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Background and Purpose—Smoking and increased levels of blood pressure (BP) substantially increase the risk of cardiovascular diseases (CVD). If these 2 risk factors have a synergistic impact on cardiovascular events, lowering BP and quitting smoking will contribute more to reducing CVD than would be expected from ignoring their interaction.

Methods—Individual participant data were combined from 41 cohorts, involving 563 144 participants (82% Asian). During a median of 6.8 years follow-up, 4344 coronary heart disease (CHD) and 5906 stroke events were recorded. Repeat measures of systolic blood pressure (SBP) were used to adjust for regression dilution bias. Hazard ratios (HRs) and 95% confidence intervals (CIs) for SBP by cigarette smoking status were estimated from Cox proportional hazard models adjusted for age and stratified by study and sex.

Results—Data suggested a log-linear relationship between SBP and all subtypes of CVD. The HRs relating SBP to both CHD and ischemic stroke were broadly similar irrespective of smoking status ($P \geq 0.1$). For hemorrhagic stroke (intracerebral hemorrhage), the HRs (95% CIs) for an additional 10 mm Hg increment in SBP were 1.81 (1.73 to 1.90) for present smokers and 1.66 (1.59 to 1.73) for nonsmokers ($P=0.003$). For every subtype of cardiovascular events, similar results were found for analyses involving only fatal events.

Conclusions—Smoking exacerbated the impact of SBP on the risk of hemorrhagic stroke. Although quitting smoking and lowering BP are both crucial for prevention of CVD, combining the 2 could be expected to have extra beneficial effect on preventing hemorrhagic stroke. **(*Stroke*. 2008;39:1694-1702.)**

Key Words: smoking ■ blood pressure ■ cardiovascular diseases ■ coronary heart disease ■ stroke

Nonoptimal levels of blood pressure (BP) and smoking are the first and second most common causes of death in the world, and, together, these 2 risk factors account for more than 20% of the global burden of premature death.[1,2] In particular, increased BP[3–7] and smoking[7–11] are major risk factors for cardiovascular diseases (CVD), including coronary heart disease (CHD) and stroke. Previous studies have indicated that smoking and increased BP interact to increase markers of cardiovascular risk, including levels of plasma fibrinogen[12] and carotid intima-media thickness.[13] Hence, a combination of raised BP and smoking may have a synergistic impact on cardiovascular events, especially those caused by atherosclerosis and thrombosis.[14] If such an interaction exists, multifactorial interventions aimed at both lowering BP and quitting smoking will contribute more to reducing CVD than expected from past data where their interaction has not been quantified.

Several epidemiological studies have examined the combined effects of nonoptimal levels of BP and smoking on cardiovascular events.[11,15–23] Some studies, at least partially, observed a synergistic effect between BP and smoking status for the risk of CVD,[15] CHD,[16–18] and stroke (predominately ischemic),[11,16,19,20] whereas other studies did not observe any such effect.[21,22] The majority of these studies were based on small datasets and crude classifications of BP and smoking status, and few examined the possible interaction effect between BP and smoking status for each subtype of CVD. For hemorrhagic stroke, only 1 case-control study[23] examined the interaction between BP and smoking status; it reported that interaction was present. Overall, however, the question as to

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whether such an interaction exists, and the nature of this interaction (synergistic or otherwise), remains unresolved. The aim of the present study was to examine this issue using data from the Asia Pacific Cohort Studies Collaboration (APCSC); an individual participant data overview of prospective cohort studies conducted in the Asia-Pacific region. The large size of the dataset provides an ideal opportunity to explore the joint associations of risk factors with cardiovascular events. In particular, the large numbers of both hemorrhagic and ischemic stroke events makes it possible to measure the risk for each subtype of stroke reliably. Additionally, APCSC provides a unique opportunity to compare the association of risk factors with cardiovascular events between Asian populations and the "Western" populations of Australia and New Zealand.

Methods

Participating Studies

Details of APCSC are described elsewhere.[24,25] Briefly, APCSC is an overview of preexisting cohort studies in the Asia-Pacific region which had at least 5000 person-years of follow-up and recorded age, sex, and BP at baseline, and vital status at the end of the follow-up. Studies were excluded from APCSC if enrolment was dependent on having a particular condition or risk factor. Additionally, for analyses in this report, only persons aged ≥20 years at study entry with information on both BP and smoking status were included.

Measurement of Baseline Variables

In most studies, BP was measured at rest in the seated position using a standard mercury sphygmomanometer. Cigarette smoking habit was self-reported at study baseline. All studies included here recorded present smoking status (present smoker or not). Some studies additionally recorded whether individuals were present, former, or never smokers, and some recorded cigarettes per day for smokers. Because most studies, including APCSC, have demonstrated that the association between systolic blood pressure (SBP) and cardiovascular events is stronger than that of other BP indices in most age and gender groups,[26,27] we analyzed data on SBP in this report. Cohorts were classified as Asian if the participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan, or Thailand and as ANZ if the participants were from Australia or New Zealand. This classification largely represented a split by ethnicity into Asians and Whites.

