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

Asia Pacific Cohort Studies Collaboration

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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 ± 1.05 mmol/l) than in Asia (4.87 ± 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

Data from observational studies[1–6] and clinical trials of lipid-lowering therapy[7–10] 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

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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.[11–13]

The Asia-Pacific region currently accounts for approximately half the global burden of cardiovascular diseases, and future projections suggest this proportion will increase.[14,15] 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.[16–19] However, there are data which indicate that population-wide levels of adverse risk factors, including cholesterol, are rising substantially in many countries in Asia.[20,21] 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.[22] 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 $\geqslant$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.[23,24] 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[24] 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 ($\leqslant$4.1, 4.2–4.6, 4.7–5.1, 5.2–5.8, and $\geqslant$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 χ^2 tests for trend.[25] 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.[26] 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 Serivce 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
Sub-Total Asia	283 544	4.86 (1.02)	40.3	46.2	5.5
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
Sub-Total ANZ[a]	68 489	5.58 (1.13)	51.9	50.9	5.7
Total	352 033	5.00 (1.09)	42.52	47.1	5.5

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

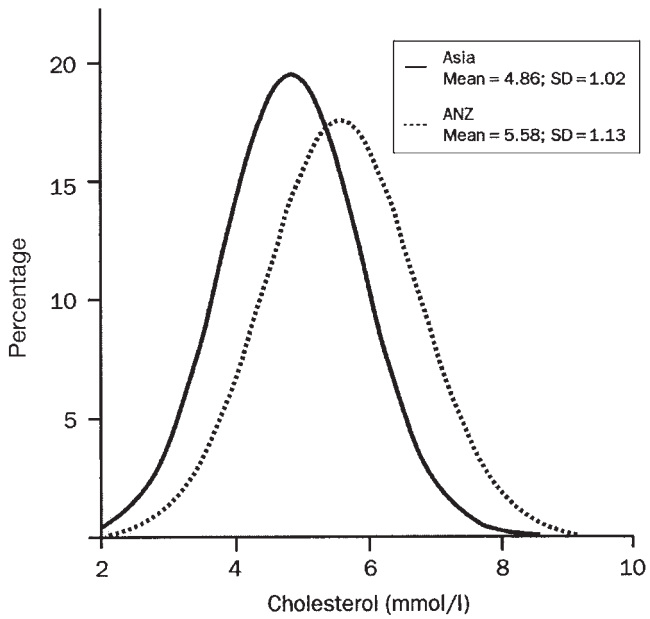

Figure 1 Distribution of baseline cholesterol among participants in Asian and Australia and New Zealand (ANZ) cohorts

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

		Fifth of cholesterol					
Variables	**No.[a]**	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)	*P*-value[b]
Mean & 95% CI							
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^2)	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
Percentage & 95% CI							
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

[a] No. of participants with data available for each variable.

[b] *P*-value for linear trend across the fifths.

Table 3 Cardiovascular events

		Deaths						Fatal or non-fatal events[a]				
Study name	**No. of subjects**	CVD[b]	Stroke	Haem.[c]	Isch.[d]	U/K-S[e]	CHD[f]	Stroke	Haem.	Isch.	U/K-S	MI[g]
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					
Sub-Total Asia	283 544	3014	1529	559	351	619	654	1504	384	603	517	493
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					
Sub-Total ANZ[h]	68 489	1827	360	55	52	253	1083	739	63	146	530	1100
Total	352 033	4841	1889	614	403	872	1737	2243	447	749	1047	1593

[a] Only studies that reported both fatal and non-fatal outcomes contributed events to this combined endpoint.

[b] Cardiovascular disease

[c] Haemorrhagic stroke.

[d] Ischaemic stroke.

[e] Stroke of unknown type or subarachnoid haemorrhage.

[f] Coronary heart disease.

[g] Myocardial infarction.

