
Chapter 7

HIGH CHOLESTEROL

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SUMMARY

Cholesterol is a fat-like substance, found in the blood stream and also in bodily organs and nerve fibres. While there are different etiological roles for various types of cholesterol, such as high and low density lipoprotein, the large majority of descriptive and epidemiological data are available only for total cholesterol levels. Therefore, in this analysis, cholesterol was defined as total serum cholesterol expressed in millimoles per litre of blood (mmol/l) a continuous variable with mean and standard deviation.

The primary outcomes assessed were ischaemic heart disease (Global Burden of Disease [GBD] study end-point 107) and non-fatal stroke (end-point 108). Ischaemic heart disease (IHD) was chosen on the basis of clear and consistent positive associations observed in cohort studies and evidence of reversibility in clinical trials of cholesterol lowering treatments. Cholesterol is positively associated with ischaemic stroke, but has a qualitatively different association with haemorrhagic stroke. As end-points must all be mapped to the GBD classification system for disease, total stroke was used in the analyses. However, application of relative risk estimates to the 14 subregions¹ were adjusted to reflect differences in stroke subtypes. Cholesterol has been observed to be inversely associated with a number of other outcomes such as cancer and chronic respiratory disease. However, evidence suggests that these associations are due to the effects of disease on cholesterol, rather than vice versa. Consequently these outcomes were not included.

Raw cholesterol data were obtained from studies after a systematic review of population-based surveys, which included about 160 surveys and almost 640 000 participants. Sex-specific associations of cholesterol with age were estimated for each of the subregions separately, based on country-weighted study estimates of mean values. There was moderate variation in the final age- and sex-specific estimates of mean cholesterol

across the 14 subregions, with the range between the highest and lowest age-specific mean cholesterol levels typically being about 2 mmol/l.

A theoretical-minimum-risk distribution of cholesterol (i.e. one that would yield the lowest population risk of adverse health outcomes) was taken as 3.8 standard deviation 0.6 mmol/l (usual) for all age, sex and subregional groups. The main basis for this estimate was the level of cholesterol down to which epidemiological relationships with cardiovascular disease outcomes are observed, and clinical trial data showing benefits from cholesterol lowering among those with below-average cholesterol levels. This theoretical minimum was also consistent with the levels of cholesterol in populations with little cardiovascular disease.

For the comparative risk assessment (CRA) analyses, observational epidemiological data were used to estimate the hazard ratios for the risk factor–disease relationship and trial meta-analyses for the time frame of risk reversibility. Data on hazard ratios for IHD were included from an overview of the ten largest observational studies conducted in populations from industrialized countries. This overview included data from 494 804 participants followed for 7–23 years, among whom 18 811 IHD events were observed. There was evidence of differences in the strength of the association by age but no difference between males and females. These data were closely similar in size and shape to the associations seen in an overview of 29 cohorts involving 353 065 participants from the Asia-Pacific region. In this individual participant meta-analysis, 2937 strokes were observed as well as 2838 IHD events. Overall, each 0.6 mmol/l lowering of usual cholesterol was associated a 27% reduction in IHD. A 1 mmol/l lowering of cholesterol was associated with a 13% (range 6–19%) reduction in total stroke, predominantly due to the effect on ischaemic stroke.

An overview of 49 trials of cholesterol lowering indicated that risk reductions in IHD of 11%, 24%, 33% and 36% are associated with a 1 mmol/l reduction in cholesterol after 1, 2, 3–5 and >5 years, respectively. Taking into account the size of the reduction in cholesterol, there was no clear difference in effects according to how the cholesterol reduction was achieved, either by diet or any one of several classes of drugs. These data indicated that in middle age, the risks associated with high cholesterol are reversed within a few years of cholesterol lowering. A meta-analysis of cholesterol lowering trials also confirmed a reduction in risk of stroke with cholesterol lowering.

The foregoing methods and assumptions allowed estimates of burden attributable to cholesterol levels of more than 3.8 mmol/l. Overall, 56% of IHD mortality and disease burden was attributable to cholesterol >3.8 mmol/l worldwide (range of 44–68% by subregion). This translated into 3 609 000 deaths in the year 2000. Also 32% of ischaemic stroke was attributable to cholesterol >3.8 mmol/l worldwide (range of 25–45% by subregion), which translated into 805 000 deaths in the year 2000.

Worldwide, 4.4 million deaths (about 7.9% of the total) and 40.4 million disability-adjusted life years (DALYs) (2.8% of the total) were estimated to be due to non-optimal cholesterol. The proportion of DALYs was lower than the proportion of deaths as most cholesterol-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths. Overall, the results suggest that a considerable proportion of cardiovascular disease is attributable to non-optimal cholesterol, defined as mean cholesterol >3.8 mmol/l, and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide. Approximately 40% of the cholesterol-related attributable burden occurred in developed subregions, 20% in low mortality developing subregions (AMR-B, EMR-B, EUR-B, EUR-C, SEAR-B, WPR-B), and a further 40% in high mortality developing subregions (AFR-D, AFR-E, AMR-D, EMR-D, SEAR-D).

In absolute terms, most of the excess burden of cardiovascular disease occurred in the populous regions, as would be expected. The relative impact of attributable deaths and DALYs—calculated as the proportion of all deaths and DALYs attributable to non-optimal cholesterol (i.e. mean >3.8 mmol/l)—was highest in the European subregions, where mean cholesterol levels were highest.

1. INTRODUCTION

Cholesterol is a fat-like substance, found in the blood stream and also in bodily organs and nerve fibres. Most cholesterol in the body is made by the liver from a wide variety of foods, but especially from saturated fats, such as those found in animal products. A diet high in saturated fat content, heredity, and various metabolic conditions such as type II diabetes, influence an individual's level of cholesterol.

1.1 CHOICE OF EXPOSURE VARIABLE

Cholesterol was described as a continuous variable, as it is commonly reported in this manner with mean and standard deviation values. The System Internationale (SI) unit for measuring cholesterol is millimoles per litre of blood (mmol/l), but in some studies, particularly those from the United States of America and Japan, it is reported in milligrams per decilitre of blood (conversion factor $1 \text{ mg/dl} = 0.02586 \text{ mmol/l}$). Total cholesterol was chosen in preference to other potential measures of risk associated with blood lipids (e.g. high density lipoprotein [HDL cholesterol] and low density lipoprotein [LDL cholesterol]) as more data and information were available on both risk factor levels and the risk-factor-disease relationship (relative risk values) for total cholesterol.

1.2 DISEASE OUTCOMES

A number of diseases are associated with non-optimal cholesterol levels. Cholesterol is thought to amplify and accelerate atherosclerosis, and influence IHD and ischaemic stroke events, but the exact mechanisms are unclear. It has been proposed that cholesterol, particularly LDL cholesterol which accounts for about 60% of total cholesterol in the circulation, is taken up by macrophages. When cholesterol levels are high, macrophages take up more cholesterol than they can metabolize and become “foam cells”. These cells are important in the early stages of atheromatous plaque formation (Bronner et al. 1995; Gorelick et al. 1997; Warlow et al. 1996).

By contrast, there is no positive association between cholesterol and haemorrhagic stroke, and some research indicates that those people with lower levels of cholesterol are at greater risk of haemorrhagic stroke (Leppala et al. 1999; Neaton et al. 1992; Yano et al. 1994). The mechanisms are unclear, but low levels of cholesterol may weaken the endothelium of small intracranial vessels which, in combination with high blood pressure, may rupture, and/or result in “osmotic fragility” of red blood cells, thereby increasing the risk of haemorrhage (Bronner et al. 1995; Iso et al. 1989; Tanaka et al. 1982; Warlow et al. 1996). Potential outcomes considered as affected by cholesterol are described below.

ISCHAEMIC HEART DISEASE

Data from prospective cohort studies have demonstrated a strong, continuous temporal association between cholesterol and IHD (APCSC 2003; Law et al. 1994b, 1994c; Lewington and MacMahon 1999; Neaton and Wentworth 1992; Neaton et al. 1992). Further, a causal association is biologically plausible and clinical trials have demonstrated reversibility (Bucher et al. 1998; LaRosa et al. 1999; Law et al. 1994b; Pignone et al. 2000; Ross et al. 1999). The GBD classification system for diseases and injuries has a category for total IHD (end-point 107 G3 ischaemic heart disease, the International Statistical Classification of Diseases, ninth revision [ICD-9] codes 410–414) (Bucher et al. 1998; LaRosa et al. 1999; Pignone et al. 2000; Ross et al. 1999).

STROKE

Data on the association between cholesterol and stroke are more complex. Most major cohort studies and overviews have shown that cholesterol is positively associated with ischaemic stroke (Anonymous 1998a; Neaton et al. 1992; PSC 1995). However, there appears to be a qualitatively different association with haemorrhagic stroke, with some studies observing a negative association (APCSC 2003; Neaton et al. 1992) and others a null association with this outcome (Suh et al. 2001). There are no specific GBD end-points for stroke subtypes, only for total

stroke (end-point 108 G4 cerebrovascular disease, ICD-9 codes 430–438). However, application of RR estimates to the subregions will reflect differences in stroke subtypes, as discussed later in this chapter.

OTHER DISEASE AND INJURY OUTCOMES

Cholesterol has been observed to be inversely associated with a number of other outcomes such as cancer and chronic respiratory disease (Law et al. 1994a). However, evidence suggests that these associations are due to the effects of disease on cholesterol, rather than vice versa (Law et al. 1994a). Consequently these outcomes were not included.

2. RISK FACTOR EXPOSURE

2.1 DATA ON CHOLESTEROL LEVELS

Data on global cholesterol levels were collated from three major sources. The first source was the MONICA study (Anonymous 1989), which collected cholesterol data from 39 collaborating centres in 22 countries and was carried out between 1979 and 1987. This study provides important information about cholesterol patterns, but does not provide a truly global overview of cholesterol distributions. It included populations that were predominantly European in origin, and did not include populations from the Eastern Mediterranean, South-East Asian or African Regions. Further, MONICA data were collected in the early 1980s, and more recent data are also available now. We therefore found it necessary to include additional cholesterol data for this analysis.

The second major source of data was a literature search using Medline and the key words “cholesterol”, “survey” “health survey” and “cross-sectional survey”. Studies were reviewed, and included in analyses if they fulfilled the following criteria:

- conducted from 1980 onwards;
- included randomly selected or representative participants;
- had a sample size of over 1000—however, a smaller sample size was acceptable in specific regions, or age groups where data were limited, if the study fulfilled the other criteria;
- described sample size and age group of participants;
- presented mean values of cholesterol by age and sex; and
- utilized a standard protocol for cholesterol measurement.

The final source of data was personal communications with researchers and study investigators. The authors had access to data from the Asia-Pacific Cohort Studies Collaboration (APCSC), a collaboration involving 37 cohorts in the Asia-Pacific region, which includes at least 5000 person-years of follow-up recorded or planned. Data on date of

birth or age, sex, and cholesterol have been recorded and collated (APCSC 1999). Cholesterol data from eligible studies that had been collected from 1980 onwards were included in the cholesterol database. In addition, authors of surveys/studies were contacted and age and sex-specific data requested, where these had not been available in the published format.

Many studies did not publish data in the format required for this project (e.g. omitting age- and sex-specific mean cholesterol levels), and unfortunately time and resource constraints limited attempts to obtain all of these data from researchers. It was also very difficult to obtain results of surveys that have only been published in local/national reports but not in peer-reviewed journals. Access to these data would have been greatly improved had these reports been more widely available in electronic formats such as on the Internet. Details of studies currently included are presented in Table 7.1.

In total, approximately 1900 abstracts were reviewed. Data from about 160 surveys (total sample size of almost 640 000 participants) have been included. Figure 7.1 illustrates data coverage by geographical region.

No data were available for AMR-D comprising Bolivia, Ecuador, Guatemala, Haiti, Nicaragua and Peru, and very limited data (studies totalling <2000 participants) for SEAR-B and EMR-D. Data on more than 50 000 participants were obtained for AMR-A, EUR-A, WPR-A and WPR-B, owing to many studies being available and large sample sizes.

Figure 7.1 Cholesterol data coverage expressed as total study sample size, by geographical region

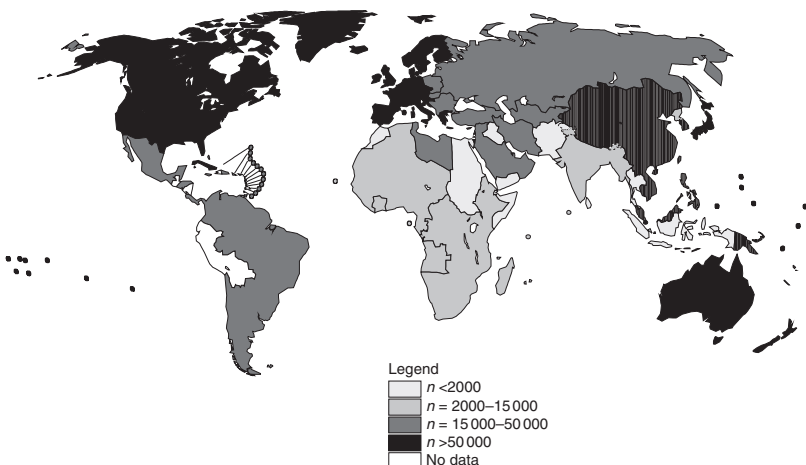


Table 7.1 Studies currently included in the cholesterol data review

<i>Subregion</i>	<i>Country or area</i>	<i>Study (reference)</i>	<i>Sample size</i>	<i>Age range (years)</i>
AFR-D	Ghana	Nyarko et al. (1994)	79	20–50
	Nigeria	Erasmus et al. (1994)	417	11–≥60
	Nigeria	Okesina et al. (1999)	500	11–≥50
	Seychelles	Bovet et al. (1991)	1 055	25–64
			2 051	
AFR-E	South Africa	Oelofse et al. (1996)	986	15–64
	South Africa	Steyn et al. (1987, 1985)	976	15–64
	United Republic of Tanzania	Kitange et al. (1993)	1 409	15–19
	United Republic of Tanzania	Swai et al. (1993)	7 272	15–≥65
	Zimbabwe	Allain et Matenga (T. Allain et al. personal communication, 2001)	261	60–≥80
			10 904	
AMR-A	Canada	Connelly et al. (1992)	1 169	42–59
	Canada	Lupien et al. (1985)	1 169	42–59
	Halifax	MONICA study (Anonymous 1989)	837	25–64
	USA	Abbott et al. (1997)	971	71–93
	USA	Brown et al. (1993)	14 521	45–64
	USA	Burke et al. (1991)	4 545	25–74
	USA	Donker et al. (1997)	1 411	7–11
	USA	Eisenberg et al. (1986)	2 477	35–64
	USA	Ettinger et al. (1992)	4 814	65–≥85
	USA	Ferrara et al. (1997)	2 339	50–≥80
	USA	Hutchinson et al. (1997)	15 743	45–64
	USA	Johnston et al. (1993)	7 836	20–≥75
	USA	Sprafka et al. (1990)	4 641	25–74
	USA	Srinivasan et al. (1991)	4 020	5–26
	USA	Wallace and Colsher (1992)	1 959	71–≥95
	USA	Yano et al. (1986)	1 363	60–≥75
Stanford	MONICA study (Anonymous 1989)	1 430	25–64	
			86 995	
AMR-B	Brazil	INCLen (Anonymous 1992b)	406	35–65
	Chile	INCLen (Anonymous 1992b)	399	35–65
	Chile	Jadue et al. (1999); L. Jadue, personal communication, 2001	1 591	25–64
	Colombia	INCLen (Anonymous 1992b)	200	35–65

continued

Table 7.1 Studies currently included in the cholesterol data review
(continued)

Subregion	Country or area	Study (reference)	Sample size	Age range (years)
	Dominican Republic	Aono et al. (1997)	2 000	20–76
	Jamaica	Wilks et al. (2001)	1 134	25–74
	Mexico	Gonzalez et al. (1999, 2001)	2 251	35–64
	Mexico	Posadas-Romero et al. (1995)	33 660	20–70
	Mexico	Yamamoto et al. (2001)	825	20–90
			42 466	
EMR-B	Bahrain	al-Mahroos et al. (2000)	2 090	40–59
	Jordan	H. Jaddou, personal communication, 2001	2 273	25–≥70
	Kuwait	Olusi et al. (1997)	751	1–≥70
	Saudi Arabia	al-Nuaim et al. (1996, 1997)	4 539	15–≥60
	Saudi Arabia	al-Nuaim (1997)	2 960	25–64
	Saudi Arabia	al Shammari et al. (1994)	1 005	<35–≥65
	Saudi Arabia	Mitwalli et al. (1994)	966	<25–≥55
	Tunisia	Ghannem et al. (2001); H. Ghannem, personal communication, 2001	1 497	13–19
			16 081	
EMR-D	Pakistan	Molla et al. (1990)	634	4–59
			634	
EUR-A	Belgium	Kesteloot et al. (1987)	18 090	<20–≥55
	Charleroi	MONICA study (Anonymous 1989)	646	25–64
	Ghent	MONICA study (Anonymous 1989)	1 260	25–64
	Denmark, Glostrup	MONICA study (Anonymous 1989)	3 780	25–64
	Finland	Lakka and Salonen (1992)	2 492	42–60
	Finland	Myllkangas et al. (1995)	2 210	45–64
	Finland	Nikkila and Heikkinen (1990)	535	85
	Finland	Nissinen et al. (1987)	6 523	25–64
	Finland	Puska et al. (1993)	1 398	25–64
	Finland	Vartiainen et al. (2000)	10 025	30–59
	Finland	Vikari et al. (1985)	3 654	3–18
	Kuopio	MONICA study (Anonymous 1989)	2 789	25–64
	Turku; Loimaa	MONICA study (Anonymous 1989)	3 283	25–64
	N. Karelia	MONICA study (Anonymous 1989)	3 138	25–64

Table 7.1 Studies currently included in the cholesterol data review
(continued)

<i>Subregion</i>	<i>Country or area</i>	<i>Study (reference)</i>	<i>Sample size</i>	<i>Age range (years)</i>
	France,			
	Haute-Garonne	MONICA study (Anonymous 1989)	1 265	25–64
	Lille	MONICA study (Anonymous 1989)	1 436	25–64
	Former German Democratic Republic,			
	Berlin-Lichtenberg	MONICA study (Anonymous 1989)	1 197	25–64
	Cottbus county	MONICA study (Anonymous 1989)	1 377	25–64
	Germany	Heinemann et al. (1995)	1 939	25–64
	Germany	Hoffmeister et al. (1994)	15 436	25–69
	Germany	Herman et al. (1988)	1 696	25–69
	Germany	MONICA study (Anonymous 1989)	1 015	25–64
	Augsburg (Rural)	MONICA study (Anonymous 1989)	2 109	25–64
	Augsburg (Urban)	MONICA study (Anonymous 1989)	1 667	25–64
	Bremen	MONICA study (Anonymous 1989)	1 625	25–64
	Rhein-Neckar	MONICA study (Anonymous 1989)	3 066	25–64
	Iceland	MONICA study (Anonymous 1989)	1 743	25–64
	Israel	Eisenberg et al. (1986)	1 588	35–64
	Israel	Greenland et al. (1993)	1 200	9–18
	Italy	Cesana et al. (1989)	1 387	25–≥55
	Italy	Nine populations (Anonymous 1981)	6 699	20–59
	Italy	Salvaggio et al. (Law and Wald 1994; Salvaggio et al. 1991)	8 953	18–65
	Italy	Vaccarino et al. (1995)	3 401	<30–≥50
	Brianza	MONICA study (Anonymous 1989)	1 647	25–64
	Friuli	MONICA study (Anonymous 1989)	1 849	25–64
	Latina	MONICA study (Anonymous 1989)	1 773	25–64
	Netherlands	Bosma et al. (1994)	3 015	45–70
	Netherlands	Vershuren et al. (1994)	41 622	20–59
	Norway	Graff-Iverson et al. (1998)	7 523	40–54
	Norway	Thune et al. (1998)	6 307	20–49
	Spain	Masia et al. (1998)	1 670	24–74
	Catalonia	MONICA study (Anonymous 1989)	2 544	25–64

continued

Table 7.1 Studies currently included in the cholesterol data review
(continued)