Outcomes

All studies reported deaths by underlying cause; a subset of studies also reported nonfatal cardiovascular events. Outcomes were classified according to the Ninth Revision of the International Classification of Diseases (ICD-9). Outcomes in this report, including fatal and nonfatal events, were CHD (ICD-9: 410 to 414) and stroke (430 to 438), divided into hemorrhagic stroke (intracerebral hemorrhage; 431.0 to 432.9), ischemic stroke (433.0 to 434.9), and other strokes. Because most studies identified events using record linkage, verification of pathological types of stroke was not routinely reported. All data provided to the Secretariat were checked for completeness and consistency and recoded, when necessary, to maximize comparability across cohorts. Summary reports were referred back to principal investigators of each collaborating study for review and confirmation.

Statistical Methods

Cox proportional hazard regression models adjusted by age and stratified by study and sex[28] were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for SBP by smoking status (nonsmokers, including former smokers, and present smokers). To determine the associations between "usual" level of SBP and the outcomes of interest, estimates were adjusted for regression dilution bias.[3,29] Repeat measurements of SBP on up to 7 occasions, between 2 and 20 years after the baseline measurement, were obtained from 16 studies for a total of 67 210 participants. These repeat measures were used to estimate a regression dilution attenuation coefficient for SBP (1.9), using a linear mixed regression model that accounted for the heterogeneity of variance between studies and within-subject correlation.[30] Log-linearity of the associations between SBP and each subtype of cardiovascular event was explored by categorical analyses in which participants were classified into 4 groups according to levels of baseline SBP (<130, 130 to 144, 145 to 159, and ≥160 mm Hg) chosen so as to have approximately equal numbers of all cardiovascular events across the groups. Corresponding 95% CIs were calculated by the "floating absolute risk method."[29] HRs and 95% CIs were also derived for a 10 mm Hg increase in the level of SBP. The interaction effect between SBP and smoking status was assessed using likelihood ratio tests comparing the models with main effects only with the models that included the interaction term.[29] In addition to analyses of the overall APCSC, predefined subgroup analyses were performed by sex, region (Asia and ANZ), and age at risk (<65 and ≥65 years).[24]

Further analyses were conducted on subsamples of the total population which had more detailed information on smoking status. In one of the subsamples, participants were classified as "present" if they smoked currently, "never smokers" if they had never smoked, and "former smokers" if they had smoked but reported having already quit at study baseline. HRs for a 10-mm Hg increase in the level of SBP were estimated for each group by this smoking status and compared using similar methods to the main analyses. Similarly, dose-response analyses were done on the subset where both the mean number of cigarettes smoked per day and never smoking were recorded, comparing never smokers with <20 and ≥20 cigarettes per day for present smokers. Groups of <20 and ≥20 were chosen to provide an approximately equal partition; 20 cigarettes corresponds to 1 standard pack.

Results

Characteristics of the Study Population

Information on SBP and smoking status was available from 41 cohorts (93% of all studies in APCSC); 32 from Asia (Table 1). Overall, 563 144 participants were included in the analysis (82% Asians; 35% female) with a mean age of 47 years. Over one-third (37%) of study participants were classified as present smokers at baseline, but the prevalence of smoking differed by sex and region: in Asia, 59% of men and 5% of women were present smokers versus 20% and 14%, respectively, in ANZ. In Asia, mean age and SBP were similar between smokers and nonsmokers (45 years versus 45 years and 122 mm Hg versus 121 mm Hg), but in ANZ, present smokers were both younger and had a lower SBP than nonsmokers: 48 years versus 54 years and 133 mm Hg versus 138 mm Hg, respectively. These mean values of age and SBP were weighted, rather than crude, averages across studies.

Information on former smoking status was available from 34 cohorts (24 in Asia). In these, 63 941 (13%) of participants were former smokers, 261 319 (51%) were never smokers, and 187 416 (37%) were present smokers. In Asian cohorts, 15% of men and 22% of women who had ever smoked had quit, compared to 68% and 59%, respectively, in ANZ. Of these 34 cohorts, 24 also recorded information on the average number of cigarettes smoked per day. Among the 97 540 present smokers in these cohorts, 44% consumed 20 cigarettes or more per day: in Asia, 44% for men and 21% for women, versus 52% and 43%, respectively, in ANZ.

