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Clustering of risk factors and the risk of incident cardiovascular disease in Asian and Caucasian populations: results from the Asia Pacific Cohort Studies Collaboration

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ABSTRACT

Objective To assess the relationship between risk factor clusters and cardiovascular disease (CVD) incidence in Asian and Caucasian populations and to estimate the burden of CVD attributable to each cluster.

Setting Asia Pacific Cohort Studies Collaboration.

Participants Individual participant data from 34 population-based cohorts, involving 314 024 participants without a history of CVD at baseline.

Outcome measures Clusters were 11 possible combinations of four individual risk factors (current smoking, overweight, blood pressure (BP) and total cholesterol). Cox regression models were used to obtain adjusted HRs and 95% CIs for CVD associated with individual risk factors and risk factor clusters. Population-attributable fractions (PAFs) were calculated.

Results During a mean follow-up of 7 years, 6203 CVD events were recorded. The ranking of HRs and PAFs was similar for Australia and New Zealand (ANZ) and Asia; clusters including BP consistently showed the highest HRs and PAFs. The BP–smoking cluster had the highest HR for people with two risk factors: 4.13 (3.56 to 4.80) for Asia and 3.07 (2.23 to 4.23) for ANZ. Corresponding PAFs were 24% and 11%, respectively. For individuals with three risk factors, the BP–smoking–cholesterol cluster had the highest HR (4.67 (3.92 to 5.57) for Asia and 3.49 (2.69 to 4.53) for ANZ). Corresponding PAFs were 13% and 10%.

Conclusions Risk factor clusters act similarly on CVD risk in Asian and Caucasian populations. Clusters including elevated BP were associated with the highest excess risk of CVD.

Strengths and limitations of this study

- ► Strengths of this study are the large sample size, prospective design and the inclusion of studies among diverse populations across the Asia-Pacific region.
- ► We did not have sufficient cardiovascular disease (CVD) events to allow for the reliable quantification of associations between risk factor clusters and the risk of major subtypes of CVD, such as coronary heart disease and stroke, or sex-specific effects within regions.
- ► Most cohorts included in the Asia Pacific Cohort Studies Collaboration were initiated around 20 years ago, before the epidemiological transition during the past few decades in Asia.

INTRODUCTION

Cardiovascular disease (CVD) is the main contributor to morbidity and mortality worldwide and over 80% of CVD deaths take place in low-income and middle-income countries.[1] Much of the burden of CVD is modifiable by adequate control of a set of key risk factors: elevated blood pressure, cigarette smoking, elevated blood lipids, excess body weight and diabetes.[2 3] The Global Burden of Disease study showed that each of these individual cardiovascular risk factors were among the top 10 causes of loss of disability-adjusted life years.[4] Large international case-control studies, INTERHEART[2] and INTERSTROKE,[3] have quantified the individual contribution of these risk factors to CVD and highlighted the substantial geographic variation in the burden of CVD attributable to particular risk factors. For instance, abdominal obesity was a great contributor to CVD risk in Western Europe, North America and South-East Asia, while it was a smaller contributor in China.[2 3]

Cardiovascular risk factors cluster within individuals and clustering of risk factors has been associated with a higher risk of CVD.[5 6] Hence, information on the risks

associated with clusters is relevant for targeting prevention, management and treatment strategies. This is particularly of relevance for Asia, as region where the burden of CVD is still rising, yet where data on the burden of risk factor clusters are limited.

The Asia Pacific Cohort Studies Collaboration (APCSC) has conducted a series of studies to evaluate the joint effects of two risk factors (combinations of excess body weight, elevated systolic blood pressure (SBP), elevated total cholesterol, diabetes and cigarette smoking) and to compare the effects in Asian and Caucasian populations.[7–16] Although several national and international guidelines on cardiovascular risk factor management use sets of individual risk factors to estimate the absolute 10-year risk, direct comparisons of risk factor clusters have not been made nor have clusters with more than two risk factors been analysed in APCSC. Therefore, the aim of the present study was to assess the relationship between multiple risk factor clusters and the risk of CVD in Asian and Caucasian populations and to estimate the burden of CVD attributable to each of these clusters.

