By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?

M R Law, N J Wald, S G Thompson

Abstract

Objective—**To estimate by how much and how quickly a given reduction in serum cholesterol concentration will reduce the risk of ischaemic heart disease.**

Design—**Data on the incidence of ischaemic heart disease and serum cholesterol concentration were analysed from 10 prospective (cohort) studies, three international studies in different communities, and 28 randomised controlled trials (with mortality data analysed according to allocated treatment to ensure the avoidance of bias).**

Main outcome measure—**Decrease in incidence of ischaemic heart disease or mortality for a 0·6 mmol/l (about 10%) decrease in serum cholesterol concentration.**

Results—**For men results from the cohort studies showed that a decrease of serum cholesterol concentration of 0·6 mmol/l (about 10%) was associated with a decrease in incidence of ischaemic heart disease of 54% at age 40 years, 39% at age 50, 27% at 60, 20% at 70, and 19% at 80. The combined estimate from the three international studies (for ages 55-64 years) was 38% (95% confidence interval 33% to 42%), somewhat greater than the cohort study estimate of 27%. The reductions in incidence of ischaemic heart disease in the randomised trials (for ages 55-64 years) were 7% (0 to 14%) in the first two years, 22% (15% to 28%) from 2·1-5 years, and 25% (15% to 35%) after five years, the last estimate being close to the estimate of 27% for the long term reduction from the cohort studies. The data for women are limited but indicate a similar effect.**

Conclusions—**The results from the cohort studies, international comparisons, and clinical trials are remarkably consistent. The cohort studies, based on half a million men and 18 000 ischaemic heart disease events, estimate that a long term reduction in serum cholesterol concentration of 0·6 mmol/l (10%), which can be achieved by moderate dietary change, lowers the risk of ischaemic heart disease by 50% at age 40, falling to 20% at age 70. The randomised trials, based on 45 000 men and 4000 ischaemic heart disease events show that the full effect of the reduction in risk is achieved by five years.**

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Introduction

In this paper we estimate the size of the reduction in risk of ischaemic heart disease produced by a given reduction in serum cholesterol concentration according to age, and the time needed to attain the full reduction in risk. We use data from observational studies[1-14] (adjusted for the two sources of underestimation as described in the preceding paper[1]) and from randomised trials.[15-46] The observational studies estimate the maximum expected long term decrease in risk of ischaemic heart disease produced by a given reduction in serum cholesterol concentration since the differences in cholesterol between individual people or between communities will have been present for many years before the data were collected. The randomised trials estimate the extent to which this maximum can be achieved in practice and how quickly.

Methods

ESTIMATING LONG TERM ASSOCIATION—OBSERVATIONAL EVIDENCE

The prospective observational studies of serum cholesterol concentration and ischaemic heart disease fall into two categories. Cohort studies examine the association between ischaemic heart disease and serum cholesterol concentration within cohorts (or groups) of people, generally by comparing subgroups within the cohort defined by ranking individual measurements of cholesterol concentration. International studies compare the incidence of ischaemic heart disease and mean serum cholesterol concentration in separate communities; the comparison is between predefined groups and entails no sorting of individual people by serum cholesterol concentration.

Cohort studies (grouping people by initial cholesterol measurements and comparing rates of ischaemic heart disease)

There are at least 60 cohort studies of serum cholesterol concentration and ischaemic heart disease, many with fewer than 100 ischaemic heart disease events. We confined our attention to the 10 largest published studies, each of which had recorded more than 350 such events (deaths and, in three studies, non-fatal infarcts) in men.[1-10] Together they recruited 494 804 men and recorded 18 811 events. The data in each of the studies were published as the incidence of or mortality from ischaemic heart disease in fifths (quintile groups) of the ranked distribution of serum cholesterol concentrations. For each study we regressed the age adjusted rate of ischaemic heart disease (in logarithms) on average cholesterol concentration across the groups. The analysis weighted the rates by the number of events but was not influenced by smoking and blood pressure, which show little association with cholesterol.[1 2 4 5]

To estimate the long term effect of a decrease in concentration of low density lipoprotein cholesterol on the risk of ischaemic heart disease from the cohort studies we adjusted for the two sources of underestimation by increasing the slope of the regression line of risk (in logarithms) on total cholesterol concentration by 61%—the estimated correction factor from the BUPA study.[1] The two components of this estimate are both generalisable. Similar estimates for regression dilution bias, the larger component, have been obtained from several studies.[1] The surrogate dilution effect, the smaller component, will be similar in the 10 studies because total cholesterol values were similar and the concentration of non-low density lipoprotein cholesterol varies little between populations,[11] so the proportion of low density lipoprotein cholesterol to total cholesterol would have been similar.

