

Does Sex Matter in the Associations between Classic Risk Factors and Fatal Coronary Heart Disease in Populations from the Asia-Pacific Region?

ASIA PACIFIC COHORT STUDIES COLLABORATION

ABSTRACT

Background: There is much interest in promoting healthy heart awareness among women. However, little is known about the reasons behind the lower rates of heart disease among women compared with men, and why this risk difference diminishes with age. Previous comparative studies have generally had insufficient numbers of women to quantify such differences reliably.

Methods: We carried out an individual participant data meta-analysis of 39 cohort studies (32 from Asian countries and 7 from Australia and New Zealand). Cox models were used to estimate hazard ratios (HR) for coronary death, comparing men to women. Further adjustments were made for several proven coronary risk factors to quantify their contributions to the sex differential. Sex interactions were tested for the same risk factors.

Results: During 4 million person-years of follow-up, there were 1989 (926 female) deaths from coronary heart disease (CHD). The age-adjusted and study-adjusted male/female HR (95% confidence interval [95% CI]) was 2.05 (1.89-2.22). At baseline, 54% of men vs. 7% of women were current smokers; hence, adjustment for smoking explained the largest component (20%) of this HR. A significant sex interaction was observed between systolic blood pressure (SBP) and CHD mortality such that a 10 mm Hg increase was associated with a 15% greater increase in the relative risk (RR) of coronary death in women compared with men ($p = 0.002$).

Conclusions: Only a small amount of the sex differential in coronary death could be explained by differences in the prevalence of classic risk factors. Alternative explanations are required to explain the age-related attenuation of the sex difference in CHD risk.

INTRODUCTION

A SUBSTANTIAL BODY OF EVIDENCE supports the hypothesis that within industrialized countries, men have a 3–5-fold greater risk of coronary heart disease (CHD) mortality than women^{1–3} and that this risk difference diminishes over time, to become only a 1–2-fold greater risk in the

eight decade of life.³ Age-related differences between men and women in the levels of classic risk factors, such as blood pressure, smoking, and cholesterol level, may partly explain the sex difference. A lack of prospective data has previously limited the ability to reliably quantify the contributions of important risk factors to CHD mortality separately for men and women.

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Interactions between sex and risk factors may account, in part, for some of the observed sex difference in CHD mortality rates. The most widely reported sex interactions have been between smoking and CHD⁴ and between diabetes and coronary risk.⁵ In both instances, however, the sex interaction appears to increase the risk among women rather than men; Hence, such interactions, if real, would act to attenuate rather than exacerbate the sex differential in CHD risk. For example, a greater proportionate effect of smoking in women has been documented, with evidence that female smokers have an approximately 50% higher relative risk (RR) of dying from vascular disease than men.⁴ Similarly, diabetes has been reported to eliminate the female advantage, with diabetic women widely considered to be at increased RR for CHD compared with diabetic men.⁵ However, a recent meta-analysis of prospective cohort studies refutes the idea of a sex-diabetes interaction.⁶ Less is known about whether sex interacts with other classic risk factors, including blood pressure, lipids, and body mass index (BMI), to modify CHD mortality risk in men and women. If sex-risk factor interactions were shown to exist, it would have substantial implications for treatment strategies and guidelines.

The Asia Pacific Cohort Studies Collaboration (APCSC) comprises a large number of prospective cohort studies in the region and was established primarily to provide reliable evidence about the effects of a variety of modifiable risk factors, including blood pressure, lipids, and diabetes, on the risks of cardiovascular diseases and other common causes of death among populations in this region.⁷ The aims of this paper are threefold: first, to quantify the contribution of individual risk factors to CHD mortality in men and women; second, to quantify how much each of the individual risk factors contributes to the excess risk difference in men; and third, to determine to what extent, if any, sex-risk factor interactions influence the risk of CHD mortality among men and women.

MATERIALS AND METHODS

Participating studies

APCSC is an overview conducted by the principal investigators of prospective studies conducted in the region. Details of the methods of study identification and data collection are de-

scribed elsewhere.⁷ Cohort studies were eligible for inclusion and were invited to participate if (1) the study population was from the Asia-Pacific region, (2) date of birth, sex, and blood pressure of each individual were recorded at baseline, and (3) at least 5000 person-years of follow-up had been completed. Studies that selected participants on the basis of the absence or presence of any specific disease or risk factor were excluded. Studies were classified as Asian if their participants were recruited from Mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan, or Thailand or ANZ if their participants were recruited from Australia or New Zealand. Each study reported deaths by underlying cause; these were mostly ascertained through data linkage. All outcomes were classified according to the ninth revision of the *International Classification of Diseases* (ICD-9). Each death was ascribed to its underlying cause as reported on the death certificate. The primary end point considered in this paper is death from CHD (ICD 410-414). All datasets were centrally checked for consistency, and where necessary, further details were sought from collaborating investigators.

