The Asia Pacific Cohort Studies Collaboration: A Decade of Achievements

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The Asia Pacific Cohort Studies Collaboration (APCSC) was established in the late 1990s when there was a distinct shortfall in evidence of the importance of risk factors for cardiovascular disease in Asia. With few exceptions, most notably from Japan, most of the published reports on cardiovascular disease in the last century were from Western countries, and there was uncertainty how far etiological associations found in the West could be assumed to prevail in the East. Against this background, APCSC was set up as a pooling project, combining individual participant data (about 600,000 subjects) from all available leading cohort studies (36 from Asia and 8 from Australasia) in the region, to fill the knowledge gaps. In the past 10 years, APCSC has published 50 peer-reviewed publications of original epidemiological research, primarily concerned with coronary heart disease, stroke, and cancer. This work has established that Western risk factors generally act similarly in Asia and in Australasia, just as they do in other parts of the world. Consequently, strategies to reduce the prevalence of elevated blood pressure, obesity, and smoking are at least as important in Asia as elsewhere—and possibly more important when the vast size of Asia is considered. This article reviews the achievements of APCSC in the past decade, with an emphasis on coronary heart disease.

The Asia Pacific Cohort Studies Collaboration (APCSC) was established at the end of the last century, when there was a plethora of high-quality evidence of the effects of several risk factors on cardiovascular disease (CVD) from Occidental populations, but scant evidence from Oriental populations [1]. This was despite CVD already being a leading cause of death in Asia. However, the pattern of CVD was, and still is, somewhat different in many Asian countries to European and North American countries. Stroke is often more common than coronary heart disease (CHD) in Asia, but not in the West, and the hemorrhagic—to—ischemic stroke rate ratio is typically higher in Asia. Furthermore, several established “Western” CVD risk factors were known to have very different distributions in Asia—for example, body mass index and cholesterol tend to be lower in Asia. So there were reasons to doubt that etiological associations confirmed, and CVD guidelines developed, in the West could be assumed for Asian populations. With the huge, and aging, populations in Asia, there was a clear need for reliable evidence on the effects of risk factors to inform policy makers in Asian countries and promote primary prevention of CVD and other noncommunicable diseases. However, the studies then completed, or

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underway, in Asia were not of a size (in terms of numbers of people or numbers of events) to provide the level of certainty required in estimates of association. Even where numbers were of reasonable size overall, they were not large enough to reliably evaluate sex- and age-specific effects.

Hence, APCSC was envisaged as a pooling project of existing studies with the remit to provide reliable evidence of the age-, sex-, and region-specific associations between classical Western risk factors and CHD, stroke, and other leading causes of death in the Asia-Pacific region. At the outset it was realized that a key output from the research would be a comparison of the associations between risk factors and diseases between the Western parts of the region (Australia and New Zealand: ANZ or Australasia) and Asia. In this way, ANZ could act as an exemplar of the West and thus allow East-West comparisons within a single platform.

THE STUDIES

Studies were eligible for inclusion in this project if they: had a study population from the Asia-Pacific region; used a prospective cohort study design; observed at least 5,000 person-years of follow-up; recorded dates of birth (or ages at baseline); recorded sex and blood pressure at baseline; and recorded dates of death (or ages at death), where appropriate. Studies were excluded if they: selected subjects on the basis of a positive disease history or diagnosis; or were judged to be of poor quality, after consultation with local experts.

Using these criteria, studies were identified by electronic searches and personal contacts, and principal investigators were invited to join by sharing their individual participant data on a range of baseline sociodemographic variables and risk factors, as well as events during follow-up. Ultimately this led to the inclusion of 44 studies, 16 from mainland China, 14 from Japan, 8 from Australia, 2 from Taiwan, 2 from Singapore, and 1 each from Hong Kong, New Zealand, South Korea, and Thailand. Unfortunately, no eligible study was found, or was willing to join, from the Indian subcontinent or the Pacific Islands. In addition to the basic requirements of providing data on potential risk factors at baseline and deaths during follow-up, 16 of the 44 studies additionally provided repeat post-baseline measurements of risk factors, 19 reported nonfatal strokes, and 16 reported nonfatal CHD events.

The study is directed by an executive committee with cross-regional coverage. Day-to-day management is undertaken through a secretariat at the George Institute in Australia.