Table 1. Study Population Characteristics by Smoking Status at Baseline

	Nonsmokers				Current Smokers			
Study Name	n	Age (years) mean (SD)	SBP (mm Hg) mean (SD)	Female (%)	n	Age (years) mean (SD)	SBP (mm Hg) mean (SD)	Female (%)
Akabane	1321	55 (8)	125 (19)	77	513	53 (7)	124 (19)	2
Anzhen	5992	54 (13)	129 (24)	69	2386	53 (12)	130 (22)	20
Anzhen02	3287	47 (8)	122 (18)	64	864	46 (8)	122 (17)	1
Beijing aging	1472	70 (9)	143 (25)	62	620	69 (8)	137 (25)	24
Capital Iron Steel Company	1367	45 (8)	125 (19)	0	3775	45 (8)	123 (19)	0
CISCH	1576	44 (7)	117 (17)	69	591	45 (8)	122 (16)	2
Civil service workers	5739	47 (5)	125 (18)	47	3501	47 (5)	126 (18)	10
CVDFACTS	4455	47 (15)	118 (19)	70	1274	48 (16)	119 (18)	4
East Beijing	806	45 (15)	125 (23)	64	322	41 (15)	124 (21)	20
EGAT	1980	43 (5)	121 (17)	38	1514	43 (5)	121 (16)	3
Fangshan	1591	47 (10)	136 (26)	86	1028	48 (10)	135 (25)	36
Guangzhou occupational	87 400	41 (6)	115 (15)	41	79 295	42 (7)	116 (14)	1
Hisayama	918	57 (12)	135 (26)	82	683	55 (10)	135 (26)	22
Hong Kong	2428	79 (7)	150 (25)	63	555	77 (6)	148 (24)	33
Kinmen	1824	63 (10)	138 (23)	64	721	64 (9)	136 (21)	9
KMIC	98 631	44 (7)	121 (14)	54	61 611	45 (7)	125 (14)	0
Konan	857	52 (16)	130 (20)	75	369	51 (16)	130 (18)	9
Miyama	756	61 (10)	134 (22)	73	317	60 (9)	130 (22)	13
Ohasama	1793	60 (11)	127 (17)	78	447	58 (12)	132 (18)	7
Saitama	2588	54 (12)	135 (20)	80	1027	55 (12)	136 (19)	17
Seven cities cohorts	7019	54 (12)	130 (25)	70	3792	54 (12)	129 (23)	26
Shanghai factory workers	5198	47 (7)	124 (21)	51	4149	50 (7)	126 (23)	5
Shibata	1573	57 (11)	130 (21)	82	777	57 (11)	133 (20)	8
Shigaraki town	2657	58 (14)	132 (19)	77	1073	56 (14)	132 (20)	16
Shirakawa	3023	48 (12)	127 (22)	79	1617	48 (12)	126 (21)	8
Singapore heart	1807	40 (13)	124 (22)	61	514	41 (14)	122 (18)	7
Singapore NHS92	2699	39 (12)	119 (19)	62	606	39 (12)	118 (17)	8
Six cohorts	10 465	44 (7)	119 (18)	76	8922	45 (7)	119 (17)	12
Tanno/Soubetsu	1214	51 (7)	134 (20)	78	764	51 (7)	132 (21)	14
Tianjin	4586	56 (13)	139 (28)	64	4749	54 (11)	134 (25)	39
Xi'an	1020	44 (6)	126 (21)	49	675	45 (6)	125 (20)	10
Yunnan	2138	58 (10)	126 (22)	9	4443	55 (9)	123 (21)	0
Total Asia	270 180	45 (10)	121 (18)	53	193 494	45 (9)	122 (17)	4
ALSA	1486	78 (6)	148 (22)	48	124	76 (6)	148 (26)	48
ANHF	7043	44 (14)	126 (18)	53	2234	41 (13)	125 (18)	45
Busselton	5155	45 (17)	138 (25)	59	2634	44 (16)	137 (24)	37
Canberra	728	77 (5)	145 (21)	46	93	76 (5)	147 (22)	39
Fletcher challenge	7899	46 (15)	127 (17)	30	2427	40 (13)	124 (15)	22
Melbourne	36 630	55 (9)	138 (20)	60	4655	53 (8)	135 (19)	47
Newcastle	4567	52 (11)	133 (20)	53	1362	50 (10)	131 (20)	40
Perth	7625	46 (13)	130 (20)	51	2605	43 (13)	129 (19)	40
WAAAAS	10 870	72 (4)	157 (21)	0	1333	71 (4)	157 (22)	0
Total ANZ	82 003	54 (14)	138 (22)	47	17 467	48 (15)	133 (22)	37
Total	352 183	47 (12)	125 (20)	52	210 961	45 (9)	123 (18)	7

SD indicates standard deviation; SBP, systolic blood pressure; ANZ, Australia and New Zealand; ALSA, Australian Longitudinal Study of Aging; ANHF, Australian National Heart Foundation; CISCH, Capital Iron and Steel Company Hospital; EGAT, Electricity Generating Authority of Thailand; KMIC, Korean Medical Insurance Corporation; NHS92, National Health Study 1992; WAAAAS, Western Australian AAA Screenees.