Variables measured at baseline

In each study, age, sex, and blood pressure at baseline were recorded. In most studies, blood pressure was measured at rest in the seated position using a standard mercury sphygmomanometer,⁸ and total cholesterol was generally measured from fasting serum.⁹ Baseline BMI, defined as weight (kg) divided by height (m²),¹⁰ was recorded. Smoking status was recorded as either current smoker or nonsmoker of cigarettes. Diabetic status was determined on the basis of either a reported history of diabetes at baseline or a fasting venous blood sample¹¹ according to the World Health Organization (WHO) definition of diabetes (i.e., fasting glucose ≥ 7.0 mmol/L or 2-hour post-glucose load ≥ 11.1 mmol/L). More detailed information about the measurement and recording of these variables is given elsewhere.⁸⁻¹¹

Statistical methods

Analyses used individual participant data and were restricted to participants aged ≥ 20 years at the time of the baseline survey. Two studies with data only from men were excluded from all analyses. Cox proportional hazard models were used to analyze age-adjusted sex effects for the relationships between known risk factors and fa-

tal CHD. All analyses were adjusted for age as a continuous variable and stratified by the cohort of origin. This method allows background risk to vary between studies but assumes that there are equal relative effects of the risk factors throughout. To determine if the associations of risk factors with fatal CHD are similar in men and women, we first examined across-study heterogeneity in the interactions between sex and risk factors, after adjustment for other risk factors, by conducting a random-effects meta-analysis of the interactions and subsequently examining the homogeneity test statistic. If there was no evidence of significant study heterogeneity, we proceeded to test for interactions between sex and risk factors combining data from all studies, first in unadjusted analyses and then after adjusting for each of the other risk factors separately and then combined. All continuous exposure variables were corrected for regression dilution.¹²

The percentage excess risk of CHD in men compared with women that was due to differences in risk factor levels was estimated by $100 \left(\frac{[HR_U - HR_A]}{[HR_U - 1]} \right) \%$ where HR_U and HR_A are, respectively, the hazard ratios for CHD comparing men with women unadjusted (\hat{u}) (except by age) and after (\hat{A}) (further) adjustment for each risk factor alone and then for all risk factors combined.¹³ Because of the limited number of CHD events in women, the high probability of finding false effects, and previous findings from APCSC that there is no regional heterogeneity in the associations between risk factors and CHD,⁸⁻¹¹ regional variations in sex interactions were not examined.

RESULTS

Characteristics of study participants

The characteristics of studies within the APCSC, after excluding those with no data on women, and the mean values of risk factors at baseline are shown in Table 1. During 4 million person-years of follow-up, there were 2915 (926 female) deaths from CHD.

The amount of information available varied for each risk factor examined (Table 2). For example, data for blood pressure were available on all 577,417 individuals; for cigarette smoking, 543,280, and for diabetes, 361,710, aged between 20 and 107 years. Information on triglycerides and high-density lipoprotein cholesterol (HDL-C) was available from a much smaller number of

individuals. The mean values for the risk factors shown in Table 2 were all highly significantly different ($p < 0.001$) between men and women. Overall, men were substantially more likely to smoke than women (54% vs. 7%), to have diabetes (7.7% vs. 3.6%), to have higher levels of triglycerides and systolic blood pressure (SBP), and to have a higher total cholesterol/HDL-C ratio. Cholesterol levels were slightly higher in women than in men but only in cohorts from ANZ. The age and BMI difference between men and women was negligible, although highly significant because of the large sample.

Sex-specific HRs for CHD

In the overall sample ($n = 577,417$), the age-adjusted and study-adjusted HR for CHD in men compared with women was 2.05 (95% CI 1.89-2.22). In the much smaller subset of individuals for whom data on all risk factors were available ($n = 58,606$), the overall age-adjusted and study-adjusted HR was 2.42 (95% CI 1.94-3.01), which was attenuated to 2.10 (95% CI, 1.68-2.45) after adjustment for all risk factors. In age-adjusted analyses, cigarette smoking, systolic blood pressure, BMI, diabetes, total cholesterol, triglycerides, and the total cholesterol/HDL-C ratio were all significantly and positively associated with CHD mortality in both men and women (Table 3).