Subregion	Country or area	Study (reference)	Sample size	Age range (years)
	Sweden	Asplund-Carlson and Carlson (1994)	1 564	40–50
	Sweden	Rosengren et al. (2000)	798	50
	Gothenburg	MONICA study (Anonymous 1989)	1 354	25–64
	Switzerland, Ticino	MONICA study (Anonymous 1989)	1 483	25–64
	Vaud; Fribourg	MONICA study (Anonymous 1989)	1 582	25–64
	United Kingdom	Brown et al. (1994)	3 939	70–≥80
	England	Bajekal et al. (1999)	11 162	16–≥75
	England	Razay et al. (1992)	1 218	40–69
	Northern Ireland, Belfast	MONICA study (Anonymous 1989)	2 327	25–64
	Scotland	Smith et al. (1989)	10 359	40–59
	Scotland, Glasgow	MONICA study (Anonymous 1989)	1 143	25–64
	Multiple sites in EUR-A	Kafatos et al. (1991)	2 114	70–79
			237 704	
EUR-B	Poland, Tarnobrzeg Voivodship	MONICA study (Anonymous 1989)	2 700	25–64
	Warsaw	MONICA study (Anonymous 1989)	2 591	25–64
	Turkey	Mahley et al. (1995); R. Mahley, personal communication, 2001	8 882	20–≥70
	Turkey	Onat et al. (1992)	3 687	30–≥70
			17 860	
EUR-C	Former Czechoslovakia	MONICA study (Anonymous 1989)	2 552	25–64
	Estonia	Olferev et al. (1990, 1991)	2 936	20–54
	Hungary	Biro et al. (1996)	2 559	18–≥60
	Hungary	Kafatos et al. (1991)	42	70–79
	Budapest	MONICA study (Anonymous 1989)	1 486	25–64
	Pecs	MONICA study (Anonymous 1989)	1 584	25–64
	Lithuania	Bosma et al. (1994)	2 149	45–70
	Russian Federation	Puska et al. (1993)	837	25–64
	The former Soviet Union ^a , Kaunas	MONICA study (Anonymous 1989)	1 462	25–64
	Novosibirsk C	MONICA study (Anonymous 1989)	2 538	25–64

Table 7.1 Studies currently included in the cholesterol data review
(continued)

<i>Subregion</i>	<i>Country or area</i>	<i>Study (reference)</i>	<i>Sample size</i>	<i>Age range (years)</i>
	Novosibirsk I	MONICA study (Anonymous 1989)	1 436	25–64
			<i>19 581</i>	
SEAR-B	Indonesia	INCLEN (Anonymous 1992b)	210	35–65
	Thailand	Bhuripanyo et al. (1993)	911	30–≥60
	Thailand	INCLEN (Anonymous 1992b)	416	35–65
			<i>1 537</i>	
SEAR-D	India	Chadha et al. (1997)	2 124	25–64
	India	Misra et al. (2001)	508	20–70
	India	Misra et al. (2001)	652	14–25
	India	Reddy et al. (1994)	380	40–≥70
			<i>3 664</i>	
WPR-A	Australia	APCSC-Busselton (APCSC secretariat, personal communication, 2001)	976	15–≥70
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	6 456	15–≥70
	Australia	Bennett and Magnus (1994)	6 096	25–64
	Australia	Boulton et al. (1995)	856	8–9
	Australia	Glikman et al. (1990)	1 743	9–15
	Australia	Simons et al. (1991)	3 182	60–≥80
	Australia	van Beurden et al. (1991)	9 238	18–98
	Newcastle	MONICA study (Anonymous 1989)	2 396	25–64
	Perth	MONICA study (Anonymous 1989)	1 758	25–64
	Japan	1990 National Survey (Sakata and Labarthe 1996)	7 836	30–≥70
	Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	1 720	15–≥70
	Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	1 834	15–≥70
	Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	2 240	30–≥60
	Japan	Choudhury et al. (1994)	832	35–59
	Japan	Okayama et al. (1993)	5 921	30–69
	Japan	Serum Lipid Survey (Anonymous 1996)	33 234	4–99
	New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	10 462	15–≥70

continued

Table 7.1 Studies currently included in the cholesterol data review
(continued)

Subregion	Country or area	Study (reference)	Sample size	Age range (years)
	New Zealand	Bullen et al. (1998)	986	65–84
	New Zealand	Flight et al. (1984)	323	14–15
	New Zealand	Mann et al. (1991)	2 363	18–64
	New Zealand	National Survey (Ministry of Health 1999)	3 223	15–≥80
	Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	2 450	15–≥70
	Singapore	Hughes et al. (1990)	2 058	18–69
			109 750	
WPR	China	APCSC-Anzhen02 (APCSC secretariat, personal communication, 2001)	4 152	30–69
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	2 019	≥70
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	37 635	15–≥70
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	19 387	30–59
	China	INCLLEN (Anonymous 1992b)	1 188	35–65
	China	Tao et al. (1992)	4 280	35–54
	China	Tian et al. (1995)	631	15–64
	China	Yang et al. (1986)	1 054	15–≥55
	China	Zhuang et al. (1986)	4 072	0–102
	Beijing	MONICA study (Anonymous 1989)	1 673	25–64
	Hong Kong SAR	Fong et al. (1994)	696	20–≥60
	Hong Kong SAR	Woo et al. (1997)	1 010	25–74
	Taiwan, China	APCSC-CVDFACTS/Two Townships (APCSC secretariat, personal communication, 2001)	7 004	0–≥70
	Papua New Guinea	Lindeberg et al. (1994)	166	20–86
	Papua New Guinea	Scrimgeour et al. (1989)	121	17–59
	Philippines	INCLLEN (Anonymous 1992b)	274	35–65
			90 057	

^a Russia in original publication.

Table 7.2 Cholesterol measuring techniques of studies included in this review

	Yes (%)	Not stated (%)
Trained staff	94	6
Approved laboratory ^a	94	6
<i>Fasting sample</i>		28
All	47	NA
Some	4	NA
None	21	NA
<i>Storage of sample</i>		43
Refrigeration	16	NA
Deep freeze	30	NA
Storage not necessary	11	NA
<i>Analysis method</i>		34
Enzymatic	56	NA
Extraction	6	NA
Other	4	NA

NA Not applicable.

^a Laboratory associated with a hospital, university or research institution.

Approximately half of the studies utilized random sampling of individuals or households, including stratified random sampling; the other half used methods such as house-to-house or workplace surveys. Response rates were documented in 72% of the studies, of which response rate was >80% in 32% of them, between 50% and 80% (including those where response was >80% in some subcategories) in 63% of them, and documented to be lower than 50% in only six studies. For completeness, full documentation of sampling method, response rate and cholesterol measuring techniques are presented in Appendix A, which is intended only for those who require more data on individual studies. A summary is given in Table 7.2.

In most studies, a laboratory was associated with a hospital, university or research institution, and the staff appeared to have received appropriate training. Whether the blood sample was taken after the individual had fasted has an impact on lipid subfractions such as triglycerides rather than on total cholesterol, but this information also provides an indication of the consistency with which samples were taken, and the degree of detail given in publications. The majority of analyses were performed using newer enzymatic techniques, rather than the older extraction analyses.

2.2 METHODOLOGY TO ESTIMATE MEAN AND STANDARD DEVIATION OF CHOLESTEROL DATA

Mean cholesterol, standard deviation, sample size and age ranges from all reviewed data sources were extracted and entered into an Excel database. Scatter plots of these cholesterol data for each subregion, utilizing the midpoints in study age categories, are presented below in Figures 7.2–7.5.

The cholesterol data obtained from published studies including various age ranges were presented by age categories that were different from those required for the CRA project. For this reason, a method was needed which would make complete use of the available data and then combine them to produce estimates for subregions and age groups. The first step was to assess the general shape of association using all the available data. Second, associations were estimated for each subregion separately where sufficient data were available. For subregions with limited data, the association was estimated using complete data available from other subregions. Finally, these subregional age–cholesterol associations for males and females were used to predict subregional cholesterol levels.

It should be noted that no step specifically estimates mean cholesterol at the country level; this approach is explained in greater detail below.

AGE–CHOLESTEROL RELATIONSHIPS

The data from the literature were first used to assess the shape of the association of cholesterol with age using SPLUS software. At this stage no assumptions were made about the shape of association and therefore non-parametric methods were applied.

Figures 7.2 and 7.3 demonstrate that there were variable amounts of data available among the different subregions, so initially analyses were limited to those subregions with the most data spread across all age groups. The six subregions thus examined were AMR-A, AMR-B, EMR-B, EUR-A, WPR-A and WPR-B. Previous analyses had demonstrated that the shape of the age–cholesterol relationship may vary depending on absolute level of cholesterol (APCSC secretariat, personal communication, 2001). Therefore, analyses of pooled data from the six subregions were stratified by overall cholesterol levels into plausible low (<4.7 mmol/l), medium (4.7–5.5 mmol/l) and high (>5.5 mmol/l) groups (Figure 7.6), as we describe below using the example of WPR-A.

The purpose of determining the overall shape of the association between cholesterol and age was to enable extrapolation to other subregions where only limited data were available. The method utilized for subregions with sparse data is detailed below. The associations between age and cholesterol for both females and males were non-linear. The association for females increased between the ages of 30 and 65 years, and then fell slightly afterwards. For males, the association increased

Figure 7.2 Scatter plots of mean cholesterol (mmol/l) against age by subregion, for females

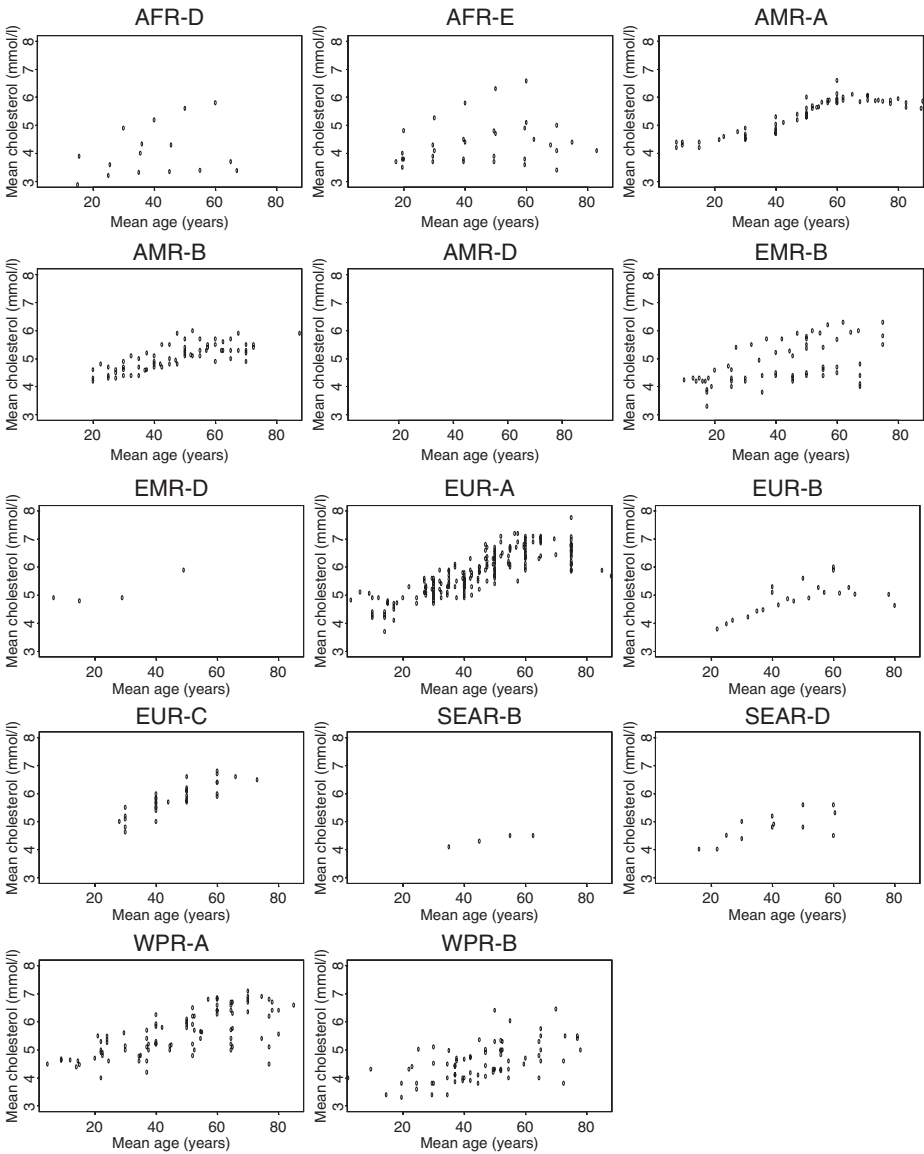


Figure 7.3 Scatter plots of mean cholesterol (mmol/l) against age by subregion, for males

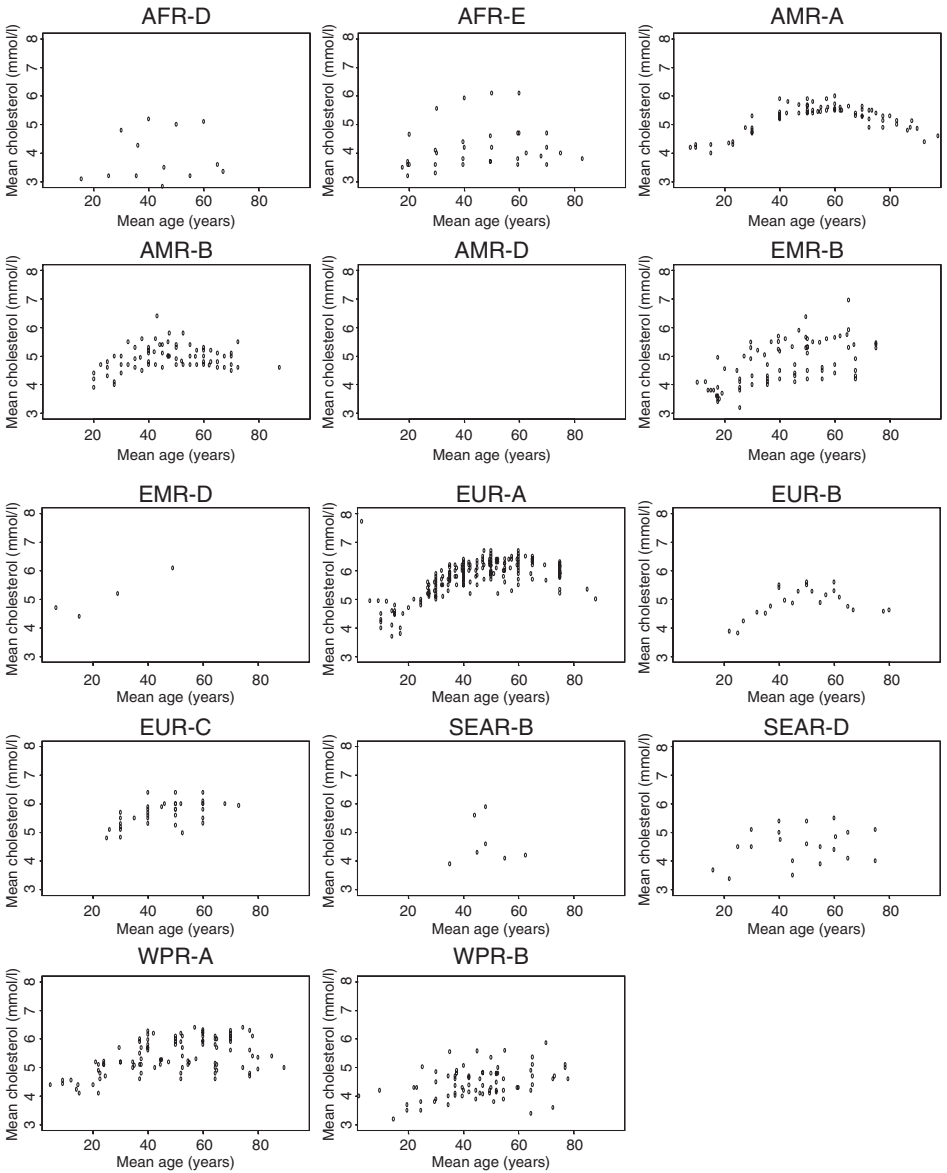


Figure 7.4 Scatter plots of mean cholesterol standard deviation (mmol/l) against age by subregion, for females

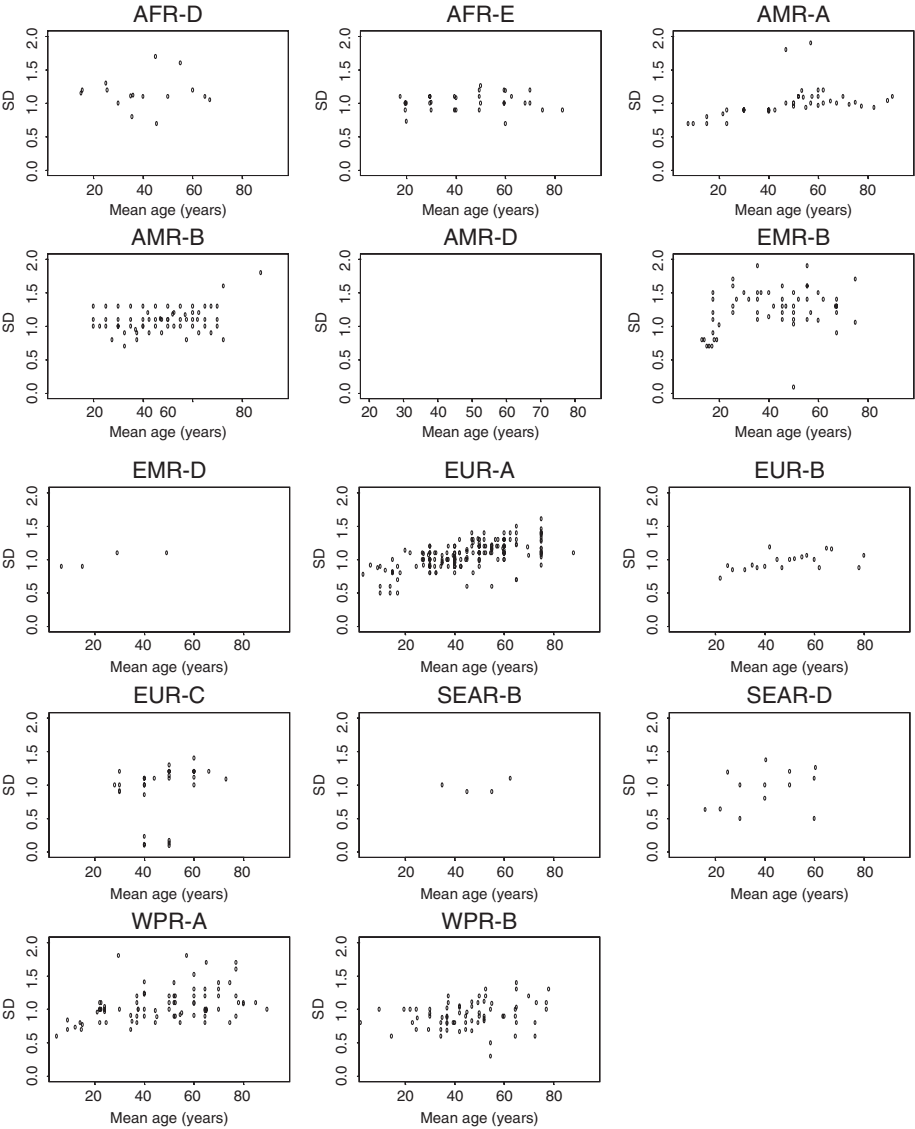


Figure 7.5 Scatter plots of mean cholesterol standard deviation (mmol/l) against age by subregion, for males

