

COHORT PROFILE

Cohort profile: the Asia Pacific Cohort Studies Collaboration

M Woodward,¹ F Barzi,¹ A Martiniuk,¹ X Fang,² DF Gu,³ Y Imai,⁴ TH Lam,⁵ WH Pan,⁶ A Rodgers,⁷ I Suh,⁸ SH Jee,⁹ H Ueshima¹⁰ and R Huxley^{1*}

How did the study come about?

Although less well recognized than in the West, cardiovascular disease (CVD) is the leading cause of disease in Asia. This is despite known differences in the distribution of risk factors for CVD in Asia, compared with Europe and North America, such as lower average total cholesterol and body mass index (BMI). The nature of CVD also tends to be different in Asia, where there are more strokes than coronary heart disease (CHD) events, and strokes are more often haemorrhagic than ischaemic, compared with the West.

By 1999 the knowledge gap in Asia was a clear impediment to progress in treating and preventing CVD in the continent. Most of the existing studies from Asia were of small size or short duration and, thus, could not provide reliable information as to the way risk factors, well-researched in the West, act upon CVD in Asia. A notable exception was the Eastern Stroke and CHD Collaborative Project,¹ which had studied the effects of diastolic blood pressure and total cholesterol on the risk of stroke and coronary disease in China and Japan. This was the starting point for the Asia Pacific Cohort Studies Collaboration (APCSC),² which extended the scope of the Eastern Project in several important ways. APCSC covers a wider geographical area, including studies from Australia and New Zealand (ANZ), which provide a 'Western' comparison group, as well as increasing numbers for certain pooled analyses. It uses individual participant, rather than summary, data, which

allows for more flexible analyses. Also, it collects data on several risk factors for CVD, not just blood pressure and total cholesterol, and records all deaths, including those due to non-cardiovascular causes.

Initial funding was provided by the New Zealand Health Research Council and the Australian National Health and Medical Research Council (NHMRC). Twin Secretariats for APCSC were established at the Clinical Trials Research Unit at the University of Auckland, New Zealand and The George Institute for International Health at the University of Sydney, Australia. In later years, Pfizer Inc. of New York provided two substantial unrestricted educational grants to APCSC. Current funding is a mixture of pharmaceutical industry funding (Pfizer), peer reviewed research council funding (NHMRC; through a programme grant), and university funding (a University of Sydney cancer research award). The Secretariat and database are now solely housed within The George Institute.

What does it cover?

The primary aims of APCSC are to determine the age-specific, sex-specific, and region-specific (Asia and ANZ) associations of major cardiovascular risk factors with

- stroke (fatal and non-fatal, ischaemic and haemorrhagic),
- CHD (fatal and non-fatal),
- total CVD.

Secondary outcomes are

- all-cause mortality and
- other major causes of death (e.g. cancer).

The primary analytical method is to use Cox proportional hazard regression models, adjusted for age and stratified by study (and where appropriate, sex) to calculate hazard ratios and confidence intervals. Continuous variables are adjusted for regression dilution error.²

Who is in the sample?

Studies are eligible for inclusion in APCSC if they are based in the Asia Pacific region, use a cohort study design, and have at least 5000 person-years of follow-up. Individuals within each study are included if they have recordings, at baseline, of date of birth (or age), sex and blood pressure, and have vital status known at the end of follow-up, together with date of death (or the age at death) where applicable. Cohorts selected on the basis of a positive disease history, or diagnosis, are excluded.

¹ The George Institute, University of Sydney, Australia.

² Department of Epidemiology and Social Medicine, Xuanwu Hospital, Capital Medical University, China.

³ Department of Evidence Based Medicine, Fuwai Hospital & CVD Institute, Chinese Academy of Medical Science & Peking Union Medical College, China.

⁴ Department of Clinical Pharmacology and Therapeutics, Tohoku University, Japan.

⁵ Department of Community Medicine, The University of Hong Kong, Hong Kong.

⁶ Institute of Biomedical Sciences, Academia Sinica, Taiwan.

⁷ Clinical Trials Research Unit, University of Auckland, New Zealand.

⁸ Department of Preventive Medicine, Yonsei University College of Medicine, Korea.

⁹ Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Korea.

¹⁰ Department of Health Science, Shiga University of Medical Science, Japan.