Sex-risk factor interactions

The magnitudes of the age-adjusted and study-adjusted associations between cigarette smoking, total cholesterol, diabetes, triglycerides, and the total cholesterol/HDL-C ratio with fatal CHD were similar in men and women. This remained true even after adjustment for other risk factors (Table 3). Because of substantial differences in the amount of information available for each of the risk factors, the adjusted analyses were restricted to the sample of individuals for whom data were available on smoking, diabetes, BMI, total cholesterol, and SBP ($n = 303,515$). In the smaller sample that had complete information on all risk factors including triglycerides and HDL-C ($n = 58,606$), the analyses were run to determine whether a sex interaction exists between these variables and fatal CHD.

We found no evidence of significant heterogeneity between the studies when we examined sex interactions with each of the risk factors. Hence, the following results are based on individual data from

TABLE 1. APCSC STUDY CHARACTERISTICS

Cohort name	n	Start year (Range)	Median follow-up (Years)	Female %	CHD deaths	
					Men	Women
Aito Town	1,717	1980–1983	15.2	56.7	9	7
Akabane	1,836	1985–1986	11.0	55.7	5	2
Anzhen	8,378	1991	4.3	55.1	35	30
Anzhen02	4,152	1992–1993	3.0	51.1	1	0
Australian Longitudinal Study of Aging	1,613	1992–1993	4.6	47.8	53	28
Australian National Heart Foundation	9,277	1989–1990	8.3	50.9	58	19
Beijing Steelworkers	8,957	1970	27.9	11.6	130	2
Busselton	7,881	1966–1981	20.5	51.9	392	296
Capital Iron and Steel Company Hospital	2,167	1992–1993	3.3	50.9	1	0
Civil Service Workers	9,319	1990–1992	6.7	33.1	1	0
CVDFACTS	5,730	1988–1996	6.0	55.3	7	6
East Beijing	1,128	1977–1994	17.1	51.4	10	10
EGAT	3,497	1985	11.4	22.8	31	2
Fletcher Challenge	10,366	1992–1994	5.8	28.0	81	33
Guangzhou Occupational	167,377	1985–1998	7.3	21.7	152	16
Hisayama	1,616	1961	24.6	56.4	24	30
Hong Kong	3,006	1985–1991	2.5	57.5	36	50
Huashan	1,868	1990–1992	2.8	52.0	2	1
Kinmen	2,793	1993–1997	2.9	48.1	8	5
KMIC	183,600	1992	4.0	37.0	104	10
Kounan Town	1,226	1987–1995	6.4	55.4	2	0
Melbourne	41,286	1990–1994	8.5	58.9	242	81
Miyama	1,078	1988–1990	6.6	55.8	1	1
Newcastle	5,934	1983–1994	9.0	50.2	103	34
Ohasama	2,240	1992–1993	4.1	63.8	6	1
Perth	10,230	1978–1994	14.4	48.3	141	54
Saitama	3,624	1986–1990	11.0	62.2	14	10
Seven Cities Cohorts	10,811	1987	2.7	54.5	44	40
Shanghai Factory Workers	9,347	1972–1978	14.0	30.6	69	17
Shibata	2,350	1977	20.0	57.7	30	37
Shigaraki Town	3,758	1991–1997	4.4	59.4	3	0
Shirakawa	4,643	1974–1979	17.5	54.3	28	17
Singapore Heart	2,325	1982–1997	14.6	49.0	23	8
Singapore NHS92	3,305	1992	6.2	51.8	17	5
Six Cohorts	19,387	1982–1986	9.0	46.7	19	8
Tanno/Soubetsu	1,984	1977	16.4	53.1	18	6
Tianjin	9,335	1984	6.1	51.3	45	51
Xi'an	1,695	1976	19.7	33.7	26	9
Yunnan	6,581	1992	4.5	3.1	18	0
Total	577,417	1961–1998	6.7	36.5	1989	926

all studies combined. There was evidence of an interaction between sex and both SBP and BMI in determining the risk of fatal CHD. Exclusion of the largest studies from these analyses ($n > 10,000$ individuals) did not alter any of the tests for interaction.