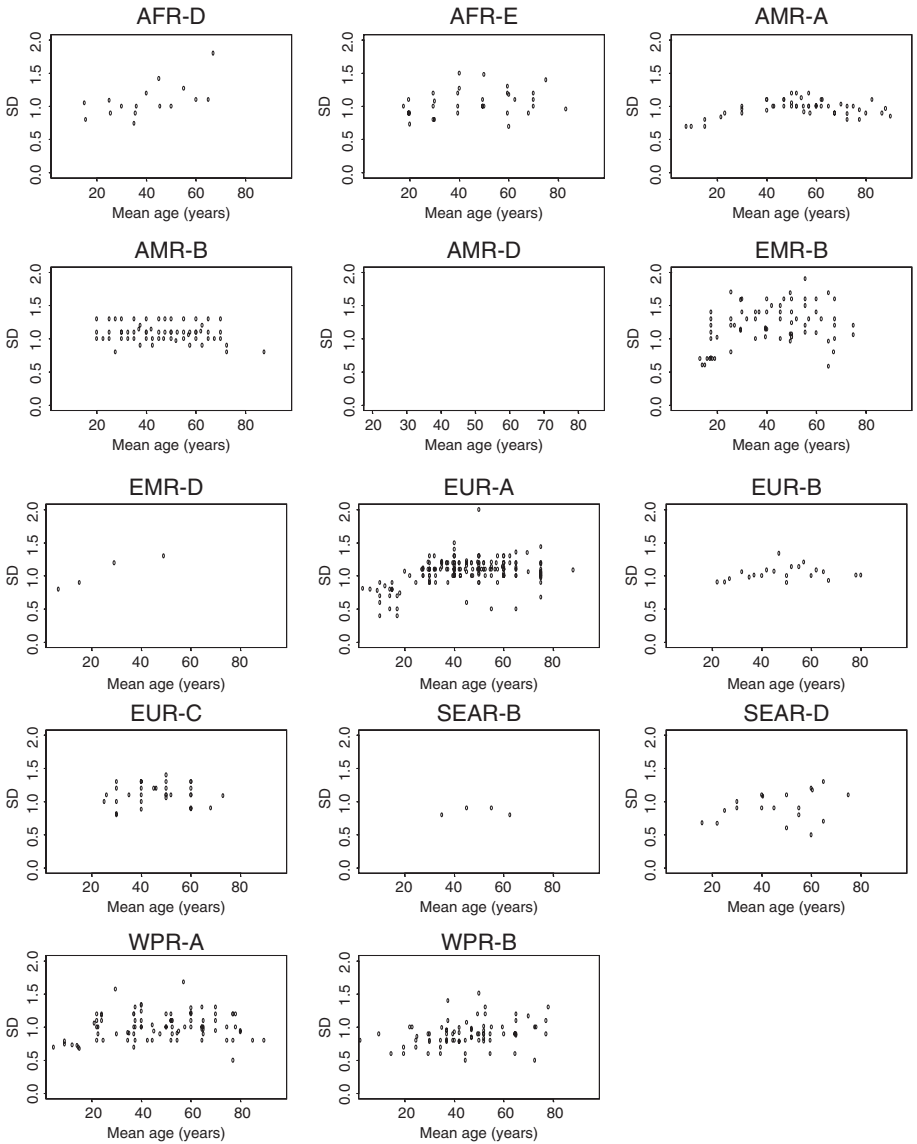
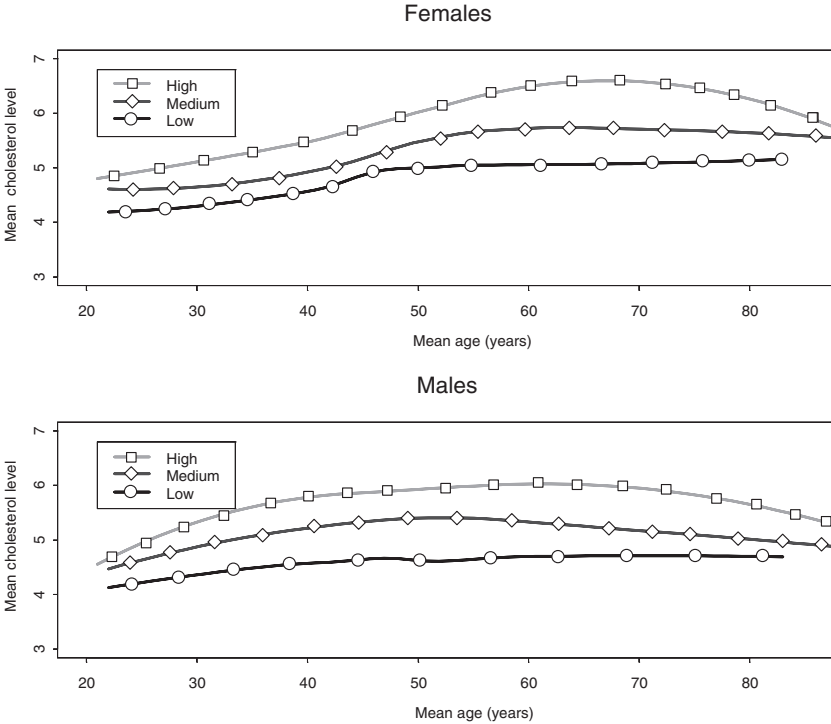


Figure 7.6 The cholesterol–age association from pooled data of six subregions^a for populations with high, medium and low cholesterol levels



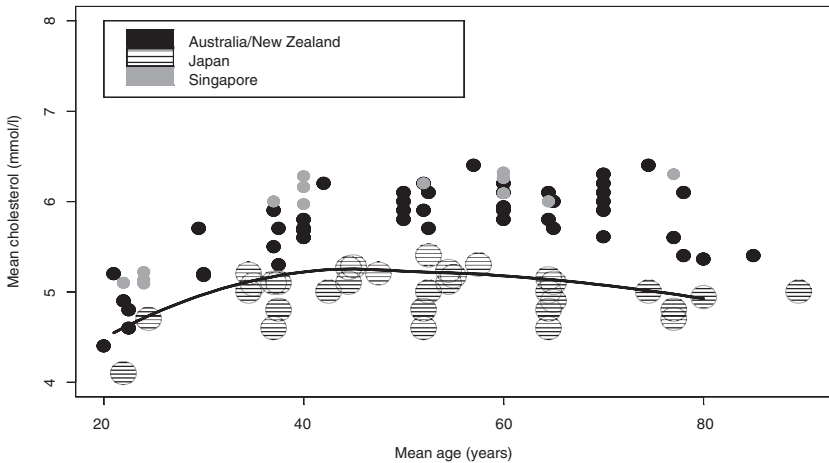
^a AMR-A, AMR-B, EMR-B, EUR-A, WPR-A and WPR-B.

Note: Overall cholesterol levels—Low = <4.7 mmol/l; Medium = 4.7–5.5 mmol/l; High = >5.5 mmol/l.

between the ages of 30 and 50 years, and then flattened before declining slightly in older age. Very little data were available in the populations aged >80 years, and therefore it is unclear whether cholesterol continues to decrease beyond the age of 70–79 years. These patterns were consistent among high, medium and low cholesterol subgroups; however, the gradient of the increase was greatest in the high cholesterol groups, and least in the low cholesterol groups.

Having established the non-linear association between age and mean cholesterol, the second step involved estimating the shape and level of this association for males and females in each subregion separately. The methodology differed by subregion depending on the available data. There were sufficient data to estimate the associations for males and females in six of the 14 subregions (AMR-A, AMR-B, EUR-A, EMR-B,

Figure 7.7 Combining cholesterol data (mmol/l) from country studies in WPR-A



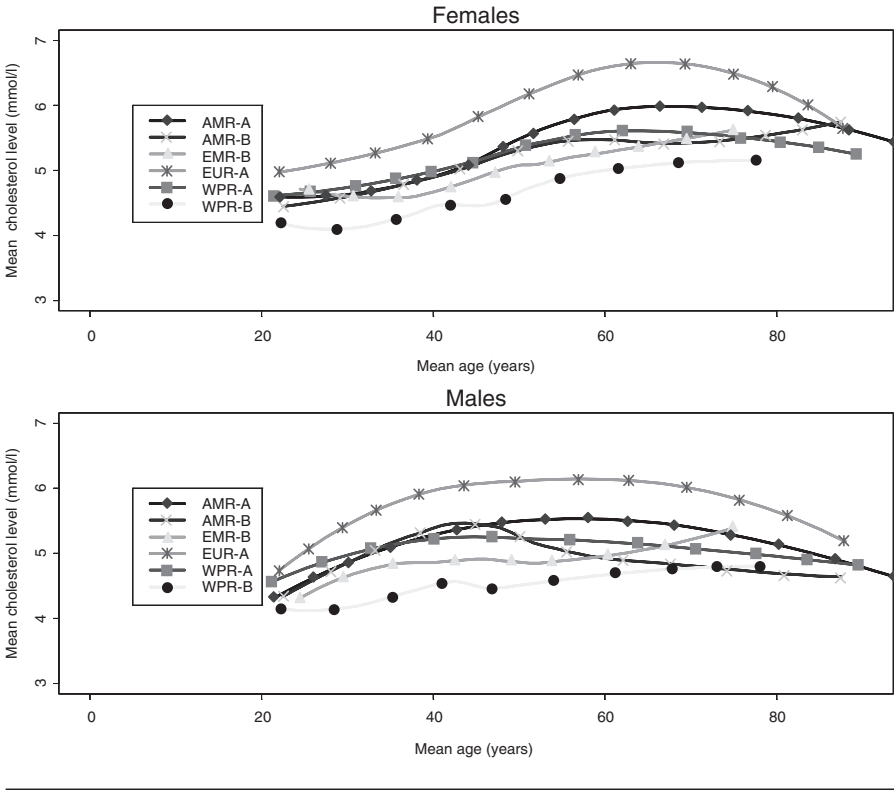
WPR-A and WPR-B). For example, for males in WPR-A, data were available from four countries (Australia, Japan, New Zealand and Singapore). The scatter plot in Figure 7.7 presents these cholesterol data at the country level.

Cholesterol data differed among and between these countries, with the size of the plot circles proportional to the population size and study size where more than one study was available within a country (Figure 7.7). Cholesterol levels were consistently lower for Japan across all age groups. The curve of best fit through these data weighted by study size within each country and by country population size within each subregion was estimated (i.e. a weighted regression line). Clearly, the fitted curve is weighted mostly to the Japanese studies due to Japan having the largest population size.

Although there was significant variation in the overall cholesterol levels between the different subregions, the shape of association across age groups was consistent for the six subregions where sufficient data were available (Figure 7.8).

For six of the remaining subregions (AFR-D, AFR-E, EUR-B, EUR-C, SEAR-B and SEAR-D), insufficient data were available to draw the age–cholesterol association accurately. Within these subregions, the available cholesterol data were pooled together to give age standardized mean levels weighted by country. That is, a single mean cholesterol level was estimated for each subregion with sparse data for males and females separately. Based on this level, one of three “age–cholesterol curves” was

Figure 7.8 The association of cholesterol with age for males and females in six subregions



chosen (Figure 7.6), and this curve was then shifted (up or down) to correspond with the calculated age adjusted mean cholesterol level for that subregion. Using this methodology, the “low cholesterol” curve (overall cholesterol <4.7 mmol/l) was used for AFR-D and AFR-E, the “middle cholesterol” curve (overall cholesterol 4.7–5.5 mmol/l) was used for EUR-B, SEAR-B and SEAR-D, and the “high cholesterol” curve (overall cholesterol >5.5 mmol/l) was used for EUR-C.

Of the two remaining subregions, no data were collected in this review for AMR-D, so data from AMR-B were used to estimate the mean cholesterol levels. In the one study for EMR-D, which included only 634 individuals, the overall mean cholesterol level was skewed by particularly high cholesterol levels in the oldest age group, compared to age patterns observed in other subregions. This was thought not to be representative of that subregion, therefore data from EMR-B were used to estimate cholesterol levels for EMR-D.

ESTIMATES OF MEAN CHOLESTEROL AND STANDARD DEVIATION

Estimates of mean cholesterol for each of the age groups were made using the age-cholesterol associations outlined above for each subregion and sex separately. Utilizing these associations, age-specific estimates for each subregion were obtained by using midpoints of each GBD age group and predicting the subregional average cholesterol levels. Cholesterol values for those aged >80 years were assumed to be the same as the 70–79 age group due to the extremely limited availability of cholesterol levels in the populations studied with a mean age >80 years. (Figures 7.2 and 7.3 demonstrate that very few subregions had any data for those with a mean age of >80 years.) A similar approach was used to estimate the standard deviations for each age, sex and subregion category. Current mean cholesterol results are presented in Table 7.3, and standard deviations are in Table 7.4.

2.3 UNCERTAINTY OF MEAN AND STANDARD DEVIATION OF CHOLESTEROL LEVELS

The uncertainty of the means and standard deviations of population distributions of cholesterol also had to be estimated. The approach described in the previous section to estimate the means and standard deviations makes as complete use as possible of all available data.

Table 7.3 Estimates of mean cholesterol levels (mmol/l) by subregion, sex and age

Subregion	Sex and age group (years)									
	Females					Males				
	30–44	45–59	60–69	70–79	≥80	30–44	45–59	60–69	70–79	≥80
AFR-D	4.6	5.1	5.2	5.2	5.2	4.5	4.7	4.7	4.7	4.7
AFR-E	4.6	5.1	5.2	5.2	5.2	4.5	4.7	4.7	4.7	4.7
AMR-A	4.8	5.6	6.0	5.9	5.9	5.2	5.5	5.5	5.2	5.2
AMR-B	4.8	5.4	5.4	5.2	5.2	5.3	5.0	4.9	4.8	4.8
AMR-D	4.8	5.4	5.4	5.2	5.2	5.3	5.0	4.9	4.8	4.8
EMR-B	4.6	5.1	5.4	5.6	5.6	4.8	4.9	5.1	5.4	5.4
EMR-D	4.6	5.1	5.4	5.6	5.6	4.8	4.9	5.1	5.4	5.4
EUR-A	5.4	6.3	6.7	6.5	6.5	5.9	6.1	6.1	5.9	5.9
EUR-B	4.6	5.3	5.5	5.4	5.4	5.0	5.1	5.2	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	6.5	5.5	5.8	5.8	5.7	5.7
SEAR-B	4.0	4.5	4.6	4.6	4.6	5.0	5.1	5.2	5.2	5.2
SEAR-D	4.9	5.7	5.8	5.7	5.7	4.8	5.0	5.0	5.0	5.0
WPR-A	4.9	5.5	5.6	5.4	5.4	5.2	5.2	5.1	5.0	5.0
WPR-B	4.3	4.8	5.1	5.1	5.1	4.5	4.6	4.7	4.8	4.8

Table 7.4 Estimates of cholesterol standard deviations (mmol/l) by subregion, sex and age

Subregion	Sex and age group (years)									
	Females					Males				
	30–44	45–59	60–69	70–79	≥80	30–44	45–59	60–69	70–79	≥80
AFR-D	1.0	1.0	1.0	1.1	1.1	0.9	1.0	1.0	1.0	1.0
AFR-E	1.0	1.0	1.0	1.1	1.1	0.9	1.0	1.0	1.0	1.0
AMR-A	0.9	1.1	1.1	1.0	1.0	1.0	1.0	1.0	0.9	0.9
AMR-B	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
AMR-D	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
EMR-B	1.4	1.4	1.4	1.2	1.2	1.4	1.4	1.3	1.1	1.1
EMR-D	1.4	1.4	1.4	1.2	1.2	1.4	1.4	1.3	1.1	1.1
EUR-A	1.0	1.2	1.2	1.1	1.1	1.2	1.2	1.1	1.1	1.1
EUR-B	1.0	1.1	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0
EUR-C	1.1	1.1	1.2	1.2	1.2	1.1	1.1	1.1	1.1	1.1
SEAR-B	0.8	0.9	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0
SEAR-D	1.0	1.1	1.1	1.1	1.1	1.0	1.0	1.0	1.0	1.0
WPR-A	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.8	0.8
WPR-B	1.0	1.1	1.3	1.2	1.2	1.1	1.1	1.2	1.1	1.1

Note: Reported standard deviations are derived from baseline cholesterol (i.e. one-off measures), which when corrected for regression dilution bias were used in all calculations on the “usual” scale.

However, there will always be errors associated with generalizing from the data collected to the subregional level. From the perspective of uncertainty, subregions can be divided into three main categories:

1. subregions where most of the countries have nationally representative surveys;
2. subregions with a lower coverage of countries and/or countries for which well designed surveys exist but on sub-national populations; and
3. subregions with countries where few studies and little or no data existed.

A subregion in which a national study is available for most of the countries would be expected to have low uncertainty (e.g. AMR-A and WPR-A). The remaining 12 subregions can be placed into either category 2 or 3, depending on the number of high-quality studies available. For these, subregional means and standard deviations were estimated from available data. Examining the heterogeneity observed between

different countries in these subregions provided a basis to quantify the uncertainty associated with data quality as well as extrapolation (see Figures 7.2 and 7.3). There may be a variety of causes underlying the heterogeneity, including sampling error and real sub-population differences. However, a subregion whose estimate is based on data from sub-national studies that suggest a wider range of mean cholesterol levels would have greater uncertainty. An example of this occurred in WPR-B, where, in the absence of a single national study for China, an estimate had to be based on all eligible studies even though there were significant differences between studies. Conversely, in WPR-A, heterogeneity is due in greater part to real population differences (i.e. Japan and Australia/New Zealand have substantially different cholesterol levels).

A simulation approach was taken to incorporate the uncertainty introduced in estimating mean cholesterol levels to reflect both sampling error as well as the variation of studies within countries. For each subregion separately, the simulation proceeded by reiterating the same weighted regression approach described earlier (i.e. weighted regression of mean cholesterol on mean age). Each iteration involved re-sampling of data points 10 000 times by treating each study as a random effect (i.e. two components of variation: study sampling error plus variation of study within country). The regression analysis was then re-iterated to obtain uncertainty distributions.

For subregions where insufficient data were available to assess the second component of variation accurately between countries, data were utilized from the data-rich subregions. Specifically, the average inter-country variation observed in AMR-A, AMR-B, EUR-A, EMR-B, WPR-A and WPR-B was applied to the remaining eight subregions.

Similar simulations were utilized to estimate the uncertainty intervals around the estimated standard deviations, the only difference being that the sampling distribution for the standard deviations was based on a chi-square in place of a normal distribution. Results from these simulations are provided in Tables 7.5 and 7.6.

2.4 THEORETICAL-MINIMUM-RISK EXPOSURE DISTRIBUTION

To make a judgment on the theoretical minimum cholesterol level, the evidence of the association between cholesterol and relative risk of cardiovascular end-points and data from “low cholesterol” populations were examined.

LOWEST RELATIVE RISK OF END-POINTS

A variety of prospective studies have examined the association between cholesterol and cardiovascular end-points. There is strong evidence that increased cholesterol is associated with increased risk of IHD, and the relationship is approximately linear on a logarithmic scale (Law 1999; Law et al. 1994b).

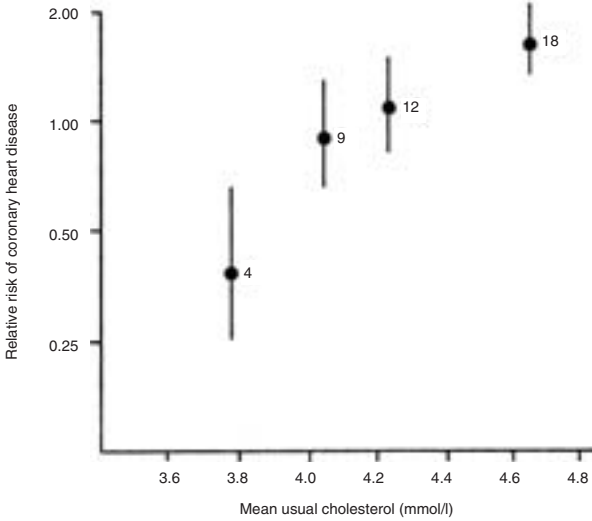
Table 7.5 Values of 95% CI for mean cholesterol (mmol/l) by subregion, sex and age

Subregion	Sex and age group (years)									
	Females				Males					
	30-44	45-59	60-69	70-79	≥80	30-44	45-59	60-69	70-79	≥80
AFR-D	(4.0-5.2)	(4.5-5.7)	(4.5-5.9)	(4.4-6.0)	(4.4-6.0)	(3.9-5.1)	(4.1-5.3)	(4.0-5.4)	(3.9-5.5)	(3.9-5.5)
AFR-E	(4.0-5.2)	(4.5-5.7)	(4.5-5.9)	(4.4-6.0)	(4.4-6.0)	(3.9-5.1)	(4.1-5.3)	(4.0-5.4)	(3.9-5.5)	(3.9-5.5)
AMR-A	(4.5-5.1)	(5.5-5.7)	(5.9-6.1)	(5.7-6.1)	(5.7-6.1)	(4.9-5.5)	(5.4-5.6)	(5.4-5.6)	(5.0-5.4)	(5.0-5.4)
AMR-B	(4.1-5.5)	(5.1-5.7)	(5.2-5.6)	(5.0-5.4)	(5.0-5.4)	(4.6-6.0)	(4.7-5.3)	(4.7-5.1)	(4.6-5.0)	(4.6-5.0)
AMR-D	(4.1-5.5)	(5.1-5.7)	(5.2-5.6)	(5.0-5.4)	(5.0-5.4)	(4.6-6.0)	(4.7-5.3)	(4.7-5.1)	(4.6-5.0)	(4.6-5.0)
EMR-B	(4.0-5.2)	(4.5-5.7)	(4.8-6.0)	(5.0-6.2)	(5.0-6.2)	(4.2-5.4)	(4.3-5.5)	(4.5-5.7)	(4.8-6.0)	(4.8-6.0)
EMR-D	(4.0-5.2)	(4.5-5.7)	(4.8-6.0)	(5.0-6.2)	(5.0-6.2)	(4.2-5.4)	(4.3-5.5)	(4.5-5.7)	(4.8-6.0)	(4.8-6.0)
EUR-A	(5.1-5.7)	(6.0-6.6)	(6.4-7.0)	(6.2-6.8)	(6.2-6.8)	(5.6-6.2)	(5.8-6.4)	(5.8-6.4)	(5.6-6.2)	(5.6-6.2)
EUR-B	(4.2-5.0)	(5.0-5.6)	(5.2-5.8)	(5.1-5.7)	(5.1-5.7)	(4.6-5.4)	(4.8-5.4)	(4.9-5.5)	(4.9-5.5)	(4.9-5.5)
EUR-C	(4.8-6.0)	(5.6-6.8)	(5.9-7.3)	(5.7-7.3)	(5.7-7.3)	(5.1-5.9)	(5.5-6.1)	(5.5-6.1)	(5.4-6.0)	(5.4-6.0)
SEAR-B	(3.4-4.6)	(3.9-5.1)	(3.9-5.3)	(3.8-5.4)	(3.8-5.4)	(4.4-5.6)	(4.5-5.7)	(4.5-5.9)	(4.4-6.0)	(4.4-6.0)
SEAR-D	(4.5-5.3)	(5.4-6.0)	(5.5-6.1)	(5.4-6.0)	(5.4-6.0)	(4.2-5.4)	(4.4-5.6)	(4.3-5.7)	(4.2-5.8)	(4.2-5.8)
WPR-A	(4.6-5.2)	(5.2-5.8)	(5.3-5.9)	(5.0-5.8)	(5.0-5.8)	(4.9-5.5)	(4.9-5.5)	(4.8-5.4)	(4.6-5.4)	(4.6-5.4)
WPR-B	(3.9-4.7)	(4.5-5.1)	(4.8-5.4)	(4.8-5.4)	(4.8-5.4)	(4.1-4.9)	(4.3-4.9)	(4.4-5.0)	(4.5-5.1)	(4.5-5.1)

