

# Cholesterol, coronary heart disease, and stroke in the Asia Pacific region

Asia Pacific Cohort Studies Collaboration

Accepted 17 January 2003

**Background** Cholesterol levels in many Asian countries are rising. Predictions of the likely effects of this on the incidence of cardiovascular diseases have mostly relied on data from Western populations. Whether the associations between total cholesterol and cardiovascular diseases are similar in Asia is not established.

**Methods** The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual-participant data meta-analysis of prospective studies from the Asia-Pacific region. Cox models were applied to the combined data from 29 cohorts to estimate the region-, sex-, and age-specific hazard ratios of major cardiovascular diseases by the fifths of total cholesterol.

**Results** At baseline, the age/sex-adjusted mean value of total cholesterol was higher in Australia and New Zealand (ANZ) ( $5.52 \pm 1.05$  mmol/l) than in Asia ( $4.87 \pm 1.05$  mmol/l). During 2 million person-years of follow-up among 352 033 individuals, 4841 cardiovascular deaths were recorded. The association of total cholesterol with coronary heart disease and stroke was similar in Asian and ANZ cohorts. Overall, each 1-mmol/l higher level of total cholesterol was associated with 35% (95% CI: 26–44%) increased risk of coronary death, 25% (95% CI: 13–40%) increased risk of fatal or non-fatal ischaemic stroke, and 20% (95% CI: 8–30%) decreased risk of fatal haemorrhagic stroke.

**Conclusions** In both Asian and non-Asian populations in the Asia-Pacific region, total cholesterol is similarly strongly associated with the risk of CHD and ischaemic, but not haemorrhagic, stroke. Rising population-wide levels of cholesterol would be expected to contribute to a substantial increase in the overall burden of cardiovascular diseases in this region.

**Keywords** Cholesterol, coronary heart disease, ischaemic stroke, haemorrhagic stroke, cardiovascular diseases, Asia-Pacific

*Writing Committee:* X Zhang, A Patel, H Horibe, Z Wu, F Barzi, A Rodgers, S MacMahon, M Woodward. *Executive Committee:* D Bennett, D Gu, H Horibe, S MacMahon, W Pan, A Rodgers, I Suh, H Ueshima, M Woodward, Z Wu, X Zhang. *Statistical Analyses:* F Barzi, D Bennett, V Parag, M Woodward. *Participating studies and principal collaborators in APCSC:* *Aito Town:* A Okayama, H Ueshima, H Maegawa; *Akabane:* N Aoki, M Nakamura, N Kubo, T Yamada; *Anzhen02:* ZS Wu; *Anzhen:* CH Yao, ZS Wu; *Beijing Steelworkers:* LS Liu, JX Xie; *Blood Donors' Health:* R Norton, S Ameratunga, S MacMahon, G Whitlock; *Busselton:* MW Knuiman; *Canberra-Queanbeyan:* H. Christensen; *Guangzhou:* YH Li; *CISCH:* J Zhou, XH Yu; *Capital Iron and Steel Company:* XG Wu; *Civil Service Workers:* A Tamakoshi; *East Beijing:* ZL Wu, LQ Chen, GL Shan; *Fangshan Farmers:* DF Gu, XF Duan; *Fletcher Challenge:* S MacMahon, R Norton, G Whitlock, R Jackson; *Guangzhou Occupational:* TH Lam, CQ Jiang; *Hisayama:* M Fujishima, Y Kiyohara, H Iwamoto; *Hong Kong:* J Woo, SC Ho; *Huashan:* Z Hong, MS Huang, B Zhou; *Kinmen:* JL Fuh; *Konara:* H Ueshima, Y Kita, SR Choudhury; *KMIC:* I Suh, SH Jee, IS Kim; *Melbourne Cohort:* 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:* XH Fang, SC Li, QD Yang; *Shanghai Factory Workers:* ZM Chen; *Shibata:* H Tanaka;

Data from observational studies<sup>1–6</sup> and clinical trials of lipid-lowering therapy<sup>7–10</sup> have provided reliable evidence regarding the importance of serum cholesterol level as a determinant of coronary heart disease (CHD) risk in mainly Caucasian populations from Europe, North America, Australia, or New Zealand. This has resulted in widespread efforts to reduce population levels of cholesterol, as well as to treat individuals at high risk

*Shigaraki:* Y Kita, A Nozaki, H Ueshima; *Shirakawa:* H Horibe, Y Matsutani, M Kagaya; *Singapore Heart Study:* K Hughes, J Lee; *Singapore 92:* D Heng, SK Chew; *Six Cohorts:* BF Zhou, HY Zhang; *Tanno/Soubetsu:* K Shimamoto, S Saitoh; *Tianjin:* ZZ Li, HY Zhang; *CVDFACTS:* WH Pan; *Xi'an:* Y He, TH Lam; *Yunnan:* SX Yao. (The underlined studies provided data used in this paper.)

Correspondence: Dr Anushka Patel, Asia-Pacific Cohort Studies Collaboration Secretariat, Institute for International Health, University of Sydney, PO Box 576, 144 Burren Street, Newtown NSW 2042, Australia. E-mail: apatel@iieh.usyd.edu.au

of CHD with lipid-lowering drugs. The associations between cholesterol level and the risk of stroke are less clear; in particular, concerns remain regarding a possible inverse association between cholesterol levels and the risk of intracerebral haemorrhage.<sup>11–13</sup>

The Asia-Pacific region currently accounts for approximately half the global burden of cardiovascular diseases, and future projections suggest this proportion will increase.<sup>14,15</sup> Particularly in Eastern Asia, cholesterol levels and the incidence of CHD are lower than in most Caucasian populations, while the incidence of stroke is higher, and includes a greater proportion of haemorrhagic stroke.<sup>16–19</sup> However, there are data which indicate that population-wide levels of adverse risk factors, including cholesterol, are rising substantially in many countries in Asia.<sup>20,21</sup> To date, predictions on future disease burden as a consequence of this have relied on knowledge of the associations between risk factors and atherothrombotic diseases in Western populations. Very few such data are available from Asia, and precise population-specific estimates of the nature and magnitude of the associations between risk factors and cardiovascular diseases in the region are lacking.

The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual-participant data overview of prospective cohort studies conducted in a number of Asian countries, Australia, and New Zealand. With several thousand events recorded, the Collaboration provides a unique opportunity to produce reliable evidence regarding the nature and size of the associations between risk factors and cardiovascular diseases, and to compare these associations between Asian and non-Asian populations. In this report, we describe the results relating to total cholesterol, and estimate the likely effects of rising population-wide levels of cholesterol on the burden of CHD and stroke in this region.

