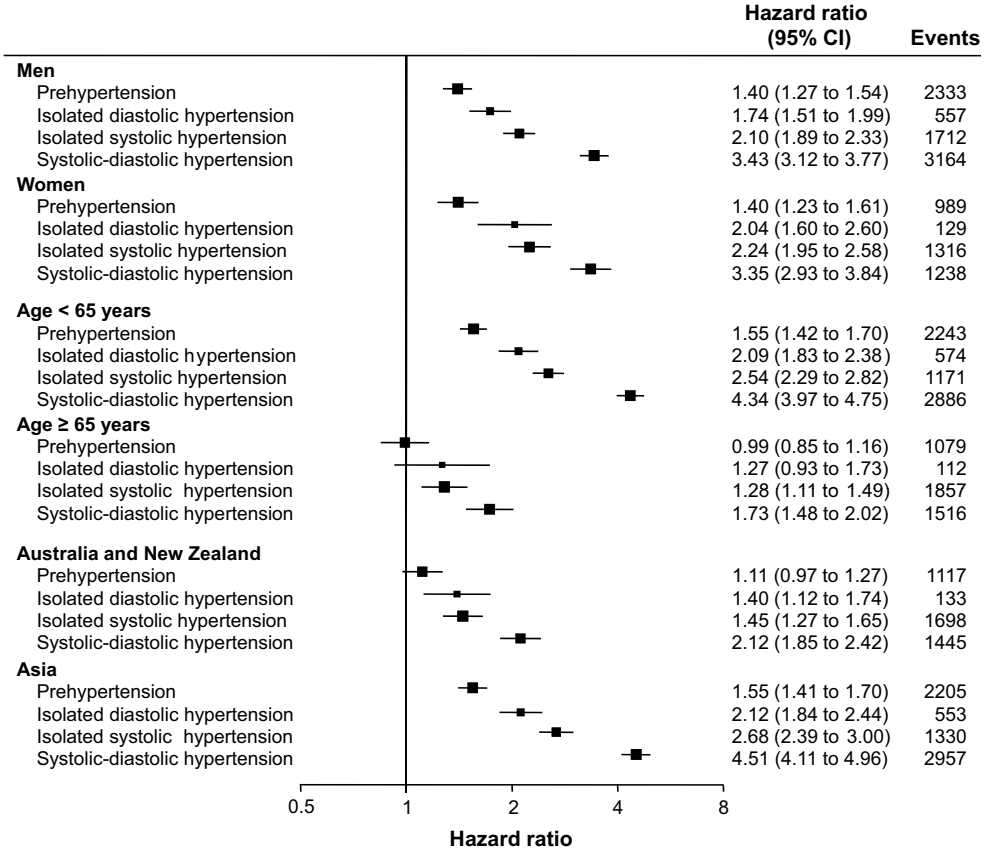

Figure 2. Effects of prehypertension and hypertension subtype on the risk of total cardiovascular disease by sex, age, and geographical region. Conventions are as for Figure 1.

here supports the findings obtained from the 2 studies conducted in China and demonstrates that the effects of IDH on the risks of CVD are generalizable to Western populations, as well as Asian populations.

In the present analysis, the highest risk of CVD was observed among patients with elevated SBP and DBP (SDH). The second highest risk was among patients with ISH, and the third highest was among those with IDH. Similar association was observed for each of the major CVD subtypes. There was also consistency in the ranking between hypertension subtypes across subgroups defined by age, sex, and geographical region. The same ranking in the effects of hypertension subtypes was also reported from other cohort studies.[19–21] The Stroke Prevention Project in China has investigated the effects of hypertension subtype on stroke among 26 587 Chinese subjects and found that HRs were 2.16 for IDH, 2.35 for ISH, and 2.96 for SDH compared with normotensives.[20] Likewise, the China Hypertension Epidemiology Follow-Up Study has demonstrated that HRs of CVD incidence were 1.59 for IDH, 1.78 for ISH, and 2.73 for SDH among 169 871 participants from China.[21] A prospective cohort study of 3267 men in Finland has also shown that HRs of stroke incidence were 1.14 for IDH, 1.36 for ISH, and 2.71 for SDH.[19] One possible reason for lower risks of CVD in IDH may involve younger age of patients with IDH than those with ISH or SDH.[16–22] These findings support the hypothesis that the risks of CVD increase in the order of IDH, ISH, and SDH.