[h] 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

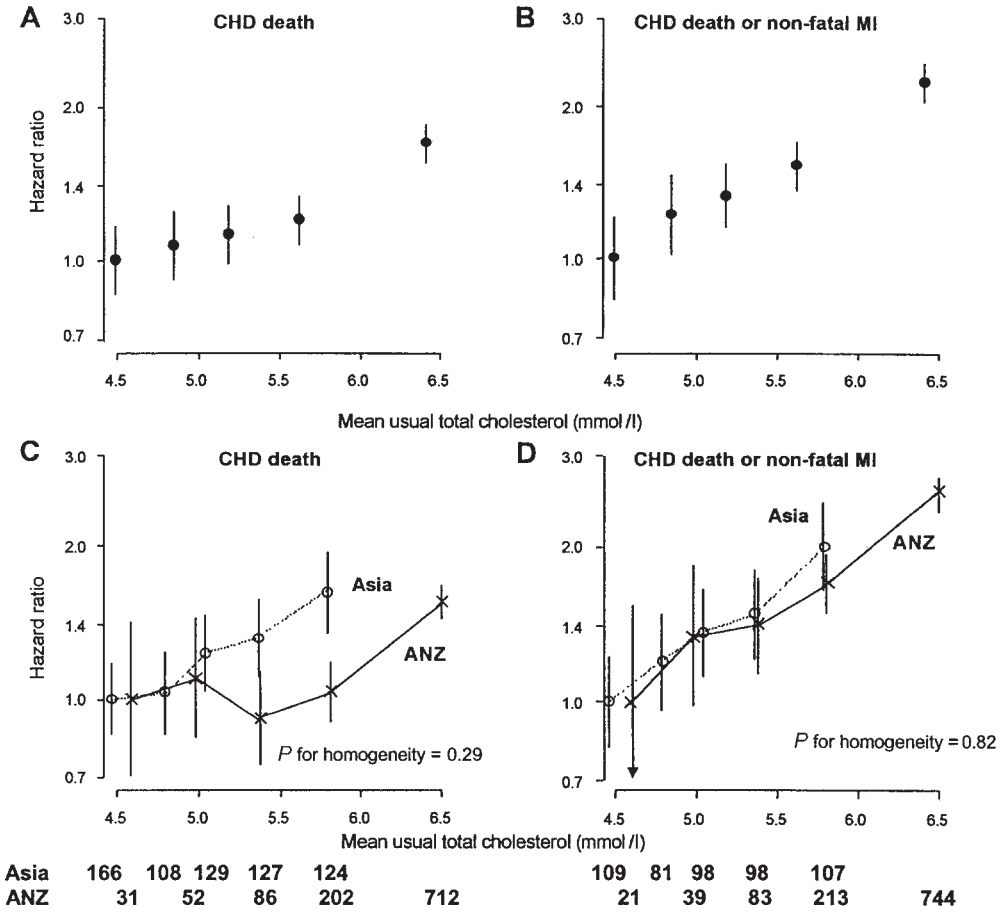

Figure 2 Association between usual cholesterol level and coronary heart disease (CHD): A—death due to CHD in the entire study population; B—death due to CHD or non-fatal myocardial infarction (MI) in the entire study population; C—death due to CHD stratified by region; D—death due to CHD or non-fatal 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