PUBLICATIONS

To date, APCSC has published 52 peer-reviewed publications [1–52]. Apart from the initial protocol [1], all were published from 2003 to 2012. These can be grouped into papers that report (at least primarily) on the following: single risk factor associations for CVD [2–13,15,18–20,24,28,38,46,47,49,51]; interactions between modifiable risk factor associations for CVD [14,30,31,34,37,40,41,48,50]; the national prevalence of risk factors and attributable risks for CVD [17,23,25,29,35]; risk factor associations for cancer [21,26,27,32,36,42–45,52]; risk factors for other diseases (diabetes [16] and kidney [39]); and smoking and all-cause mortality [33]. This totals 50 primary research papers in the last decade. In addition, a profile of the study was published in 2006 [22].

METHODS

Every study has provided individual participant data, and analyses are performed taking all the data as a single entity (sometimes called a “1-step method” for meta-analysis). Compared with the 2-step method that is necessary when pooling published parameters, individual participant data has the advantage of allowing greater flexibility in model building, especially when interactions are included; conversely, it is less well suited to consideration of heterogeneity between studies. Associations between risk factors and outcomes are estimated using Cox proportional hazards models, stratified [53] by study and sex. All results are at least age-adjusted; most publications show results after adjustment for other risk factors that are potential confounders. Associations of all continuous variables are adjusted for regression dilution using information from repeat measures [53] from those studies within APCSC that have appropriate data. The floating absolute risk technique [53] is used to produce confidence intervals around the point estimates of hazard ratios. Typically, associations are estimated both after grouping the risk factor into ordinal groups, such as its quarters, and when taking the variable in its continuous form. Interactions between risk factors are tested by adding cross-multiplication terms to the Cox models. Results from Asia and ANZ are compared, again, by adding cross-multiplication terms (here, involving region) to Cox models. Attributable risks are estimated, by country, using nationally
representative (not APCSC) data for prevalence [17,23,25,29] or distributions [35] and APCSC data for estimated relative risks.

RESULTS

Altogether, APCSC includes 600,443 subjects, of whom almost 600,000 are aged 20 years or over (Table 1). The average levels of risk factors tend to be worse in ANZ than in Asia, except for smoking, which is more common in Asia; although this hides a huge differential between the sexes—smoking is typically common among men, but rare among women, in Asia [17]. As expected, the fatal stroke/CHD ratio is much higher in Asia (around 2:1) than in ANZ (around 1:3) and the fatal hemorrhagic/ischemic stroke ratio is also higher in Asia (around 2:1) than in ANZ (around 3:2).

Primary associations. Figure 1 shows age-adjusted associations for 6 leading risk factors for fatal CHD. Allowing for random error, the associations seen for all 6 risk factors are very similar in Asia and ANZ. Only for systolic blood pressure (SBP) was there evidence of an interaction ($P = 0.002$). For total cholesterol (TC), high-density lipoprotein cholesterol, triglycerides, and SBP, the relationship with fatal CHD was approximately log-linear, with a shallower slope for SBP in ANZ than in Asia. For body mass index (BMI), the shape of the relationship was clearly nonlinear in ANZ, in Asia, the same J-shape was suggested, but not as clearly. There was also a clear dose-response relationship for smoking status in both regions: never smokers having the least and current smokers the most risk of a fatal CHD.

The hazard ratio for diabetes compared with no diabetes was, similarly, much the same (around 2) for both subregions ($p$ for interaction $= 0.42$). Multiple adjusted results showed much the same similarities, with the same exception of a significant difference for SBP between regions [11].

Interactions between risk factors. The APCSC papers on interactions between the major modifiable cardiovascular risk factors, published to date, have reported on the joint risks for CHD and stroke for all but one of the 10 2-way combinations of BMI, diabetes, smoking, SBP, and TC. As above, here only results for CHD will be summarized.

In 5 (diabetes and BMI [48], diabetes and smoking [41], diabetes and SBP [31], diabetes and TC [30], SBP and smoking [34]) of the 9 combinations studied, there was no evidence ($P > 0.10$) of (multiplicative) interaction. Hence, when any of these 2-way combinations of risk factors are taken together, the APCSC results suggest that the effect of one risk factor can broadly be assumed to act the same whatever the level of the other risk factor. All the same, having a combination of 2 “bad” levels always appears to be worse than having just a single bad level.