Another key result from the present analysis was the heterogeneity in the effects of prehypertension and hypertension subtypes on different types of CVD and heterogeneity in the effects of each BP category across subgroups defined by age or geographical region. These findings are directly in line with the results of large-scale observational studies that had identified smaller effects of BP on the risks of coronary heart disease than on the risks of stroke, stronger effects of BP on intracerebral hemorrhage than on the risks of ischemic stroke, and stronger effects of BP on CVD among younger or Asian subjects compared with older or Western subjects.[4,5,34] Although there were no clear effects of prehypertension on CVD among subjects aged ≥65 years in the present analysis, similar findings were also reported from other cohort studies.[14,33] The regional difference observed in the present analysis might be explained, at least in part, by the fact that Asian subjects were younger than Western subjects (mean, 46 versus 53 years) despite our adjustment for age, and stroke, which was more strongly associated with BP than coronary heart disease, was more common in Asian studies than in ANZ studies. Heterogeneity in the effects of each BP category in the present analyses are also consistent with the results of randomized, controlled trials, which demonstrated heterogeneity in the magnitude of the effects of BP-lowering treatment on different types of CVD or across subgroups defined by age or region.[35–40]

The strengths of APCSC include the large amount of data and the strong collaboration, involving several ethnic groups.

As far as we are aware, this is the largest study to report the effects of prehypertension and hypertension subtypes on the risks of CVD. The number of individuals involved in the present analysis of APCSC means that the overall estimates are more precise than those in most previous studies. The main weaknesses of APCSC relate to nonstandardization of data collection methods. All of the cohorts were begun before the collaboration was initiated, without a common protocol. This might have introduced variations in measurement error in determining BP levels and possible misclassification of events, particularly with respect to stroke subtype. Reliable verification of stroke subtype requires imaging or autopsy data, and although it is likely that such information formed the basis of most reporting, this could not always be confirmed.

Perspectives

In the Asia-Pacific region, prehypertension and all of the hypertension subtypes were significantly associated with increased risks of CVD. Because a large portion of the population is classified as prehypertension or hypertension, population strategy to lower BP at the community level, such as salt reduction in commercial products, civil engineering to facilitate walking, and a systematic large-scale educational effort, are essential for reduction in the global burden of CVD. Furthermore, BP-lowering treatment should be initiated, and target BP levels recommended by current guidelines[7–9] adopted, among all patients who require drug treatment, irrespective of hypertension subtype (IDH, ISH, and SDH).[41]

Sources of Funding

This study was supported by a National Health and Medical Research Council of Australia program grant (358395). The study in Korea was supported by a grant of the Korea Healthcare Technology Research and Development Project of the Ministry of Health and Welfare, Republic of Korea (A102065). H.A. holds an Australian Research Council Future Fellowship.

Disclosures

None.