## Methods

### Participating studies

The design of the APCSC, an overview (meta-analysis) of prospective observational studies, has been described elsewhere.<sup>22</sup> Study eligibility criteria included being based in the Asia-Pacific region, and having at least 5000 person-years of follow-up. Studies were excluded if the study population was selected on the basis of the presence of any disease or risk factor. In this paper, only those studies with baseline measures of total cholesterol are included. Studies were classified as Asian if their participants were recruited from China, Japan, Korea, or South East Asia, or from 'ANZ' if their participants were recruited from Australia or New Zealand. Definitions of region were based only on the geographical location of the cohort, and not on the ethnic origin of individual participants.

### Measurement of baseline variables

Total cholesterol was measured at baseline in 25 of the 37 studies included in the APCSC database at the end of 2001. Of these studies, seven (five in Asia and two in ANZ) also obtained repeat cholesterol measurements on up to seven occasions. Cholesterol measurements were determined using serum samples, and these were obtained while fasting in approximately 93% of participants. As these studies were initiated over a long period of time (1966–1994), the methods and instruments used for measuring cholesterol varied. Information regarding method of

cholesterol analysis was available from 15 studies comprising 68% of all participants; amongst these, 96% of cholesterol levels were determined using enzymatic methods. In each study, age, sex, and blood pressure at baseline were recorded. Wherever available, baseline body mass index (BMI), smoking status, alcohol consumption, and the presence or absence of diabetes were also recorded.

### Outcomes

All studies reported deaths by underlying cause; a subset of studies also reported non-fatal cardiovascular disease events. Outcomes were classified according to the Ninth Revision of the International Classification of Diseases (ICD-9). The fatal outcomes considered in this analysis were: CHD (ICD-9: 410–414); total stroke (430–438); haemorrhagic stroke (431.0–432.9); and ischaemic stroke (433.0–434.9). Two composite outcomes were also considered: death due to CHD or non-fatal myocardial infarction (MI), and fatal or non-fatal stroke. Since most studies used record linkage with official sources, verification of strokes was not routinely reported. However, 9 of the 25 studies included in this analysis provided information on stroke verification; in these 9 studies, stroke sub-type was determined on the basis of imaging, lumbar puncture or autopsy in 515 of 606 cases (85%).

### Statistical methods

All analyses used individual-participant data, and were restricted to individuals aged  $\geq 20$  years at the time of the baseline survey. To assess the association of 'usual' cholesterol level with the outcomes of interest, baseline cholesterol measurements were adjusted to account for regression dilution bias.<sup>23,24</sup> Repeat measurements of cholesterol were obtained from approximately 7% of participants between 1 and 18 years following the baseline measurement. These repeat measures were used to estimate regression dilution attenuation coefficients, using a linear mixed regression model that accounted for the heterogeneity of variance between studies, within-subject correlation, and the varying time intervals between measurements. The attenuation coefficients derived by this method were similar for men and women, and between age groups, but differed significantly between regions. Thus, region-specific attenuation coefficients<sup>24</sup> were used for all separate analyses in Asian (2.30) and in ANZ (1.60) populations, while the overall population coefficient (1.70) was used for all other analyses.

For grouped analyses, individuals were classified according to approximately equal fifths of baseline cholesterol for the entire study population ( $\leq 4.1$ , 4.2–4.6, 4.7–5.1, 5.2–5.8, and  $\geq 5.9$  mmol/l). Trends in mean values of other major continuous cardiovascular risk factors across these fifths were assessed through simple linear regression, coding the groups in rank order. Trends in percentages for binary risk factors were assessed similarly using  $\chi^2$  tests for trend.<sup>25</sup> Cox proportional hazards regression models were used to estimate hazard ratios (HR), with corresponding 95% CI calculated using the 'floating absolute risk' method in order to provide a CI for the reference group.<sup>26</sup> Log-linearity of cholesterol associations was explored through the analysis of fifths of cholesterol, and summarized through the HR and 95% CI for a 1-mmol/l increase in usual cholesterol.

All analyses reported here were stratified by study and sex, and adjusted for time-dependent age at risk, systolic blood pressure, and smoking status. For the subset of participants in

**Table 1** Major characteristics of studies

| Study name                       | No. of subjects | Cholesterol, mean (sd) (mmol/l) | Women %      | Mean age (years) | Median follow-up (years) |
|----------------------------------|-----------------|---------------------------------|--------------|------------------|--------------------------|
| Aito Town                        | 1672            | 4.62 (0.85)                     | 56.6         | 51.0             | 15.2                     |
| Akabane                          | 1826            | 4.98 (0.92)                     | 55.8         | 54.0             | 11.0                     |
| Anzhen 02                        | 4141            | 4.72 (0.87)                     | 51.0         | 47.0             | 3.0                      |
| Capital Iron and Steel Company   | 4772            | 4.83 (1.00)                     | 0.0          | 45.3             | 12.5                     |
| Civil Service Workers            | 9303            | 5.19 (0.92)                     | 33.1         | 46.7             | 6.7                      |
| Fangshan                         | 815             | 4.58 (1.05)                     | 66.9         | 46.9             | 2.7                      |
| Hisayama                         | 1539            | 4.07 (0.95)                     | 56.5         | 54.0             | 24.6                     |
| Hong Kong                        | 194             | 5.26 (0.96)                     | 52.1         | 79.0             | 2.5                      |
| Huashan                          | 1595            | 4.66 (0.89)                     | 54.4         | 52.9             | 2.9                      |
| KMIC                             | 183 216         | 4.94 (0.98)                     | 37.0         | 44.1             | 5.5                      |
| Kounan Town                      | 1220            | 4.88 (0.87)                     | 55.3         | 51.8             | 6.4                      |
| Miyama                           | 414             | 5.11 (0.89)                     | 62.1         | 59.2             | 6.6                      |
| Ohasama                          | 1907            | 5.00 (0.87)                     | 64.8         | 58.2             | 4.1                      |
| Saitama                          | 3623            | 5.00 (0.87)                     | 62.2         | 54.5             | 10.3                     |
| Seven Cities                     | 17 999          | 4.87 (1.28)                     | 55.3         | 56.1             | 2.7                      |
| Shanghai Factory Workers         | 8997            | 4.16 (0.86)                     | 31.0         | 48.4             | 14.0                     |
| Shibata                          | 2319            | 4.63 (1.20)                     | 57.6         | 56.8             | 20.0                     |
| Shigaraki                        | 3748            | 5.00 (0.90)                     | 59.6         | 57.2             | 4.4                      |
| Shirakawa                        | 4634            | 4.63 (0.90)                     | 54.3         | 48.0             | 17.5                     |
| Singapore 92                     | 3330            | 5.35 (1.05)                     | 51.7         | 38.8             | 6.2                      |
| Six Chinese                      | 14 483          | 4.19 (0.92)                     | 48.5         | 45.0             | 8.4                      |
| Tanno/Soubetsu                   | 1968            | 4.94 (0.92)                     | 53.4         | 51.1             | 16.4                     |
| CVDFACTS                         | 5522            | 4.97 (1.16)                     | 55.5         | 47.1             | 6.0                      |
| Xi'an                            | 1686            | 4.61 (0.90)                     | 33.8         | 44.4             | 19.5                     |
| Yunnan Tin Miner                 | 2621            | 4.31 (0.78)                     | 4.0          | 54.3             | 4.5                      |
| <b>Sub-Total Asia</b>            | <b>283 544</b>  | <b>4.86 (1.02)</b>              | <b>40.3</b>  | <b>46.2</b>      | <b>5.5</b>               |
| Busselton                        | 7401            | 5.87 (1.28)                     | 52.1         | 45.3             | 20.5                     |
| Fletcher Challenge               | 10 224          | 5.36 (1.15)                     | 27.9         | 44.4             | 4.8                      |
| Melbourne Cancer                 | 41 137          | 5.53 (1.05)                     | 58.9         | 54.8             | 5.6                      |
| Perth                            | 9727            | 5.78 (1.22)                     | 47.3         | 45.4             | 14.4                     |
| <b>Sub-Total ANZ<sup>a</sup></b> | <b>68 489</b>   | <b>5.58 (1.13)</b>              | <b>51.9</b>  | <b>50.9</b>      | <b>5.7</b>               |
| <b>Total</b>                     | <b>352 033</b>  | <b>5.00 (1.09)</b>              | <b>42.52</b> | <b>47.1</b>      | <b>5.5</b>               |