Cardiovascular Outcomes

In total, there were 3 907 543 person-years of follow-up; the median follow-up was 6.8 years (6.8 years for present smokers and 6.7 years for nonsmokers) but, for both present smokers and nonsmokers, it was shorter in Asia (6.8 years versus 6.0 years) than in ANZ (8.3 years versus 8.2 years; Table 2). In addition to information on fatal events available from all cohorts, data on nonfatal CHD events were available from 14 studies and on nonfatal strokes from 12 studies. During follow-up, 4344 CHD (1569 in Asia) and 5906 stroke (4218 in Asia) fatal and nonfatal events were recorded: 76% (n=3282) of CHD events were fatal. Over 80% of CHD events were myocardial infarction. Of all stroke events, 2001 (1550 in Asia) were classified as ischemic and 1645 (1441 in Asia) as hemorrhagic: 30% (n=608) of ischemic stroke and 73% (n=1207) of stroke events were fatal. Diagnosis of ischemic or hemorrhagic stroke was documented by CT/MRI/autopsy investigations in 56% of fatal and 65% of nonfatal, strokes. The percentage of CHD among all CVD (CHD plus stroke) was similar between smokers and nonsmokers (40% versus 44%): these percentages in ANZ (61% versus 64%) were more than double those in Asia (29% versus 25%). The percentage of hemorrhagic strokes among all strokes was similar between smokers and nonsmokers (30% versus 26%): these percentages were higher in Asia (34% versus 34%) than in ANZ (13% versus 12%).

The Association Between SBP and CHD by Smoking Status

The HR for CHD increased log-linearly with higher levels of SBP in both smokers and nonsmokers (Figure 1A). The HRs (95% CIs) comparing the top to the bottom group of SBP were 2.27 (2.05 to 2.52) for present smokers and 2.20 (2.05 to 2.36) for nonsmokers. The HR for a 10-mm Hg increase in SBP level was also similar for present smokers and nonsmokers (Figure 2): 1.29 (1.24 to 1.34) and 1.24 (1.21 to 1.28), respectively (probability value for interaction=0.14). The coronary HRs for present smokers and nonsmokers were similar in all sex, age, and region subgroups. Similar results (not shown) were found for analyses involving fatal events only.

In the subsample of studies for which information on former smokers was available, the HRs for CHD associated with a 10-mm Hg increase in SBP were similar for present smokers and never smokers. However, the HR was lower in former smokers than in present or never smokers: 1.28 (1.22 to 1.33) for present smokers, 1.14 (1.09 to 1.20) for former smokers, and 1.30 (1.25 to 1.35) for never smokers (probability value for interaction=0.0001). In the subsample of studies with information on cigarette consumption, the HRs for CHD tended to increase with increasing consumption of cigarettes: 1.27 (1.21 to 1.32) for never smokers, 1.30 (1.19 to 1.43) for <20 cigarettes per day, and 1.41 (1.28 to 1.54) for ≥20 cigarettes per day (probability value for interaction=0.11).

The Association Between SBP and Ischemic Stroke by Smoking Status

Similar to CHD, there was no evidence of an interaction between BP and smoking for risk of ischemic stroke: the HR for ischemic stroke increased log-linearly with higher levels of SBP in both present smokers and nonsmokers (Figure 1B). The HRs (95% CIs) comparing the highest with the lowest group of SBP were 3.71 (3.22 to 4.27) for present smokers and 3.82 (3.43 to 4.26) for nonsmokers. The HR for a 10-mm Hg increase in SBP level was similar for present smokers and nonsmokers in all subgroups (Figure 2). Overall HRs (95% CIs) were 1.50 (1.43 to 1.57) for present smokers and 1.47 (1.41 to 1.53) for nonsmokers (probability value for interaction=0.53). Similar results (not shown) were found for analyses involving fatal events only.

In the subsample with information on former smokers, the HR for a 10-mm Hg increase in SBP was similar for present smokers, former smokers, and never smokers: 1.44 (1.36 to 1.52), 1.41 (1.29 to 1.53), and 1.41 (1.34 to 1.49), respectively (probability value for interaction=0.86). Among those participants with information on cigarettes per day there was marginally nonsignificant evidence of an increasing effect of SBP with increasing cigarette consumption. The HRs were 1.30 (1.20 to 1.41) for never smokers, 1.47 (1.26 to 1.70) for <20 cigarettes per day, and 1.62 (1.34 to 1.97) for ≥20 cigarettes per day (probability value for interaction=0.06).

The Association Between SBP and Hemorrhagic Stroke by Smoking Status

The HR for hemorrhagic stroke increased with higher levels of SBP in both present smokers and nonsmokers (Figure 1C). There was evidence to support a synergistic effect of smoking on the association between SBP and hemorrhagic stroke risk: the HRs (95% CIs) for hemorrhagic stroke comparing the group with the highest to that with the lowest SBP values were 9.32 (8.15 to 10.67) for present smokers and 7.05 (6.27 to 7.92) for nonsmokers. The excess risk of hemorrhagic stroke associated with a 10-mm Hg higher SBP level increased in present smokers compared with nonsmokers by 15 percentage points (ie, 81% versus 66%) (Figure 2): 1.81 (1.73 to 1.90) versus 1.66 (1.59 to 1.73); probability value for interaction=0.003. Subgroup analysis found indications of this synergistic effect in most subgroups, although it was statistically significant only for men (P=0.01), in Asian study centers (P=0.05), and individuals aged 65 years or over (P=0.008) (Figure 2). Restricting the analysis to fatal hemorrhagic events resulted in a similar pattern: HR (95% CI) for a 10-mm Hg increase in SBP was 1.82 (1.72 to 1.92) for present smokers and 1.67 (1.59 to 1.75) for nonsmokers (probability value for interaction=0.01).