In both age-adjusted and study-adjusted analyses, SBP was more strongly associated with fatal CHD in women than in men, such that a 10 mm Hg increase in SBP was associated with a 35% increase in risk in women compared with a 20% increase in men. To ascertain whether this interaction was a consequence of competing risk with stroke,

we subsequently tested for a sex interaction between SBP and fatal stroke and observed a significant interaction ($p < 0.001$) such that an increase in blood pressure was more strongly associated with fatal stroke in men compared with women.

In unadjusted analyses, BMI was more strongly associated with fatal CHD in men, such that a 2-unit increase in BMI was associated with a 10% increased risk in men compared with 3% in women. After adjustment for SBP, cholesterol, and diabetes, the association between BMI and CHD was attenuated so that BMI was no longer an in-

TABLE 2. DISTRIBUTION OF VASCULAR RISK FACTORS

Variable ^a	Men			Women		
	n	Mean	95% CI	n	Mean	95% CI
Age (years)	366,569	45.4	45.3–45.4	210,848	46.3	46.2–46.3
SBP (mm Hg)	366,569	124.1	124.1–124.2	210,848	121.3	121.2–121.3
BMI (kg/m ²)	232,642	23.7	23.7–23.7	174,957	23.4	23.4–23.5
Total cholesterol (mmol/L)	214,446	5.06	5.06–5.07	158,721	5.10	5.10–5.11
Triglycerides (mmol/L)	49,203	1.58	1.57–1.59	44,505	1.30	1.29–1.31
Total cholesterol/HDL-C ratio	42,249	4.56	4.54–4.58	35,161	3.97	3.95–3.99
Diabetes (%)	208,634	7.7	7.5–7.7	153,076	3.6	3.5–3.7
Current smoking (%)	348,761	54.4	54.1–54.6	194,519	6.7	6.6–6.8

^aAll variables adjusted for age.

dependent predictor of CHD in women. This, however, may be due to overadjustment of intermediary variables that lie on the causal pathway between BMI and CHD (Table 3).

Figure 1 illustrates what proportion of the excess risk of CHD mortality in men vs. women is explained by each the risk factors alone and by all the risk factors combined. Cigarette smoking was the single largest contributor, explaining approximately 20% of the excess CHD risk, chiefly as a result of the vast difference in cigarette smoking rates (54% in men vs. 7% in women). Sex differences in the total cholesterol/HDL-C ratio, diabetes, and triglycerides explained 6%, 3%, and 2% of the excess risk, respectively. By comparison, adjustment for total cholesterol increased the HR in men relative to women, as a consequence of women having an overall higher age-adjusted mean total cholesterol level (Table 2). Similarly, adjustment for SBP also increased the HR despite the fact that, overall, the age-adjusted mean level of SBP was significantly greater in men than in women (Table 2). Rather, the increase in the HR, after adjusting for SBP, was due to its much stronger interaction with CHD in women compared with men. Simultaneous adjustment for all risk factors reduced the excess risk of fatal CHD in men compared with women by 23%.

DISCUSSION

Findings from this present study indicate that the strength of association between classic CHD risk factors, such as cigarette smoking, lipids and diabetes, with fatal CHD is similar in magnitude for both men and women. There was some evidence to suggest that a sex-specific interaction existed between SBP and fatal CHD. In this study, a 10 mm Hg increase in SBP was associated with a 35% increased risk of fatal CHD among women

but with only a 20% increased risk among men. However, this may be an artifact due to competing risks between stroke and CHD, as in this study, an increase in blood pressure was more strongly associated with the risk of incurring a fatal stroke in men than in women.

Few published reports have commented on the existence of sex differences in the associations between risk factors and CHD, with the exceptions of diabetes and smoking, which have been the subject of much debate in the literature. For example, a meta-analysis of 10 prospective cohort studies concluded that diabetes was more strongly associated with CHD risk in women than in men.¹⁴ However, a more recent meta-analysis of 8 prospective studies that had adjusted for other CHD risk factors concluded that the risk of CHD was similar in both sexes, RR 2.3 (95% CI 1.9–2.8) in men vs. 2.9 (95% CI 2.2–3.8) in women.⁶ In this current study, the RR of fatal CHD associated with diabetes tended to be greater in women than in men, although it was not significantly so, possibly because of the small number of fatal events among individuals with diabetes.