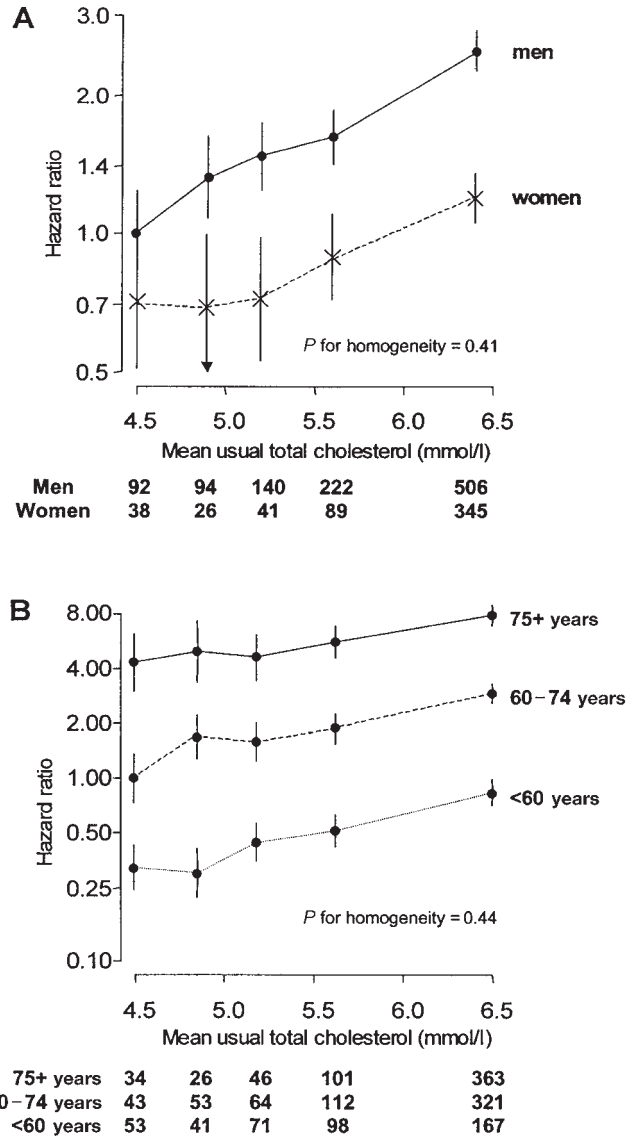

Figure 3 Association between usual cholesterol level and death due to coronary heart disease (CHD) and non-fatal myocardial infarction (MI), stratified by: A—gender; B—age at baseline. The hazard ratio for the lowest fifth of cholesterol is fixed at 1.0 for men in Figure 3A, and in the group aged 60–74 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.[1–6] 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.