Table 7.6 Values of 95% CI for standard deviation of cholesterol (mmol/l) by subregion, sex and age

Subregion	Sex and age group (years)									
	Females					Males				
	30-44	45-59	60-69	70-79	≥80	30-44	45-59	60-69	70-79	≥80
AFR-D	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.9-1.3)	(0.9-1.3)	(0.7-1.1)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)
AFR-E	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.9-1.3)	(0.9-1.3)	(0.7-1.1)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)
AMR-A	(0.8-1.0)	(1.0-1.2)	(1.0-1.2)	(0.9-1.1)	(0.9-1.1)	(0.9-1.1)	(0.9-1.1)	(0.9-1.1)	(0.8-1.0)	(0.8-1.0)
AMR-B	(1.0-1.2)	(1.0-1.2)	(1.1-1.3)	(1.0-1.4)	(1.0-1.4)	(1.0-1.2)	(1.0-1.2)	(1.0-1.2)	(0.9-1.3)	(0.9-1.3)
AMR-D	(1.0-1.2)	(1.0-1.2)	(1.1-1.3)	(1.0-1.4)	(1.0-1.4)	(1.0-1.2)	(1.0-1.2)	(1.0-1.2)	(0.9-1.3)	(0.9-1.3)
EMR-B	(1.2-1.6)	(1.1-1.7)	(1.2-1.6)	(1.0-1.4)	(1.0-1.4)	(1.2-1.6)	(1.1-1.7)	(1.1-1.5)	(0.9-1.3)	(0.9-1.3)
EMR-D	(1.2-1.6)	(1.1-1.7)	(1.2-1.6)	(1.0-1.4)	(1.0-1.4)	(1.2-1.6)	(1.1-1.7)	(1.1-1.5)	(0.9-1.3)	(0.9-1.3)
EUR-A	(0.9-1.1)	(0.9-1.5)	(1.0-1.4)	(1.0-1.2)	(1.0-1.2)	(1.1-1.3)	(0.9-1.5)	(0.9-1.3)	(1.0-1.2)	(1.0-1.2)
EUR-B	(0.8-1.2)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)
EUR-C	(0.9-1.3)	(0.9-1.3)	(1.0-1.4)	(1.0-1.4)	(1.0-1.4)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)
SEAR-B	(0.6-1.0)	(0.7-1.1)	(0.7-1.1)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)
SEAR-D	(0.8-1.2)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.9-1.3)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)	(0.8-1.2)
WPR-A	(0.7-1.1)	(0.8-1.0)	(0.8-1.0)	(0.8-1.0)	(0.8-1.0)	(0.7-1.1)	(0.8-1.0)	(0.8-1.0)	(0.7-0.9)	(0.7-0.9)
WPR-B	(0.7-1.3)	(0.9-1.3)	(1.2-1.4)	(1.0-1.4)	(1.0-1.4)	(0.8-1.4)	(0.9-1.3)	(1.1-1.3)	(0.9-1.3)	(0.9-1.3)

Figure 7.9 The association between cholesterol and IHD in the Shanghai Factory Workers Study



Source: Reprinted, by permission of the publisher, from Chen et al. (1991). Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *British Medical Journal*, **303**:276–282.

In populations from industrialized countries (e.g. Europe and North America), this relationship has seldom been demonstrated below a cholesterol level of 4.5–5.0 mmol/l (Chen et al. 1991). However, in other populations such as China, data suggest that this relationship may continue, without a threshold, below cholesterol levels of about 4.0 mmol/l (Chen et al. 1991; Law and Wald 1994; Law et al. 1994b) (Figure 7.9). Based on this evidence it would be feasible to set a theoretical minimum of usual cholesterol of at least 3.8 mmol/l.

Another source of data is clinical trials of cholesterol lowering from recent meta-analyses. Trials included in these overviews achieved substantial reduction in cholesterol with no adverse effects. The reductions are summarized in Table 7.7. These reductions of cholesterol also occurred in the lowest cholesterol group, i.e. those with baseline mean cholesterol of about 5.0 mmol/l. The aggregated data from trials therefore indicate that a substantial reduction in cholesterol is possible, across different baseline cholesterol levels, without risk of substantial adverse effects.

Further, the recently completed large-scale Heart Protection study (Heart Protection Study Collaborative Group 2002a, 2002b) demonstrated that cholesterol lowering in those with average or below average

Table 7.7 Reduction in cholesterol achieved by trials of statins

<i>Trial</i>	<i>Baseline mean cholesterol (mmol/l)</i>	<i>Mean cholesterol reduction (%)</i>	<i>Final mean cholesterol (mmol/l)</i>
LRC	7.5	9	6.9
HHS	7.4	10	6.7
WOSCOPS	7.0	20	5.6
4S	6.8	26	5.0
AFCAPS/TexCAPS	5.7	19	4.6
LIPID	5.6	18	4.6
CARE	5.4	20	4.3

Source: LaRosa et al. (1999) and Pignone et al. (2000).

total cholesterol levels was still associated with reduced risk of cardiovascular disease. This trial included over 20 000 participants and found no evidence of a threshold level below which lowering cholesterol did not produce a lower risk.

LOW CHOLESTEROL POPULATIONS

An alternative source of data relevant to setting a theoretical minimum comes from examining mean cholesterol levels in studies of so-called “unacculturated” populations with little cardiovascular disease and low cholesterol levels (Poulter and Sever 1994). Unacculturated generally refers to those populations that are relatively isolated and have preserved their lifestyle over many generations.

An overview of typical cholesterol values in men aged 45–64 years in different populations noted that while mean cholesterol ranged from 5.5 to 7.0 mmol/l in many industrialized populations, it was much lower in hunter-gatherer societies where mean values were as low as 3.0–3.5 mmol/l (Law 1999; Law and Wald 1994). Data from individual studies around the world that have focused on these “low cholesterol” populations are summarized in Table 7.8. In the Shanghai study, there was a strongly positive and apparently independent relation between cholesterol concentration and death from IHD, even at these lower levels (Chen et al. 1991) (Figure 7.10).

Typically, the data show that there is a very low prevalence of cardiovascular disease in these populations, which exhibit an absence of obesity due to diets low in salt, cholesterol and fat (particularly animal fat), and a lifestyle requiring heavy physical labour (Barnes 1965; Carvalho et al. 1989; Connor et al. 1978; He et al. 1991a, 1991b; Page et al. 1974; Poulter and Sever 1994; Sever et al. 1980). There is also evidence of low blood pressure levels, and no age-related rise in either cholesterol or blood pressure levels. Data from these studies indicate that many of these populations have mean cholesterol levels of about

Table 7.8 Cholesterol levels in low cholesterol populations

<i>Country (reference)</i>	<i>Population</i>	<i>Mean cholesterol levels</i>	<i>Patterns with age</i>
<i>Africa</i>			
Tanganyika ^a (Mann et al. 1964)	Masai tribe (mostly males) with virtually no cardiovascular disease.	3.0–3.7 mmol/l; >5.2 mmol/l rare	No evidence of increasing cholesterol with advancing age
<i>Americas</i>			
Mexico (Casdorph 1972; Connor et al. 1978)	Tarahumara Indians who lived in the mountains	3.0–3.5 mmol/l	No age-related rise in cholesterol
<i>Western Pacific</i>			
China (Fan et al. 1990)	An ecological study of 6 500 individuals rural China	3.3 mmol/l	—
China (Chen et al. 1991)	9 021 males and females aged 35–64 years at baseline in urban Shanghai	3.1–5.4 mmol/l (baseline) 3.8–4.6 mmol/l (3 years)	— —
Papua New Guinea (Barnes 1965)	The isolated Bomai and Yongamuggi people	3.4–3.6 mmol/l for males and females	—
Solomon Islands (Page et al. 1974)	Six tribal societies with varying levels of acculturation	3.0–3.7 mmol/l in least acculturated groups	No age-related rise in cholesterol
— No data.			
^a Country name correct as at time of study.			

3.8 mmol/l or lower. Therefore, setting a theoretical minimum at 3.8 mmol/l is justified based on all of the data.

SAFETY OF LOW CHOLESTEROL LEVELS

Concerns have been expressed over whether lowering cholesterol may be harmful, and therefore setting a theoretical minimum too low may have adverse consequences. Some data have suggested a negative association between cholesterol and haemorrhagic stroke (Iso et al. 1989); however, a recent analysis has suggested that this is in fact more likely to be a null association (Suh et al. 2001). It should also be noted that even if there were a small increase in risk of haemorrhagic stroke for people with very low cholesterol levels, this would be outweighed overall by the benefits resulting from lower risk of IHD (Bucher et al. 1998; Law et al. 1994a).

There is no strong consistent evidence that low or reduced cholesterol concentrations increase mortality from non-cardiovascular diseases such as cancer or infection (Law et al. 1994a). Overviews of trials have not

detected increases in causes of non-cardiovascular disease mortality (Hebert et al. 1997; LaRosa et al. 1999) despite achieving relatively large decreases in cholesterol. In many cases, the apparent association is actually due to disease causing low cholesterol rather than vice versa (Law et al. 1994a). A recent meta-analysis of trials found no convincing evidence that the risk of “non-illness”-related mortality (deaths from suicide, accident or trauma) was strongly associated with cholesterol lowering (Muldoon et al. 2001).

Finally, data relating to low cholesterol levels come from research on those with heterozygous familial hypobetalipoproteinaemia. These individuals have cholesterol levels as low as 2.0–3.0 mmol/l and a prolonged life expectancy, as coronary artery disease is avoided—but no recognized adverse effects from the low cholesterol (Law 1999).

STANDARD DEVIATION OF THE THEORETICAL-MINIMUM-RISK EXPOSURE DISTRIBUTION

The choice of standard deviation around the theoretical minimum was based on examining the relationship of the standard deviation and mean of cholesterol using all available data from our review of the literature (Figure 7.10). From this illustration, a distribution with a mean of 3.8 mmol/l would typically have a standard deviation of 0.9 mmol/l (baseline), which equates to 0.6 mmol/l (usual).

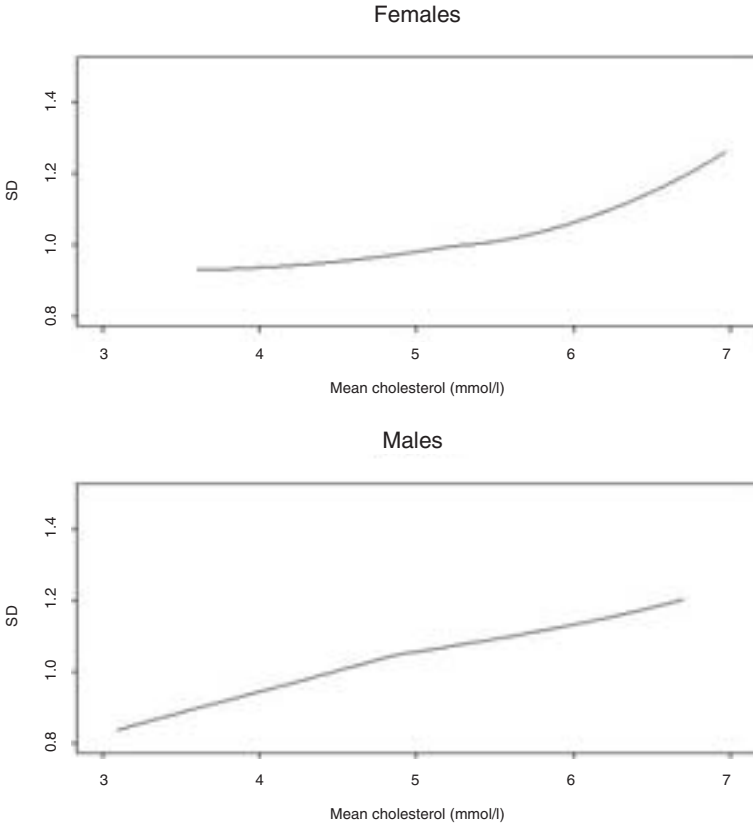
3. CHOLESTEROL–DISEASE RELATIONSHIPS

Data on the relationship between cholesterol and disease outcomes come from two main types of studies (MacMahon 1994). Prospective observational studies provide data from which the effects of prolonged cholesterol differences can be estimated (MacMahon et al. 1990), that is, hazard ratios. Trials provide data about the effects of short-term cholesterol reduction (Collins et al. 1990), or risk reversal. Results from prospective observational studies will be considered first.

3.1 DATA SOURCES FOR HAZARD RATIOS

Observational studies have been conducted in a variety of settings that examine the association between cholesterol and disease. However, the results of many of these individual studies are limited. Many observational studies have small sample sizes or an insufficient number of end-points, and therefore lack the power required to provide reliable estimates of associations for different population subgroups (e.g. sex and age groups) and/or specific diagnostic categories (MacMahon et al. 1990). Individual studies do not always provide information on the direction of the association at lower cholesterol levels, making it difficult to assess whether the observed association is continuous or has a threshold level. In addition, these studies frequently do not standardize the size of the association for bias and confounding—in particular,

Figure 7.10 Association between mean cholesterol and standard deviation for review data



regression dilution bias (MacMahon et al. 1990). This bias occurs when associations are calculated from “one-off” measures of cholesterol rather than “usual” cholesterol. (There is further discussion of this bias in the next section.)

Overviews or meta-analysis of observational studies, or meta-analyses, overcome many of the size limitations of individual studies. At the time of writing four major overviews have been conducted that included data on cholesterol, and their main design features are summarized in Table 7.9.

In contrast to the first three meta-analyses, which utilized tabular data, the APCSC (1999) involved analyses of individual participant data. Therefore, it can more reliably adjust for confounding and provide more reliable estimates of hazard ratios.

Table 7.9 Characteristics of major cholesterol cohort study overviews

<i>Study characteristics</i>	<i>Law et al. (1994b)</i>	<i>Prospective Studies Collaboration (PSC 1995)</i>	<i>Eastern Collaborative Research Group (Anonymous 1998a)</i>	<i>Asia-Pacific Cohort Studies Collaboration (APCSC secretariat, personal communication, 2001)</i>
Aims	To estimate by how much and how quickly a given reduction in cholesterol concentration will reduce the risk of IHD	To assess the relationship between BP and total blood cholesterol and stroke, and determine how the strength of the relationship between BP and stroke varied with age	To assess the relationship between BP and total blood cholesterol and stroke in Asian populations, and determine whether the strength of the relationship varied with type of stroke	To produce region, age- and sex-specific blood pressure and cholesterol associations for stroke (including subtypes), IHD, and total cardiovascular disease
Number of studies included	10	45	18	29
Regions included	England, Scotland, Europe, Hawaii and Israel	Asia, Australia, Europe, Hawaii, the Middle East and USA	China (13 cohorts), Japan (5)	Australia (3), mainland China (9), Hong Kong SAR (1), Japan (12), New Zealand (1), Republic of Korea (1), Singapore (1), Taiwan, China (1)
Number of participants	494804	450000	124774	353065
% male	100%	61%	61%	57%
Age range (years)	35–84	15–99	18–98	20–107
Mean age at baseline	Not available	Not available	48 years	47 years
Follow-up	Range of 7–23 years	Range of 5–30 years, mean 15 years	Range unknown, mean 9 years	Range of <1–29 years, mean 7 years

BP Blood pressure.

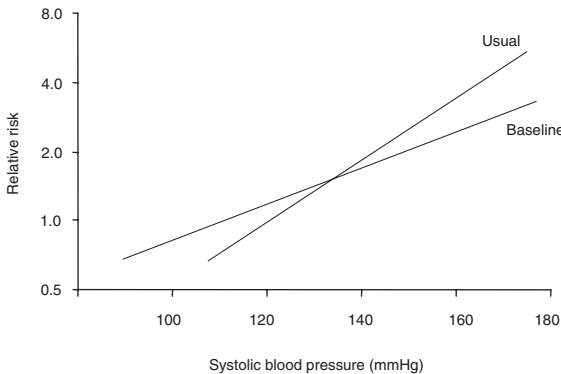
Of the four overviews, only two included analyses for the IHD end-point; Law et al. (1994b) and APCSC (APCSC secretariat, personal communication, 2001). The former will be used as the primary data source for relative risk estimates of IHD due to the greater sample size. Three overviews included data on cholesterol and stroke (Anonymous 1998a; APCSC secretariat, personal communication, 2001; PSC 1995). However, only APCSC analyses were based on individual participant data and provided age-specific analyses of total stroke and stroke subtypes. It will therefore be the primary data source for relative risk estimates of stroke.

3.2 ANALYSIS ISSUES

An important factor that must be accounted for with estimates of the association between cholesterol and cardiovascular end-points from observational data is regression dilution bias. This bias occurs because baseline or one-off measures of cholesterol are subject to random fluctuations, due partly to the measurement process, and partly to any real but temporary deviations at the baseline from the usual cholesterol level (MacMahon et al. 1990). Therefore, baseline cholesterol values have a wider distribution than the “usual” cholesterol values. With repeated measures there is a “regression to the mean” of values (MacMahon 1994), whereby an initially extreme observation tends to become less abnormal with replication (Strachan and Rose 1991).

This imprecision in measurement not only influences distribution, but also affects the association with disease outcomes (MacMahon et al. 1990). Figure 7.11 illustrates the effect of regression dilution

Figure 7.11 Effects of regression dilution bias on the association between blood pressure and relative risk of cardiovascular disease



bias for blood pressure, but the same would be true for cholesterol. The baseline distribution has a shallower slope than usual cholesterol on the curve-relation of cholesterol to relative risk of disease. Analyses have suggested that correcting for regression dilution bias increases the slope of the association by as much as 61% (Law et al. 1994c). If this bias is not corrected, the strength of the association between cholesterol and disease incidence is underestimated (“regression dilution bias”) (MacMahon 1994). This systematically dilutes the apparent importance of cholesterol and can result in systematic and substantial underestimation of risk of disease with usual cholesterol (MacMahon et al. 1990).

The size of the dilution is directly related to the extent to which cholesterol measurements are subject to regression to the mean. Several major meta-analyses conducted in recent years aimed to address these limitations with correction for regression dilution bias (Anonymous 1998a; APCSC 1999; PSC 1995). It is possible to use repeated measures on cholesterol to obtain an estimate of the attenuation factor in order to correct for this bias in the analysis. An attenuation factor of 1.82 was calculated from remeasurement data in the Prospective Studies Collaboration (PSC) (1995), and 1.90 in the Eastern study (Anonymous 1998a). In the APCSC, analyses of remeasurement data from cohorts estimated that the correction factor was 1.8. (APCSC secretariat, personal communication, 2001). Here, use of the term “usual cholesterol” indicates that the association between cholesterol and the disease end-point has been corrected for regression dilution bias.

The surrogate dilution effect is another factor that should be considered specifically in cholesterol studies. This effect arises because observational studies underestimate the effect of lower cholesterol relative to the trials (Law et al. 1994c). In a cohort study, a 1 mmol/l lower cholesterol concentration is associated with about 0.67 mmol/l of LDL, but in cholesterol lowering trials, a 1 mmol/l lower total cholesterol is usually comparable to 1 mmol/l lower LDL. Law et al. (1994c) adjusted for both regression dilution bias and the surrogate dilution effect in their analyses, and the final correction factor was 1.61.

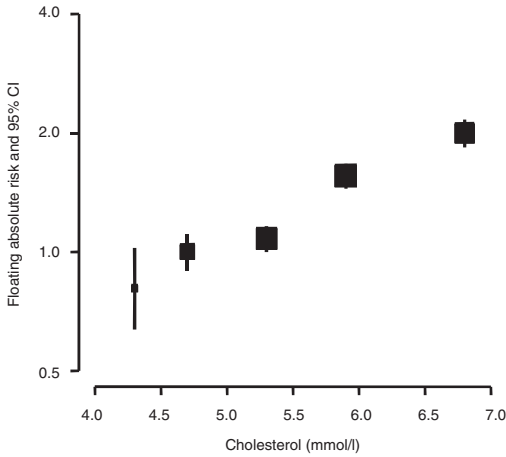
3.3 ESTIMATES OF CHOLESTEROL–DISEASE RELATIONSHIPS

A summary of the results of the four prospective study overviews is presented in Table 7.10, and each of these end-points will now be considered in detail.

CHOLESTEROL AND IHD

Analyses from the APCSC overview (APCSC secretariat, personal communication, 2001) and that by Law et al. (1994b) demonstrated that the relative risk of IHD increased with increasing cholesterol level, and that the association was roughly linear when plotted on a log scale (Figure 7.12 and 7.13).

Figure 7.12 Usual cholesterol level and risk of IHD in the Asia-Pacific region



Source: APCSC data (APCSC secretariat, personal communication, 2001).

This means that the proportional difference in risk associated with a given absolute difference in usual cholesterol is similar at all levels of cholesterol, at least within the range studied. This continuous association showed no evidence of a threshold level of cholesterol, below which lower levels of cholesterol are no longer associated with lower relative risks of IHD (down to almost 4.0 mmol/l). Further, there was no evidence of an upper threshold level above which the relative risk of IHD increased much more rapidly (Anonymous 1998a; APCSC secretariat, personal communication, 2001; Law et al. 1994c; PSC 1995).