* Corresponding author. The George Institute, University of Sydney, Australia. E-mail: rhuxley@george.org.au

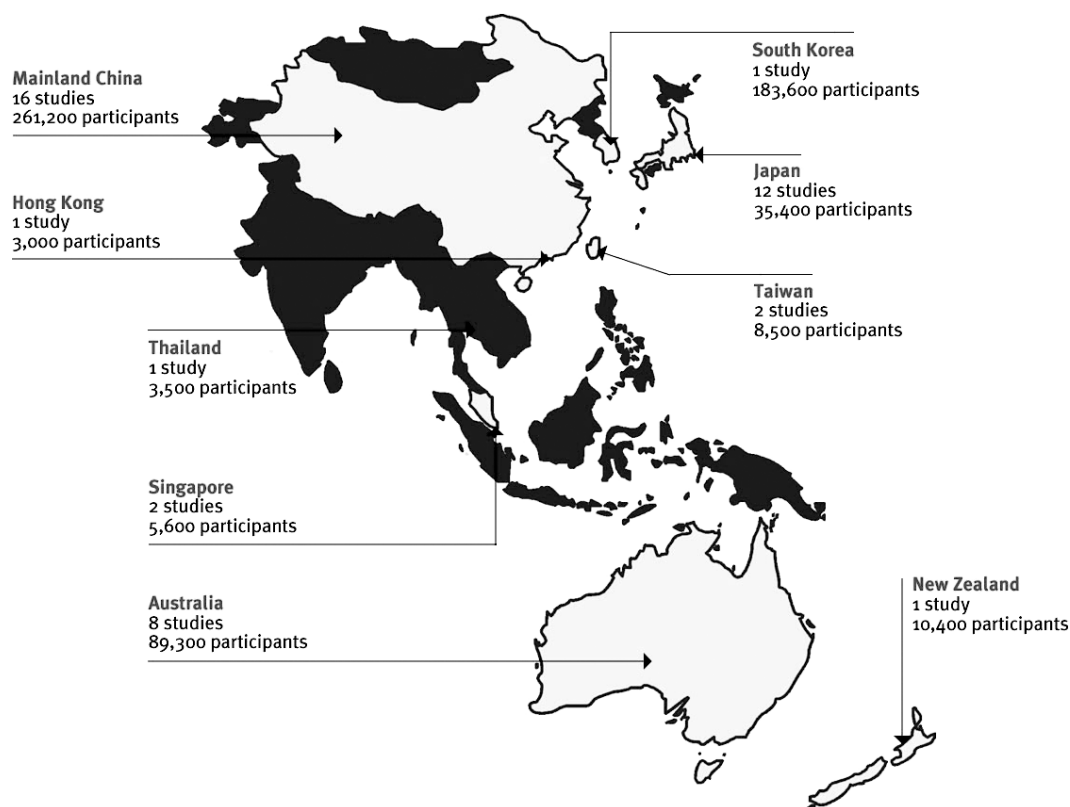


Figure 1 Map showing studies in the Asia Pacific Cohort Studies Collaboration

Studies were identified by a range of methods, including searches of electronic databases (MEDLINE and EMBASE), scrutiny of abstracts and proceedings of meetings, and by personal enquiry among collaborators and colleagues. For each identified eligible study, the principal investigators (PIs) were invited to participate. Figure 1 shows the distribution of studies included in the APCSC database at the time of the third datalock, in April 2006 (previous datalocks were in 2000 and 2003). Study names, and names of PIs, are given in the acknowledgements; this includes two studies that have agreed to join APCSC but have yet to qualify according to the entry criteria. The studies in Figure 1 are the only ones included in the remainder of this article.

How often have they been followed-up?

APCSC studies are free to contribute whatever data they like to the Collaboration. Of the 44 studies, 28 have only provided baseline data; 16 have additionally provided data on one repeat enumeration and six have contributed more than one repeat set of measurements, up to a maximum of seven repeats. The median follow-up is 6.7 years and the longest follow-up of any individual, not yet deceased, is 36 years.

What has been measured?

Baseline

As the primary outcomes in this collaboration are cardiovascular, the baseline risk factors collected are all the

well-established risk factors for CVD. Table 1 gives a list of these risk factors, with numbers of individual data points. Methods used to measure risk factors varied; for instance 13 studies gave glucose from fasting samples and six from non-fasting. Wherever possible, methods and classifications were standardized. Several studies provided further variables, such as social classifications and ethnicity, but these were not consistently reported and are not amenable for analyses.