METHODS

The APCSC is an individual participant data overview comprising 44 cohort studies in the Asia Pacific region. Details of the APCSC, and characteristics of the included studies have been described previously.[17] Studies from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan or Thailand were classified as Asian, while studies from Australia and New Zealand (ANZ) were classified as Caucasian. For the present study, only those studies with information on smoking status, blood pressure, total cholesterol and body mass index (BMI) were included (34 studies). The prevalence of diabetes was relatively low in the included studies (6% in Asia, and 4% in ANZ), which can in part be explained by the inclusion of studies that conducted their baseline surveys before the rapid rise in the prevalence of diabetes. For that reason, clusters with diabetes were not included. Participants with known coronary heart disease (CHD) and stroke at baseline were excluded. The primary study outcome was the incidence of fatal or non-fatal CVD (International Classification of Diseases Ninth Revision 410–414, 430–438).

Cardiovascular risk factors

Methods of measurement of baseline risk factors have been described previously.[17] Smoking status was determined from self-report questionnaires. BMI was calculated from measured body weight (in kilograms) divided by measured height (in metres) squared. Overweight was defined as a BMI ≥25 kg/m^2.[18] Elevated blood pressure was defined as SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg,[19] and elevated cholesterol was defined as total cholesterol ≥5.2 mmol/L.[20]

Statistical analyses

HRs and 95% CIs for different risk factor clusters were estimated from Cox proportional hazards regression models. The models were adjusted for age and stratified by sex and study. To facilitate comparisons, we also assessed the corresponding associations for individual risk factors. The reference group consisted of individuals without any of the four risk factors. The population attributable fractions (PAFs) for CVD due to risk factor clusters were calculated using the observed prevalence estimates and the HRs as described above. The formula was[21]:

$$\frac{prevalence*(HR-1)}{1+prevalence*(HR-1)}$$

Risk factor clusters were mutually exclusive in calculating the HRs, but were not mutually exclusive in calculating the PAFs. Prevalences and PAFs were estimated separately by region, and, in secondary analyses, by sex. As a sensitivity analysis, individuals with a history of diabetes were excluded.

RESULTS

Baseline characteristics

Overall, 314 024 individuals were included in the analyses, of whom 74% were from Asia, and 59% were men (table 1 and online supplementary etable 1). Participants in Asia were 4 years younger (mean age, 47 years) than those in ANZ. Caucasian participants had higher levels of BMI, SBP and total cholesterol. Smoking was more common in Asian participants, which was due to high smoking rates in men.

Risk factors and risk factor clusters and in relation to cardiovascular events

During a mean follow-up of 7 years, 6203 CVD events were recorded. The ranking of HRs by individual risk factors and risk factor clusters was similar in ANZ and Asia (figure 1 and table 2). The blood pressure–smoking cluster had the highest HR in people with two risk factors (HR (95% CI): 4.13 (3.56 to 4.80) in Asia and 3.07 (2.23 to 4.23) in ANZ and the cholesterol–overweight cluster had the lowest HR: 1.25 (0.94 to 1.65) in Asia and 1.79 (1.39 to 2.29) in ANZ. For individuals with three risk factors, the blood pressure–smoking–cholesterol cluster had the highest (HR 4.67 (3.92 to 5.57) in Asia and 3.49 (2.69 to 4.53) in ANZ; the smoking–cholesterol–overweight cluster had the lowest HR (2.00 (1.51 to 2.67) in Asia and 3.30 (2.51 to 4.35) in ANZ). HRs in individuals with four risk factors were 5.66 (4.61 to 6.95) in Asia and 4.35 (3.38 to 5.59) in ANZ. Rankings of HRs were broadly similar between sexes (figure 2 and table 2).