Overall, the analyses in both the APCSC (APCSC secretariat, personal communication, 2001) and by Law et al. (1994b) suggested that a 0.6 mmol/l lower cholesterol was associated with 24–27% lower risk of IHD. There was no evidence of a difference in the size of the association between males and females or fatal and non-fatal IHD end-points.

Age has an important influence on the size of the cholesterol–end-point relationship, as the associations are steeper for those in younger age groups. (This also largely accounts for the apparent heterogeneity between the cholesterol–IHD associations in the cohorts in Figure 7.13.) This limits the ability to compare directly the overall relative risk estimates across the overviews, as it is only appropriate to compare age-specific results. The gradient of the cholesterol–IHD association varies with age at baseline, the gradient being much steeper for younger

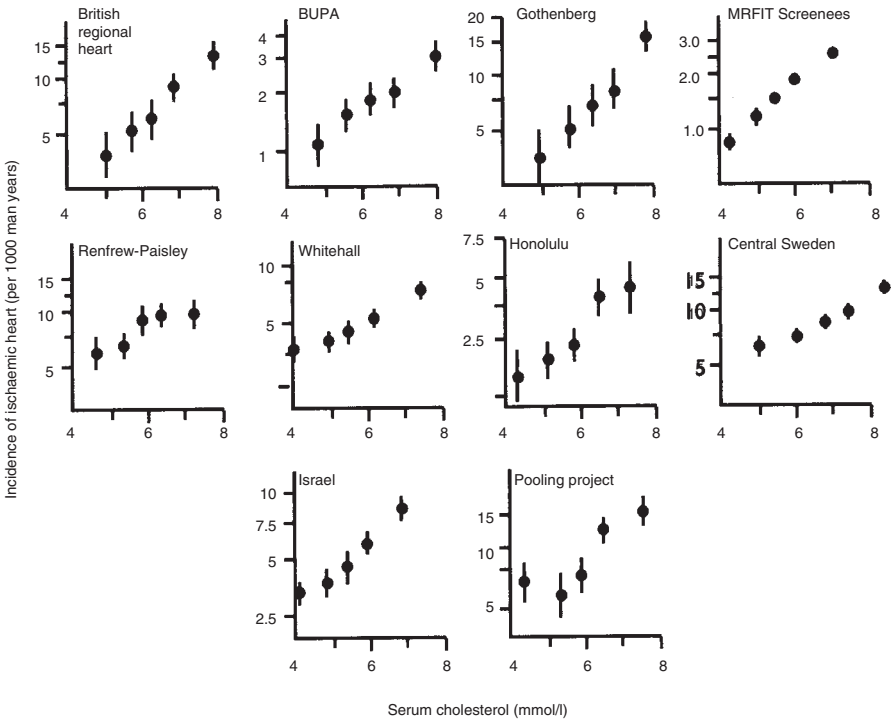
Table 7.10 Summary results of major cohort study overviews

Study end-points	Law et al. (1994b)	Prospective Studies Collaboration (PSC 1995)	Eastern Collaborative Research Group (Anonymous 1998a)	Asia-Pacific Cohort Studies Collaboration (APCSC secretariat, personal communication, 2001)
IHD end-points	1881 IHD events recorded	—	—	2838 IHD events, 1607 (57%) fatal
	0.6 mmol/l ↓ cholesterol associated with overall reduction of IHD of 27% from 10 studies combined	—	—	0.6 mmol/l ↓ cholesterol RR = 0.76 (95% CI 0.73–0.79) (24% reduction in IHD)
Stroke end-points	—	13 397 participants were recorded as having had a stroke	1798 strokes, 995 (55%) fatal, 39% had data on subtype of which 42% haemorrhagic	2937 strokes, 56% fatal
	—	1 mmol/l ↑ cholesterol RR = 0.98 (95% CI 0.94–1.01)	0.6 mmol/l ↓ cholesterol RR = 0.92 (95% CI 0.72–1.17) (8% reduction in stroke)	1 mmol/l ↓ cholesterol RR = 0.87 (95% CI 0.81–0.94) (13% reduction in stroke)

Key: ↑, raised; ↓, decreased.

— No data.

Figure 7.13 Incidence of ischaemic heart disease and usual cholesterol level in 10 cohort studies



Source: Reprinted, by permission of the publisher, from Law et al. (1994b) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal*, 308:367–372.

age groups. While the proportional change in IHD risk per unit change in cholesterol is less extreme in old age than in middle age, the relationship remains positive for all age groups (APCSC secretariat, personal communication, 2001; Law et al. 1994b). It is therefore necessary to use age-specific estimates for hazard ratios in all cholesterol analyses for CRA.

The results of both overviews are relatively consistent, but due to the larger number of participants and end-points in the review by Law et al. (1994b), these relative risk estimates, transformed for application to GBD age groups, were used in the analyses of this chapter. Table 7.11 presents relative risks from the overview by Law et al. (1994b) transformed into GBD age groups for a 1 mmol/l difference in usual cholesterol.

Table 7.11 Relative risk of IHD associated with a 1 mmol/l difference in usual cholesterol

Age group (years)	Relative risk (95% CI)
30–44	0.51 (0.36–0.73)
45–59	0.50 (0.45–0.56)
60–69	0.70 (0.62–0.79)
70–79	0.77 (0.69–0.86)
≥80	0.75 (0.67–0.84)

Source: Modified from overview by Law et al. (1994b).

CHOLESTEROL AND STROKE

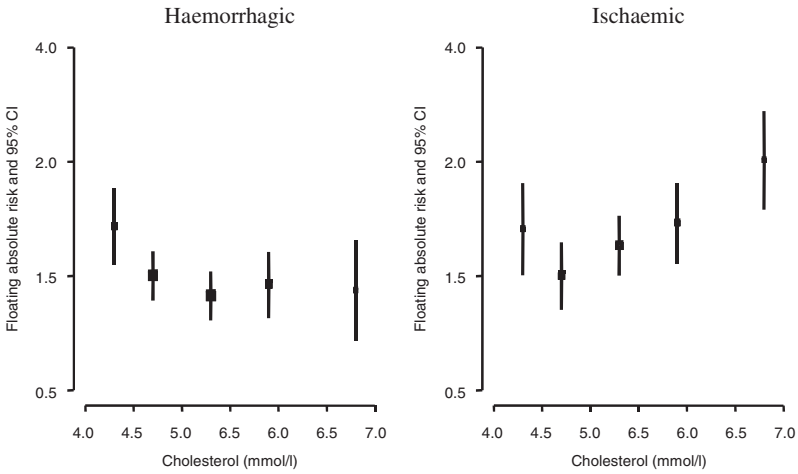
Few data are available on the association between cholesterol and stroke, and the relationship is more complex. Many individual cohorts and the PSC have found no association between cholesterol and risk of stroke death (PSC 1995). However, recent meta-analyses and other studies have reported that this apparent null association may be principally due to a quantitatively different association between cholesterol and the two major types of stroke—haemorrhagic and ischaemic. A variety of studies have attempted to clarify these associations. Table 7.12 summarizes some of the largest cohort studies undertaken, with several hundred recorded stroke events by subtype.

Several of these studies showed evidence of a positive association between cholesterol and risk of ischaemic stroke (Anonymous 1998a; Benfante et al. 1994; Iso et al. 1989; Jorgensen et al. 1995; Leppala et al. 1999; Neaton et al. 1992, 1993; Yano et al. 1994). Other individual studies failed to find an association between cholesterol and ischaemic stroke (Nakayama et al. 1997; Szatrowski et al. 1984; Tanaka et al. 1982), but the extent of misclassification of stroke subtype was uncertain in these studies. The association of cholesterol with haemorrhagic stroke is less clear, with some analyses suggesting either a negative (Anonymous 1998a; Iso et al. 1989; Leppala et al. 1999; Neaton et al. 1992, 1993; Yano et al. 1989, 1994) or null association (Iribarren et al. 1996; Suh et al. 2001).

Analyses from the APCSC show the different association of cholesterol with stroke subtypes (Figure 7.14); a positive association for ischaemic stroke and a negative/null association for haemorrhagic stroke. In the CRA analyses, data from the APCSC overview were used, given the size and availability on individual data.

The age-specific relative risks of haemorrhagic and ischaemic stroke with a 1 mmol/l difference in usual cholesterol are presented in Table 7.13.

Figure 7.14 Usual cholesterol level and risk of haemorrhagic and ischaemic stroke



Source: APCSC data (APCSC secretariat, personal communication, 2001).

Overall, APCSC data indicated that the association of cholesterol with stroke varies with age at baseline, the gradient being much steeper for younger age groups. As discussed in relation to IHD, this means that the proportional change in stroke risk per unit change in cholesterol is less extreme in old age than in middle age (APCSC secretariat, personal communication, 2001). It is therefore necessary to use age-specific estimates for hazard ratios in all cholesterol analyses for CRA. There was no evidence of differences in the association between males and females, so sex-specific estimates are not necessary.

Despite having data from the APCSC, it is difficult to incorporate the different cholesterol-stroke subtype associations into CRA analyses as the only GBD end-point for stroke relates to total stroke. It is not possible to conduct analyses for ischaemic and haemorrhage stroke independently, and it is not appropriate simply to apply the relative risk for total stroke events to all 14 subregions, since there is evidence that the relative proportions of haemorrhagic and ischaemic stroke vary among them (Anderson et al. 1993; Bamford et al. 1990; Chen et al. 1992; Giroud et al. 1991; Hung 1993; Jeng et al. 1998; Nakayama et al. 1997; Suzuki et al. 1987; Thrift et al. 2001; Wu et al. 1992). Analyses of total stroke must therefore be modified to reflect these differing proportions, and the different types of association between cholesterol and stroke

Table 7.12 Data from major cohort studies on the association between cholesterol and risk of stroke subtype

Study	Participants	Ischaemic stroke	Haemorrhagic stroke
The American MRFIT study (Iso et al. 1989; Neaton et al. 1992, 1993)	350 000 males At 6 years, 230 fatal strokes had occurred At 12 years, 765 stroke deaths had occurred	Risk of death was significantly increased with increasing cholesterol at both points of follow-up	Risk of haemorrhagic stroke death highest in those with lowest cholesterol (if DBP ≥ 90 mmHg) at 6 and 12 years
American Kaiser Permanente Study (Iribarren et al. 1996)	61 756 individuals At 16 years 386 haemorrhagic strokes recorded	—	No relationship among those aged 40–64 years Negative association between low cholesterol and risk of haemorrhagic stroke in elderly males
British Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Leppala et al. 1999)	28519 males aged 50–69 years At 8 years 1 057 males had a stroke	Cholesterol was associated with increased risk of cerebral infarction at levels ≥ 7 mmol/l	Cholesterol was inversely associated with the risk of intracerebral haemorrhage (Leppala et al. 1999)
Copenhagen Stroke Study (Jorgensen et al. 1995)	Included over 1 000 males who had suffered a stroke	Cholesterol was positively associated with risk of ischaemic stroke	—
A cohort study in Sweden (Gatchev et al. 1993)	54 000 participants At 20 years, 347 haemorrhagic strokes had been reported	—	Relative risk for cerebral haemorrhage increased with decreasing cholesterol level in females, but the risk function was U-shaped in males
Honolulu Heart Program (Benfante et al. 1994; Yano et al. 1989, 1994)	Over 6 000 Japanese males in Hawaii followed for 15 years (252 ischaemic strokes) Over 7 000 of these males followed for 18 years (116 haemorrhagic strokes)	A continuous increase in isch. stroke rates with increasing levels of cholesterol	An inverse association between cholesterol and the risk of haemorrhagic stroke, at least in males with cholesterol in the lowest quintile
Korea Medical Insurance Corporation study (Suh et al. 2001)	114 793 males in the Republic of Korea, aged 35–59 years followed for 6 years	—	No overall association between the relative risk of intracerebral haemorrhage and total cholesterol
Eastern Stroke and CHD Collaborative project (Anonymous 1998a)	Overview of 18 cohort studies in China and Japan, 11 studies, >60 000 participants included data on stroke subtype (494 non-haemorrhagic and 404 haemorrhagic strokes)	A positive association between cholesterol and non-haemorrhagic stroke	An inverse association between cholesterol and haemorrhagic stroke (Anonymous 1998a)

— No data.

Table 7.13 Relative risk of stroke with a 1 mmol/l difference in usual cholesterol

Age group (years)	Risk of stroke event	
	Haemorrhagic stroke relative risk (95% CI)	Ischaemic stroke relative risk (95% CI)
30–44	1.03 (0.64–1.64)	0.66 (0.34–1.26)
45–59	1.09 (0.92–1.28)	0.66 (0.56–0.77)
60–69	1.13 (0.90–1.41)	0.77 (0.65–0.92)
70–79	1.08 (0.84–1.40)	0.92 (0.76–1.10)
≥80	1.43 (0.99–2.07)	0.84 (0.70–1.00)

Source: APCSC data (APCSC secretariat, personal communication, 2001).

subtype. It was therefore necessary to estimate subregion- and age-specific proportions of ischaemic and haemorrhagic fatal and non-fatal strokes so that weighted RR values could be applied. (An assumption was made that these are the same for males and females.)

Several steps were undertaken to estimate stroke subtype proportions, and these are outlined in Appendix B. They included using data from “gold-standard” studies of stroke incidence, and other observational data on stroke subtypes by subregion. Having estimated the relative percentage of stroke subtypes by age, sex and subregion, the APCSC values of RR for ischaemic stroke were smoothed and then weighted as per these percentages. (Smoothed RRs for the five age groups were 0.61, 0.69, 0.76, 0.82 and 0.90.) No association was found between cholesterol and haemorrhagic stroke.

3.4 RISK REVERSAL

As already alluded to, prospective observational studies provide data on the association between cholesterol and stroke and IHD, but they do not provide data on the impact of cholesterol lowering on these outcomes over time (MacMahon et al. 1990). From prospective studies alone, it is not possible to tell whether outcomes are reversible, or whether the association reflects, to some extent, irreversible cumulative effects of cholesterol differences that have persisted for years (Collins and Peto 1994).

The results from randomized clinical trials do provide data on reversibility. They are relevant to assessing how rapidly, and to what extent, the epidemiologically expected reductions in stroke and IHD are produced by lowering cholesterol levels (Collins and Peto 1994; Collins et al. 1990). They therefore provide estimates of the proportion of the potential long-term benefit from a particular cholesterol difference that may be expected within a few years of cholesterol lowering.

DATA SOURCES ON RISK REVERSAL

A variety of trials have studied the impact of cholesterol lowering. However, as with blood pressure lowering trials, individual studies usually lacked sufficient power to reliably detect moderate changes in events (Collins and Peto 1994; Collins et al. 1990; He and Whelton 2000). To accurately detect small but potentially important differences in risk reduction of cardiovascular disease (e.g. 10–15%), it is necessary for trials to record many hundreds of end-points. Since most have not achieved this, overviews are necessary to provide more accurate estimates of the impact of cholesterol lowering on stroke and IHD. Results from these overviews will contribute to estimates of “risk reversibility”.

A number of cholesterol lowering trials as well as major meta-analyses of such trials have been undertaken (Atkins et al. 1993; Blauw et al. 1997; Bucher et al. 1998; Byington et al. 2001; Crouse et al. 1997, 1998; Hebert et al. 1995, 1997; Holme 1990; LaRosa et al. 1999; Law et al. 1994b; Pignone et al. 2000; Ross et al. 1999; M. Law, personal communication, 2001). Most of these trials assessed the impact of lowering cholesterol on IHD, but data are also available on stroke. Results of an updated meta-analysis of all trials included in these previous overviews are given in Tables 7.14–7.16.

*ESTIMATES OF RISK REVERSAL**Cholesterol and risk of IHD*

Trials of cholesterol lowering may be broadly grouped into “dietary interventions”, “non-statin drugs” (e.g. fibrates), and “statin drugs”. Many individual trials and a number of meta-analyses (including the updated meta-analysis) have analysed the association between cholesterol lowering and IHD. Overall, the trials have demonstrated a significant reduction in risk of IHD for those treated.

The current and previous meta-analyses of the early trials demonstrated a risk reduction in those treated of about 10–15%, with dietary interventions or non-statin drugs such as fibrates or resins (Atkins et al. 1993; Bucher et al. 1998; Holme 1990). Later trials with statins, that achieved larger reductions in cholesterol, produced risk reductions of up to 25–30% (Table 7.14) (Bucher et al. 1998; LaRosa et al. 1999; Pignone et al. 2000; Ross et al. 1999). One recently published overview included diet, fibrates, resins and statins (Bucher et al. 1998), but most recent meta-analyses have limited their analyses to statins. The review suggested that the effects of statins on risk reduction could be greater than other agents, but cautioned that analyses were based on between-study treatment comparisons rather than within study comparisons. Therefore, any apparent differences in drug efficacy may have been due to other factors such as differences in study design or populations. For example, participants in statin trials tended to be older, with higher event rates than on other trials, which may partly be responsible for differences in trial

Table 7.14 Clinical trials of cholesterol lowering by dietary interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
DART (Burr et al. 1989; Law et al. 1994b)	1018	1015	—	—	132	144	56.6	0.0	0.3	2.0	—	0.91 (0.73–1.14)
Hjermann et al. (1981)	604	628	3	3	19	36	45.0	0.0	>1.0	6.5	1.04 (0.21–5.13)	0.55 (0.32–0.95)
Los Angeles (Dayton et al. 1968)	424	422	13	22	45	67	65.5	0.0	0.9	8.0	0.59 (0.30–1.15)	0.67 (0.47–0.95)
MRC (Anonymous 1968)	199	194	2	0	45	51	—	0.0	1.00	3.7	4.87 (0.24–100.90)	0.86 (0.61–1.22)
MRC (Research Committee to the Medical Council 1965)	123	129	—	—	43	44	—	0.0	0.5	6.0	—	1.02 (0.73–1.44)
Minnesota (Frantz et al. 1975, 1989; Law et al. 1994b)	4922	4853	—	—	131	121	50.0	51.5	0.7	5.0	—	1.07 (0.84–1.36)
Oslo (Leren 1970)	206	206	7 ^a	5 ^a	79	94	45.0	0.0	1.1	11.0	1.40 (0.45–4.34)	0.84 (0.67–1.06)
STARS (Law et al. 1994b; Watts et al. 1992)	60	30	0	1	3	5	51.0	0.0	1.1	3.0	0.17 (0.01–4.04)	0.30 (0.08–1.17)
St Mary's (Law et al. 1994b; Rose et al. 1965)	28	52	0	0	8	11	56.8	—	0.6	2.0	—	1.45 (0.67–3.17)
Sydney (Law et al. 1994b; Woodhill et al. 1978)	221	237	—	—	37	24	49.0	0	0.3	5.0	—	1.65 (1.02–2.67)
	7805	7766	25	34	542	597	50.9 ^b	32.5	0.7 ^b	5.6 ^b	0.80 (0.48–1.32)	0.92 (0.82–1.02)

Key: A, active treatment group; C, control group.

— No data.

^a Only fatal events reported.

^b "Weighted mean" totals (weighted by person-years of follow-up).

Table 7.15 Clinical trials of cholesterol lowering by other non-statin interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
Adhesion and Hutchison ^a (1972)	47	48	25	27	—	—	—	31.6	0.6	3.5	0.95 (0.66–1.36)	—
CLAS (Blankenhorn et al. 1987)	94	94	0	0	1	5	54.2	0.0	1.3	2.0	—	0.20 (0.02–1.68)
Coronary Drug Project (Anonymous 1975)	2222	2789	231	311	596	839	54.0	0.0	0.6	6.0	1.01 (0.73–1.41)	0.89 (0.82–0.97)
Dorr et al. (1978)	1 149	1 129	0 ^c	1 ^c	19	31	53.9	52.0	0.5	2.1	0.33 (0.01–8.03)	0.60 (0.34–1.06)
FATS (Brown et al. 1990; Law et al. 1994b)	94	52	0	0	2	0	46.7	0.0	1.5	2.5	—	2.79 (0.14–57.03)
Gross and Figueredo (1973)	23	29	0 ^f	1 ^c	1	0	57.1	71.2	0.6	3.0	0.42 (0.02–9.78)	3.75 (0.16–87.98)
Helsinki (Frick et al. 1987)	2051	2030	6 ^c	4 ^c	56	84	47.3	0.0	0.7	5.0	1.48 (0.42–5.25)	0.66 (0.47–0.92)
Lipid Research Clinic (Anonymous 1984)	1 906	1 900	17	14	155	187	47.0	0.0	0.7	7.4	1.21 (0.60–2.45)	0.83 (0.67–1.01)
McCaughan ^b (Law et al. 1994b; McCaughan 1981)	88	30	0	0	2	3	49.8	0.0	0.7	1.0	—	0.23 (0.04–1.30)
Miettinen (Miettinen et al. 1985)	612	610	0	8	19	9	48.0	0.0	0.5	5.0	0.06 (0.00–1.01)	2.10 (0.96–4.61)

Newcastle (Anonymous 1971b)	244	253	—	—	57	94	52.0	19.5	0.6	5.0	—	0.63 (0.48–0.83)
NHLBI (Brensike et al. 1984; Law et al. 1994b)	59	57	—	—	8	11	46.1	19.0	0.9	5.0	—	0.70 (0.30–1.62)
POSCH (Buchwald and Campos 1995; Buchwald et al. 1990)	421	417	14	15	82	125	51.0	9.3	1.5	9.7	0.92 (0.45–1.89)	0.65 (0.51–0.83)
Scottish (Anonymous 1971a)	350	367	—	—	59	79	53.0	20.7	0.6	6.0	—	0.78 (0.58–1.06)
Stockholm (Carlson and Rosenhamer 1988)	279	276	6	5	82	123	59.0	20.4	0.8	5.0	1.19 (0.37–3.84)	0.66 (0.53–0.83)
Veterans (Detre and Shaw 1974; Law et al. 1994b)	145	284	—	—	42	69	51.0	0.0	0.6	5.0	—	1.19 (0.86–1.65)
WHO (Anonymous 1978, 1980)	5331	5296	25	17	167	208	45.0	0.0	0.6	5.3	1.14 (0.79–2.70)	0.80 (0.65–0.97)
	15115	15661	155	169	1348	1867	48.6 ^d	5.6%	0.7 ^d	5.8 ^d	1.01 (0.82–1.24)	0.82 (0.77–0.87)

Key: A, active treatment group; C, control group.