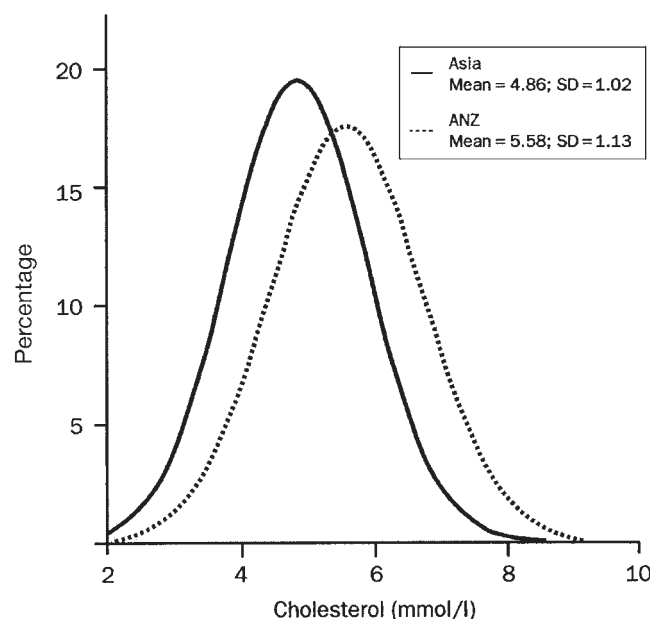
<sup>a</sup> Australia and New Zealand.

whom baseline data on diabetes status, alcohol consumption, and BMI were available, further adjustment was made for these variables. However, these additional adjustments had very little effect and so are not reported here.

## Results

The 29 cohorts from 25 studies in the APCSC with data on baseline cholesterol are summarized in Table 1. The analyses included 352 033 individuals with almost 2 million person-years of follow-up, which represented 83% of the entire APCSC study population. The mean age of participants at baseline was 47 years, and 42% were women. Compared with participants in the ANZ studies, the Asian cohort tended to be younger (46 years versus 51 years) and be represented by fewer women (40% versus 52%).

The distribution of baseline cholesterol levels for the Asian and ANZ participants respectively is shown in Figure 1. The age- and sex-adjusted mean cholesterol value for ANZ participants was 5.52 mmol/l (95% CI: 5.51–5.53 mmol/l), and 4.87 mmol/l (95% CI: 4.86–4.88 mmol/l) for Asian participants. The mean cholesterol value was similar in men (4.80 mmol/l, 95% CI: 4.79–4.81) and women (4.82 mmol/l, 95% CI: 4.82–4.83). The age- and sex-adjusted levels of major cardiovascular risk factors within study population fifths of baseline cholesterol are summarized in Table 2. Age, systolic blood pressure, BMI, the prevalence of current alcohol consumption, and diabetes all



**Figure 1** Distribution of baseline cholesterol among participants in Asian and Australia and New Zealand (ANZ) cohorts

increased with increasing total cholesterol, but smoking prevalence was unrelated to cholesterol levels.

**Table 2** Distribution of major risk factors by baseline cholesterol fifth, adjusted by age and sex

| Variables                            | No. <sup>a</sup> | Fifth of cholesterol |                     |                     |                     |                     | P-value <sup>b</sup> |
|--------------------------------------|------------------|----------------------|---------------------|---------------------|---------------------|---------------------|----------------------|
|                                      |                  | 1 (≤4.1 mmol/l)      | 2 (4.2–4.6 mmol/l)  | 3 (4.7–5.1 mmol/l)  | 4 (5.2–5.8 mmol/l)  | 5 (≥5.9 mmol/l)     |                      |
| <b>Mean &amp; 95% CI</b>             |                  |                      |                     |                     |                     |                     |                      |
| Age (years)                          | 352 033          | 45.2 (45.1–45.2)     | 45.6 (45.6–45.7)    | 46.5 (46.4–46.6)    | 48.0 (47.9–48.0)    | 50.4 (50.3–50.4)    | <0.0001              |
| Body mass index (kg/m <sup>2</sup> ) | 337 838          | 22.4 (22.40–22.45)   | 23.00 (22.97–23.02) | 23.37 (23.34–23.39) | 23.93 (23.90–23.95) | 24.72 (24.69–24.74) | <0.0001              |
| Systolic blood pressure (mmHg)       | 352 033          | 122.4 (122.2–122.5)  | 123.6 (123.4–123.7) | 124.6 (124.5–124.8) | 126.2 (126.1–126.3) | 129.3 (129.2–129.4) | <0.0001              |
| <b>Percentage &amp; 95% CI</b>       |                  |                      |                     |                     |                     |                     |                      |
| Current smoking                      | 327 854          | 38.3 (37.8–38.8)     | 36.4 (35.9–36.9)    | 36.3 (35.8–36.7)    | 36.0 (35.4–36.5)    | 36.7 (36.2–37.1)    | 0.38                 |
| Current alcohol consumption          | 307 998          | 43.7 (43.2–44.3)     | 49.1 (48.5–49.7)    | 51.2 (50.7–51.8)    | 53.6 (53.0–54.2)    | 56.4 (55.8–57.0)    | <0.0001              |
| History of diabetes                  | 123 605          | 2.1 (1.9–2.4)        | 2.7 (2.5–2.9)       | 3.0 (2.8–3.3)       | 3.1 (2.9–3.4)       | 3.5 (3.3–3.7)       | <0.0001              |