References

1. World Health Organization. *The Atlas of Heart Disease and Stroke*. Geneva, Switzerland: World Health Organization; 2004.
2. World Health Organization. *Preventing Chronic Disease: A Vital Investment*. Geneva, Switzerland: World Health Organization; 2005.
3. Lawes CM, Vander Hoorn S, Rodgers A, for the International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008;371:1513–1518.
4. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
5. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular diseases in the Asia-Pacific region. *J Hypertens*. 2003;21: 707–716.
6. Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension*. 2003;42:69–75.
7. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, and the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
8. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A. 2007 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). *J Hypertens*. 2007;25:1105–1187.
9. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clement D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, van Zwieten PA, Viigimaa M, Zanchetti A. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121–2158.
10. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2011 update–a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
11. Agyemang C, van Valkengoed I, van den Born BJ, Stronks K. Prevalence and determinants of prehypertension among African Surinamese, Hindustani Surinamese, and White Dutch in Amsterdam, the Netherlands: the SUNSET Study. *Eur J Cardiovasc Prev Rehabil*. 2007;14:775–781.
12. Rodgers A, Ezzati M, Vander Hoorn S, Lopez AD, Lin RB, Murray CJ. Distribution of major health risks: findings from the Global Burden of Disease Study. *PLoS Med*. 2004;1:e27.
13. He J, Gu D, Chen J, Wu X, Kelly TN, Huang JF, Chen JC, Chen CS, Bazzano LA, Reynolds K, Whelton PK, Klag MJ. Premature deaths attributable to blood pressure in China: a prospective cohort study. *Lancet*. 2009;374:1765–1772.
14. 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.
15. Kaplan NM, Victor RG., *Kaplan's Clinical Hypertension*. Philadelphia, PA: Lippincott Williams and Wilkins; 2010.
16. Petrovitch H, Curb JD, Bloom-Marcus E. Isolated systolic hypertension and risk of stroke in Japanese-American men. *Stroke*. 1995;26:25–29.
17. Nielsen WB, Lindenstrom E, Vestbo J, Jensen GB. Is diastolic hypertension an independent risk factor for stroke in the presence of normal systolic blood pressure in the middle-aged and elderly? *Am J Hypertens*. 1997;10:634–639.
18. Hozawa A, Ohkubo T, Nagai K, Kikuya M, Matsubara M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prognosis of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of blood pressure at home: the Ohasama Study. *Arch Intern Med*. 2000;160:3301–3306.
19. Strandberg TE, Salomaa VV, Vanhanen HT, Pitkala K, Miettinen TA. Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. *J Hypertens*. 2002;20:399–404.
20. Fang XH, Zhang XH, Yang QD, Dai XY, Su FZ, Rao ML, Wu SP, Du XL, Wang WZ, Li SC. Subtype hypertension and risk of stroke in middle-aged and older Chinese: a 10-year follow-up study. *Stroke*. 2006; 37:38–43.
21. Kelly TN, Gu D, Chen J, Huang JF, Chen JC, Duan X, Wu X, Yau CL, Whelton PK, He J. Hypertens subtype and risk of cardiovascular disease in Chinese adults. *Circulation*. 2008;118:1558–1566.
22. Fang J, Madhavan S, Cohen H, Alderman MH. Isolated diastolic hypertension: a favorable finding among young and middle-aged hypertensive subjects. *Hypertension*. 1995;26:377–382.
23. Franklin SS, Wilkinson IB, McEniery CM. Unusual hypertensive phenotypes: what is their significance? *Hypertension*. 2012;59:173–178.
24. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*. 2001;37:869–874.
25. Asia Pacific Cohort Studies Collaboration. Determinants of cardiovascular disease in the Asia Pacific region: protocol for a collaborative overview of cohort studies. *Cardiovasc Dis Prev*. 1999;2:281–289.