— No data.

^a This was not strictly a randomized trial but is included in many meta-analyses. Exclusion of this trial does not significantly alter the overall RR and 95% CI.

^b This was a multi-factorial trial but is included in many meta-analyses. Exclusion of this trial does not significantly alter the overall RR and 95% CI.

^c Only fatal events reported.

^d "Weighted mean" totals (weighted by person-years of follow-up).

Table 7.16 Clinical trials of cholesterol lowering by statin interventions

Trial	Participants		Stroke		IHD		Mean age (years)	% female	Cholesterol reduction	Follow-up	RR (95% CI)	
	A	C	A	C	A	C					Stroke	IHD
4S (Anonymous 1994b, 1995)	2221	2223	70	98	464	691	59.0	18.6	1.8	5.4	0.71 (0.53–0.97)	0.67 (0.61–0.74)
ACAPS (Furberg et al. 1994a)	460	459	0	5	5	9	61.7	48.5	0.9	2.8	0.09 (0.01–1.64)	0.55 (0.19–1.64)
AFCAPS/TEXCAPS (Downs et al. 1998)	3304	3301	—	—	57	95	58.3	15.0	1.1	5.2	—	0.60 (0.43–0.83)
CARE (Sacks et al. 1996)	2081	2078	54	78	212	274	59.0	13.8	1.1	5.0	—	0.77 (0.65–0.91)
CCAIT (Crouse et al. 1998; Waters et al. 1993; Waters et al. 1994)	165	164	2	0	7	7	53.0	19.0	1.0	2.0	4.97 (0.24–102.74)	0.99 (0.36–2.77)
EXCEL (Bradford et al. 1990, 1991; Crouse et al. 1998; Shear et al. 1992)	6582	1663	10	1	47	18	56.0	41.0	1.6	0.9	2.53 (0.32–19.72)	0.66 (0.38–1.13)
HPS (Heart Protection Study Collaborative Group 2002a, 2002b)	10269	10267	444	585	898	1212	—	24.7	1.3	5.0	0.76 (0.67–0.86)	0.74 (0.68–0.80)
KAPS (Salonen et al. 1995)	224	223	2	4	3	8	57.5	0.0	1.2	3.0	0.50 (0.09–2.69)	0.37 (0.10–1.39)
KLIS (Anonymous 2000)	2219	1634	47	41	65	47	58.0	0.0	0.5	5.0	0.84 (0.56–1.28)	1.02 (0.70–1.47)

LIPID (Anonymous 1998b; White et al. 2000)	4512	4502	169	204	557	715	620	16.8	1.0	6.1	0.83 (0.68–1.01)	0.78 (0.70–0.86)
LRT (Weintraub et al. 1994)	203	201	0	1	14	5	62.0	28.0	2.0	4.0	0.33 (0.01–8.05)	2.77 (1.02–7.55)
MAAS (Anonymous 1994a; Crouse et al. 1998; Dumont 1993)	193	188	1	2	11	7	55.3	11.8	1.5	4.0	0.49 (0.04–5.33)	1.53 (0.61–3.86)
MARS (Blankenhorn et al. 1993)	134	136	0	0	22	31	58.0	9.0	1.8	2.2	—	0.72 (0.44–1.18)
PLAC1 (Byington et al. 1995; Pitt et al. 1995)	206	202	0	2	8	17	57.0	22.5	1.3	3.0	0.20 (0.01–4.06)	0.46 (0.20–1.05)
PLAC2 (Crouse et al. 1992, 1995, 1998; Furberg et al. 1994b)	75	76	1	3	4	10	61.7	14.6	1.3	3.0	0.34 (0.04–3.17)	0.41 (0.13–1.24)
PMSG (Anonymous 1993)	530	532	0	3	0	7	55.0	23.3	1.2	0.5	0.11 (0.01–2.07)	0.07 (0.00–1.17)
REGRESS (Jukema et al. 1995)	450	435	3	5	8	13	55.7	0.0	1.3	2.0	0.58 (0.14–2.41)	0.59 (0.25–1.42)
Sahni (Law et al. 1994b; Sahni et al. 1991)	79	78	0	0	3	4	60.2	30.5	0.7	1.0	—	0.74 (0.17–3.20)
WOSCOPS (Anonymous 1992a; Shepherd et al. 1995)	3302	3293	46	51	174	248	55.2	0.0	1.1	4.9	0.90 (0.61–1.34)	0.70 (0.58–0.84)
	37209	31655	849	1083	2599	3418	58.8 ^a	14.6%	1.2 ^a	5.1 ^a	0.77 (0.70–0.84)	0.73 (0.70–0.77)

Key: A, active treatment group; C, control group.

— No data.

^a "Weighted mean" totals (weighted by person-years of follow-up).

results (Bucher et al. 1998). Another review is more relevant in addressing this issue. It examined the proportional reduction in risk from each trial titrated to a cholesterol reduction of 0.6 mmol/l as a yardstick. There was a dose–response relationship with bigger reductions in risk in trials attaining bigger cholesterol reductions, and statins tended to achieve greater reduction in total cholesterol. It was clear however, that for each method of lowering cholesterol (different drugs, diet and surgery), the proportional reduction in risk was close to that expected from the cholesterol reduction, suggesting little difference in relative effect of agents (Law et al. 2003).

Evidence from meta-analyses suggested that there were similar benefits from cholesterol lowering for males and females, and fatal and non-fatal events, but there was no evidence of age attenuation (LaRosa et al. 1999; Law et al. 1994b). However, trials are often not powered for such age subgroup analysis and often include only a narrow age band. On the whole, no substantial evidence has been presented for a significant difference in risk reduction of IHD between trials among those individuals with or without a prior history of cardiovascular disease (Atkins et al. 1993; Crouse et al. 1997, 1998; Hebert et al. 1997; Holme 1990; LaRosa et al. 1999; Law et al. 1994b).

Further important results from meta-analyses of cholesterol reduction trials relate to the time frame of the achieved benefits. A major overview published by Law et al. (1994b) included 28 trials of diet and non-statin drugs, 45 254 individuals and 4421 deaths from IHD. It demonstrated that most of the benefits were evident after 5 years of sustained cholesterol lowering. In the first two years, a 0.6 mmol/l reduction in cholesterol was associated with a 7% (95% CI 0–14%) lower risk of IHD, but after 5 years, it was 25% (15–35%) (Law et al. 1994b). An updated overview which included more cholesterol lowering trials including statins has confirmed these patterns with a 1.0 mmol/l reduction in LDL cholesterol associated with a 11% (95% CI 4–18%) lower risk of IHD at year 1. At 2 years this increased to 24% (17–30%), at 3–5 years it was 33% (28–37%), and after 5 years it was 36% (26–45%). (Law et al. 2003).

Most other reviews have not reported events according to duration of treatment, and instead only give an “average” risk reduction for the entire period of follow-up. A risk reduction of 20% after 5 years of follow-up, for example, for a given age group is a combined risk reduction for 1, 2, 3, 4 and 5 years, rather than a true representation of the risk reduction for a cohort of people after 5 years of treatment, which would be greater than 20%. These data are a vital component to interpreting the time frames and extent of reversibility. The majority of the benefit of cholesterol lowering was achieved after 5 years (Law et al. 1994b). At this time, virtually all of the risk predicted by the observational studies had been reversed. There is no evidence that the effects of

cholesterol lowering on risk of IHD differ between males and females (Byington et al. 2001; LaRosa et al. 1999; Law et al. 1994b).

Cholesterol and risk of stroke

Early observational studies, trials and overviews did not find an association between cholesterol and stroke. Part of the reason for this was that the analyses involved total stroke, and “concealed” differences in the type of association between cholesterol and each stroke subtype (Crouse et al. 1998). Early trials also only achieved small reductions in cholesterol and included few, mostly fatal, stroke events, which made the influence of cholesterol lowering difficult to detect (Crouse et al. 1998; Law 1999). Trials also tended to be of short duration, so that the long-term reduction in stroke was “diluted” by the absence of an early effect (Law 1999).

Data from individual trials are presented in Tables 7.14–7.16. As with IHD end-points, there were similar risk reduction in males and females and no evidence of age attenuation (Byington et al. 2001). However, trials were often not powered for this subgroup analysis and included only a narrow age-band.

The larger, more recent trial overviews have found a positive association between cholesterol and total stroke, and the size of the risk reduction in more recent overviews was about 20–25% (Blauw et al. 1997; Bucher et al. 1998; Crouse et al. 1997, 1998; Hebert et al. 1997; Ross et al. 1999). Overviews have also noted a stronger association with non-fatal strokes (which comprise a higher proportion of ischaemic strokes) than fatal strokes (which comprise a greater proportion of haemorrhagic strokes) (Atkins et al. 1993; Blauw et al. 1997; Byington et al. 2001; Ross et al. 1999). One of the most recent overviews performed subgroup analysis and suggested different associations between cholesterol and haemorrhagic and ischaemic strokes (Byington et al. 2001), as predicted by the observational data.

In summary, the data from clinical trials of cholesterol lowering indicated that after 5 years, a reduction of approximately 0.6 mmol/l of cholesterol resulted in reversal of most or all of the epidemiologically expected risk for IHD (about 27%). Interpretation is more difficult for stroke as many studies have combined ischaemic and haemorrhagic strokes into one category, when the association of cholesterol with ischaemic stroke differs from that of haemorrhagic stroke. Even when stroke subtype is specified, there will likely be differing rates of misclassification of stroke subtype between studies. However, more recent trial overviews appear to concur with the epidemiological data and suggest that total stroke risk can be reversed, but associations differ by stroke subtype. Unfortunately, analyses have not specifically analysed results by duration, so similar time frames for the cholesterol-IHD association will have to be used. These time frames for reversibility from trials will be

used in CRA analyses, but the relative risk estimates from cohort studies will be used in preference to those from trials for both stroke and IHD. Cohort studies are much larger than the trials, their statistical power is greater, and they are also better able to examine associations across a wide range of cholesterol values (Law 1999). Furthermore, age-specific estimates are more readily available.

4. RESULTS

4.1 ATTRIBUTABLE FRACTION

The “attributable fraction” refers to the proportion of disease burden that would theoretically not have occurred if the population distribution of cholesterol had been equal to that of the theoretical minimum (mean cholesterol = 3.8mmol/l).

STROKE

Globally, 32% of ischaemic stroke was attributable to a total cholesterol level >3.8 mmol/l (range of 25–45% by subregion). Subregions with the lowest attributable fractions included AFR-D, AFR-E and WPR-B. In contrast, EUR-C and EUR-A had the highest values. In most subregions, the attributable fractions were slightly lower for males than females.

ISCHAEMIC HEART DISEASE

Globally, 56% of IHD was attributable to a total cholesterol level >3.8 mmol/l (range of 44–68% by subregion). Subregions with the lowest attributable fractions included AFR-D, SEAR-B and WPR-B. In contrast, EUR-C and EUR-A had the highest values.

4.2 ATTRIBUTABLE DISEASE BURDEN

For the year 2000, the World Health Organization (WHO) estimated that there were 55.9 million deaths and 1455 million DALYs worldwide; approximately 22% of these deaths and 7% of these DALYs were due to ischaemic heart disease and stroke. The burden of disease was distributed across the developed and developing world (e.g. about one quarter of all stroke deaths and one third of IHD deaths occurred in the least developed regions), and predominantly affected those aged >60 years.

The “attributable burden” refers to the number of deaths or DALYs that would theoretically not have occurred if the population distribution of cholesterol had been equal to that of the theoretical minimum (mean cholesterol = 3.8mmol/l). In total, the attributable burden equated to 805 000 stroke deaths, and about 3.6 million IHD deaths. For DALYs, these figures were 8.3 million stroke DALYs, and 32.1 million IHD DALYs (Table 7.17).

Table 7.17 Attributable deaths and DALYs for cholesterol >3.8 mmol/l by subregion and cardiovascular end-point

Subregion	Deaths (000s)		DALYs (000s)	
	Stroke	IHD	Stroke	IHD
AFR-D	18	68	219	738
AFR-E	21	68	267	767
AMR-A	33	317	377	2086
AMR-B	31	136	448	1 425
AMR-D	3	15	47	150
EMR-B	7	75	89	836
EMR-D	26	188	287	2 037
EUR-A	96	451	779	2 600
EUR-B	45	235	474	1 984
EUR-C	176	729	1 637	5 683
SEAR-B	18	94	224	1 016
SEAR-D	145	851	1 542	9 548
WPR-A	20	58	219	389
WPR-B	165	322	1 724	2 847
World	805	3 609	8 332	32 105

Worldwide this means that 4.4 million deaths (about 7.9% of the total) and 40.4 million DALYs (2.8% of the total) were estimated to be due to non-optimal cholesterol. The proportion of DALYs was lower than the proportion of deaths, as most cholesterol-related cardiovascular disease events occurred in middle or old age, so the years of life lost due to premature mortality and years of life lost due to disability is a smaller percentage of the total DALYs than of the total deaths.

The age group with the greatest attributable deaths for both males and females was 70–79 years. The number of attributable deaths then declined, reflecting the smaller denominator population, and the smaller total number of events in the oldest age group. For DALYs, this decline occurred sooner, as there are less years of life lost and years of life lived with disability with advancing age.

For each end-point, the attributable deaths were higher for males than females for the age groups 30–44 and 45–59 years. In contrast, attributable deaths were higher for females in the oldest age groups, 70–79 and ≥80 years. There was a similar trend for attributable DALYs. This was due to older females having higher mean cholesterol (and therefore greater attributable fraction) than males, and there are also a larger

number of cardiovascular deaths occurring in older females compared to older males.

STROKE

The subregions with the highest attributable ischaemic stroke burden were EUR-C (176 000 deaths, 1.6 million DALYs), WPR-B (165 000 deaths, 1.7 million DALYs) and SEAR-D (145 000 deaths, 1.5 million DALYs).

ISCHAEMIC HEART DISEASE

The subregions with the highest attributable IHD burden were SEAR-D (851 000 deaths, 9.6 million DALYs) and EUR-C (729 000 deaths, 5.7 million DALYs).

Overall, approximately 40% of attributable DALYs occurred in the most developed subregions (16.2 million), 40% (15.6 million) in high mortality developing subregions, and 20% (8.6 million) in low mortality developing subregions. A higher proportion of these deaths and DALYs were from IHD than stroke in all subregions.

These results indicate where most of the worldwide attributable cardiovascular disease burden occurred, and provide any given subregion with an indication of absolute size of the attributable burden. However, the age structure, population size, and the number of estimated events occurring in a subregion, influences the ranking of subregions by absolute number of attributable deaths and DALYs. The relative impact of the attributable DALYs indicates that between about 2–25% of all deaths and 0.5–12% of all DALYs across the subregions were attributable to non-optimal cholesterol. Approximately 16% of all deaths and 8% of all DALYs were attributable to excess cardiovascular disease in developed subregions, and about 5% and 2% in high and low mortality developing subregions, respectively.

5. DISCUSSION

5.1 ATTRIBUTABLE DEATHS AND DISEASE BURDEN

The analyses in this chapter suggest that globally, a substantial proportion of cardiovascular disease is attributable to non-optimal cholesterol, defined as mean cholesterol >3.8 mmol/l. Overall, about one third of ischaemic stroke and over half of IHD was attributable to non-optimal cholesterol. The attributable fractions were higher in the more developed parts of the world than the least developed regions, as would be expected given the higher cholesterol levels.

Worldwide, 4.4 million deaths (about 7.9% of the total) and 40.4 million DALYs (2.8% of the total) were estimated to be due to non-optimal cholesterol. Overall, the results suggest that a considerable proportion of cardiovascular disease is related to non-optimal cholesterol

and this translates into an important portion of deaths and years of life lost to deaths and disability worldwide.

5.2 ATTRIBUTABLE DEATHS AND DISEASE BURDEN BY SUBREGION

In absolute terms, most of the excess burden of cardiovascular disease occurred in subregions WPR-B, SEAR-D and EUR-C; approximately 10–20% of worldwide attributable deaths and DALYs occurred in these subregions. The relative impact that attributable deaths and DALYs have in different subregions may also be calculated as the proportion of all deaths and DALYs attributable to non-optimal cholesterol (i.e. mean $>3.8\text{mmol/l}$) within each specific subregion. Overall, between 2% and 25% of all deaths and 0.5 and 12% of all DALYs across subregions were attributable to non-optimal cholesterol. This excess burden was highest in European subregions where mean cholesterol levels were highest.

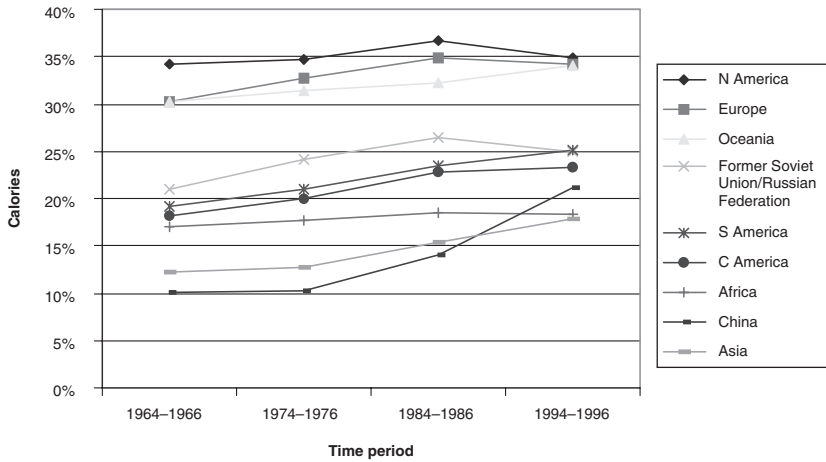
6. TRENDS IN MEAN CHOLESTEROL LEVELS OVER TIME BY AGE, SEX AND SUBREGION

The CRA project includes estimates of avoidable burden, that is, the reduction in future burden that would be observed if current levels of exposure to a risk factor were reduced to those specified by a counterfactual distribution of exposure. To perform these calculations an estimate must be made of cholesterol distributions in the future under a “business-as-usual” scenario. This requires estimates of changes in current cholesterol levels 10, 20 and 30 years into the future by age, sex and subregion.

Several basic steps were necessary to produce these estimates and each one to some extent dictated the next. First, the literature was reviewed to assess what we already know about trends in cholesterol in different populations. Second, subregions were categorized into broad groupings based on likely direction of changes in cholesterol levels over time. Third, the future trends in cholesterol distribution were estimated.

6.1 LITERATURE REVIEW OF CHOLESTEROL TRENDS OVER TIME

There is evidence in the literature that risk factors such as cholesterol change over time, and a variety of studies from different world regions and populations have demonstrated increases and decreases in cholesterol levels (Capewell et al. 2000; Dobson et al. 1999; Evans et al. 2001; Law and Wald 1994; McGovern et al. 1996; Sakata and Labarthe 1996; Sigfusson et al. 1991; Suh 2001; Tuomilehto et al. 1991; Vartiainen et al. 1994, 2000). These data were reviewed by subregion. In addition, data on fat intake from the Food and Agriculture Organization of the United Nations (FAO) were reviewed as fat intake correlates with mean cholesterol levels. Changes in mean cholesterol levels in recent literature relate predominantly to AMR-A, EUR-A and WPR-A.

Figure 7.15 Percentage of total calories from fat per capita per day

The best available FAO data (www.fao.org) cover the whole world, but the country groupings differ from those of WHO. FAO data may be presented as the total number of calories supplied as fat per day, or percentage of daily calories supplied as fat (Figure 7.15). (These data only relate to total fat, and have not been subdivided further, e.g. into saturated or animal fat vs unsaturated fat.)

AMR-A AND EUR-A

Studies in the United Kingdom of Great Britain and Northern Ireland (Capewell et al. 1999; Law and Wald 1994), the United States (Law and Wald 1994; McGovern et al. 1996), Finland (Tuomilehto et al. 1991; Vartiainen et al. 1994, 2000), Iceland (Sigfusson et al. 1991) and other parts of Europe (Law and Wald 1994) have documented reductions in mean cholesterol levels. In the more recent studies from the 1980s onwards, these decreases have been approximately 0.02–0.03 mmol/l of cholesterol per year in males and females (Capewell et al. 2000; Dobson et al. 1999; Evans et al. 2001; McGovern et al. 1996; Vartiainen et al. 2000). FAO data also show a levelling or decline of mean cholesterol levels recently in North America (AMR-A) and Europe (EUR-A). The direction of these trends correlates with those demonstrated for blood pressure in the same studies.