In 2 combinations of risk factors (smoking and BMI [40], smoking and TC [37]), there was

| Table 1. Summary statistics for APCSC participants aged 20 years or more |
|-----------------------------|-----------------------------|
|                             | Asia (n = 500,819) | Australia and New Zealand (n = 98,790) |
| Baseline variables          |                             |
| Women, %                    | 33.7                       | 45.7                       |
| Age, yrs (range)            | 45.0 ± 9.5 (20–107)        | 53.2 ± 14.4 (20–104)       |
| Systolic blood pressure, mm Hg | 121.3 ± 17.7             | 136.9 ± 22.1              |
| Diastolic blood pressure, mm Hg | 77.7 ± 10.7              | 79.2 ± 12.7               |
| Total cholesterol (mmol/l)  | 4.9 ± 0.98                 | 5.6 ± 1.13                |
| HDL cholesterol (mmol/l)    | 1.35 ± 0.38                | 1.45 ± 0.38               |
| Triglycerides (mmol/l)      | 1.44 ± 1.04                | 1.41 ± 1.07               |
| Body mass index, kg/m²      | 22.9 ± 2.9                 | 26.3 ± 4.3                |
| Smoking, %                  | 41.6                       | 17.6                       |
| Diabetes, %                 | 3.4                        | 4.2                        |
| Number of deaths (median follow-up) | (6.1 yrs) | (8.3 yrs)               |
| Total                       | 17,648                     | 7,897                      |
| CHD                         | 1,341                      | 1,855                      |
| Stroke*                     | 2,851                      | 613                        |
| Hemorrhagic stroke          | 1,276                      | 114                        |
| Ischemic stroke             | 591                        | 79                         |

Values are mean ± SD unless otherwise indicated. CHD, coronary heart disease; HDL, high-density lipoprotein.
* Many strokes were not classified by subtype.
evidence of synergism. Among current smokers there was a 13% higher risk of CHD associated with a 2 kg/m² higher level of BMI compared with a 9% additional risk amongst nonsmokers ($P = 0.04$ for the interaction). Similarly, among current smokers there was a 54% higher risk of CHD for a 1-SD (1.06 mmol/l) higher level of TC compared with a 38% additional risk for nonsmokers ($P = 0.02$ for the interaction). Hence, concurrent smoking seems to exacerbate the ill effects of high levels of both adiposity and blood cholesterol level. If this is more widely true, it suggests that application of standard cardiovascular risk scores may underestimate risk for smokers. A corollary is that quitting smoking with either lowering of SBP or better control of lipids may have even greater benefit than would be expected from past projections.
In the final 2 cases (SBP and BMI [50], SBP and TC [14]), there was evidence of antagonism. The effects of SBP on CHD, although always substantial and log-linear, tended to diminish as BMI increased ($P = 0.01$ for the interaction). For example, a 10-mm Hg higher SBP was associated with a 27% higher risk among people with “healthy” BMI (18.5 to 22.9 kg/m$^2$) compared with a 17% higher risk among overweight people (BMI: 25 to 29.9 kg/m$^2$). Similarly, the log-linear effects of SBP diminished systematically as TC level increased ($P < 0.001$ for the interaction). For example, a 10-mm Hg higher SBP was associated with a 34% higher risk among those with TC $<$ 4.75 mmol/l compared with 21% among those with TC $>$ 6.25 mmol/l. Thus, though not undermining the importance of these risk factors, this suggests that when the effects of SBP are considered along with either BMI or TC, some allowance should be made for mutual attenuation of effects.

Comparison of these contrasting results should take account of the relatively low power when tests are performed on dichotomous variables, such as diabetes and smoking. More generally, although APCSC has a large sample, which allows us to reliably examine the effect modification of one risk factor on another, it is still not large enough for more detailed analyses of interactions involving more than two risk factors or to reliably compare the interaction effects of modifiable risk factors across region, age, or sex groups. Furthermore, unlike in Figure 1, fatal and nonfatal events were combined in the analyses testing interactions to increase the available power. With more data, reliable conclusions for 2-way interactions would be possible for fatal CHD, and fatal stroke, alone.

**Attributable risk.** Figure 2 shows estimates of attributable risks (AR) for CHD, hemorrhagic and ischemic stroke mortality for 8 selected countries in the Asia-Pacific region, and 3 selected risk factors, using the most recent national data available when the APCSC papers were published (2006/2007). Blood pressure is an especially strong determinant of both the major stroke subtypes, but most particularly...
hemorrhagic stroke, which has AR approaching 50% in some countries. Differences between countries were not great, reflecting the widespread importance of high blood pressure for all CVD across the entire Asia-Pacific region. For overweight or obesity (BMI of 30 kg/m² or more), ARs were smaller for hemorrhagic stroke than for either CHD or ischemic stroke, and both Australia and New Zealand had much higher ARs than any Asian country for which data were available. As already noted, the prevalence of smoking for men is much higher than for women in many Asian countries; hence, ARs are presented here separately for women and men. Due to these differences in prevalence in Asia, and the contrasting situation in ANZ where the prevalence of smoking is very similar between sexes, the pattern of AR by country goes in opposite directions by sex. For women, ARs are higher in ANZ than in Asia, but for men they are lower. Hemorrhagic stroke has lower ARs due to smoking than those for CHD or ischemic stroke; the AR for the latter pair are broadly similar.