Prevalence and PAFs

The prevalence of individual risk factors and risk factor clusters and associated PAFs are shown in table 2, figure 3 and online supplementary etable 2. Clusters

Table 1 Baseline characteristics of study participants included in the present analyses, by study

Study name	Baseline, yrs	N (% women)	Age, yrs	SBP, mm Hg	High BP, %	Smoker, %	TC, mmol/L	High TC, %	BMI, kg/m^2	High BMI, %	FU, yrs	No. events
Aito Town	1980–1983	964 (57)	51 (10)	137 (23)	49	29	4.7 (0.9)	24	23.2 (2.9)	25	15	18
Akabane	1985–1986	1651 (56)	54 (8)	125 (19)	21	28	5.0 (0.9)	38	22.9 (2.7)	20	11	96
Anzhen	1992–1993	4004 (51)	47 (8)	122 (18)	22	21	4.7 (0.9)	26	24.2 (3.2)	37	3	17
Capital Iron & Steel Company	1974–1980	4290 (0)	45 (8)	123 (19)	31	74	4.9 (1.0)	33	23.3 (2.6)	23	13	237
Beijing Aging	1992	1182 (51)	69 (8)	141 (25)	61	29	4.4 (1.0)	19	23.8 (3.4)	35	4	34
Civil Service Workers	1990–1992	8537 (33)	47 (5)	126 (18)	22	38	5.2 (0.9)	46	22.8 (2.5)	17	7	3
Frangshan	1992	814 (67)	47 (9)	133 (25)	36	39	4.6 (1.1)	25	25.1 (3.7)	48	3	10
Hong Kong	1991	115 (48)	79 (7)	148 (23)	75	17	5.3 (0.9)	49	22.8 (2.7)	22	2	6
Huashan	1990–1992	1680 (53)	53 (11)	127 (21)	30	24	4.7 (0.9)	25	23.8 (3.1)	32	2	16
Konan	1987–1995	980 (55)	50 (15)	130 (19)	32	30	4.9 (0.9)	34	22.5 (2.6)	17	6	11
KMIC	1992	156565 (33)	44 (7)	123 (14)	22	39	5.0 (0.9)	36	23.2 (2.4)	21	4	1311
Guangzhou Occupational	1985–1997	4287 (32)	43 (7)	114 (16)	11	45	5.3 (1.2)	49	23.0 (3.0)	22	8	10
Ohasama	1992–1993	1692 (65)	57 (11)	127 (17)	32	20	5.0 (0.9)	39	23.5 (2.9)	29	4	35
Seven Cities Cohorts	1987	4855 (58)	57 (10)	133 (25)	41	32	5.1 (1.5)	40	23.6 (3.3)	29	5	198
EGAT	1985	3318 (23)	43 (5)	121 (16)	20	43	5.8 (1.1)	69	23.4 (2.9)	26	10	43
Shigaraki Town	1991–1997	3113 (60)	56 (14)	132 (19)	34	29	5.0 (0.9)	40	22.9 (2.8)	21	4	5
Shirakawa	1974–1979	4081 (54)	48 (12)	127 (21)	28	35	4.7 (0.9)	23	22.0 (2.5)	12	17	127
Singapore Heart	1982–1997	1979 (49)	41 (13)	124 (21)	24	22	5.9 (1.2)	70	24.2 (4.0)	36	12	100
Six Cohorts	1982–1986	12458 (47)	45 (7)	119 (18)	14	43	4.2 (0.9)	12	21.5 (2.2)	7	8	147
Tannno/Soubetsu	1977	1915 (53)	51 (7)	134 (20)	41	38	4.9 (1.0)	36	23.8 (3.1)	30	15	51
CVDFACTS	1988–1996	5072 (55)	47 (15)	118 (19)	21	22	5.0 (1.2)	38	23.8 (3.2)	31	6	30
Singapore NHS92	1992	2893 (51)	40 (12)	119 (18)	18	18	5.4 (1.0)	55	23.9 (3.8)	33	6	62
Miyama	1988–1990	372 (63)	59 (9)	129 (23)	37	22	5.1 (0.9)	44	22.7 (2.7)	17	7	0
Saitama	1986–1990	3167 (62)	54 (12)	135 (20)	45	28	5.0 (1.0)	38	22.8 (2.6)	18	10	55
Hisayama	1961	1307 (55)	55 (11)	134 (26)	36	44	4.1 (1.0)	12	22.1 (2.4)	12	18	320
Shibata	1977	2048 (58)	56 (11)	131 (21)	44	33	4.6 (1.2)	28	22.8 (2.8)	19	16	209
Yunnan	1992	2346 (4)	54 (9)	123 (21)	27	68	4.3 (0.8)	12	22.4 (2.6)	15	4	24
Subtotal Asia		*235685 (37)*	*46 (9)*	*123 (17)*	*24*	*38*	*4.9 (1.0)*	*35*	*23.1 (2.6)*	*22*	*5*	*3175*
Newcastle	1983–1994	5237 (51)	51 (10)	132 (19)	36	23	5.8 (1.1)	69	26.6 (4.4)	61	9	108
ANHF	1989–1990	8548 (51)	43 (13)	126 (18)	27	24	5.5 (1.1)	60	25.4 (4.1)	48	8	56
Perth	1978–1994	9169 (47)	45 (13)	130 (20)	36	25	5.8 (1.2)	64	25.3 (3.8)	47	13	199
Melbourne	1990–1994	38390 (60)	54 (9)	137 (20)	46	11	5.5 (1.1)	60	26.9 (4.4)	64	9	277
Fletcher Challenge	1992–1994	9840 (28)	44 (14)	126 (17)	26	24	5.4 (1.1)	53	26.5 (4.1)	60	6	576