26. Woodward M, Barzi F, Martiniuk A, Fang X, Gu DF, Imai Y, Lam TH, Pan WH, Rodgers A, Suh I, Jee SH, Ueshima H, Huxley R. Cohort profile: the Asia Pacific Cohort Studies Collaboration. *Int J Epidemiol*. 2006;35:1412–1416.
27. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297.
28. Liszka HA, Mainous AG III, King DE, Everett CJ, Egan BM. Prehypertension and cardiovascular morbidity. *Ann Fam Med*. 2005;3:294–299.
29. Hsia J, Margolis KL, Eaton CB, Wenger NK, Allison M, Wu L, LaCroix AZ, Black HR, for the Women's Health Initiative Investigators. Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation*. 2007;115:855–860.
30. Conen D, Ridker PM, Buring JE, Glynn RJ. Risk of cardiovascular events among women with high normal blood pressure or blood pressure progression: prospective cohort study. *BMJ*. 2007;335:432.
31. Murakami Y, Hozawa A, Okamura T, Ueshima H, and the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan Research Group (EPOCH-JAPAN). Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension*. 2008;51:1483–1491.
32. Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, Murakami Y, Ohashi Y, Ueshima H, Imai Y, the Japan Arteriosclerosis Longitudinal Study (JALS) group. Stroke risk and antihypertensive drug treatment in the general population: the Japan Arteriosclerosis Longitudinal Study. *J Hypertens*. 2009;27:357–364.
33. Ishikawa Y, Ishikawa J, Ishikawa S, Kajii E, Schwartz JE, Pickering TG, Kario K, and the Jichi Medical School Cohort Investigators Group. Prehypertension and the risk for cardiovascular disease in the Japanese general population: the Jichi Medical School Cohort Study. *J Hypertens*. 2010;28:1630–1637.
34. Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, MacMahon S, Neal B, for the PROGRESS Collaborative Group. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS Trial. *J Hypertens*. 2006;24:1201–1208.
35. Perry HM Jr, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probstfield JL, for the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 2000;284:465–471.
36. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041.
37. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
38. Rodgers A, Chapman N, Woodward M, Liu L-S, Colman S, Lee A, Chalmers J, MacMahon S, on behalf of the PROGRESS Collaborative Group. Perindopril-based blood pressure lowering in individuals with cerebrovascular disease: consistency of benefits by age, sex and region. *J Hypertens*. 2004;22:653–659.
39. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ*. 2008;336:1121–1123.
40. Arima H, Anderson C, Omae T, Liu L, Tzourio C, Woodward M, MacMahon S, Neal B, Rodgers A, Chalmers J, for the PROGRESS Collaborative Group. Perindopril-based blood pressure lowering reduces major vascular events in Asian and Western participants with cerebrovascular disease: the PROGRESS Trial. *J Hypertens*. 2010;28:395–400.
41. Arima H, Anderson C, Omae T, Woodward M, Hata J, Murakami Y, Macmahon S, Neal B, Chalmers J, for the PROGRESS Collaborative Group. Effects of blood pressure lowering on major vascular events among patients with isolated diastolic hypertension: the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) Trial. *Stroke*. 2011;42:2339–2341.

ONLINE SUPPLMENT

EFFECTS OF PREHYPERTENSION AND HYPERTENSION SUBTYPE ON CARDIOVASCULAR DISEASE IN THE ASIA-PACIFIC REGION

Asia Pacific Cohort Studies Collaboration

Writing Committee: Hisatomi Arima, Yoshitaka Murakami, Tai Hing Lam, Hyeon Chang Kim, Hirotsugu Ueshima, Jean Woo, Il Suh, Xianghua Fang, Mark Woodward

The George Institute for Global Health, University of Sydney (H.A., Y.M., M.W.), Sydney, Australia; School of Public Health / Department of Community Medicine, The University of Hong Kong (T.H.L.), Hong Kong, China; Department of Preventive Medicine, Yonsei University College of Medicine (H.C.K., I.S.), Seoul, Korea; Department of Preventive Medicine, Northwestern University Feinberg School of Medicine (H.C.K.), Chicago, USA; Department of Health Science, Shiga University of Medical Science (H.U.), Shiga, Japan; Division of Geriatrics, Department of Medicine and Therapeutics, The Chinese University of Hong Kong (J. W.), Hong Kong, China; Department of Epidemiology and Social Medicine, Xuanwu Hospital, Capital Medical University (X.F.), Beijing, China; and Department of Epidemiology, Johns Hopkins University, Baltimore, USA (M.W.).

Short title: Prehypertension, hypertension subtype and CVD

Author for correspondence:
Professor Mark Woodward
The George Institute for Global Health, University of Sydney
Postal address: PO Box M201, Missenden Road, NSW 2050, AUSTRALIA
Street address: Level 10, KGV building, RPA Hospital, Missenden Road, NSW 2050, AUSTRALIA
Telephone: +61-2-9993-4500
Facsimile: +61-2-9993-4502
Email: markw@georgeinstitute.org.au