<sup>a</sup> No. of participants with data available for each variable.<sup>b</sup> P-value for linear trend across the fifths.**Table 3** Cardiovascular events

| Study name                       | No. of subjects | Deaths           |             |                    |                    |                    |                  | Fatal or non-fatal events <sup>a</sup> |            |            |             |                 |
|----------------------------------|-----------------|------------------|-------------|--------------------|--------------------|--------------------|------------------|--|------------|------------|-------------|-----------------|
|                                  |                 | CVD <sup>b</sup> | Stroke      | Haem. <sup>c</sup> | Isch. <sup>d</sup> | U/K-S <sup>e</sup> | CHD <sup>f</sup> | Stroke                                 | Haem.      | Isch.      | U/K-S       | MI <sup>g</sup> |
| Aito Town                        | 1672            | 55               | 24          | 5                  | 0                  | 19                 | 15               |  |            |            |             |                 |
| Akabane                          | 1826            | 36               | 12          | 1                  | 9                  | 2                  | 7                | 38                                     | 5          | 16         | 17          | 28              |
| Anzhen 02                        | 4141            | 2                | 1           | 1                  | 0                  | 0                  | 1                | 16                                     |            | 14         | 2           | 1               |
| Capital Iron and Steel Company   | 4772            | 109              | 69          | 47                 | 16                 | 6                  | 40               | 165                                    | 64         | 92         | 9           | 82              |
| Civil Service Workers            | 9303            | 13               | 2           | 1                  | 0                  | 1                  | 1                |  |            |            |             |                 |
| Fangshan                         | 815             | 2                | 1           | 0                  | 0                  | 1                  | 0                | 8                                      | 2          | 5          | 1           | 2               |
| Hisayama                         | 1539            | 287              | 168         | 50                 | 93                 | 25                 | 50               | 313                                    | 62         | 221        | 30          | 85              |
| Hong Kong                        | 194             | 15               | 4           | 0                  | 0                  | 4                  | 7                |  |            |            |             |                 |
| Huashan                          | 1595            | 13               | 6           | 3                  | 3                  | 0                  | 3                | 16                                     | 6          | 10         | 0           | 3               |
| KMIC                             | 183 216         | 566              | 287         | 144                | 14                 | 129                | 127              | 331                                    |            |            | 331         | 141             |
| Kounan Town                      | 1220            | 26               | 13          | 3                  | 2                  | 8                  | 3                |  |            |            |             |                 |
| Miyama                           | 414             | 1                | 0           | 0                  | 0                  | 0                  | 0                |  |            |            |             |                 |
| Ohasama                          | 1907            | 16               | 5           | 2                  | 0                  | 3                  | 4                | 42                                     | 10         | 27         | 5           |                 |
| Saitama                          | 3623            | 120              | 55          | 15                 | 27                 | 13                 | 24               |  |            |            |             |                 |
| Seven Cities                     | 17 999          | 337              | 123         | 87                 | 30                 | 6                  | 62               | 220                                    | 119        | 99         | 2           |                 |
| Shanghai Factory Workers         | 8997            | 373              | 249         | 0                  | 0                  | 249                | 81               |  |            |            |             |                 |
| Shibata                          | 2319            | 338              | 202         | 36                 | 74                 | 92                 | 66               |  |            |            |             |                 |
| Shigaraki                        | 3748            | 29               | 13          | 2                  | 1                  | 10                 | 3                |  |            |            |             |                 |
| Shirakawa                        | 4634            | 162              | 72          | 28                 | 28                 | 16                 | 44               | 87                                     | 30         | 39         | 18          | 64              |
| Singapore 92                     | 3330            | 33               | 6           | 2                  | 2                  | 2                  | 22               | 44                                     | 5          | 14         | 25          | 33              |
| Six Chinese                      | 14483           | 215              | 87          | 61                 | 16                 | 10                 | 19               | 131                                    | 65         | 56         | 10          | 31              |
| Tanno/Soubetsu                   | 1968            | 72               | 33          | 16                 | 10                 | 7                  | 23               | 93                                     | 16         | 10         | 67          | 23              |
| CVDFACTS                         | 5522            | 59               | 29          | 8                  | 7                  | 14                 | 12               |  |            |            |             |                 |
| Xi'an                            | 1686            | 80               | 41          | 24                 | 15                 | 2                  | 35               |  |            |            |             |                 |
| Yunnan Tin Miner                 | 2621            | 55               | 27          | 23                 | 4                  | 0                  | 5                |  |            |            |             |                 |
| <b>Sub-Total Asia</b>            | <b>283 544</b>  | <b>3014</b>      | <b>1529</b> | <b>559</b>         | <b>351</b>         | <b>619</b>         | <b>654</b>       | <b>1504</b>                            | <b>384</b> | <b>603</b> | <b>517</b>  | <b>493</b>      |
| Busselton                        | 7401            | 1170             | 253         | 32                 | 42                 | 179                | 668              | 641                                    | 57         | 127        | 457         | 973             |
| Fletcher Challenge               | 10224           | 108              | 16          | 1                  | 1                  | 14                 | 68               | 98                                     | 6          | 19         | 73          | 127             |
| Melbourne Cancer                 | 41137           | 254              | 32          | 12                 | 5                  | 15                 | 161              |  |            |            |             |                 |
| Perth                            | 9727            | 295              | 59          | 10                 | 4                  | 45                 | 186              |  |            |            |             |                 |
| <b>Sub-Total ANZ<sup>h</sup></b> | <b>68 489</b>   | <b>1827</b>      | <b>360</b>  | <b>55</b>          | <b>52</b>          | <b>253</b>         | <b>1083</b>      | <b>739</b>                             | <b>63</b>  | <b>146</b> | <b>530</b>  | <b>1100</b>     |
| <b>Total</b>                     | <b>352 033</b>  | <b>4841</b>      | <b>1889</b> | <b>614</b>         | <b>403</b>         | <b>872</b>         | <b>1737</b>      | <b>2243</b>                            | <b>447</b> | <b>749</b> | <b>1047</b> | <b>1593</b>     |

<sup>a</sup> Only studies that reported both fatal and non-fatal outcomes contributed events to this combined endpoint.<sup>b</sup> Cardiovascular disease.<sup>c</sup> Haemorrhagic stroke.<sup>d</sup> Ischaemic stroke.<sup>e</sup> Stroke of unknown type or subarachnoid haemorrhage.<sup>f</sup> Coronary heart disease.<sup>g</sup> Myocardial infarction.<sup>h</sup> Australia and New Zealand.

## Outcomes

During follow-up, 4841 (34%) of all deaths were assigned an underlying cardiovascular cause (Table 3). Of these, 1889 deaths

were due to stroke (1529 in Asia, 360 in ANZ), and 1737 were due to coronary disease (654 in Asia, 1083 in ANZ). In Asian cohorts, stroke and coronary disease accounted for 51% and

22% of cardiovascular deaths respectively; in ANZ cohorts, stroke caused 20%, and coronary disease 59%, of cardiovascular deaths. Non-fatal events were recorded in 15 studies for stroke (1436 events), and 13 studies for MI (716 events). Subclassification into ischaemic or haemorrhagic stroke was provided for only 54% and 51% of all fatal and non-fatal strokes respectively. Of those strokes classified, 44% in Asia and 35% in ANZ were haemorrhagic.