Continued

Table 1 Continued

Study name	Baseline, yrs	N (% women)	Age, yrs	SBP, mm Hg	High BP, %	Smoker, %	TC, mmol/L	High TC, %	BMI, kg/m^2	High BMI, %	FU, yrs	No. events
Busselton	1966–1981	6250 (52)	44 (16)	138 (24)	44	34	5.9 (1.3)	68	24.7 (3.6)	40	25	1755
ALSA	1992–1993	905 (51)	77 (6)	149 (22)	67	9	5.8 (1.2)	70	25.8 (3.8)	55	5	57
Subtotal ANZ		*78 339 (52)*	*50 (13)*	*134 (20)*	*40*	*18*	*5.6 (1.1)*	*61*	*26.3 (4.3)*	*58*	*10*	*3028*
Total		**314 024 (41)**	**47 (10)**	**126 (18)**	**28**	**33**	**5.1 (1.0)**	**42**	**23.9 (3.4)**	**31**	**7**	**6203**

High blood pressure was defined as SBP ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, high TC was defined as a TC level ≥5.2 mmol/L and high BMI was defined as a BMI ≥25 kg/m^2.
ALSA, Australian Longitudinal Study of Ageing; ANHF, Australian National Heart Foundation; ANZ, Australia and New Zealand; BMI, body mass index; BP, blood pressure; CVDFACTS, CardioVascular Disease risk FACtor Two-township Study; EGAT, Electricity Generating Authority of Thailand; FU, follow-up; KMIC, Korean Medican Insurance Corporation; OW, overweight; SBP, systolic blood pressure; Singapore NHS92, Singapore National Health Survey 1992; TC, elevated total cholesterol; yrs, years.

including smoking had the highest PAFs in Asian men, with a PAF of 37% for the blood pressure–smoking cluster. The blood pressure–cholesterol cluster had the highest PAF in men in ANZ (30%), followed by the blood pressure–overweight (28%), and smoking–cholesterol (20%) clusters. The blood pressure–cholesterol and blood pressure–overweight clusters had the highest PAFs in women in both regions; the PAFs were 17% and 13% in Asian women and 36% and 34% in women from ANZ. The prevalence of smoking in Asian women is very low, which explains the comparatively low PAFs for risk factor clusters involving smoking.

The main findings did change minimally after exclusion of individuals with a history of diabetes (online supplementary etables 3 and 4).

DISCUSSION

This study of over 320 000 individuals in the Asia-Pacific region found that the ranking of the relations between clusters of major modifiable risk factors for CVD and risk of cardiovascular events was similar in Asia and ANZ. In both regions, the greatest excess risks of CVD were found in clusters involving elevated blood pressure. However, differences in the prevalence of risk factors between sexes and regions led to variation in the burden of CVD attributable to risk factor clusters.

The present study is the first to examine the relationships between clusters of two, three or four risk factors and cardiovascular events. We confirm that all combinations of risk factors are related to an increased risk of CVD, and that the risk increases in the presence of additional risk factors. Through direct comparisons, we identified that the most hazardous clusters for CVD where those that included high blood pressure. Furthermore, we expanded the evidence by showing that clusters act broadly similar on the risk of CVD in Asian and Caucasian populations.