The HR for a 10-mm Hg increase in SBP was higher in present smokers than in former smokers and never smokers: 1.87 (1.77 to 1.97) versus 1.55 (1.40 to 1.71) and 1.68 (1.58 to 1.78), respectively (probability value for interaction=0.0008). In the subsample with information on cigarettes per day, the HRs increased with higher dose of smoking: 1.60 (1.47 to 1.75) for never smokers, 1.85 (1.65 to 2.08) for <20 cigarettes per day, and 1.95 (1.72 to 2.22) for ≥20 cigarettes per day (probability value for interaction=0.01).

A sensitivity analysis using only data from participants (n=126 956) in which information on the use of antihypertensive medication status at study baseline was available indicated that further adjustment for use of antihypertensive

Table 2. Fatal and Nonfatal Cardiovascular Events by Smoking Status

	Nonsmokers					Current Smokers				
			Stroke					Stroke		
Study Name	Median FUP	CHD	Isch	Hem	Others	Median FUP	CHD	Isch	Hem	Others
Akabane	11.0	15	9	5	11	11.0	13	7		6
Anzhen	4.3	50	74		7	4.3	15	32	20	3
Anzhen02	3.0		11	43		3.0	1	3	1	1
Beijing aging	4.8				61	4.8				25
Capital Iron Steel Company	12.5	13	15	20		12.5	70	77	45	9
CISCH	3.3	9			6	3.3	5			3
Civil service workers	6.7					6.7	1		1	1
CVDFACTS	6.1	10	6	5	10	5.8	3	1	3	4
East Beijing	16.0	12	10	8	2	17.4	8	4	3	1
EGAT	11.4	9			8	11.4	24			8
Fangshan	3.6	2	15	6	4	3.6	3	5	2	2
Guangzhou occupational	7.3	60		68	37	7.2	106		99	58
Hisayama	25.1	40	129	29	19	22.6	49	101	39	11
Hong Kong	2.5	73	5	14	41	2.5	13	1	2	10
Kinmen	2.9	6			8	2.9	4			6
KMIC	4.0	107	187	161	150	4.0	171	245	164	147
Konan	6.4		6	2	2	6.4	2	1	1	
Miyama	6.6	1	2		2	6.6	1	4	1	1
Ohasama	4.1	2	21	9	4	4.1	5	16	2	2
Saitama	11.0	14	19	9	10	10.0	10	8	6	3
Seven cities cohorts	2.7	51	66	109	6	2.7	33	51	73	2
Shanghai factory workers	14.0	33			114	14.0	53			141
Shibata	20.0	40	46	23	62	20.0	27	31	13	34
Shigaraki town	4.4	2	2	2	1	4.4	1	2		6
Shirakawa	17.5	29	18	20	12	17.5	36	21	11	5
Singapore heart	14.7	40	16	6	37	14.2	26	6	1	9
Singapore NHS92	6.2	22	11	1	19	6.2	11	3	3	8
Six cohorts	9.0	6	33	50	7	8.3	41	71	41	6
Tanno/Soubetsu	16.4	8	7	7	5	16.4	16	3	9	2
Tianjin	6.1	65	58	97	43	6.1	49	64	90	22
Xi'an	19.7	12	8	17	2	19.7	23	7	7	
Yunnan	4.5	7	5	42		4.5	11	7	51	1
Total Asia	6.0	738	779	753	690	6.8	831	771	688	537
ALSA	4.7	77	7	8	34	3.3	4			3
ANHF	8.4	55	1		10	8.3	22	1		5
Busselton	26.5	767	153	57	407	26.5	480	85	40	207
Canberra	9.6	106	5	4	23	8.4	14	1	1	4
Fletcher challenge	5.7	202	56	7	101	5.8	71	11	2	17
Melbourne	8.5	262	10	28	43	8.7	61	1	7	11
Newcastle	8.5	78	3	6	15	9.4	59		3	7
Perth	14.4	127	3	7	29	14.4	68	1	3	20
WAAAAS	3.2	285	98	29	86	3.2	37	15	2	11
Total ANZ	8.2	1959	336	146	748	8.3	816	115	58	285
Total	6.7	2697	1115	899	1438	6.8	1647	886	746	822

FUP indicates follow-up (years); CHD, coronary heart disease; Isch, ischemic; Hem, hemorrhagic; ANZ, Australia and New Zealand; ALSA, Australian Longitudinal Study of Aging; ANHF, Australian National Heart Foundation; CISCH, Capital Iron and Steel Company Hospital; EGAT, Electricity Generating Authority of Thailand; KMIC, Korean Medical Insurance Corporation; NHS92, National Health Study 1992; WAAAAS, Western Australian AAA Screenees; Blanks indicate that the event was not reported for that study.