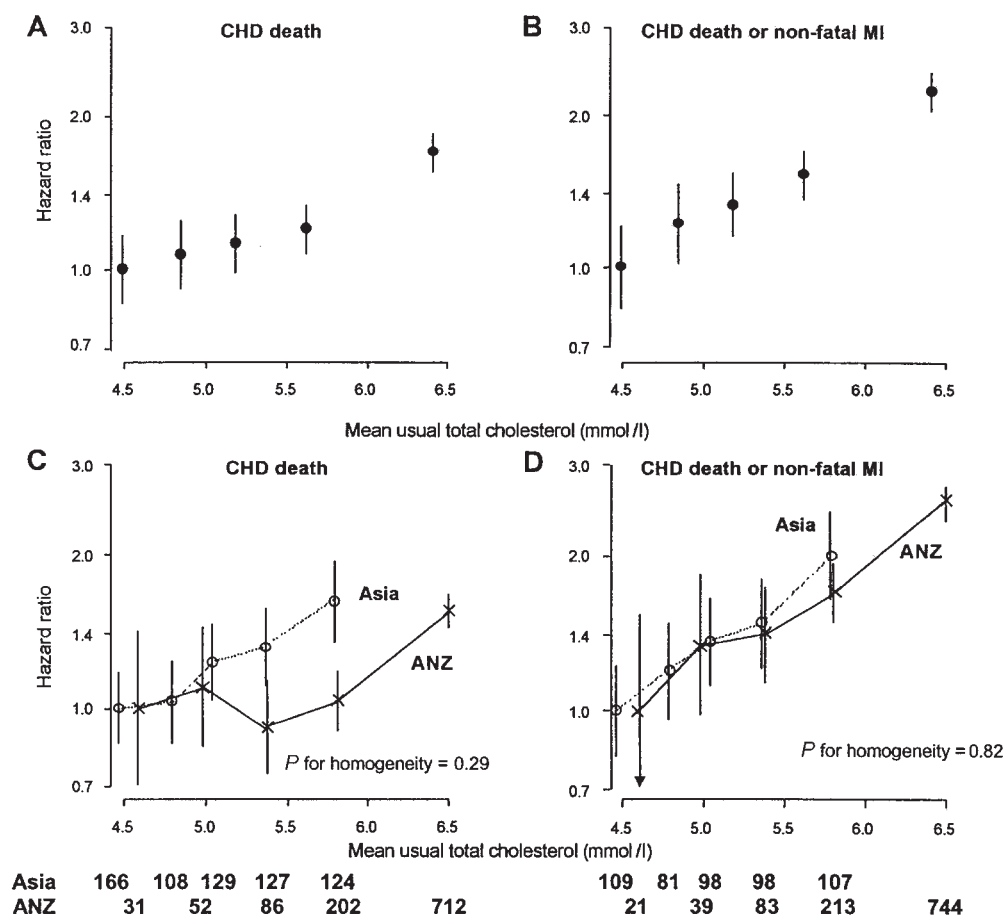
### Cholesterol and risk of coronary heart disease

There was a continuous, positive association between usual cholesterol levels and the risk of CHD, which persisted after adjustment for age, sex, blood pressure, and smoking. For each 1-mmol higher than usual cholesterol level, the risk of coronary death was approximately 35% (95% CI: 26–44%) greater (Figure 2A), while the risk of the combined outcome of non-fatal MI or coronary death was 45% (95% CI: 35–55%) higher (Figure 2B). The HR for coronary death associated with a 0.7-mmol/l increase in usual cholesterol (the mean difference between Asian and ANZ cohort values) was 1.23 (95% CI: 1.18–1.29). The association between usual cholesterol and CHD was similar in

ANZ and Asia (Figures 2C and 2D), and there was no evidence of heterogeneity by age or sex (Figure 3). Exclusion of the studies contributing most events in each region (the Korean Medical Insurance Corporation (KMIC) study with ~20% of fatal coronary events in Asia, and the Busselton Study with ~70% of fatal coronary events in ANZ) did not materially alter the point estimates of association.

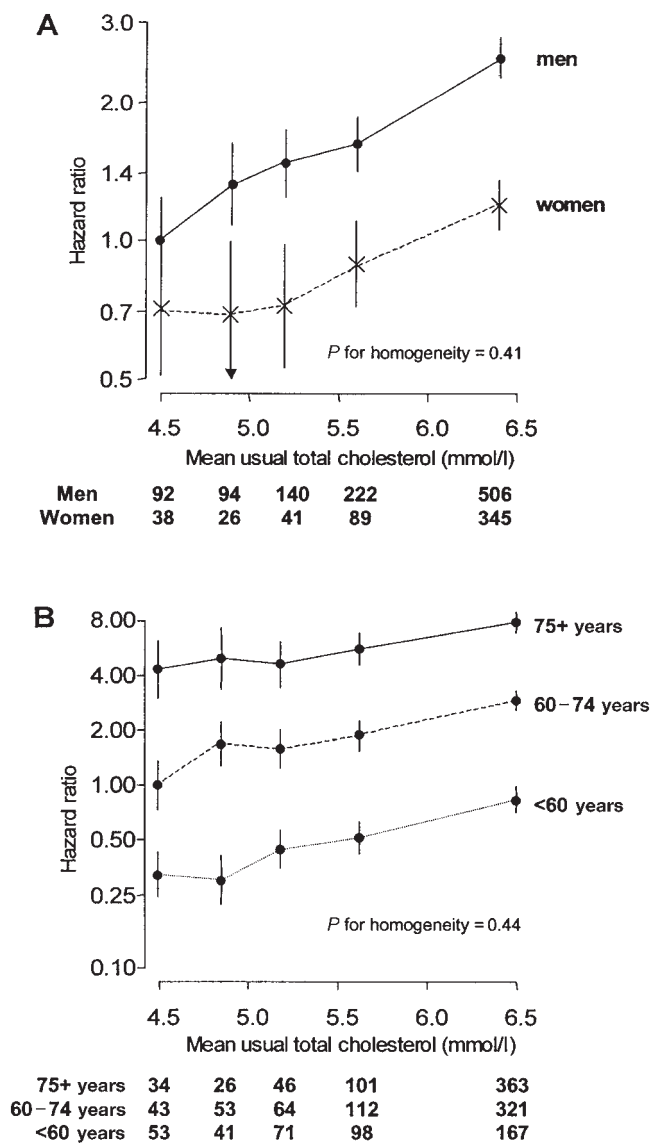
### Cholesterol and risk of stroke

Overall, no association between usual cholesterol and risk of fatal stroke was observed (Figure 4A). However, when the combined outcome of fatal or non-fatal stroke was considered, weak evidence of a positive log-linear association emerged (Figure 4B). Each 1-mmol/l higher level of cholesterol was associated with a 7% (95% CI: 0.9–14%) greater risk of fatal or non-fatal stroke. When compared with those in the lowest fifth of usual cholesterol level, the risk of fatal or non-fatal stroke among individuals belonging to the highest fifth was increased by about 20% (HR = 1.2, 95% CI: 1.1–1.3). Significant heterogeneity ( $P=0.03$ ) between Asia and ANZ was observed for the association between cholesterol and fatal stroke (Figure 4C). This