**DISCUSSION**

This synopsis has reviewed some of the previously published results from APCSC, with a particular focus on CHD. Further details are available from the published papers. After a decade of research, APCSC has a considerable portfolio of results and recommendations that have been influential in setting national guidelines and have contributed results to international forums, such as the World Health Organization’s Global Burden of Disease study [54] and the Institute of Medicine’s initiative to improve global cardiovascular health [55]. The research has not only greatly extended knowledge of chronic disease risk factors in Asia, but also has produced more precise estimates of the effects of some risk factors than had previously been available, for example, on triglycerides [7]. Due to the relatively low incidence in Western populations, risk factors for stroke, and particularly hemorrhagic stroke, have not been studied as thoroughly as CHD has been. The Asian studies in APCSC had a high frequency of stroke events; thus, APCSC has contributed importantly to epidemiological knowledge about stroke and its risk factors.

Moreover, in addition to producing valuable region-specific estimates of associations between risk factors and chronic disease, the large number of women (well over 200,000) included in the collaboration has enabled us to reliably explore sex differences in the relationships between risk factors and outcomes. For example, several papers have shown higher relative risks associated with diabetes and cigarette smoking for CHD and other chronic conditions in women than in men. The APCSC findings have contributed to the growing body of evidence suggesting that there are fundamental sex-differences in how certain risk factors exert their effects on subsequent chronic disease risk [56,57].

APCSC has, undoubtedly, been a trendsetting project. APCSC researchers are based in 9 countries or regions, speak at least 5 major primary languages, and are from several professions—predominantly clinical, statistical, and epidemiological. It is a tribute to all concerned that such a disparate group of researchers has collaborated so successfully and achieved so much in a comparatively short space of time. Perhaps most importantly, the APCSC has been an important focus for the training of Asian researchers. APCSC workshops have been held in China, South Korea, and Hong Kong and have been attended by students and healthcare professionals from the region that sought to benefit from an intensive course in cardiovascular epidemiology. These courses focused on the innovative statistical methods used in APCSC, including modern methods in meta-analysis. Furthermore, APCSC still has valuable, yet-untapped, resources with extensive data on risk factors, such as alcohol consumption and socioeconomic status, yet to be analyzed. An extensive program of future research has been mapped out to include greater use of the data as a practical basis for the evaluation of contemporary methodology in biostatistics, for example, continuing the use of these data to compare methods for missing value imputation [58].

APCSC is not, however, without its drawbacks, most of which stem from the use of existing datasets. First, many of the cohorts began in the 1980s; CVD treatment and risk factor profiles have changed considerably in the many Asian countries that are undergoing economic and epidemiological transitions. Second, reporting of risk factors is not always consistent, both in terms of coverage (high-density lipoprotein cholesterol, for example, is only recorded in 25 of the 44 cohorts) and methodology. This is a particular problem when analyzing nonclinical variables, such as alcohol and social class, which are recorded differently in different geo-ethnic populations. Third, repeat measurements are only available from a minority of cohorts; even then, the frequency of remeasurement is not consistent, so that only limited longitudinal analyses are possible. Fourth,
only one study had a biobank available for use by the collaboration, so we have been unable to reliably analyze novel biomarkers, such as C-reactive protein. Fifth, outcomes were recorded in several different ways, including by contacting subjects, or their relatives, and record linkage. Lack of information on nonfatal outcomes from many cohorts lowered statistical power and could have introduced bias when all events were pooled in some analyses. The level of disaggregation in cause of death also varies. Most studies used International Classification of Diseases (ICD) codes, but without consistency in which version was used, and although we were able to harmonize all coding to ICD-9, this could also have introduced a degree of bias in estimation. Differential diagnoses are a particular problem for subtyping stroke; for instance, not all studies had access to imaging.

To solve some of these problems, a new Asian collaboration in CVD, LIFECARE (Life Course Study in Cardiovascular Disease Epidemiology) [59], has been formed, involving longitudinal studies in 4 countries. This has a common set of questions and scheduled repeat recording of risk factor levels, as well as a biobank. However, it remains to be seen whether funding will allow hard outcomes to be collected, and, if so, whether follow-up will be long enough to obtain precise estimates. Perhaps the future lies more in using routinely collected health system data to draw epidemiological inferences. In this respect, Asia could lead the world with the existing huge medical insurance databases in South Korea that have already been used for epidemiological analyses (the Korean Heart Study; paper submitted) and Taiwan (the Taiwan MJ Health study) [60].

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