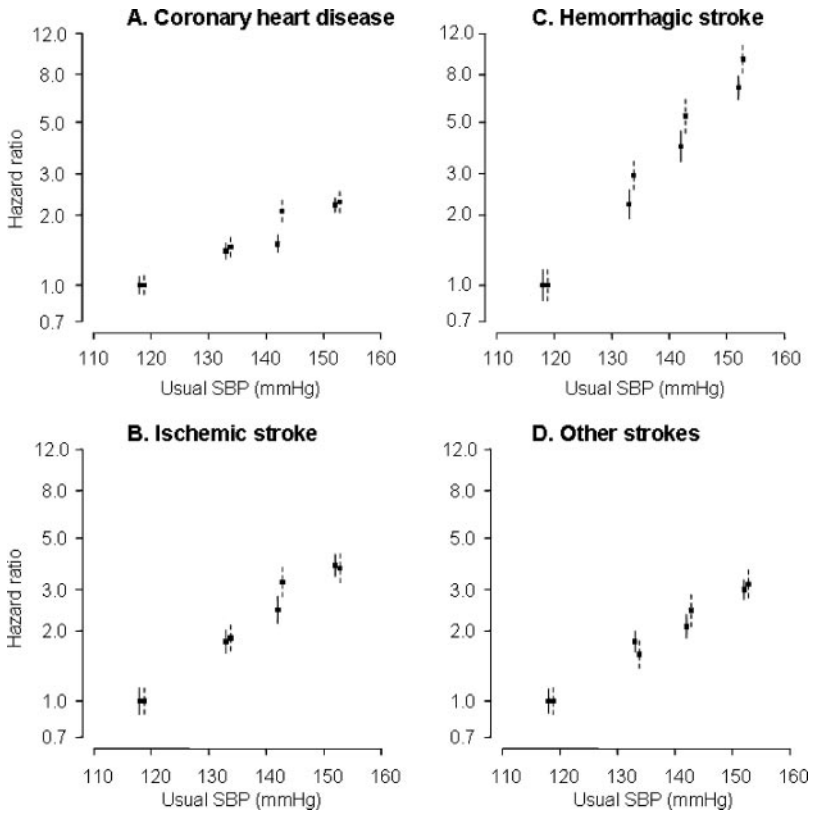

Figure 1. Associations between usual systolic blood pressure (SBP) and overall events by smoking status for: (A) coronary heart disease, (B) ischemic stroke, (C) hemorrhagic stroke, and (D) other strokes. The hazard ratio (95% confidence interval) for the lowest group of SBP is fixed at 1.0, separately for present smokers and nonsmokers. Analyses are adjusted by age and stratified by study and sex. The dashed (right) and continuous (left) lines represent present smokers and nonsmokers, respectively. (Probability values for log-linearity <0.0001 for all.)

medication did not attenuate the difference in risk estimates between present smokers and nonsmokers. The HR (95% CI) for a 10-mm Hg increase in SBP was 1.42 (1.24 to 1.63) for present smokers and 1.23 (1.11 to 1.36) for nonsmokers, after age adjustment (probability value for interaction=0.09), and 1.39 (1.21 to 1.60) and 1.20 (1.09 to 1.33), respectively, after age and use of antihypertensive medication adjustment (probability value for interaction=0.08).

The Association Between SBP and Other Strokes by Smoking Status

For completeness, Figure 1D shows the categorical analyses for other strokes. As with ischemic and hemorrhagic strokes, the HR increased with higher levels of SBP in both present smokers and nonsmokers. The HRs (95% CIs) comparing the highest with the lowest group of SBP were 3.17 (2.76 to 3.64) for present smokers and 3.01 (2.76 to 3.64) for nonsmokers. The HRs (95% CIs) for a 10-mm Hg increment in SBP level were 1.40 (1.33 to 1.47) in present smokers and 1.36 (1.31 to 1.41) in nonsmokers (probability value for interaction=0.33).

Discussion

The present study demonstrates a log-linear relationship of SBP with every subtype of CVD, for both smokers and nonsmokers, with no evidence of a threshold effect down to usual levels of SBP of 115 mm Hg. For hemorrhagic stroke, there was evidence that SBP and smoking have a synergistic effect such that smoking increases the excess risk associated with a 10-mm Hg increment in SBP by about 15 percentage points. Our data suggest that this interaction may be specific to men and older participants, but is unlikely to be specific to region because of the marginal differences between smokers and nonsmokers in both Asia and ANZ apparent from Figure 2. By comparison, the excess relative risk associated with increments in SBP for both CHD and ischemic stroke was broadly similar for smokers and nonsmokers.