**Figure 2** Association between usual cholesterol level and coronary heart disease (CHD): A—death due to CHD in the entire study population; B—death due to CHD or non-fatal myocardial infarction (MI) in the entire study population; C—death due to CHD stratified by region; D—death due to CHD or non-fatal MI stratified by region. In Figures 2C and 2D, the hazard ratio for the lowest fifth of cholesterol is fixed at 1.0 separately for Asia and Australia and New Zealand (ANZ).  $P$ -values for test of homogeneity are shown. The number of events within each fifth of cholesterol is shown separately for Asia and ANZ below Figures 2C and 2D. Analyses are stratified by study and sex, and adjusted for age at risk, systolic blood pressure, and smoking





**Figure 3** Association between usual cholesterol level and death due to coronary heart disease (CHD) and non-fatal myocardial infarction (MI), stratified by: A—gender; B—age at baseline. The hazard ratio for the lowest fifth of cholesterol is fixed at 1.0 for men in Figure 3A, and in the group aged 60–74 years in Figure 3B.  $P$ -values for test of homogeneity are shown. The number of events within each fifth of cholesterol is shown beneath each Figure. Analyses are stratified by study and sex, and adjusted for age at risk, systolic blood pressure, and smoking

heterogeneity appears to reflect an unusually low risk associated with the lowest fifth of cholesterol in ANZ; the HR remained approximately constant over the other cholesterol fifths. There was no evidence of any regional difference in the association between usual cholesterol levels and risk of the composite outcome of fatal or non-fatal stroke (Figure 4D). Again, repeat analysis after exclusion of KMIC in Asia and the Busselton study in ANZ resulted in similar estimates of the association between cholesterol and stroke.

There were substantial differences in the relationship between cholesterol and the risks of ischaemic and haemorrhagic stroke.

While there was the appearance of a positive association between cholesterol and the risk of fatal ischaemic stroke (Figure 5A), this was not statistically significant. However, each 1-mmol/l higher level of usual cholesterol was associated with a 25% (95% CI: 13–40%) greater risk of fatal or non-fatal ischaemic stroke (Figure 5B). When compared with the lowest fifth of usual cholesterol levels, the risk for this combined outcome was about 50% higher for those belonging to the highest fifth (hazard ratio = 1.5, 95% CI: 1.3–1.8).

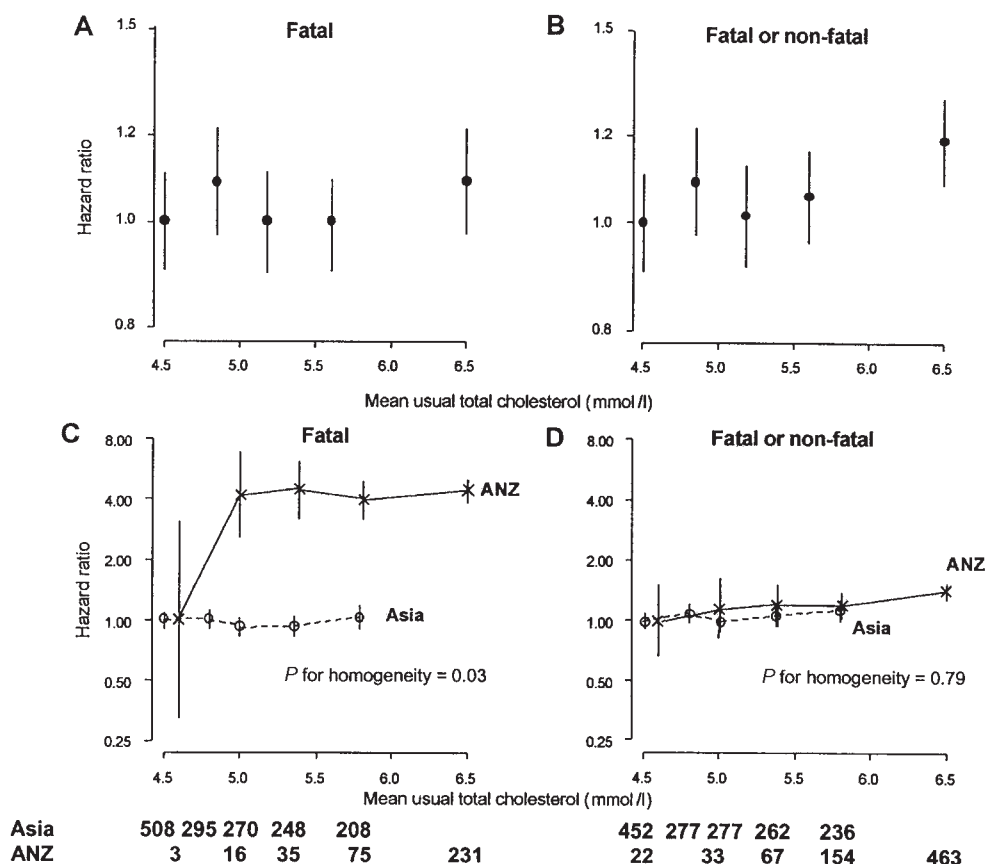
In contrast, there was evidence of an inverse association between usual cholesterol levels and risk of death due to haemorrhagic stroke (Figure 5C). The test for log-linearity was significant; each 1-mmol/l higher value of cholesterol was associated with a 20% (95% CI: 8–30%) lower risk of haemorrhagic stroke death. The HR for haemorrhagic stroke death associated with a 0.7-mmol/l increase in usual cholesterol (the mean difference between Asian and ANZ cohort values was 0.86 [95% CI: 0.78–0.94]). However, the excess risk appears to be mostly confined to those below the second quintile of cholesterol (<5.0 mmol/l). There were fewer studies and fewer events included in the analysis of the composite endpoint of fatal or non-fatal haemorrhagic stroke; for this outcome no definite association with cholesterol levels was observed (Figure 5D).

## Discussion

These data confirm a strong, positive, and continuous log-linear association between usual serum cholesterol levels and the risk of developing CHD. In terms of stroke risk, we found evidence of an association with cholesterol for the combined fatal and non-fatal outcome, but not for fatal stroke alone. There was a significant positive association between cholesterol and the risk of fatal or non-fatal ischaemic stroke, and a weaker negative association between cholesterol and the risk of fatal haemorrhagic stroke.