High blood pressure, smoking, unfavourable lipid levels, high BMI and diabetes are each independently related to an increased risk of CVD, and the more risk factors are present in an individual, the higher these risks are. Previous reports from the APCSC on the joint effects of several combinations of two risk factors broadly showed that the risk of CVD increased at all combinations, with an indication for synergism for some CVD subtypes.[7–16] For example, where high SBP is an important risk factor for CVD in people with and without diabetes and irrespective of levels of BMI,[9 15] it may be more strongly related to the risk of CVD at lower levels at TC.[7] Similarly, smoking seemed to exacerbate the impact of high SBP on the risk of haemorrhagic stroke[10] and that of BMI, TC and high-density lipoprotein cholesterol on the risk of CHD.[11 12] Hence, effective strategies that target combinations of specific risk factors, such as smoking cessation and weight loss

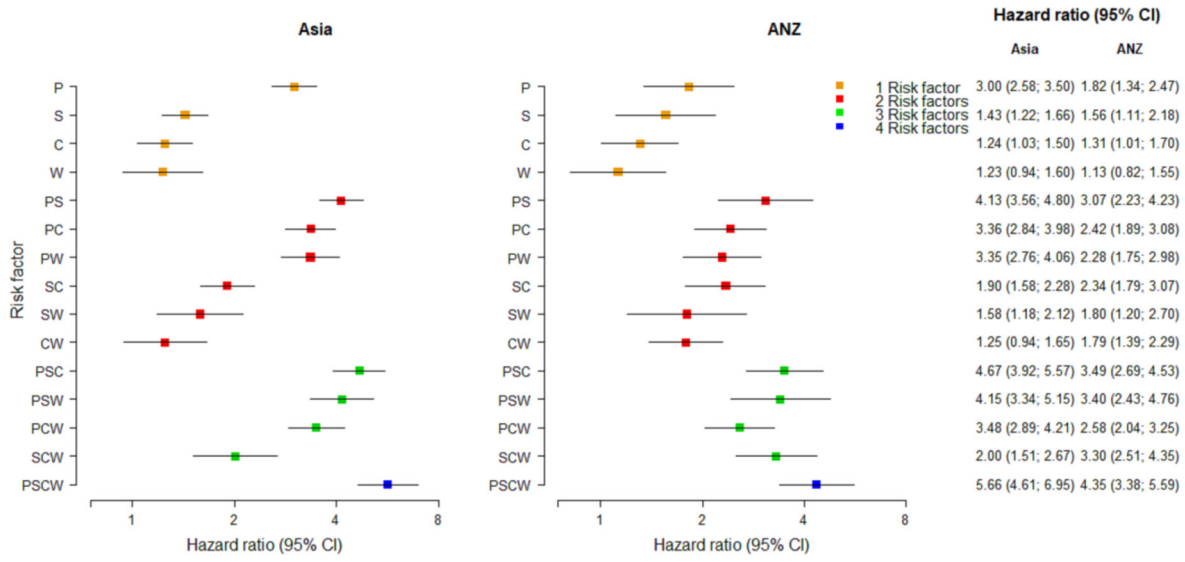

Figure 1 HRs and 95% CIs for incident cardiovascular disease associated with risk factors and risk factor clusters by region. Analyses are adjusted for age, and stratified by sex and study. Individuals without any elevated risk factor were the reference group. ANZ, Australia and New Zealand; P, high blood pressure; S, current smoking; C, high total cholesterol (TC), W, high body mass index (BMI). High blood pressure was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, high TC was defined as a TC level ≥5.2 mmol/L and high BMI was defined as a BMI≥25 kg/m^2.

or blood pressure reduction, could have a greater impact than anticipated on reducing the burden of CVD.