The prevailing cause of CHD and ischemic stroke is occlusion of the coronary and cerebral arteries due to atherosclerosis and thrombosis.[14] Some previous reports suggest that nonoptimal levels of BP combined with smoking may promote atherothrombogenesis.[12,13] Kiyohara and colleagues[16] observed an interaction effect between BP and smoking status for CHD in women but not in men, and 1 study[17] observed such an effect in women. Meanwhile, 1 study[18] observed such an effect in men. In a case-control study, Ohgren and colleagues[19] reported an interaction effect between BP and smoking status for all strokes (78% of which were ischemic). Two Japanese studies[11,16] observed such a potentiation for ischemic stroke among men (but not women[16]), as did the British Regional Heart Study,[20] in which the majority of strokes would be expected to be ischemic in origin. By contrast, 2 studies[21,22] in populations where ischemic stroke predominates did not observe such a potentiation for all strokes. These null findings are consistent with our results based on the simple assessment of present smoking status (ie, present/nonsmokers, and present/former/never smokers), suggesting that smoking does not exacerbate the association between SBP and the risk of CHD and ischemic stroke. Furthermore, as most of the previous studies used a relatively crude classification of smoking and hypertensive status, previous positive findings of an interaction may have been attributable to chance alone. There was however some sug-

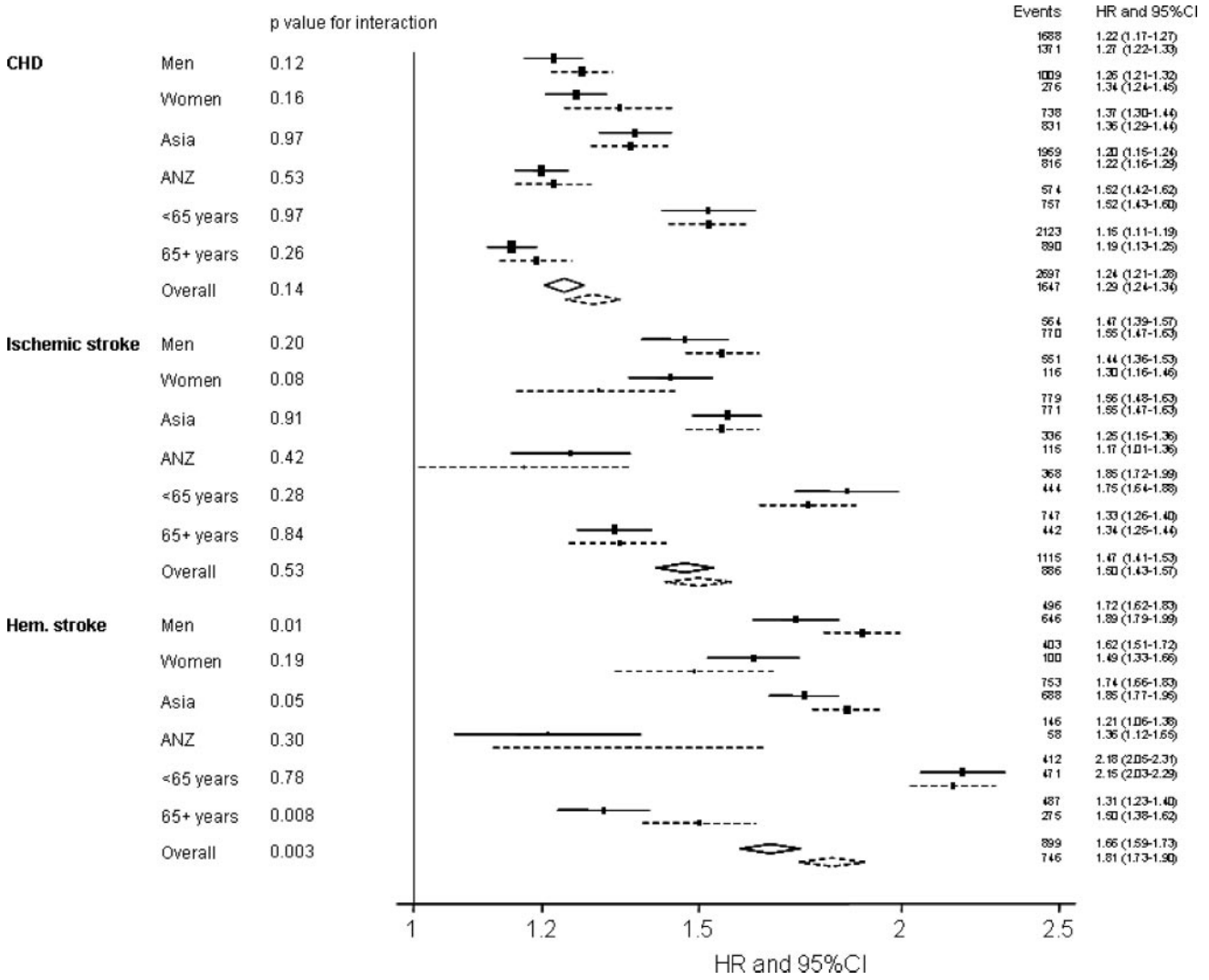

Figure 2. Hazard ratios (HRs) associated with a 10-mm Hg increase in usual systolic blood pressure for coronary heart disease (CHD), ischemic stroke, and hemorrhagic (Hem) stroke, in present smokers and nonsmokers, by sex, region, age, and overall. Analyses are adjusted by age and stratified by study and sex. The horizontal lines (or widths of diamonds for overall results) show 95% confidence intervals (CIs). The probability values shown are for the test of interaction between systolic blood pressure and smoking status. The dashed (lower) and continuous (upper) lines represent present smokers and nonsmokers, respectively.