WPR-A

Reduction in mean cholesterol levels has been documented in New Zealand and Australia (Capewell et al. 2000; Dobson et al. 1999; Law

and Wald 1994). In contrast, there appears to have been an increase in mean cholesterol levels in Japan since the 1980s (Law and Wald 1994; Okayama et al. 1993; Sakata and Labarthe 1996) in the order of about 0.03–0.04 mmol/l per year (Sakata and Labarthe 1996). This would result in an overall increase in cholesterol levels in WPR-A, owing to the larger population size of Japan. WPR-A covers countries that would be included by FAO in Asia (Japan) and Oceania (Australia, New Zealand and the Pacific), where trends in fat consumption indicate that cholesterol levels are increasing.

EUR-B AND EUR-C

Some decreases in cholesterol have been recorded recently in parts of eastern Europe (Bobak et al. 1997), but the data are limited. The FAO region that covers the former Soviet Union and the Russian Federation most closely maps to EUR-B and C, and also suggests a levelling off and possible decline in fat consumption.

WPR-B

Mean cholesterol levels appear to be increasing in China and in the Republic of Korea (Evans et al. 2001; Suh 2001), which correlates with increases in fat consumption in China.

OTHER SUBREGIONS

Very few data were available on several developing subregions (AFR-D, E, AMR-B, D, EMR-B, D, SEAR-B and D); however, certain data demonstrated that as regions become more industrialized or “acculturated”, risk factor profiles such as blood pressure and cholesterol change. This is particularly evident in migration studies conducted in a variety of settings (Poulter and Sever 1994), such as Africa (Poulter et al. 1988, 1990), China (He et al. 1991a, 1991b), and the Pacific (Joseph et al. 1983; Salmond et al. 1985, 1989), which suggest that blood pressure and cholesterol levels rise after people migrate to more urbanized “acculturated” settings. The trends are as follows.

AMR-B and D: FAO data from Central and South America suggest that overall, fat consumption is increasing.

EMR-B and D; SEAR-B and D: These subregions are all included in the FAO grouping of Asia where levels of fat consumption are increasing.

AFR-D and E: FAO data suggest small increases in fat consumption.

6.2 POTENTIAL CATEGORIES OF CHOLESTEROL CHANGE

Data presented above indicate that mean cholesterol levels appear to be decreasing in many of the most developed subregions, while they are increasing or plateauing in less developed subregions. However, estimating how long the current trends will continue and quantifying the changes is difficult.

A published meta-analysis assessed the quantitative importance of dietary fat to blood concentrations of total cholesterol (Clarke et al. 1997). However, these results are difficult to extrapolate to FAO data as they relate to isocaloric replacement of fats by carbohydrates. The FAO data demonstrated not only increasing caloric fat intake, but also increasing caloric intake from other sources and overall. Therefore, the same associations do not apply. The following potential scenario was therefore based on current evidence of time trends, and previously documented changes in mean cholesterol levels.

Owing to the limited data available, these estimates are susceptible to a high degree of uncertainty. A wide range of factors could influence future risk factor levels, and it is difficult to capture these factors even with sophisticated modelling. A decision was thus made to use a relatively simple, but transparent method for the purposes of these analyses.

ESTIMATES OF MEAN CHOLESTEROL LEVELS OVER TIME

Table 7.18 presents an overview of the cholesterol trends over time, by subregion. The following estimates summarize mean cholesterol levels by subregion, sex and age, currently and in 2010, 2020 and 2030 (Tables 7.19–7.22).

Table 7.18 Scenario for changes in mean cholesterol levels (mmol/l) by subregion over the next 10, 20 and 30 years^a

Subregion	2000 to 2010	2010 to 2020	2020 to 2030	Comment
AMR-A	↓ 0.3 mmol/l	↓ 0.3 mmol/l	↓ 0.2 mol/l	↓ attenuating over time
EUR-A	↓ 0.3 mmol/l	↓ 0.3 mmol/l	↓ 0.2 mol/l	↓ attenuating over time
WPR-A	↑ 0.2 mmol/l	→ plateau	↓ 0.1 mol/l	↑ due to influence of Japan over next 10 years, then plateau and start to decrease
AMR-B, D	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
EUR-B, C	→ plateau	↓ 0.1 mol/l	↓ 0.1 mol/l	→ plateau initially then start to decrease as some evidence on this already happening in some regions
WPR-B	↑ 0.3 mmol/l	↑ 0.2 mmol/l	↑ 0.1 mmol/l	↑ attenuating over time
SEAR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
EMR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau
AFR	↑ 0.2 mmol/l	↑ 0.1 mmol/l	→ plateau	↑ attenuating over time, then plateau

Key: ↑, increase; ↓, decrease; →, plateau.

^a Assumes the same absolute change in cholesterol for all age and sex subgroups.

Table 7.19 Current CRA estimates of mean cholesterol (mmol/l) by subregion, sex and age

Subregion	Sex and age group (years)							
	Females				Males			
	30–44	45–59	60–69	70–79 ^a	30–44	45–59	60–69	70–79 ^a
AFR-D	4.6	5.1	5.2	5.2	4.5	4.7	4.7	4.7
AFR-E	4.6	5.1	5.2	5.2	4.5	4.7	4.7	4.7
AMR-A	4.8	5.6	6.0	5.9	5.2	5.5	5.5	5.2
AMR-B	4.8	5.4	5.4	5.2	5.3	5.0	4.9	4.8
AMR-D	4.8	5.4	5.4	5.2	5.3	5.0	4.9	4.8
EMR-B	4.6	5.1	5.4	5.6	4.8	4.9	5.1	5.4
EMR-D	4.6	5.1	5.4	5.6	4.8	4.9	5.1	5.4
EUR-A	5.4	6.3	6.7	6.5	5.9	6.1	6.1	5.9
EUR-B	4.6	5.3	5.5	5.4	5.0	5.1	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	5.5	5.8	5.8	5.7
SEAR-B	4.0	4.5	4.6	4.6	5.0	5.1	5.2	5.2
SEAR-D	4.9	5.7	5.8	5.7	4.8	5.0	5.0	5.0
WPR-A	4.9	5.5	5.6	5.4	5.2	5.2	5.1	5.0
WPR-B	4.3	4.8	5.1	5.1	4.5	4.6	4.7	4.8

^a The same cholesterol levels apply to those aged ≥ 80 years.

Table 7.20 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2010

Subregion	Sex and age group (years)							
	Females				Males			
	30–44	45–59	60–69	70–79 ^a	30–44	45–59	60–69	70–79 ^a
AFR-D	4.8	5.3	5.4	5.4	4.7	4.9	4.9	4.9
AFR-E	4.8	5.3	5.4	5.4	4.7	4.9	4.9	4.9
AMR-A	4.5	5.3	5.7	5.6	4.9	5.2	5.2	4.9
AMR-B	5.0	5.6	5.6	5.4	5.5	5.2	5.1	5.0
AMR-D	5.0	5.6	5.6	5.4	5.5	5.2	5.1	5.0
EMR-B	4.8	5.3	5.6	5.8	5.0	5.1	5.3	5.6
EMR-D	4.8	5.3	5.6	5.8	5.0	5.1	5.3	5.6
EUR-A	5.1	6.0	6.4	6.2	5.6	5.8	5.8	5.6
EUR-B	4.6	5.3	5.5	5.4	5.0	5.1	5.2	5.2
EUR-C	5.4	6.2	6.6	6.5	5.5	5.8	5.8	5.7
SEAR-B	4.2	4.7	4.8	4.8	5.2	5.3	5.4	5.4
SEAR-D	5.1	5.9	6.0	5.9	5.0	5.2	5.2	5.2
WPR-A	5.1	5.7	5.8	5.6	5.4	5.4	5.3	5.2
WPR-B	4.6	5.1	5.4	5.4	4.8	4.9	5.0	5.1

^a The same cholesterol levels apply to those aged ≥ 80 years.

Table 7.21 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2020

Subregion	Sex and age group (years)							
	Females				Males			
	30–44	45–59	60–69	70–79 ^a	30–44	45–59	60–69	70–79 ^a
AFR-D	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AFR-E	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AMR-A	4.2	5.0	5.4	5.3	4.6	4.9	4.9	4.6
AMR-B	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
AMR-D	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
EMR-B	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EMR-D	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EUR-A	4.8	5.7	6.1	5.9	5.3	5.5	5.5	5.3
EUR-B	4.5	5.2	5.4	5.3	4.9	5.0	5.1	5.1
EUR-C	5.3	6.1	6.5	6.4	5.4	5.7	5.7	5.6
SEAR-B	4.3	4.8	4.9	4.9	5.3	5.4	5.5	5.5
SEAR-D	5.2	6.0	6.1	6.0	5.1	5.3	5.3	5.3
WPR-A	5.1	5.7	5.8	5.6	5.4	5.4	5.3	5.2
WPR-B	4.8	5.3	5.6	5.6	5.0	5.1	5.2	5.3

^a The same cholesterol levels apply to those aged ≥ 80 years.

Table 7.22 Estimates of mean cholesterol (mmol/l) by subregion, sex and age in 2030

Subregion	Sex and age group (years)							
	Females				Males			
	30–44	45–59	60–69	70–79 ^a	30–44	45–59	60–69	70–79 ^a
AFR-D	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AFR-E	4.9	5.4	5.5	5.5	4.8	5.0	5.0	5.0
AMR-A	4.0	4.8	5.2	5.1	4.4	4.7	4.7	4.4
AMR-B	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
AMR-D	5.1	5.7	5.7	5.5	5.6	5.3	5.2	5.1
EMR-B	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EMR-D	4.9	5.4	5.7	5.9	5.1	5.2	5.4	5.7
EUR-A	4.6	5.5	5.9	5.7	5.1	5.3	5.3	5.1
EUR-B	4.4	5.1	5.3	5.2	4.8	4.9	5.0	5.0
EUR-C	5.2	6.0	6.4	6.3	5.3	5.6	5.6	5.5
SEAR-B	4.3	4.8	4.9	4.9	5.3	5.4	5.5	5.5
SEAR-D	5.2	6.0	6.1	6.0	5.1	5.3	5.3	5.3
WPR-A	4.9	5.5	5.6	5.4	5.2	5.2	5.1	5.0
WPR-B	4.9	5.4	5.7	5.7	5.1	5.2	5.3	5.4

^a The same cholesterol levels apply to those aged ≥ 80 years.

ACKNOWLEDGEMENTS

Particular thanks are due to the Asia-Pacific Cohort Studies Collaboration secretariat, and all study collaborators for allowing us to access and analyse their data for estimates of relative risk. The Prospective Studies Collaboration assisted with analyses and provided unpublished data on relative risk estimates that could be compared with those presented here.

The authors are grateful to Varsha Parag and Derrick Bennett for biostatistical support. Angela Hurley provided valuable research assistance and Clarissa Gould-Thorpe provided secretarial support.

NOTE

- 1 See preface for an explanation of this term.

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APPENDIX A: SAMPLING METHODS, RESPONSE RATE AND CHOLESTEROL MEASURING TECHNIQUES OF STUDIES INCLUDED IN CHOLESTEROL DATA REVIEW

Africa

Subregion	Country or area	Study reference	Sampling methods	Response rate	Cholesterol measurement
AFR-D	Ghana	Nyarko et al. (1994)	Employees from the University of Ghana were randomly selected	*	Trained staff & certified lab All fasting samples Storage of sample unnecessary, enzymatic analysis
	Nigeria	Erasmus et al. (1994)	Recruitment from a rural village	82%	Trained staff & certified lab Non-fasting samples Storage of sample unnecessary, extraction analysis
	Nigeria	Okesina et al. (1999)	Houses in villages selected randomly, then individuals randomly selected	*	All fasting samples ?where sample stored, enzymatic-colorimetric analysis
	Seychelles	Bovet et al. (1991)	Age and sex stratified random sample from national census	84-89%	Certified lab All fasting samples Sample stored in freezer, enzymatic analysis

AFR-E	South Africa	Oelofse et al. (1996)	A stratified proportional sample from target population using census data	*	Trained staff Non-fasting samples Sample stored in fridge, enzymatic analysis
	South Africa	Steyn et al. (1985, 1987)	A stratified sample by age and sex from census data	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	United Republic of Tanzania	Kitange et al. (1993)	Whole population in four villages, and a random sample in another four villages	60–94%	Certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	United Republic of Tanzania	Swai et al. (1993)	Community-based survey of eight villages in three regions in rural United Republic of Tanzania	90.9–96%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Zimbabwe	Allain and Matenga (T. Allain et al., personal communication, 2001)	Stratified sampling	*	Trained staff & certified lab Some fasting samples Sample analysed immediately ? method

* Data unavailable.

? Specific details not given.

Americas

Subregion	Country or area	Study reference	Sampling methods	Response rate	Cholesterol measurement
AMR-A	Canada	Connelly et al. (1992)	Probability sample from health insurance register	60–70%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Canada	Lupien et al. (1985)	Random sample from provincial electoral register	60%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II)
	Halifax	MONICA study (Anonymous 1989)	Sample from public health service register	41–63%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	USA	Abbott et al. (1997)	Sample from long-term study	*	Trained staff & certified lab All fasting samples Sample stored in fridge, ?method of analysis (LRC program)
	USA	Brown et al. (1993)	Sample from four communities	42–68%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	USA	Burke et al. (1991)	Clusters of 40 households in the metropolitan area were randomly selected	*	Trained staff & certified lab Non-fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
	USA	Donker et al. (1997)	Sample by age and race from survey of school-age children	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (Technicon Autoanalyzer: LRC program)

USA	Eisenberg et al. (1986)	Random sample from population register	74–85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (LRC program)
USA	Ettlinger et al. (1992)	Random sample from health care register	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
USA	Ferrara et al. (1997)	Stratified sample by age and sex using community study	80%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
USA	Hutchinson et al. (1997)	Random sample from study centres	*	Trained & certified staff All fasting samples Sample stored in freezer, enzymatic analysis
USA	Johnson et al. (1993)	Stratified sample from four separate national surveys	67–84%	Trained staff & certified lab Some fasting samples Sample stored in freezer, enzymatic analysis
USA	Sprafka et al. (1990)	Clusters of 1 000 households in the metropolitan area were randomly selected	68%	Trained staff & certified lab Non-fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
USA	Srinivasan et al. (1991)	Sample from specific bi-racial community	65–85%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis (Technicon Autoanalyzer II: LRC program)
USA	Wallace and Colsher (1992)	Sample from cohort studies using target population from two counties	50–80%	Trained staff & certified lab Some fasting samples ?where sample stored, ?method of analysis (derived and not directly measured)

continued

Americas (continued)

Subregion	Country or area	Study reference	Sampling methods	Response rate	Cholesterol measurement
	USA	Yano et al. (1986)	Random sample from cohort studies	86%	Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis (LRC program)
	Stanford	MONICA study (Anonymous 1989)	Sample from commercial household directory	66%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, extraction analysis
AMR-B	Brazil	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	82–92%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Chile	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	67–76%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Chile	Jadue et al. (1999), L. Jadue, personal communication, 2001	Stratified sample	*	Trained staff All fasting samples Immediate analysis enzymatic analysis
	Colombia	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	83%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

Dominican Republic	Aono et al. (1997)	Clusters of 2 000 individuals from public health regions were randomly selected	72–77%	Trained staff & certified lab ?fasting sample Sample stored in freezer, ?method of analysis
Jamaica	R. Wilks et al., personal communication, 2001	Stratified sampling from Sparush Town	64%	Trained staff All fasting samples ?where sample stored, ?method of analysis
Mexico	Gonzalez et al. (1999), C. Gonzalez, personal communication, 2001	Random sample of population from a selected area—a complete household survey was performed	80.2%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis
Mexico	Posadas-Romero et al. (1995)	Random sample from population register	58%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
Mexico	L. Yamamoto et al., personal communication, 2001	Random stratified sample in Mexico City	87%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis

AMR-D

* Data unavailable.

? Specific details not given.

Eastern Mediterranean

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
EMR-B	Bahrain	al-Mahroos et al. (2000)	Stratified sample by age from national population register	62%	Trained staff & ?certified lab Some fasting samples ?where sample stored, enzymatic analysis
	Jordan	H. Jaddou, personal communication, 2001	Stratified sample from the population	62%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Kuwait	Olusi et al. (1997)	Sample taken from outpatient requests	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Saudi Arabia	al-Nuaim et al. (1996, 1997)	Stratified cluster random sample from target population using census data	92%	Trained staff & certified lab ?fasting sample Sample stored in freezer, enzymatic calorimetric analysis
	Saudi Arabia	al-Nuaim (1997)	Stratified random sample from target population using census data	92%	Trained staff & certified lab ?fasting sample Sample stored in freezer, enzymatic calorimetric analysis

Saudi Arabia	al-Shammari et al. (1994)	Random sample from family practice health clinics	*	Trained staff & certified lab Some fasting samples ?where sample stored, enzymatic analysis
Saudi Arabia	Mitwalli et al. (1994)	Random sample as males were invited to participate in cholesterol screening campaign at several public gatherings in Riyadh City	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
Tunisia	Ghannem et al. (2001), H. Ghannem, personal communication, 2001	Random stratified sample of schoolchildren from the urban region of Sousse	95.4%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
EMR-D	Pakistan	Molla et al. (1990)	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis

* Data unavailable.

? Specific details not given.

Europe

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
EUR-A	Belgium	Kesteloot et al. (1987)	Sample from a survey performed in the Belgian army	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Charleroi	MONICA study (Anonymous 1989)	Sample from population register	59%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Ghent	MONICA study (Anonymous 1989)	Sample from public health service register	54–57%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Denmark, Glostrup	MONICA study (Anonymous 1989)	Sample from population register	79–80%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Finland	Lakka and Salonen (1992)	Random sample from selected region	83%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	Finland	Mylkangas et al. (1995)	Stratified random sample from population register	79%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Finland	Nikkila and Heikkinen (1990)	Sample from health survey	*	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
	Finland	Nissinen et al. (1987)	Random sample from population of two areas using the national population register	76–80%	Trained staff & certified lab ?fasting sample Storage not necessary, enzymatic analysis

Finland	Puska et al. (1993)	Stratified random sample from population register	68–81%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
Finland	Vartiainen et al. (2000)	Stratified random sample from population register	70–85%	Trained staff & certified lab ?fasting sample
Finland	Vikari et al. (1985)	Multicentre study using random selected children and adolescents	*	Storage not necessary, enzymatic analysis Trained staff & certified lab All fasting samples
Kuopio	MONICA study (Anonymous 1989)	Sample from population register	85%	Sample stored in freezer, enzymatic analysis Trained staff & certified lab All fasting samples
Turku; Loimaa	MONICA study (Anonymous 1989)	Sample from population register	86%	Sample stored in fridge, enzymatic analysis Trained staff & certified lab All fasting samples
N. Karelia	MONICA study (Anonymous 1989)	Sample from population register	80%	Sample stored in fridge, enzymatic analysis Trained staff & certified lab All fasting samples
France Haute-Garonne	MONICA study (Anonymous 1989)	Sample from population register	86%	Sample stored in fridge, enzymatic analysis Trained staff & certified lab All fasting samples
Lille	MONICA study (Anonymous 1989)	Sample from communities & electoral roll	65–80%	Sample stored in freezer, enzymatic analysis Trained staff & certified lab All fasting samples
Germany	Heinemann et al. (1995)	Random sample from urban and rural population	*	Sample stored in freezer, enzymatic analysis Trained staff & certified lab ?fasting samples ?where sample stored, enzymatic analysis

continued

Europe (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
	Germany	Herman et al. (1988)	Random sample from health survey	71%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (Boehringer Mannheim CHOD-PAP)
	Germany	Hoffmeister et al. (1994)	Randomly selected districts on resident registries	69%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
	Germany	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	72%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
	Augsburg (Rural)	MONICA study (Anonymous 1989)	Sample from population register	82–84%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Augsburg (Urban)	MONICA study (Anonymous 1989)	Sample from population register	76–80%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Bremen	MONICA study (Anonymous 1989)	Sample from resident register	71%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Rhein-Neckar	MONICA study (Anonymous 1989)	Sample from population register	74%	?Trained staff & ?certified lab ?fasting sample ?where sample stored, enzymatic analysis