The major shift in causes of death and disability from infectious diseases to non-communicable diseases and increases in life expectancy seen over the past decades pose major challenges on the capacities of health systems globally. These challenges are most profound in low-income and middle-income countries where the burden of CVD is the largest, competing health threats are still present and resources are most limited.[22] Prevention of CVD through targeting its major modifiable risk factors is arguably the most cost-effective way to reduce the burden of CVD. From the public health perspective, our findings indicate that the largest burden of CVD is attributable to elevated blood pressure and smoking, suggesting that interventions on curbing smoking habits and managing blood pressure levels could have major benefits in terms of reducing the burden of CVD worldwide. However, local contexts need to be considered. Taking smoking, for example, implementing effective smoking bans, raising taxes and the price of tobacco have been effective ways to reduce tobacco use in low-income and middle-income countries.[23] In contrast, bans on advertising in the mass media to denormalise smoking and behavioural interventions at the individual level are current strategies to reduce the smoking prevalence in high-income countries, where bans on smoking in public places have largely been implemented. Reduction in dietary salt intake is another major strategy to avert the burden of elevated blood pressure; such strategies need to be tailored to the national situation given substantial differences in dietary habits globally. The risk factor clusters with overweight did not rank as high as anticipated. The relatively low PAFs found in our study may be due to the lower prevalence of overweight some decades ago, when the measurements of BMI were done. Since then, the prevalence of overweight and obesity has dramatically increased globally. While further follow-up of existing cohorts and new cohorts are needed to monitor the obesity epidemic and the evolution of the relative risks, contemporary information on the burden of the risk factors and their clustering should become available to local authorities when trying to target their own needs and priorities. Yet, surveillance of the prevalence of risk factor clusters is not available for many countries.