gestion of an interaction for CHD and ischemic stroke when restricting the present analysis to those studies with information on cigarette consumption, in agreement with an earlier study[11] which reported that the risk of ischemic stroke increased more strongly with higher dose of smoking among individuals with hypertension compared with those without. By contrast, another study[21] reported that the smoking dose-related risk for all strokes was similar for both those with and without hypertension.

Unlike CHD and ischemic stroke, the prevailing cause of hemorrhagic stroke is rupture resulting from fragility (including microaneurysms) of the intracerebral penetrating arteries caused by nonoptimal levels of BP or amyloid angiopathy.[31,32] This accounts for the stronger association between BP and hemorrhagic stroke risk compared with CHD, although the risk related to increased levels of BP is similar for ischemic and hemorrhagic stroke.[4,5] By contrast, the excess risk attributable to smoking for hemorrhagic stroke is less than it is for either CHD or ischemic stroke.[9–11] As regards a pathophysiological mechanism behind the interaction for hemorrhagic stroke observed in the present study, we can only speculate that smoking may promote the weakening of the intracranial blood vessels caused by high levels of BP or amyloid angiopathy. Only Thrift and colleagues[23] have examined the interaction between BP and smoking status for hemorrhagic stroke events. In this case-control study, a significant synergistic interaction was observed only in men, which is consistent with our findings. The sex-specific effect that we observed may have been a chance finding as a consequence of the few events among the smaller population of female smokers (n=14 031), compared with male smokers (n=196 930). The regional specificity may result from the difficulty in observing hemorrhagic stroke events due to a much smaller number participants and a lower event rate of hemorrhagic stroke in ANZ (204 events per 99 470 ANZ participants) compared with Asia (1411 events per 463 674

Asian participants). However, neither of these explanations would explain the age-specific significant effect, wherein the interaction only occurred among those aged 65 years or over: 883 events for <65 years and 762 events for ≥65 years.

The present study has some limitations. First, some cohorts in APCSC do not have information on other risk factors for CVD at baseline, restricting our ability to adjust for important covariates which may explain the observed interaction effects between BP and smoking. Serum total cholesterol, which is positively associated with CHD and ischemic stroke events, and inversely with hemorrhagic stroke events,[33] was available on 353 158 individuals; data on other potentially useful covariates was less common. However, adjustment for total cholesterol had negligible impact on any of the reported results (not shown). Second, we had limited data on daily dose of smoking and little information on how smoking status changed during follow-up, which did not allow any reliable analyses of follow-up smoking status comparable to our treatment of SBP. Third, the main analysis was not adjusted for antihypertensive medication status because of a lack of this information for more than 70% of participants, although the sensitivity analysis suggests that it may have little material impact on the results. Finally, there was lack of standardization of methods and procedures among the participating studies in APCSC, because the participating studies were originally independent of each other. For instance, only 56% of fatal and 65% of nonfatal strokes were objectively (using CT/MRI or autopsy findings) classified as ischemic or hemorrhagic in origin. The Hisayama study in Japan,[34] 1 of the APCSC participating studies, investigated the accuracy of diagnosis of each subtype of CVD using autopsies in the 1960s, 1970s, and 1980s. The accuracy of diagnosis was similar for ischemic and hemorrhagic stroke (confirmation rate 60% to 70%), which was better than the accuracy for CHD (46%).[34] Therefore, misclassification of stroke subtype may have introduced bias the extent of which would have varied across the studies.

In conclusion, we have shown that a combination of present smoking and nonoptimal levels of BP appears to have a synergistic impact on the risk of hemorrhagic stroke, at least among men and in the elderly, although the underlying pathophysiological mechanism is unclear, and we cannot exclude that similar synergism may occur among younger people and women. Furthermore, we cannot affirm the absence of interaction between BP and smoking for CHD and ischemic stroke. Further studies allowing for better verification of pathological types of stroke, better assessment of smoking status and other variables, and using a larger and more standardized dataset, are warranted to determine whether the interaction between BP and smoking really exists for each subtype of CVD, what mechanism explains the interaction, and how specific it is to demographic groups. Although quitting smoking and lowering BP are both crucial for prevention of CVD, combining the two could be expected to have extra beneficial effect on preventing hemorrhagic stroke. Thus, smoking cessation initiatives should be targeted more rigorously for hypertensive patients to prevent hemorrhagic stroke.

Appendix

The Asia Pacific Cohort Studies Collaboration

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Disclosures

None.

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