Former German Democratic Republic, Berlin-Lichtenberg	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	70-80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
Cottbus county	MONICA study (Anonymous 1989)	Sample from national X-ray screening register	77%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
Iceland	MONICA study (Anonymous 1989)	Sample from national roster	76%	Trained staff & certified lab All fasting samples Storage not necessary, extraction analysis
Israel	Eisenberg et al. (1986)	Random sample from population register	72-81%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis (LRC program)
Israel	Greenland et al. (1993)	Random sample of school-age children from population register	*	Trained staff & certified lab All fasting samples Storage not necessary, ?method of analysis (Gilford automated instrument)
Italy	Cesana et al. (1989)	Sample from routine screening of bank employees	*	?Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Italy	Nine populations (Anonymous 1981)	Random sample of nine populations from eight regions	62%	Trained staff & certified lab All fasting sample ?where sample stored, ?method of analysis

continued

Europe (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
Italy	Italy	Salvaggio et al. (Law and Wald 1994; Salvaggio et al. 1991)	Sample from a study on preventative medicine	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Italy	Italy	Vaccarino et al. (1995)	All employees of IBM asked to participate	45%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
Brianza	Brianza	MONICA study (Anonymous 1989)	Sample from population register	70–71%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
Friuli	Friuli	MONICA study (Anonymous 1989)	Sample from regional health roll	80–82%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
Latina	Latina	MONICA study (Anonymous 1989)	Sample from electoral rolls	76%	Trained staff & certified lab All fasting samples
Netherlands	Netherlands	Vershuren et al. (1994)	Random sample of population selected from the municipal registry of each town	50–57%	Sample stored in fridge, enzymatic analysis Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
Netherlands	Netherlands	Bosma et al. (1994)	Sample taken from a 10-year follow-up to the Kaunus-Rotterdam Intervention Study (KRIS)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Norway	Norway	Graff-Iverson et al. (1998)	Sample from health survey	89%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis

Norway	Thune et al. (1998)	Population-based cohort study	81%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
Spain	Masia et al. (1998)	Two-stage population random sample stratified by age from census data	73%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Catalonia	MONICA study (Anonymous 1989)	Sample from population register	76–79%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
Sweden	Asplund-Carlson and Carlson (1994)	Selected at random from population register	63%	Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis (Boehringer Mannheim)
Sweden	Rosengren et al. (2000)	Selected at random	55–76%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
Gothenburg	MONICA study (Anonymous 1989)	Sample from population register	84–86%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Switzerland, Ticino	MONICA study (Anonymous 1989)	Sample from population register	79–83%	?Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
Vaud; Fribourg	MONICA study (Anonymous 1989)	Sample from population register	61–69%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
United Kingdom	Brown et al. (1994)	Sample from health survey	55%	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis

continued

Europe (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
	United Kingdom	Mann et al. (1988)	Opportunistic case finding from GP lists and random sampling from age-sex registers	73%	Trained staff & certified lab Some fasting samples ?where sample stored, enzymatic analysis
	England	Bajekal et al. (1999)	Community sample	Not stated	Trained & certified staff Standard sphg one cuff 2 measures taken sitting after 5 mins rest, R arm
	England	Razay et al. (1992)	Stratified random sample from regional health survey	73%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Northern Ireland, Belfast	MONICA study (Anonymous 1989)	Sample from GP lists	57–70%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Scotland	Smith et al. (1989)	Sample taken from selected districts, then random sampling from GP lists	*	Trained staff & certified lab Non-fasting samples ?where sample stored, enzymatic analysis
	Scotland, Glasgow	MONICA study (Anonymous 1989)	Sample from GP lists	50–64%	Trained staff & certified lab Non-fasting samples Sample stored in fridge, enzymatic analysis
	Multiple sites in EUR-A	Kafatos et al. (1991)	Stratified random sample by age and sex of target population from 11 countries	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic-colorimetric analysis

EUR-B	Poland, Tarnobrzeg Voivodship	MONICA study (Anonymous 1989)	Sample from electoral register	70–80%	Trained staff & certified lab All fasting samples Sample stored in freezer, direct analysis
	Warsaw	MONICA study (Anonymous 1989)	Sample from electoral register	74%	Trained staff & certified lab All fasting samples Sample stored in fridge, direct analysis
	Turkey	Mahley et al. (1995), R. Mahley, personal communication, 2001	Random sample of six regions in Turkey	*	Trained staff & certified lab All fasting sample Sample stored in freezer, enzymatic analysis
	Turkey	Onat et al. (1992)	Random sample from population register	85%	Trained staff & certified lab Some fasting samples ?where sample stored, enzymatic analysis
EUR-C	Former Czechoslovakia	MONICA study (Anonymous 1989)	Random sample from population register	*	Trained staff & certified lab All fasting samples Sample stored in fridge, direct analysis
	Estonia	Olferev et al. (1990, 1991)	Random sample from population register	70–72%	?Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Hungary	Biro et al. (1996)	Random sample from Budapest and seven counties in Hungary	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Hungary	Kafatos et al. (1991)	Stratified random sample by age and sex of target population from 11 countries	*	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic-colorimetric analysis

continued

Europe (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
	Budapest	MONICA study	Sample from population register (Anonymous 1989)	75–80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, direct analysis
	Pecs	MONICA study	Sample from population register (Anonymous 1989)	70–80%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, enzymatic analysis
	Lithuania	Bosma et al. (1994)	Sample taken from a 10-year follow-up to the Kaunas-Rotterdam Intervention Study (KRIS)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Russian Federation	Puska et al. (1993)	Stratified random sample from population registers	77–92%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	The former Soviet Union ^a , Kaunas	MONICA study (Anonymous 1989)	Sample from GP lists	70%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis
	Novosibirsk	MONICA study (Anonymous 1989)	Sample from electoral list	69%	Trained staff & certified lab All fasting samples Sample stored in freezer, extraction analysis

* Data unavailable.

? Specific details not given.

^a Russia in original publication.

South-East Asia

<i>Subregion</i>	<i>Country or area</i>	<i>Study reference</i>	<i>Sampling</i>	<i>Response rate</i>	<i>Cholesterol measurement</i>
SEAR-B	Indonesia	INCLN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	70%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Thailand	Bhuripanyo et al. (1993)	Stratified random sample from community survey	79%	Trained staff & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
	Thailand	INCLN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	70–73%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
SEAR-D	India	Reddy et al. (1994)	Sampled from electoral register	48–76%	Trained staff & certified lab All fasting samples
	India	Chadha et al. (1997)	Cluster random sample from target population	*	Storage not necessary, ?method of analysis ?Trained staff & ?certified lab ?fasting sample ?where sample stored, ?method of analysis
	India	Misra et al. (2001), A. Misra, personal communication, 2001	Stratified systematic random sampling using electoral list	40%	Trained staff & ?certified lab All fasting samples Storage not necessary, enzymatic analysis
	India	A. Misra, personal communication, 2001	Multistage cluster sampling from 20 schools and colleges located in south Delhi	100%	Trained staff & ?certified lab All fasting samples Storage not necessary, enzymatic analysis

* Data unavailable.

? Specific details not given.

Western Pacific

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
WPR-A	Australia	APCSC-Busseton (APCSC secretariat, personal communication, 2001)	A stratified random sample representative of population	*	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Australia	APCSC-Perth (APCSC secretariat, personal communication, 2001)	Stratified random sampling of Perth metropolitan area	>70%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Australia	Bennett and Magnus (1994)	Systematic probability sample from electoral roles	75%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Australia	Boulton et al. (1995)	Cross-sectional sample of schoolchildren from South Australia	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	Australia	Gliksman et al. (1990)	Two-stage probability sampling of all school children in Australia	*	Trained staff & certified lab All fasting samples Sample stored in fridge, ?method of analysis (LRC program)
	Australia	Simons et al. (1991)	Sample from regional population	73%	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Australia	van Beurden et al. (1991)	Sample from community screening sessions	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

Newcastle	MONICA study (Anonymous 1989)	Sample from electoral register	68-82%	Trained staff & certified lab All fasting samples Sample stored in fridge, extraction & enzymatic analysis
Perth	MONICA study (Anonymous 1989)	Sample from electoral register	81-84%	Trained staff & certified lab All fasting samples Sample stored in fridge, extraction & enzymatic analysis
Japan	APCSC-Aito Town (APCSC secretariat, personal communication, 2001)	Random sample of Aito town residents	75%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Japan	APCSC-Akabane (APCSC secretariat, personal communication, 2001)	All residents living in Akabane town	77.6%	Trained staff & certified lab All fasting samples ?sample stored in freezer, ?method of analysis
Japan	APCSC-Ohasama (APCSC secretariat, personal communication, 2001)	Non-hospitalized adults in Ohasama invited to participate	50%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Japan	Choudhury et al. (1994)	Sample from population register	88%	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
Japan	Okayama et al. (1993)	Randomly selected from national census	81-89%	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis

continued

Western Pacific (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
	Japan	Robinson et al. (Law and Wald 1994; Robinson et al. 1992)	Sample from medical centre	*	Trained staff & certified lab All fasting samples ?where sample stored, enzymatic analysis
	Japan	Serum lipid Survey (Anonymous 1996)	Sample from 39 institutes from various districts	*	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	Japan	1990 National Survey (Sakata and Labarthe 1996)	Randomly selected from National Health Survey districts	81.5%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
	New Zealand	APCSC-Fletcher challenge (APCSC secretariat, personal communication, 2001)	Employees of one centre, and random sample from electoral roll	74%	Trained staff & certified lab Non-fasting samples Storage not necessary, enzymatic analysis
	New Zealand	Bullen et al. (1998)	Age stratified random sampling from electoral rolls	66–68%	Trained staff & certified lab Non-fasting samples Sample not necessary, enzymatic analysis
	New Zealand	Flight et al. (1984)	Randomly chose schools then students	81%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	New Zealand	Mann et al. (1991)	Random sample from electoral roll	94%	Trained staff & certified lab Fasting samples Sample stored in freezer, enzymatic analysis

New Zealand	National Survey (Ministry of Health 1999)	Random sample of individuals from random households constructed from census data	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, ?method of analysis
Auckland	MONICA study (Anonymous 1989)	Sample from electoral register	81%	Trained staff & certified lab Non-fasting samples Sample stored in freezer, extraction analysis
Singapore	APCSC-Singapore Heart Survey (APCSC secretariat, personal communication, 2001)	Random sampling of population of Singapore	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Singapore	Hughes et al. (1990)	Random sample of census districts, units, houses, then individuals (weighted)	52-66%	Trained staff & certified lab All fasting samples Sample stored in fridge, enzymatic analysis
WPR-B	China	APCSC-Anzhen 02 (APCSC secretariat, personal communication, 2001)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	APCSC-Hong Kong SAR (APCSC secretariat, personal communication, 2001)	85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	APCSC-Seven Cities cohort (APCSC secretariat, personal communication, 2001)	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

continued

Western Pacific (continued)

Subregion	Country or area	Study reference	Sampling	Response rate	Cholesterol measurement
	China	APCSC-Six Cohorts (APCSC secretariat, personal communication, 2001)	Cluster sampling of six cohorts in villages, including farmers of Shanxi, Shaanxi, Guangxi, Jiangsu province, minors of Hebei province and fishermen of Zhejiang	≥85%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	76–99%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
	China	Tao et al. (1992)	Cluster sampling from four regions in China	87–88%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	China	Tian et al. (1995)	Random survey of population in Tianjin	96%	Trained staff & certified lab All fasting samples Storage not necessary, enzymatic analysis
	China	Yang et al. (1986)	Sample from Beijing region	*	Trained staff & certified lab Non-fasting samples Sample stored in freezer, ?method of analysis
	China	Zhuang et al. (1986)	Sample from specific region using urban and rural population	*	Trained staff & certified lab All fasting samples ?where sample stored, ?method of analysis
	Beijing	MONICA study (Anonymous 1989)	Sample from register of households	89–90%	Trained staff & certified lab ?fasting sample

Hong Kong SAR	Fong et al. (1994)	Sample from population register	*	?where sample stored, ?method of analysis Trained staff & certified lab All fasting samples Sample stored in freezer, ?method of analysis
Hong Kong SAR	Woo et al. (1997)	Random selection, asked to participate by telephone call	40%	Trained staff & certified lab ?fasting sample ?where sample stored, enzymatic analysis
Taiwan, China	APCSC-CVDFACTS/Two Townships (APCSC secretariat, personal communication, 2001)	Two townships in Taiwan, China	*	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis
Papua New Guinea	Lindeberg et al. (1994)	Randomly selected within specific age range during a period of seven weeks—some non-randomized subjects included due to low participation	45–63%	Trained & certified lab All fasting samples Sample stored in freezer, ?method of analysis
Papua New Guinea	Scrimgeour et al. (1989)	Randomly selected from three rural communities and one urban community	58–64% (F) 52–60% (M)	Trained & certified lab All fasting samples Sample stored in freezer, enzymatic analysis
Philippines	INCLEN (Anonymous 1992b)	Random sample of males from 12 centres in 7 countries	91%	Trained staff & certified lab ?fasting sample ?where sample stored, ?method of analysis

* Data unavailable.

? Specific details not given.

APPENDIX B: METHODOLOGY FOR ESTIMATING STROKE SUBTYPES BY AGE, SEX, SUBREGION AND FATAL AND NON-FATAL EVENTS

Subregional- and age-specific proportions of ischaemic and haemorrhagic fatal and non-fatal strokes were estimated so that weighted RRs could be applied. Based on published data, an assumption was made that these are the same for males and females. Several steps were undertaken to estimate stroke subtype proportions, and these are outlined below.

STEP 1. ASSESS AGE PATTERNS OF HAEMORRHAGIC AND ISCHAEMIC STROKE

The most reliable data on age patterns of stroke subtypes are available from a small selection of “gold standard” incidence studies, most of which were included in a review (Sudlow and Warlow 1997). These studies include the Melbourne stroke study (Thrift et al. 2001), Oxfordshire stroke project (Bamford et al. 1990), Perth community stroke study (Anderson et al. 1993) and the Dijon study (Giroud et al. 1991). Broadly, similar age patterns have also been seen in other studies.

Utilizing the combined age-specific data from these four studies, the percentage of ischaemic strokes in 10-year age categories is presented in Figure B.1. (The number of strokes in the youngest age group is small compared to the other age groups and is therefore less reliable.)

Figure B.1 Percentage of ischaemic strokes by age using data from four “gold standard” studies with linear regression line

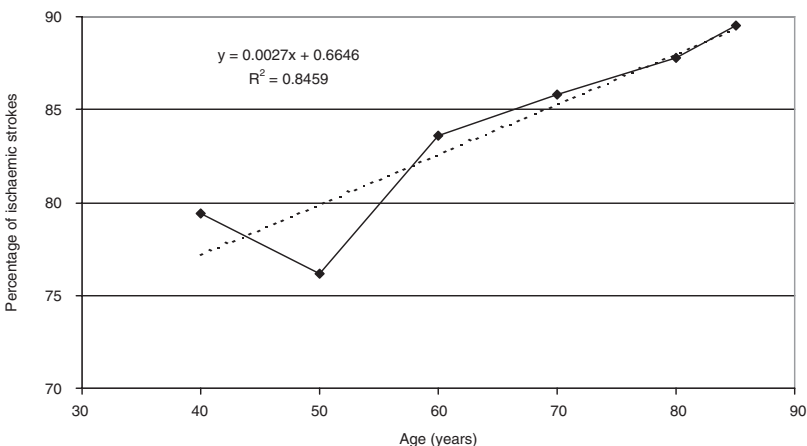


Table B.1 Estimates of the proportion of stroke subtypes by age

Stroke subtypes	Age group (years)				
	30-44	45-59	60-69	70-79	≥80
% ischaemic	77	81	84	87	89
% haemorrhagic	23	19	16	13	11

The linear regression was then used to estimate the proportions of ischaemic stroke by GBD age groups using the midpoint in each GBD age category. The remaining strokes were classified as haemorrhagic (Table B.1).

STEP 2. ESTIMATE THE AGE-SPECIFIC SUBTYPE PROPORTIONS FOR FATAL AND NON-FATAL EVENTS

Table B.1 relates to total strokes, but these proportions will differ for fatal and non-fatal strokes as the case fatality rates for the ischaemic and haemorrhagic strokes are different. The “gold standard” incidence studies (Sudlow and Warlow 1997) suggest that the one-month case fatality rates range from 10% to 23% (crude average = 14%) for ischaemic stroke, and 35% to 54% (crude average = 45%) for haemorrhagic stroke. If it is assumed that these case fatality rates apply for all age groups, these crude percentages can be applied to each age group to provide estimates of the overall proportion of stroke subtypes for fatal and non-fatal events (Table B.2).

These percentages may then be converted in proportions of ischaemic and haemorrhagic stroke within the fatal and non-fatal categories for each age group (Table B.3).

Table B.2 Estimates of subtype proportions for fatal and non-fatal events by age

Age group (years)	Total stroke (%)		Fatal stroke (%)		Non-fatal stroke (%)	
	Ischaemic	Haemorrhagic	Ischaemic	Haemorrhagic	Ischaemic	Haemorrhagic
30-44	77	23	11	10	66	13
45-59	81	19	11	9	70	10
60-69	84	16	12	7	72	9
70-79	87	13	12	6	75	7
≥80	89	11	12	5	77	6

Table B.3 Percentage of stroke subtypes within fatal and non-fatal categories

Age group (years)	Fatal stroke (%)		Non-fatal stroke (%)	
	Ischaemic	Haemorrhagic	Ischaemic	Haemorrhagic
30–44	51	49	84	16
45–59	57	43	87	13
60–69	62	38	89	11
70–79	68	32	91	9
≥80	72	28	93	7

STEP 3. ESTIMATE HOW THESE AGE-SPECIFIC SUBTYPE PROPORTIONS CAN BE APPLIED TO DIFFERENT REGIONS

The age-specific subtype proportions in Table B.3 would only apply to subregions such as AMR-A and EUR-A, from where the data on which the estimates were based came. Estimates were also required for other subregions. The literature suggests that haemorrhagic stroke is relatively more common (about 30–40% of all strokes) in Japan (Nakayama et al. 1997; Suzuki et al. 1987), China (Chen et al. 1992; Wu et al. 1992) and Taiwan, China (Hung 1993; Jeng et al. 1998) and lower in countries in North America and Europe (about 10–15% of all strokes) (Sudlow and Warlow 1997). Unfortunately, reliable data on the remainder of the world are extremely limited or non-existent, and there are no internally consistent WHO estimates available.

The level of cholesterol is important in determining the overall ratio of ischaemic to haemorrhagic strokes in any world region (APCSC 1999). Subregions may therefore be crudely ranked based on their mean cholesterol levels, grouped into three basic subregional categories, and average percentages of haemorrhagic stroke applied. An example is given in Table B.4.

Table B.4 Subregional grouping by mean cholesterol and percentage haemorrhagic stroke^a

Subregional grouping	Cholesterol level	Overall % haemorrhagic stroke
AMR-A, EUR-A, EUR-C	≥5.8 mmol/l	15
AFR-D, AFR-E, AMR-B, AMR-D, EMR-B, EMR-D, EUR-B, SEAR-D, WPR-A	5.1–5.7 mmol/l	20
SEAR-B, WPR-B	≤5.0 mmol/l	30

^a Based on mean cholesterol levels for individuals aged 60–69 years.

The case fatality rates used previously (14% ischaemic, 45% haemorrhagic) are applicable to WPR-A, AMR-A and EUR-A, but case fatality would be higher in other subregions. Limited data are available, but when case fatality rates of 20% for ischaemic stroke and 60% for haemorrhagic stroke (Chen et al. 1992; Li et al. 1985) are applied to other subregions, five potential scenarios result (Table B.5).

These proportions may then be translated into age-specific proportions for fatal and non-fatal ischaemic and haemorrhagic strokes (Table B.6).

Table B.5 Subregional grouping by mean cholesterol and percentage haemorrhagic stroke

<i>Subregional grouping</i>	<i>% haemorrhagic stroke</i>	<i>Ischaemic stroke case fatality (%)</i>	<i>Haemorrhagic case fatality (%)</i>
EUR-A, AMR-A	15	14	45
EUR-C	15	20	60
WPR-A	20	14	45
EMR-B, EMR-D, EUR-B, AFR-D, AFR-E, AMR-B, AMR-D, SEAR-D	20	20	60
SEAR-B, WPR-B	30	20	60

Table B.6 Proportion of fatal and non-fatal stroke subtypes by age and subregion

<i>Age group (years)</i>	<i>Fatal stroke (%)</i>		<i>Non-fatal stroke (%)</i>	
	<i>Ischaemic</i>	<i>Haemorrhagic</i>	<i>Ischaemic</i>	<i>Haemorrhagic</i>
<i>EUR-A, AMR-A</i>				
30–44	51	49	84	16
45–59	57	43	87	13
60–69	62	38	89	11
70–79	68	32	91	9
≥80	72	28	93	7
<i>EUR-C</i>				
30–44	53	47	87	13
45–59	59	41	90	10
60–69	64	36	91	9
70–79	69	31	93	7
≥80	73	27	94	6

continued

Table B.6 Proportion of fatal and non-fatal stroke subtypes by age and subregion (*continued*)

Age group (years)	Fatal stroke (%)		Non-fatal stroke (%)	
	Ischaemic	Haemorrhagic	Ischaemic	Haemorrhagic
<i>WPR-A</i>				
30–44	41	59	78	22
45–59	48	52	82	18
60–69	53	47	85	15
70–79	60	40	88	12
≥80	64	36	90	10
<i>EMR-B, EMR-D, EUR-B, AFR-D, AFR-E, AMR-B, AMR-D, SEAR-D</i>				
30–44	43	57	82	18
45–59	50	50	85	15
60–69	55	45	88	12
70–79	61	39	91	9
≥80	66	34	92	8
<i>SEAR-B, WPR-B</i>				
30–44	28	72	70	30
45–59	35	65	77	23
60–69	41	59	81	19
70–79	49	51	85	15
≥80	54	46	88	12