Strengths of this study include its large sample size, prospective design and the inclusion of studies among diverse populations across the Asia-Pacific region. Some limitations of this study need to be acknowledged. First, despite the large sample size, we did not have sufficient CVD events to allow for reliable quantification of associations between risk factor clusters and the risk of major subtypes of CVD, such as CHD and stroke, or sex-specific effects within regions. However, CHD and stroke share many of the same risk factors, and preventive strategies to target clusters are likely to be beneficial in preventing both outcomes in both sexes and across regions. While the number of participants from Asian cohorts was greater than from ANZ cohorts, the number of CVD events, and associated statistical power, was broadly similar between regions. Next, most cohorts from APCSC were initiated around 20 years ago and one might question its suitability

Table 2 HRs (95% CIs), prevalence and population attributable fractions (PAFs) for incident cardiovascular disease associated with risk factors and risk factor clusters by sex and region

	ANZ			Asia		
	HR (95% CI)	Prevalence	PAF, %	HR (95% CI)	Prevalence	PAF, %
Men						
P	1.79 (1.22 to 2.63)	42.5	25.1	2.44 (1.95 to 3.06)	27.8	28.6
S	1.51 (1.01 to 2.27)	23.3	10.7	1.41 (1.16 to 1.71)	13.8	19.3
C	1.33 (0.94 to 1.88)	60.3	16.5	1.19 (0.90 to 1.56)	61.5	6.5
W	1.06 (0.71 to 1.58)	64.5	3.8	1.07 (0.73 to 1.58)	51.0	1.7
PS	2.70 (1.83 to 4.00)	8.8	13.0	4.02 (3.32 to 4.86)	3.8	31.2
PC	2.50 (1.81 to 3.46)	28.7	30.1	3.01 (2.36 to 3.84)	28.1	19.2
PW	2.23 (1.60 to 3.11)	31.6	28.0	3.09 (2.37 to 4.03)	24.6	16.5
SC	2.71 (1.94 to 3.79)	14.6	20.0	1.80 (1.45 to 2.24)	8.6	14.3
SW	1.65 (1.03 to 2.64)	13.6	8.1	1.47 (1.06 to 2.02)	5.8	5.5
CW	1.87 (1.37 to 2.57)	41.9	26.8	1.23 (0.83 to 1.83)	34.9	2.5
PSC	3.16 (2.27 to 4.42)	6.1	11.7	4.38 (3.54 to 5.42)	3.0	17.4
PSW	3.44 (2.31 to 5.11)	5.9	12.6	3.81 (2.97 to 4.90)	2.1	11.6
PCW	2.51 (1.86 to 3.39)	21.8	24.7	3.25 (2.50 to 4.24)	18.7	9.6
SCW	2.94 (2.09 to 4.13)	9.2	15.2	1.94 (1.42 to 2.65)	4.1	5.2
PSCW	4.32 (3.16 to 5.92)	4.2	12.3	5.44 (4.29 to 6.90)	1.7	9.5
Women						
P	1.79 (1.07 to 2.97)	37.5	22.7	3.61 (2.90 to 4.49)	16.8	30.5
S	1.60 (0.83 to 3.05)	13.8	7.6	1.42 (0.87 to 2.33)	3.0	1.3
C	1.25 (0.83 to 1.87)	61.5	13.2	1.27 (0.98 to 1.63)	33.4	8.2
W	1.15 (0.67 to 2.00)	51.0	7.3	1.39 (0.95 to 2.03)	17.8	6.5
PS	4.95 (2.79 to 8.79)	3.8	13.1	4.78 (3.20 to 7.14)	0.9	3.1
PC	2.22 (1.51 to 3.27)	28.1	25.5	3.57 (2.80 to 4.56)	7.8	16.7
PW	2.16 (1.37 to 3.40)	24.6	22.2	3.51 (2.62 to 4.70)	6.0	13.1
SC	1.47 (0.90 to 2.38)	8.6	3.9	2.79 (1.51 to 5.17)	1.0	1.8
SW	2.15 (0.90 to 5.16)	5.8	6.3	2.49 (0.91 to 6.79)	0.7	1.0
CW	1.47 (0.97 to 2.22)	34.9	14.0	1.20 (0.80 to 1.80)	8.3	1.6
PSC	3.91 (2.56 to 5.96)	3.0	8.0	8.22 (4.79 to 14.10)	0.3	2.3
PSW	2.80 (1.40 to 5.58)	2.1	3.7	8.49 (4.58 to 15.74)	0.3	1.9
PCW	2.41 (1.65 to 3.53)	18.7	20.9	3.50 (2.65 to 4.63)	3.2	7.5
SCW	3.95 (2.45 to 6.38)	4.1	10.8	1.62 (0.40 to 6.54)	0.3	0.2
PSCW	3.83 (2.48 to 5.92)	1.7	4.6	5.00 (2.20 to 11.35)	0.1	0.5