Table S1. Characteristics of study population

Study	Country	Baseline years	n	Female (%)	Age (years) Mean	Age (years) SD	SBP (mmHg) Mean	SBP (mmHg) SD	DBP (mmHg) Mean	DBP (mmHg) SD	Cholesterol (mmol/l) Mean	Cholesterol (mmol/l) SD	Current smoker (%)	Mean follow up years	Number of events CHD	Number of events IS	Number of events HS	Number of events CVD
Anzhen02	China	1992-93	4140	51	47	8	122	18	78	11	4.7	0.9	21	3	1	14	1	17
Beijing Aging	China	1992	1682	50	69	8	141	25	82	12	4.4	1.0	31	4	0	0	0	149
Capital Iron & Steel Company	China	1974-80	4423	0	46	7	124	19	81	12	4.9	1.0	74	13	74	86	61	220
Fangshan	China	1991-92	834	67	47	9	132	25	79	13	4.6	1.0	39	3	2	5	2	12
Guangzhou Occupational	China	1985-97	15641	36	44	7	114	16	76	10	5.3	1.2	43	8	20	0	18	60
Huashan	China	1990-92	1805	52	53	12	126	21	76	11	4.6	0.9	25	3	3	10	6	23
Seven Cities Cohorts	China	1987	6372	57	58	10	134	25	83	13	5.0	1.5	34	6	66	100	124	453
Shanghai Factory Workers	China	1972	9017	31	48	7	125	22	79	12	4.2	0.9	44	14	81	0	0	373
Six Cohorts	China	1982-86	14503	48	45	7	118	17	76	10	4.2	0.9	42	8	30	56	65	270
Xi'an	China	2964	1695	34	44	6	126	21	83	12	4.6	0.9	40	18	35	15	24	80
Yunnan	China	1992	2626	4	54	9	122	21	80	13	4.3	0.8	69	4	5	4	23	55
Hong Kong	Hong Kong	1985-91	175	52	78	5	149	22	80	12	5.3	0.9	18	2	4	0	0	12
Aito Town	Japan	1980-83	1094	59	51	9	137	23	80	13	4.7	0.9	28	15	10	0	4	39
Akabane	Japan	1985-86	1832	56	54	8	125	19	74	12	5.0	0.9	28	11	28	16	5	79
Civil Service Workers	Japan	1990-92	9225	33	47	5	126	18	75	11	5.2	0.9	38	7	1	0	1	12
Hisayama	Japan	1961	1545	56	56	11	135	26	78	13	4.1	1.0	43	19	88	224	66	438
Konan	Japan	1987-95	1106	56	54	14	131	19	79	11	4.9	0.9	30	6	2	7	3	24
Miyama	Japan	1988-90	413	62	59	9	129	23	77	12	5.1	0.9	24	7	0	0	0	1
Ohasama	Japan	1992-93	1905	65	58	11	127	17	72	12	5.0	0.9	21	4	4	27	10	52
Saitama	Japan	1986-90	3554	63	55	11	135	20	80	12	5.0	1.0	28	10	24	27	15	119
Shibata	Japan	1977	2328	58	57	11	131	21	78	12	4.6	1.2	33	16	67	75	36	340
Shigaraki Town	Japan	1991-97	3715	59	57	14	132	20	78	12	5.0	0.9	29	4	3	4	2	28
Shirakawa	Japan	1974-79	4389	54	50	11	127	22	77	13	4.7	0.9	35	17	65	39	31	192
Tanno/Soubetsu	Japan	1977	1970	53	51	7	133	20	82	10	4.9	1.0	39	15	24	10	16	73
Singapore Heart	Singapore	1982-97	1707	50	46	11	127	23	78	12	6.1	1.2	22	11	61	21	7	128
Singapore NHS92	Singapore	1992	2469	53	44	10	121	20	71	12	5.5	1.0	18	6	33	13	4	76
KMIC	South Korea	1992	160236	33	44	7	122	14	80	10	5.0	0.9	38	4	278	432	325	1416
CVDFACTS	Taiwan	1988-96	4729	55	51	13	120	19	76	11	5.0	1.2	22	6	12	7	7	58
EGAT	Thailand	1985	3488	23	43	5	121	16	75	11	5.8	1.1	43	10	33	0	0	51
TOTAL ASIA			268618	37	46	9	123	17	79	11	4.9	1.0	38	6	1054	1192	856	4850
Australian Longitudinal Study of Aging	Australia	1992-93	1107	48	77	6	149	22	79	11	5.8	1.2	8	5	58	3	8	136
Australian National Heart Foundation	Australia	1989-90	7469	51	48	11	128	19	80	11	5.7	1.1	23	8	76	1	0	111
Busselton	Australia	1966-81	5561	51	52	14	143	26	80	13	6.1	1.3	33	24	1178	223	89	2011
Melbourne	Australia	1990-94	41139	59	55	9	138	20	77	12	5.5	1.1	11	9	323	11	35	550
Newcastle	Australia	1983-94	5729	50	52	10	133	20	80	11	5.9	1.1	23	9	134	3	8	198
Perth	Australia	1978-94	8470	47	48	11	132	20	82	11	5.9	1.2	24	13	186	4	10	294
Fletcher Challenge	New Zealand	1992-94	8477	28	48	13	127	17	78	11	5.5	1.1	22	6	261	66	9	448
TOTAL ANZ			77952	52	53	11	135	21	78	12	5.6	1.1	17	10	2216	311	159	3748
TOTAL			346570	41	48	10	126	19	79	11	5.1	1.1	34	7	3270	1503	1015	8598