Findings from the current study suggest a trend toward increased CHD risk in women who smoked compared with male smokers, although the test for interaction with sex was not significant ($p = 0.29$). Women who smoke have been reported to have an approximate 50% increased risk of incurring a cardiovascular event compared with male smokers.^{2,4,15,16} In contrast, Jousilahti et al.,³ in a large prospective Finnish cohort, reported no sex interaction with smoking, as did the Renfrew-Paisley prospective cohort in Scottish adults.¹⁷ Two major limitations within the APCSC are the lack of information on duration of smoking and the limited information on the number of cigarettes smoked by individuals. Fur-

TABLE 3. UNADJUSTED AND ADJUSTED HRs^a AND 95% CIs RELATING VASCULAR RISK FACTORS WITH CHD MORTALITY IN MEN AND WOMEN

Risk factor	n	increase	Unit	Unadjusted						Adjusted					
				Women			Men			Women			Men		
				95% CI	HR	95% CI	p value ^b	n	HR	95% CI	HR	95% CI	p value ^b	95% CI	p value ^b
Cigarette smoking	543,280	Current vs. not		1.51	1.37–1.66	1.69	1.44–1.99	0.23	303,515	1.66 ^c	1.46–1.87	1.73 ^c	1.40–2.14	0.29	
SBP	577,417	10 mm Hg		1.27	1.22–1.32	1.38	1.32–1.44	0.002	303,515	1.20 ^d	1.14–1.26	1.35 ^d	1.28–1.43	0.0005	
BMI	407,599	2 kg/m ²		1.10	1.07–1.13	1.03	1.00–1.06	0.001	303,515	1.04 ^e	1.01–1.07	0.97 ^e	0.93–1.00	0.005	
Total cholesterol	373,167	1 mmol/L ^f		1.41	1.31–1.51	1.33	1.21–1.45	0.28	303,515	1.37 ^g	1.26–1.49	1.26 ^g	1.13–1.41	0.30	
Diabetes	361,710	Yes vs. No		1.85	1.55–2.20	2.23	1.73–2.88	0.28	303,515	1.77 ^h	1.47–2.13	2.00 ^h	1.47–2.72	0.61	
Log triglycerides ⁱ	93,708	0.55 mmol/L ^f		1.76	1.49–2.08	1.66	1.28–2.16	0.71	58,606	1.16 ^j	0.91–1.46	1.60 ^j	1.11–1.30	0.14	
Total cholesterol/HDL-C ratio	77,410	1.85 ^f		1.22	1.15–1.29	1.29	1.19–1.39	0.29	58,606	1.36 ^k	1.17–1.58	1.15 ^k	0.93–1.42	0.20	

^aHRs adjusted for age and stratified by study.

^bp value for interaction.

^cAdjusted for BSP, BMI, total cholesterol, and diabetes.

^dAdjusted for cigarette smoking, BMI, total cholesterol, and diabetes.

^eAdjusted for cigarette smoking, SBP, total cholesterol, and diabetes.

^fUnit increase for total cholesterol, log triglycerides, and total cholesterol/HDL-C ratio is equal to 1 SD.

^gAdjusted for cigarette smoking, SBP, BMI, and diabetes.

^hAdjusted for cigarette smoking, SBP, BMI, and total cholesterol.

ⁱLog triglycerides, natural log transformation of triglycerides.

^jAdjusted for cigarette smoking, SBP, BMI, diabetes, and total cholesterol/HDL-C ratio.

^kAdjusted for cigarette smoking, SBP, BMI, diabetes, and log triglycerides.