Repeat values

Values from repeat sampling have been provided for many continuous measures: the number of individuals with repeat measures for blood pressure = 48 113, total cholesterol ($n = 21\ 575$), HDL-cholesterol ($n = 7629$), triglycerides ($n = 10\ 734$), BMI ($n = 21\ 305$), and glucose ($n = 4396$). The median time to resampling was 3 years. From these data, regression dilution coefficients were calculated² using the MacMahon-Peto non-parametric method.^{2,3} These were 1.9 for systolic blood pressure, 2.1 for diastolic blood pressure, 1.7 for total cholesterol, 1.9 for HDL-cholesterol, 1.8 for triglycerides, 1.2 for BMI, and 1.6 for glucose.

Outcomes

Data on deaths were available for every study participant, according to the entry criteria. Figure 2 shows the underlying cause of death (taken as the sole cause of death in APCSC), where available. Different studies used different methods of coding, such as various incarnations of the International

Table 1 Numbers of observations for each variable, age range, and percentage female, by region, Asia Pacific Cohort Studies Collaboration

	Asia	ANZ	All
Total	513 022	87 421	600 443
Blood pressure			
Systolic	513 022	87 421	600 443
Diastolic	513 022	87 421	600 443
Heart rate	58 629	54 052	112 681
Tobacco			
Current cigarette smoking	478 875	87 283	566 158
Other tobacco smoking	28 669	24 628	53 297
Years of smoking cigarettes	96 790	10 190	106 980
Alcohol			
Current drinking	471 158	82 697	553 855
Lipids			
Total cholesterol	295 868	84 615	380 483
Triglycerides	79 886	18 588	98 474
High density lipoprotein cholesterol	56 161	24 162	80 323
Low density lipoprotein cholesterol	10 717	2896	13 613
Glucose	214 819	50 526	265 345
Anthropometric			
Hip	8270	29 013	37 283
Waist	8306	25 548	33 854
Weight	344 448	86 467	430 915
Height	424 736	86 064	510 800
BMI	343 498	86 035	429 533
Medical history			
Coronary disease	111 966	87 092	199 058
Stroke	114 104	81 378	195 482
Diabetes	100 240	82 336	182 576
Medications			
Cholesterol-reducing	13 902	19 592	33 494
Blood pressure-reducing	59 964	69 587	129 551
Ethnicity	42 069	67 682	109 751
Education level	235 709	74 634	310 343
Occupation	197 676	13 587	211 263
% Female ^a	35.7	45.3	35.7
Age range ^a	20–107	20–104	20–107

^a Age and sex were recorded for everyone.

Classification of Diseases (ICD). Indeed, studies may have used different ICD codes in different periods. Some studies used rather broader classifications than others; hence, the proliferation of unknown classifications at lower levels in Figure 2. Cause of death was unknown, or unreported, in 1021 (4%) of cases. Non-fatal events were requested for stroke (provided by 19 cohorts) and CHD (16 cohorts). Non-fatal stroke events by subtype were reported by 17 cohorts. Methods for obtaining information on non-fatal events differed across the studies but

was mainly due to either self-report in repeat questionnaires or by review of medical records.

What has it found? Key findings and publications

At the time of writing, 21 papers have been published, or are about to be published, from APCSC, while more than a dozen further papers are in various stages of processing. The latter, unpublished research, includes reports on cancer outcomes. Published papers have shown that all the major cardiovascular risk factors work at least as strongly in Eastern as in Western populations.⁴ Given the enormous size of the populations concerned, this result is important, since it implies that Western research and treatment regimens have relevance in Asia. Policies for prevention must, however, be specific to the populations, given the cultural differences even within Asia. Blood pressure seems to be a key risk factor for stroke and CHD in Asia, with hazard ratios, after adjusting for other risk factors, that are considerably greater than those in ANZ.⁴ APCSC has shown that blood pressure,⁵ cholesterol,⁶ and glucose⁷ have log-linear relationships with CHD; results that often only become clear with large datasets. Most risk factors for CVD have been found to have greater hazard ratios in younger age groups and to work similarly between the sexes. An exception to the latter is diabetes; in this case APCSC data have helped to provide conclusive evidence of higher coronary relative risks in women.⁸

What are the main strengths and weaknesses?