Aside from providing unique data involving Asian cohorts, the APCSC has many other advantages. The combination of data from numerous cohorts results in a large number of events, thus providing precise estimates of association. The use of individual-participant data and the availability of repeat cholesterol measures in a number of cohorts also provides the opportunity to limit systematic error due to regression dilution bias. We found that the use of population-specific attenuation factors to correct the effects of regression dilution bias had a substantial effect on our estimates of association, while adjustment for major confounding variables had relatively little effect. The calculated attenuation factor for Asia was higher than that for ANZ; this probably reflects greater variation in measurement error in determining cholesterol levels in Asia. Another important potential for bias resides in misclassification of events, particularly with respect to stroke subtype. Reliable verification of subtype requires imaging or autopsy data, and while it is likely that such information formed the basis of most reporting, this could not always be confirmed.

Numerous other observational studies, particularly in men, have demonstrated a strong, continuous, graded, and independent association between cholesterol and the risk of CHD.<sup>1–6</sup> The current data clearly extend these findings to Asian populations with substantially lower average levels of cholesterol, and confirm that effects are similar in men and women.

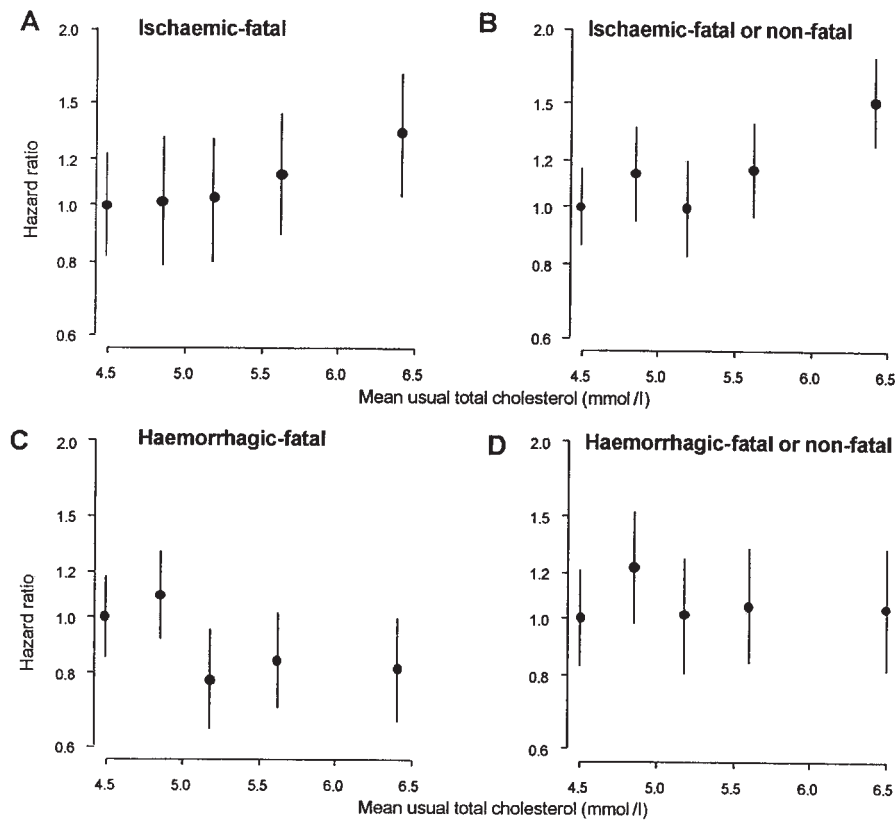


**Figure 4** Association between usual cholesterol level and stroke: A—any fatal stroke in the entire study population; B—any fatal or non-fatal stroke in the entire study population; C—any fatal stroke stratified by region; D—any fatal or non-fatal stroke stratified by region. In Figures 4C and 4D, the hazard ratio for the lowest fifth of cholesterol is fixed at 1.0 separately for Asia and Australia and New Zealand (ANZ). *P*-values for test of homogeneity are shown. The number of events within each fifth of cholesterol is shown separately for Asia and ANZ below Figures 4C and 4D. Analyses are stratified by study and sex, and adjusted for age at risk, systolic blood pressure, and smoking

Unlike CHD, the relationship between cholesterol level and the risk of stroke is complex. The APCSC data suggest that the lack of association between cholesterol and the overall risk of fatal stroke is due to a positive association between cholesterol and ischaemic stroke, partially counter-balanced by a weaker negative association between cholesterol and haemorrhagic stroke. The association with ischaemic stroke appears stronger and more conclusive; the lack of association for the endpoint of fatal stroke is likely explained by a higher case-fatality rate associated with haemorrhagic stroke,<sup>27</sup> and thus disproportionate representation of this stroke sub-type among fatal outcomes. This is consistent with the finding of a positive association between cholesterol and total stroke risk when both fatal and non-fatal events are considered. Furthermore, the 1.5:1.0 ratio of non-fatal to fatal stroke observed in the current analysis (based only on those cohorts that reported both fatal and non-fatal outcomes) is somewhat lower than that expected from surveillance data.<sup>28</sup> This is consistent with underreporting of non-fatal events (which are more likely to be ischaemic), and may have resulted in underestimation of the true association between cholesterol and total stroke. Again, we did not find any clear evidence of regional differences in any of these associations.

Other observational data have variably demonstrated a weak positive or a lack of any association between cholesterol levels and the risk of stroke.<sup>12,13,29–36</sup> However, most studies were conducted in Caucasian populations at relatively low risk of stroke, and thus with limited power to detect moderate yet meaningful associations, and many failed to examine associations with stroke sub-types. Some studies have reported clear evidence of a positive log-linear association between cholesterol and the risk of cerebral infarction,<sup>12</sup> while others suggest that the excess risk is confined to those individuals with the highest cholesterol levels, generally within the top 5% of the distribution.<sup>33–35</sup> An association between lower cholesterol and an increased risk of haemorrhagic stroke has also been reported elsewhere,<sup>12,13,30,34,37,38</sup> although not consistently so.<sup>39</sup> While the current analysis provides some evidence in support of such an inverse association, the results indicate that the association is comparatively weak, and that the excess risk of haemorrhagic stroke appears mostly confined to individuals with the lowest cholesterol levels.

The difference in average baseline cholesterol level between ANZ and Asian cohorts in the APCSC was approximately 0.7 mmol/l. While it is important to recognize that these cohorts are not necessarily representative samples of the populations



**Figure 5** Association between usual cholesterol level and stroke subtype: A—fatal ischaemic stroke; B—fatal or non-fatal ischaemic stroke; C—fatal haemorrhagic stroke; D—fatal or non-fatal haemorrhagic stroke. Analyses are stratified by study and sex, and adjusted for age at risk, systolic blood pressure, and smoking

from which they were drawn, this average cholesterol difference is consistent with data from published cross-sectional surveys.<sup>40–42</sup> The current data suggest that a 0.7-mmol/l increase in average cholesterol levels in the Asian populations represented in APCSC could result in an approximate 25–30% increase in the incidence of CHD, and a 15–20% increase in the incidence of ischaemic stroke, which would not be counter-balanced by a possible 10–15% decrease in the incidence of haemorrhagic stroke. Such predictions are based on changes in cholesterol levels only, and do not account for the influence of likely changes in the levels of other cardiovascular risk factors. Furthermore, as well as increasing the overall mortality due to CHD and stroke, rising population levels of cholesterol would be expected to result in a far greater burden of stroke-related disability. This is especially true since ischaemic stroke, which is expected to increase both in absolute numbers and relative to haemorrhagic stroke, has a comparatively lower case-fatality rate.