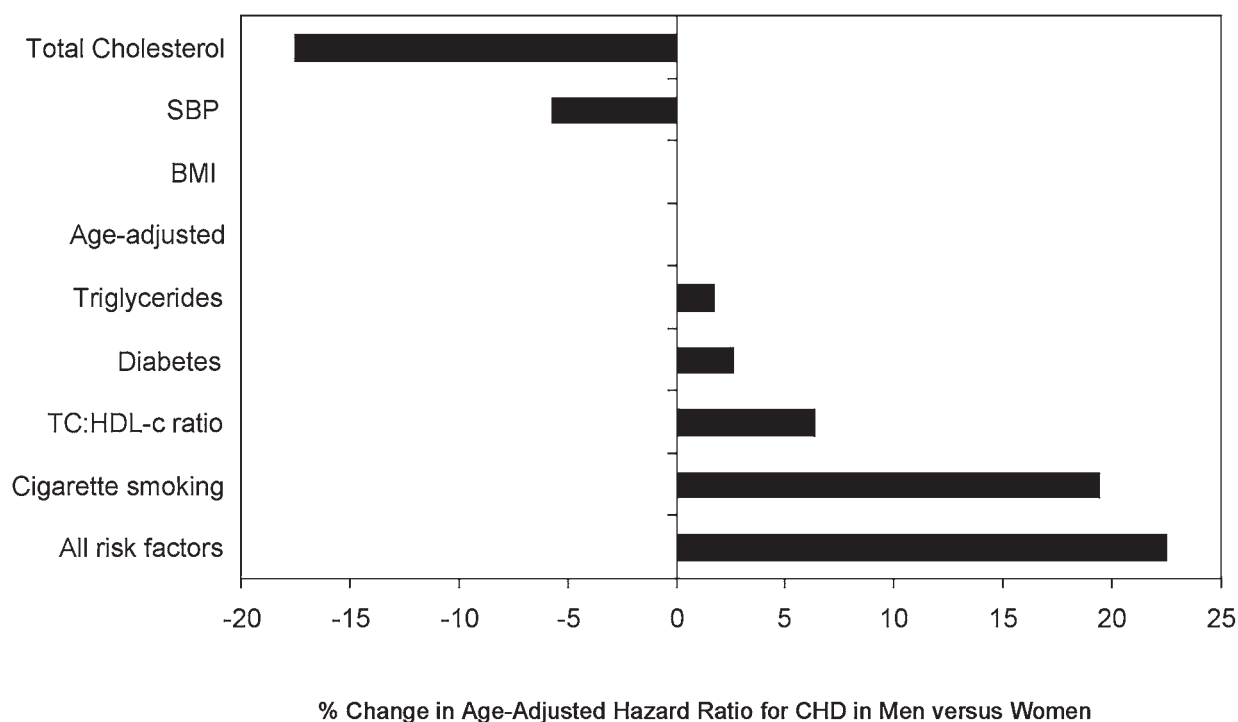


FIG. 1. Percentage of the age-adjusted CHD mortality HR for sex (men vs. women) explained by each of the risk factors alone and by all risk factors combined. (0% explained corresponds to the HR for sex adjusted for age only. All other adjustments also include age adjustment.)

ther analyses, exploiting this limited information, are reported elsewhere.¹⁸ In Asia, women have only recently started to smoke.¹⁹ Hence, it is probable that the RR of smoking in women obtained from these current analyses is likely to underestimate the true effect. Our finding that there was no sex differential associated with total cholesterol and HDL-C accords with the few other studies that have commented on the relationship.^{2,3}

In this current study, differences in levels of the classic cardiovascular risk factors explained nearly a quarter of the excess CHD risk in men compared with women. Of these, the sex difference in the rate of cigarette smoking was the single most important determinant of the excess CHD risk in men. Differences in the levels of triglycerides, diabetes, and the total cholesterol/HDL-C ratio explained only a small proportion of the excess risk. These findings contrast with those of Jousilahti et al.,³ who reported that a sex difference in the total cholesterol/HDL-C ratio and smoking explained most of the risk factor-associated excess CHD risk. However, Johnson²⁰ concluded that differences in smoking, total cholesterol, glucose intolerance, and blood pressure did not account for the observed sex difference in CHD risk within the Framingham cohort.

Because of a lack of data on the use of prescribed medication in study participants, we were unable to evaluate the impact on CHD risk of any treatment differences between men and women. Recent evidence suggests that women are undertreated compared with men with respect to cardiovascular risk factors. For example, in a recent study from Norway, only 35% of women with diabetes or cardiovascular disease were prescribed a statin compared with 45% of men with similar medical histories.²¹ Similar findings were reported from the United Kingdom Prospective Diabetes Study,²² where women with diabetes were significantly less likely to use aspirin compared with men. The consequence of any treatment bias that favors men would be to underestimate the contribution of classic risk factors to the sex differential.

A further limitation of APCSC is the lack of data on new and emerging CHD risk factors. It is possible that differences in the levels of novel risk factors, such as fibrinogen, C-reactive protein, and other inflammatory agents, may contribute to some of the excess CHD risk observed in men. Sex hormones may account for some of the sex differential in CHD risk. Prior to the menopause, at around the age of 50 years, women are at considerably lower risk of CHD compared with men, but

the sex difference in coronary risk gradually diminishes with increasing age,²³ possibly as a consequence of the postmenopausal decline in sex hormones.²⁴

CONCLUSIONS

In this large prospective database of studies from the Asia-Pacific region, only a small amount of the sex differential in CHD could be explained by differences in the prevalence of classic risk factors. Future studies are required to elucidate the mechanisms responsible for the attenuation of the age-related sex difference in CHD risk.

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