The great strengths of APCSC include the large amount of raw data and the strong collaboration, involving several ethnic groups. Day-to-day management is undertaken by a dedicated group in Sydney and the project is overseen by an Executive Committee, an elected representative group from across the countries involved. Three meetings of the entire collaboration have been held so far, as well as extra meetings of the Executive Committee. Some of the current funding has been used to hold a training workshop in Korea, with further funding earmarked for two similar workshops in China and Taiwan. Research publications are published in the name of the Collaboration, with writing committees that include representatives from across the geographical spread of APCSC. Language difficulties in China have been addressed by translating key documents, such as the regular APCSC newsletters, while five of the publications have been translated and submitted for re-publication in a Chinese medical journal. An APCSC website has been set up, with many special features available only to the collaborators. All these factors have helped maintain such a diverse collaboration for several years.

The main weaknesses of APCSC relate to non-standardization of data collection methods. All the cohorts were begun before the Collaboration was initiated, without a common protocol. This has the potential to introduce bias when analysing continuous exposure variables, particularly when comparing subgroups that may be unequally distributed

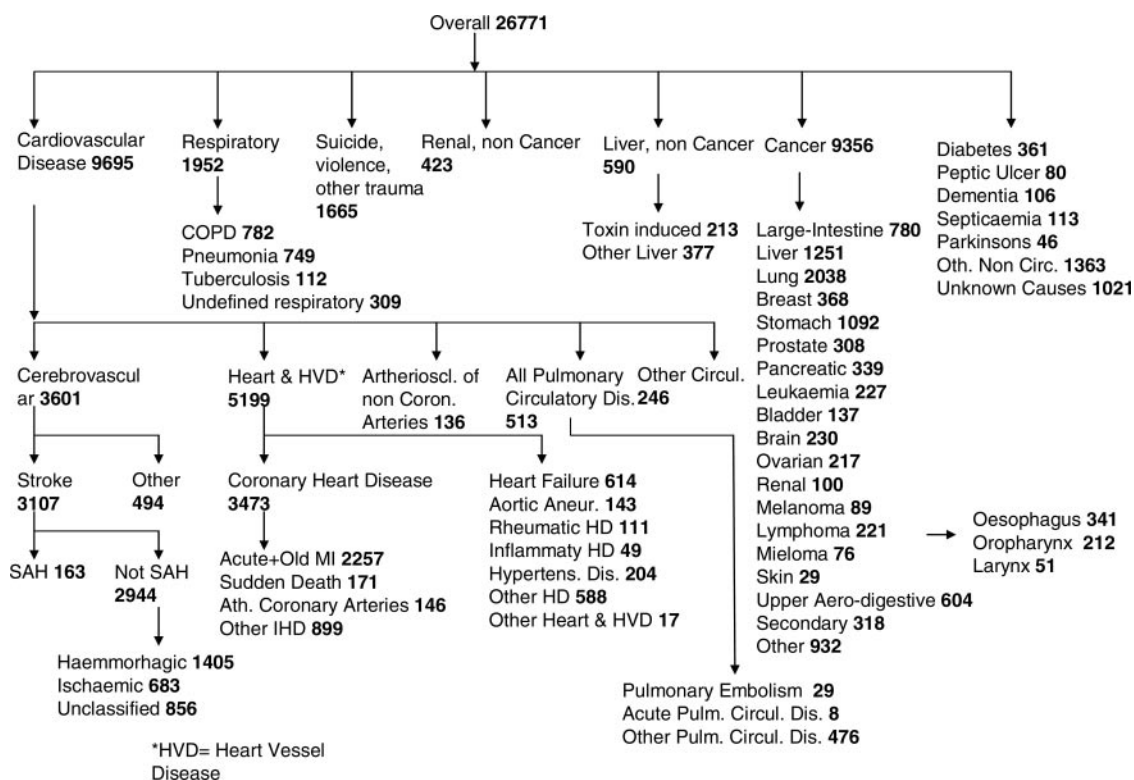


Figure 2 Fatal events, by cause, recorded in the Asia Pacific Cohort Studies Collaboration

amongst the studies and makes analysis of categorical variables crude or impractical. Outcome variables have similar issues; for example, stroke subtypes are not always reported, are verified using different techniques in different studies (or at different times within the same study), and either do or do not include non-fatal events. Pooling studies with outcome data of such different quality and quantity requires assumptions, which may not always be well-founded.

Can I get hold of the data? Where can I find out more?

The data are held by the Sydney Secretariat and are not available for use by outsiders, including the sponsors. Members of the Collaboration who wish to work on the data have to do so in Sydney, having obtained prior approval from the Executive Committee. Further details on APCSC, including a full list of publications, are available from the Website: www.apcsc.info.