In summary, this study provides reliable data that indicate adverse changes in population-wide levels of cholesterol in many parts of Asia are likely to result in substantial increases in the incidence of atherothrombotic vascular diseases. The effects are likely to be similar to those observed during the ‘epidemic’ of cardiovascular diseases observed in most Western countries several decades ago, with the potential to adversely influence the health of a large proportion of the global population. Action to arrest further increases, or preferably to reduce, cholesterol levels in the Asia-Pacific region is vital.

## Acknowledgement

**Funding/Support:** This project has received grants from the National Health and Medical Research Council of Australia and the Health Research Council of New Zealand.



## KEY MESSAGES

- There is a strong, independent, positive, and continuous association between cholesterol levels and the risk of coronary heart disease among populations from the Asia Pacific region.
- The relationship between cholesterol and the risk of stroke is more complex, with a positive association for ischaemic stroke, and a weaker negative association for haemorrhagic stroke.
- Despite substantially lower average cholesterol levels in Asian countries, these associations are similar in Asian and non-Asian populations of the region.
- Rising population-wide cholesterol levels are likely to contribute to an increased incidence of atherothrombotic coronary and cerebrovascular diseases in the Asia Pacific region.

## References

- Stamler J, Daviglius ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 2000;**284**:311–18.
- Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316 099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992;**152**:56–64.
- Verschuren WM, Jacobs DR, Bloemberg BP *et al*. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *JAMA* 1995;**274**:131–36.
- Navas-Nacher EL, Colangelo L, Beam C, Greenland P. Risk factors for coronary heart disease in men 18 to 39 years of age. *Ann Intern Med* 2001;**134**:433–39.
- Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. *Circulation* 1996;**93**:450–56.
- Sharrett AR, Ballantyne CM, Coady SA *et al*. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density sub-fractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001;**104**:1108–13.
- Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;**308**:367–72.
- Simes J, Furberg CD, Braunwald E *et al*. Effects of pravastatin on mortality in patients with and without coronary heart disease across a broad range of cholesterol levels. The Prospective Pravastatin Pooling Project. *Eur Heart J* 1997;**23**:207–15.
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study Group (4S). *Lancet* 1994;**344**:1383–89.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;**360**:7–22.
- Ueshima H, Iida M, Shimamoto T *et al*. Multivariate analysis of risk factors for stroke: eight-year follow-up study of farming villages in Akita, Japan. *Prev Med* 1980;**9**:722–40.
- Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350 977 men screened for the Multiple Risk Factor Intervention Trial. *N Engl J Med* 1989;**320**:904–10.
- Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998;**352**:1801–07.
- Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997;**349**:1269–76.
- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997;**349**:1498–504.
- Khor GL. Cardiovascular epidemiology in the Asia-Pacific region. *Asia Pacific J Clin Nutr* 2001;**10**:76–80.
- Sekikawa A, Kuller LH, Ueshima H *et al*. Coronary heart disease mortality trends in men in the post World War II birth cohorts aged 35–44 in Japan, South Korea and Taiwan compared with the United States. *Int J Epidemiol* 1999;**28**:1044–49.
- Chen D, Roman GC, Wu GX *et al*. Stroke in China (Sino-MONICA-Beijing study) 1984–1986. *Neuroepidemiology* 1992;**11**:15–23.
- Kimura Y, Takishita S, Muratani H *et al*. Demographic study of first-ever stroke and acute myocardial infarction in Okinawa, Japan. *Intern Med* 1998;**37**:736–45.
- Okayama A, Ueshima H, Marmot MG, Elliott P, Yamakawa M, Kita Y. Different trends in serum cholesterol levels among rural and urban populations aged 40–59 in Japan from 1960 to 1990. *J Clin Epidemiol* 1995;**48**:329–37.
- The Collaborative Study Group on Trends of Cardiovascular Diseases in China and Preventive Strategy. Current status of major cardiovascular risk factors in Chinese population and their trends in the past two decades. *Ch J Cardiol* 2001;**29**:74–78.
- Asia Pacific Cohort Studies Collaboration. Determinants of cardiovascular disease in the Asia Pacific region: protocol for a collaborative overview of cohort studies. *CVD Prevent* 1999;**2**:281–89.
- 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.
- Clarke R, Shipley M, Lewington S *et al*. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150**:341–53.
- Woodward M. *Epidemiology: Study Design and Data Analysis*. Boca Raton: Chapman and Hall/CRC, 1999.
- Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991;**10**:1025–35.
- Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS). *Stroke* 2001;**32**:1732–38.

- <sup>28</sup> Thorvaldsen P, Kuulasmaa K, Rajakangas AM, Rastenyte D, Sarti C, Wilhelmsen L. Stroke trends in the WHO MONICA project. *Stroke* 1997;**28**:500–06.
- <sup>29</sup> Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995;**346**:1647–53.
- <sup>30</sup> Rodriguez BL, D'Agostino R, Abbott RD *et al.* Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: A comparison of incidence and risk factor effects. *Stroke* 2002;**33**:230–36.
- <sup>31</sup> Njolstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. *Circulation* 1996;**94**:2877–82.
- <sup>32</sup> Berger K, Schulte H, Stogbauer F, Assmann G. Incidence and risk factors for stroke in an occupational cohort: the PROCAM Study. Prospective Cardiovascular Muenster Study. *Stroke* 1998;**29**:1562–66.
- <sup>33</sup> Lindstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. *BMJ* 1994;**309**:11–15.
- <sup>34</sup> Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke* 1999;**30**: 2535–40.
- <sup>35</sup> Wannamethee SG, Shaper AG, Ebrahim S. HDL-Cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke* 2000;**31**:1882–88.
- <sup>36</sup> Hart CL, Hole DJ, Smith GD. The relation between cholesterol and haemorrhagic or ischaemic stroke in the Renfrew/Paisley study. *J Epidemiol Community Health* 2000;**54**:874–75.
- <sup>37</sup> Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. *Stroke* 1996;**27**:1993–98.
- <sup>38</sup> Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke* 1989;**20**:1460–65.
- <sup>39</sup> Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. *Lancet* 2001;**357**:922–25.
- <sup>40</sup> Tian HG, Nan Y, Liang XQ *et al.* Relationship between serum lipids and dietary and non-dietary factors in a Chinese population. *Eur J Clin Nutr* 1995;**49**:871–82.
- <sup>41</sup> Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980–1989. *Med J Aust* 1994;**161**:519–27.
- <sup>42</sup> Tao S, Li Y, Xiao Z *et al.* Serum lipids and their correlates in Chinese urban and rural populations of Beijing and Guangzhou. *Int J Epidemiol* 1992;**21**:893–903.