HRs are adjusted for age and stratified by study. Individuals without any elevated risk factor were the reference group. Combinations of risk factors were not mutually exclusive in calculating the prevalence and population attributable fractions. ANZ, Australia and New Zealand; P, high blood pressure; S, current smoking; C, high total cholesterol (TC); W, high body mass index (BMI). High blood pressure was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, high TC was defined as a TC level ≥5.2 mmol/L and high BMI was defined as a BMI ≥25 kg/m^2.

to address current cardiovascular profiles, given the well-recognised epidemiological transition during the past few decades in Asia. However, the main purpose of this study was to evaluate the aetiological relationships of clusters on risk of CVD, which are less likely to change over time. The historical nature of the data also precluded reliable analysis of clusters involving diabetes, which is a much commoner risk factor in current times. Data on prediabetes were also not available. Finally, ethnicity was not recorded in all studies. However, where we know it, less than 0.5% of participants in Australia and New Zealand had an Asian ancestry. Hence, we feel that domicile is a reasonable proxy for ethnicity in our data.

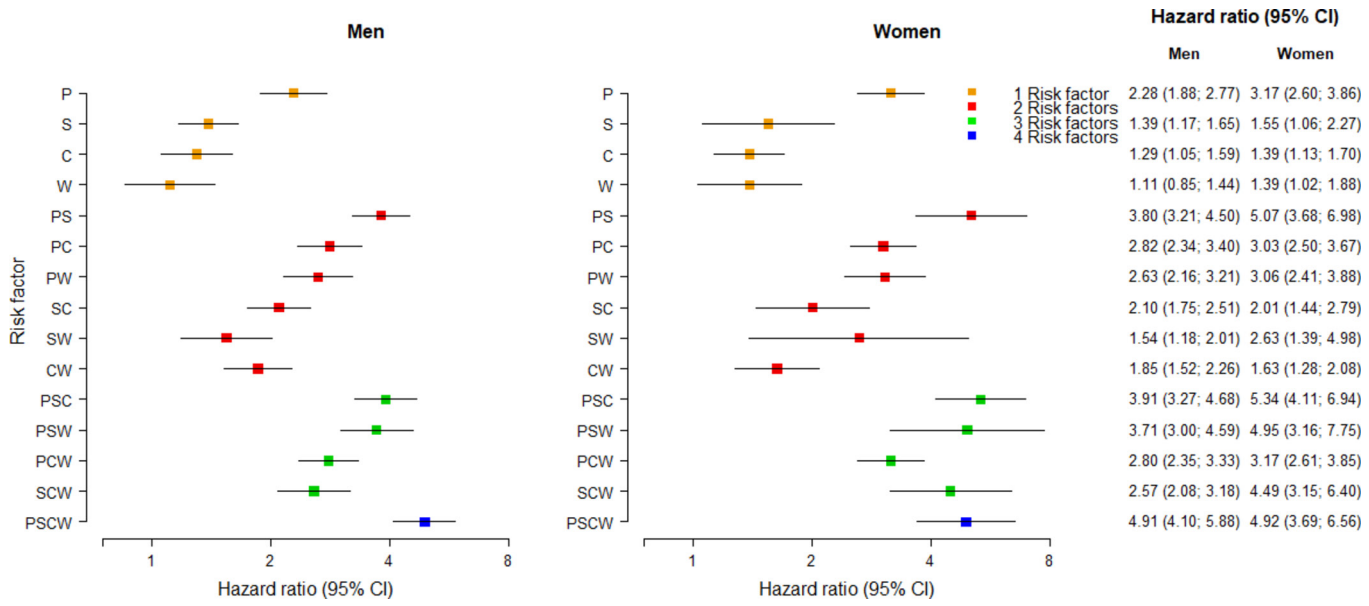

Figure 2 HRs and 95% CIs for incident cardiovascular disease associated with risk factors and risk factor clusters by sex. Conversions as in figure 1.

In conclusion, clusters of major modifiable risk factors act similarly on the risk of CVD in Asian and Caucasian populations. Risk factor clusters including elevated blood pressure were associated with the highest excess risk of CVD.

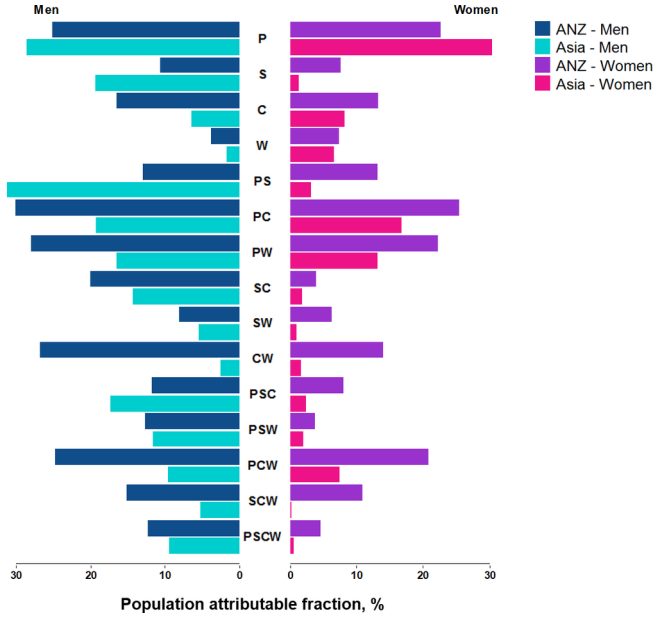

Figure 3 Population attributable fractions of risk factors and risk factor clusters for cardiovascular disease by sex and region. ANZ, Australia and New Zealand; P, high blood pressure; S, current smoking; C, high total cholesterol (TC); W, high body mass index (BMI). High blood pressure was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. High TC was defined as a TC level ≥5.2 mmol/L. High BMI was defined as a BMI≥25 kg/m^2. Combinations of risk factors were not mutually exclusive.

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Contributors SAEP, XW, MLB, IV and MW conceived the study. T-HL, HCK, SH, TN, MK and MW retrieved the study data, along with other principal collaborators in the Asia Pacific Cohort Studies Collaboration. SAEP and XW did the statistical analyses and drafted the manuscript. SAEP, XW, T-HL, HCK, SH, TN, MK, IV, MLB and MW participated in data interpretation, made important revisions to the draft manuscript and read and approved the final manuscript.

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