Acknowledgements

APCSC is sponsored by Pfizer Inc., the NHMRC, and the University of Sydney. Thanks to Konrad Jamrozik for his corrections to an earlier version of this article. Any remaining errors are the responsibility of the authors. APCSC executive committee: M. Woodward, X. Fang, D.F. Gu, Y. Imai, T.H. Lam, W.H. Pan, A. Rodgers, I. Suh, H.J. Sun, H. Ueshima. APCSC participating studies and principal investigators: Aito

Town: A. Okayama, H. Ueshima; H. Maegawa; Akabane: M. Nakamura, N. Aoki; Anzhen02: Z.S. Wu; Anzhen: C.H. Yao, Z.S. Wu; Australian Longitudinal Study of Aging: G. Andrews; Australian National Heart Foundation: T.A. Welborn; Beijing Aging: Z. Tang; Beijing Steelworkers: L.S. Liu, J.X. Xie; Blood Donors' Health: R. Norton, S. Ameratunga, S. MacMahon, G. Whitlock; Busselton: M.W. Knuiman; Canberra-Queanbeyan: H. Christensen; Capital Iron and Steel Company: X.G. Wu; CISCH: J. Zhou, X.H. Yu; Civil Service Workers: A. Tamakoshi; CVDFACTS: W.H. Pan; East Beijing: Z.L. Wu, L.Q. Chen, G.L. Shan; Electricity Generating Authority of Thailand (EGAT) and EGAT2: P. Sritara; Fangshan: D.F. Gu, X.F. Duan; Fletcher Challenge: S. MacMahon, R. Norton, G. Whitlock, R. Jackson; Guangzhou: Y.H. Li; Guangzhou Occupational: T.H. Lam, C.Q. Jiang; Hisayama: M. Fujishima, Y. Kiyohara, H. Iwamoto; Hong Kong: J. Woo, S.C. Ho; Huashan: Z. Hong, M.S. Huang, B. Zhou; Kinmen: J.L. Fuh; Konan: H. Ueshima, Y. Kita, S.R. Choudhury; KMIC: I. Suh, S.H. Jee, I.S. Kim; Melbourne: G.G. Giles; Miyama: T. Hashimoto, K. Sakata; Newcastle: A. Dobson; Ohasama: Y. Imai, T. Ohkubo, A. Hozawa; Perth: K. Jamrozik, M. Hobbs, R. Broadhurst; Saitama: K. Nakachi; Seven Cities: X.H. Fang, S.C. Li, Q.D. Yang; Shanghai Factory Workers: Z.M. Chen; Shibata: H. Tanaka; Shigaraki Town: Y. Kita, A. Nozaki, H. Ueshima; Shirakawa: H. Horibe, Y. Matsutani, M. Kagaya; Singapore Heart: K. Hughes, J. Lee; Singapore NHS92: D. Heng, S.K. Chew; Six Cohorts: B.F. Zhou, H.Y. Zhang; Tanno/Soubetsu: K. Shimamoto, S. Saitoh; Tianjin: Z.Z. Li, H.Y. Zhang; Western Australia AAA Screenees: P. Norman, K. Jamrozik; Xi'an: Y. He, T.H. Lam; Yunnan: S.X. Yao.

References

- ¹ The Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998;**352**:1801–07.
- ² Woodward M. *Epidemiology: Study Design and Data Analysis*. 2nd edn. Boca Raton, FL: Chapman and Hall/CRC Press, 2005.
- ³ MacMahon S, Peto R, Cutler J *et al*. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;**335**:765–74.
- ⁴ Asia Pacific Cohort Studies Collaboration. A comparison of the associations between risk factors and cardiovascular disease in Asia and Australasia. *Eur J Cardiovasc Prev Rehabil* 2005;**12**:484–91.
- ⁵ Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003;**21**:707–16.
- ⁶ Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease and stroke in the Asia Pacific region. *Int J Epidemiol* 2003;**32**:563–572.
- ⁷ Asia Pacific Cohort Studies Collaboration. Blood glucose and the risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care* 2004;**27**:2836–42.
- ⁸ Huxley R, Barzi F, Woodward M. The impact of type-2 diabetes on coronary risk differs by sex: a meta-analysis of 37 prospective cohort studies. *BMJ* 2006;**332**:73–77.