SD indicates standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; IS, ischemic stroke; HS, hemorrhagic stroke; CVD, cardiovascular disease; ANZ, Australia and New Zealand.

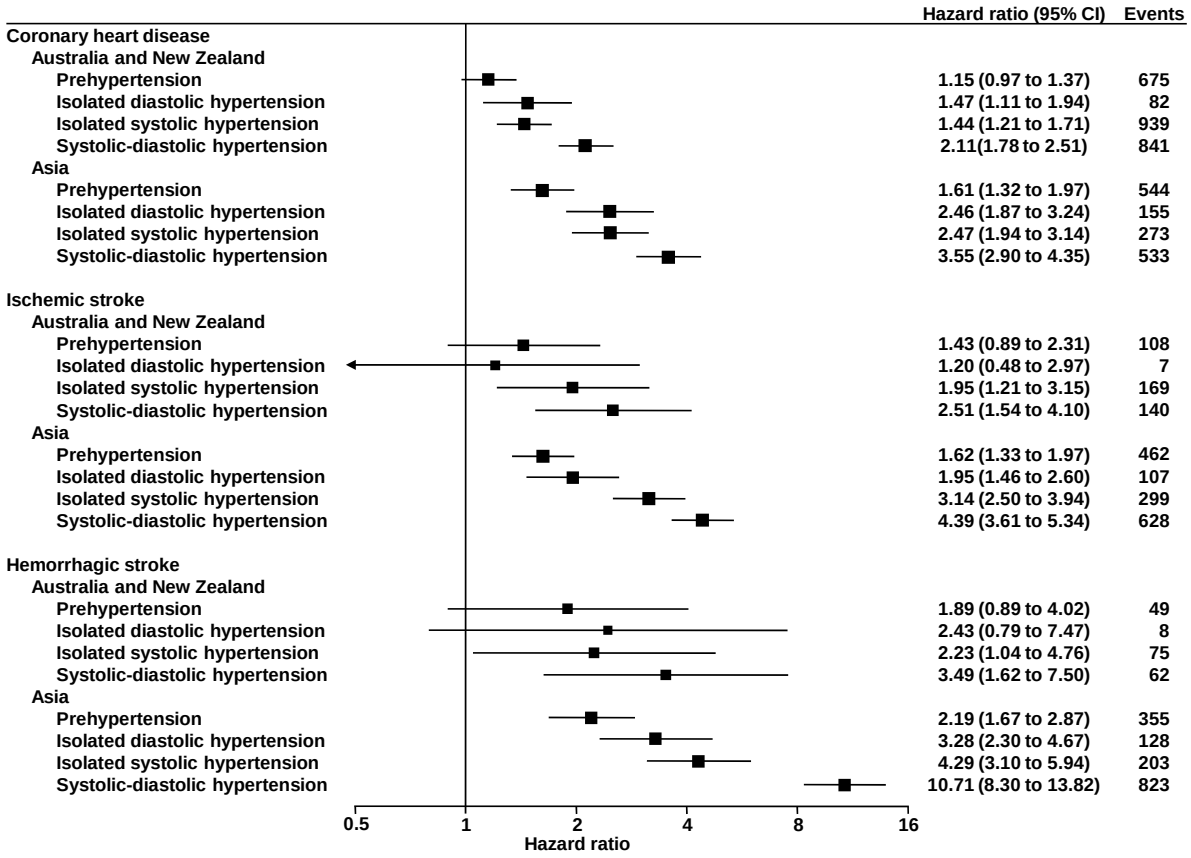

Figure S1. Effects of prehypertension and hypertension subtype on the risk of coronary heart disease, ischemic stroke and hemorrhagic stroke by geographical region

Hazard ratios were adjusted for age, total cholesterol and smoking and stratified by sex and study. Normal blood pressure was used as the reference group. The center of each solid box is plotted against the point estimate and the horizontal lines are drawn to the 95% confidence limits. Areas of the boxes are proportional to the reciprocal of the variance of the estimates. 95% CI indicates 95% confidence interval.

Appendix S1: Asia Pacific Cohort Studies Collaboration membership

APCSC Executive Committee

M. Woodward (Chair), X. Fang, D.F. Gu, R. Huxley, Y. Imai, H.C. Kim, T.H. Lam, W.H. Pan, A. Rodgers, I. Suh, H. Ueshima

Participating Studies and Principal Collaborators in APCSC

Aito Town: A. Okayama, H. Ueshima, H. Maegawa; Akabane: M. Nakamura, N. Aoki; Anzhen02: Z.S. Wu; Anzhen: C.H. Yao, Z.S. Wu; Australian Longitudinal Study of Aging: Mary Luszcz; Australian National Heart Foundation: T.A. Welborn; Beijing Aging: Z. Tang; Beijing Steelworkers: L.S. Liu, J.X. Xie; Blood Donors' Health: R. Norton, S. Ameratunga, S. MacMahon, G. Whitlock; Busselton: M.W. Knuiman; Canberra-Queanbeyan: H. Christensen; Capital Iron and Steel Company: X.G. Wu; CISCH: J. Zhou, X.H. Yu; Civil Service Workers: A. Tamakoshi; CVDFACTS: W.H. Pan; East Beijing: Z.L. Wu, L.Q. Chen, G.L. Shan; Electricity Generating Authority of Thailand: P. Sritara; Fangshan: D.F. Gu, X.F. Duan; Fletcher Challenge: S. MacMahon, R. Norton, G. Whitlock, R. Jackson; Guangzhou: Y.H. Li; Guangzhou Occupational: T.H. Lam, C.Q. Jiang; Hisayama: Y. Kiyohara, Y. Doi, T. Ninomiya; Hong Kong: J. Woo, S.C. Ho; Huashan: Z. Hong, M.S. Huang, B. Zhou; Kinmen: J.L. Fuh; Konan: H. Ueshima, Y. Kita, S.R. Choudhury; KMIC: I. Suh, S.H. Jee, I.S. Kim; Melbourne: G.G. Giles; Miyama: T. Hashimoto, K. Sakata; Newcastle: A. Dobson; Ohasama: Y. Imai, T. Ohkubo, A. Hozawa; Perth: the late K. Jamrozik, M. Hobbs, R. Broadhurst; Saitama: K. Nakachi; Seven Cities: X.H. Fang, S.C. Li, Q.D. Yang; Shanghai Factory Workers: Z.M. Chen; Shibata: H. Tanaka; Shigaraki Town: Y. Kita, A. Nozaki, H. Ueshima; Shirakawa: H. Horibe, Y. Matsutani, M. Kagaya; Singapore Heart: K. Hughes, J. Lee; Singapore NHS92: D. Heng, S.K. Chew; Six Cohorts: B.F. Zhou, H.Y. Zhang; Tanno/Soubetsu: K. Shimamoto, S. Saitoh; Tianjin: Z.Z. Li, H.Y. Zhang; Western Australia AAA Screenees: P. Norman, the late K. Jamrozik; Xi'an: Y. He, T.H. Lam; Yunnan: S.X. Yao.