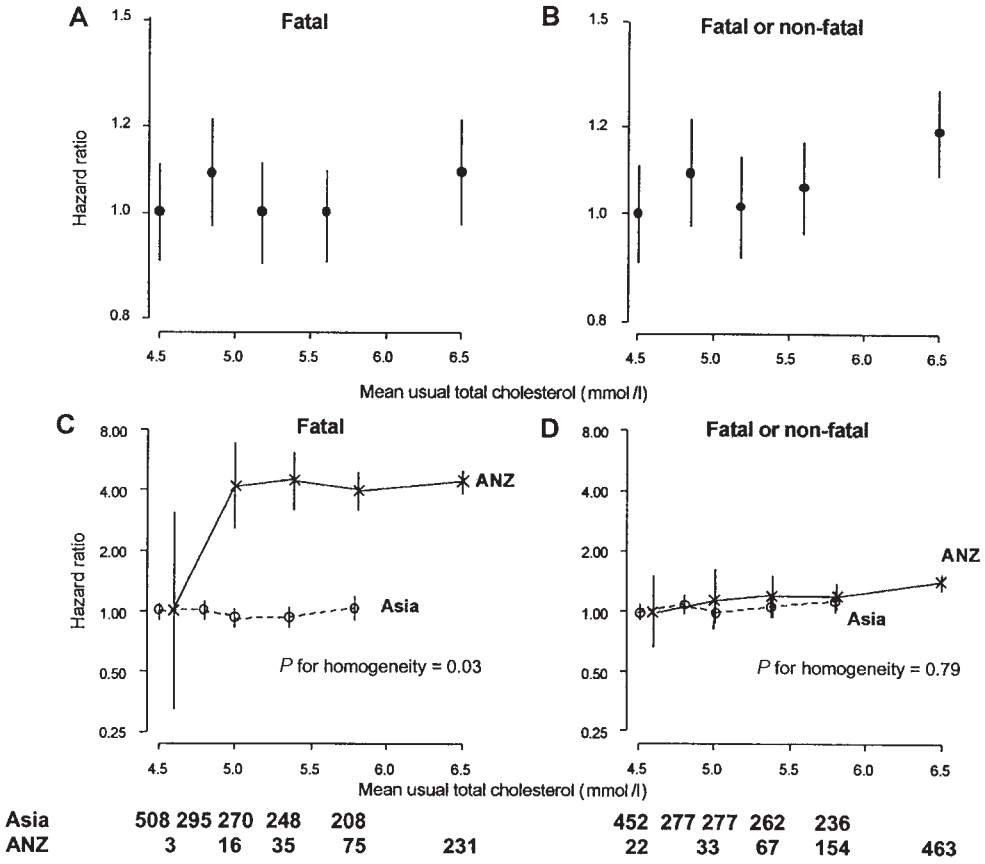

Figure 4 Association between usual cholesterol level and stroke:
A—any fatal stroke in the entire study population; B—any fatal or non-fatal stroke in the entire study population; C—any fatal stroke stratified by region; D—any fatal or non-fatal stroke stratified by region. In Figures 4C and 4D, the 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,[27] 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.[28] 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.[12,13,29–36] 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,[12] 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.[33–35] An association between lower cholesterol and an increased risk of haemorrhagic stroke has also been reported elsewhere,[12,13,30,34,37,38] although not consistently so.[39] 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

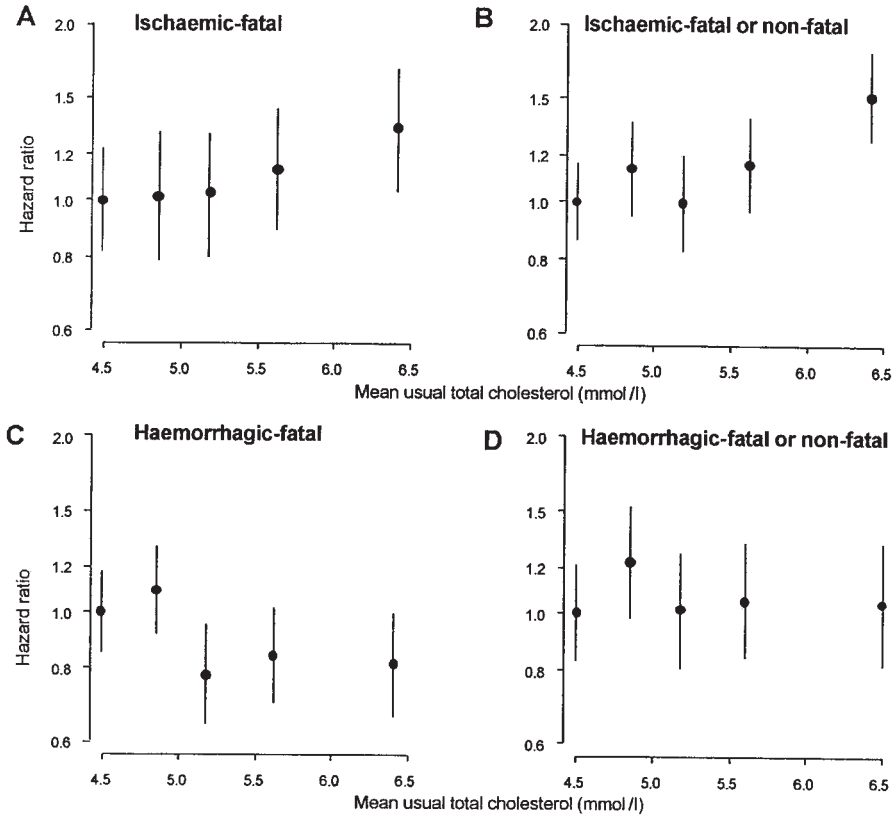

Figure 5 Association between usual cholesterol level and stroke subtype: A—fatal ischaemic stroke; B—fatal or non-fatal ischaemic stroke; C—fatal haemorrhagic stroke; D—fatal or non-fatal haemorrhagic stroke. Analyses are stratified by study and sex, and adjusted for age at risk, systolic blood pressure,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

from which they were drawn, this average cholesterol difference is consistent with data from published cross-sectional surveys.[40–42] 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 counterbalanced 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.

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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.

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