International studies (comparing rates of ischaemic heart disease between communities with varying mean cholesterol concentrations)

The seven countries study measured serum cholesterol concentrations and recorded mortality from ischaemic heart disease prospectively among men living in 16 communities in seven countries.[12 13] The Ni-Hon-San study similarly compared three communities of Japanese men living in Japan, Honolulu, and San Francisco.[14] A third study compared age specific mortality from ischaemic heart disease between 17 countries for which the national average serum cholesterol concentration could be determined from published surveys.[11] For each study we regressed the incidence of or mortality from ischaemic heart disease (in logarithms) in the constituent communities on the cholesterol concentration associated with mean risk in each community. This value is greater than the mean cholesterol concentration (because the association with ischaemic heart disease is log-linear); we estimated it as the mean cholesterol concentration plus a factor, $\frac{1}{2}\sigma^2 b$, calculated from the standard deviation of the concentration in the community, σ, and the regression coefficient, b. The analysis weighted the age adjusted rates for ischaemic heart disease by the number of ischaemic heart disease events and used multiple regression to allow for the confounding effects of smoking and blood pressure. The international studies are not influenced by the underestimation affecting cohort studies. Regression dilution bias is avoided because cholesterol concentrations were not used to divide people into groups, and the differences in mean total cholesterol concentration between communities reflect similar differences in mean low density lipoprotein cholesterol concentration (as the residual non-low density lipoprotein cholesterol concentration is similar across different communities with widely varying total serum cholesterol concentrations[11]).

ESTIMATING HOW QUICKLY MAXIMUM REDUCTION IN RISK OF ISCHAEMIC HEART DISEASE CAN BE ATTAINED—RANDOMISED CONTROLLED TRIALS

We identified randomised controlled trials of reduction in cholesterol concentration (by drugs, diet, or ileal bypass surgery) and ischaemic heart disease events (deaths and non-fatal infarcts). We included 28 published trials that recorded at least one death and documented a reduction in serum cholesterol concentration of at least 1%.[15-46] Together they recruited 46 254 men and recorded 4241 events. Most trials measured only total cholesterol concentration, but the interventions produced similar absolute reductions in concentrations of total and low density lipoprotein cholesterol with little change in non-low density lipoprotein cholesterol.[19,29,31,32,43,46-49] Diagnostic criteria for death from ischaemic heart disease and non-fatal myocardial infarction were similar in the different trials, and diagnoses were made without knowledge of treatment allocation. Data on mortality were analysed on the basis of allocated treatment, whether or not treatment was received (intention to treat), thereby avoiding bias. With unpublished data on mortality provided by the coordinators of nine of the trials, vital status (alive or dead) at the end of the trial was known for over 99% of all the subjects randomly allocated to interventions in the 28 trials. Data on non-fatal myocardial infarcts were generally not available for subjects who were lost to follow up. Two trials were extended by inviting subjects to continue beyond the planned finishing date[16,29] but since many declined the random allocation was lost, so we did not include the additional events.

To estimate how quickly the risk of ischaemic heart disease falls after reduction in cholesterol concentration we determined the numbers of ischaemic heart disease events in the trials in three time periods, ≤2, 2·1-5, and 5·1-12 years after entry. Trial coordinators kindly provided unpublished data for eight trials, and numbers of events were estimated by using published survival curves for two trials.[38,41] The average reduction in ischaemic heart disease over each time period was estimated by a logistic regression analysis that combined the odds ratios from each trial to obtain a summary relative odds estimate (close to the relative risk as the event rates were low). Each trial was weighted by the mean difference in total cholesterol concentration between treated and control groups. We performed analyses on subgroups of drug and dietary trials and trials of men with and without ischaemic heart disease (angina or previous non-fatal infarction) on entry; authors supplied separate data for two trials that recruited men with and without ischaemic heart disease.[34,35]

The results of both the observational studies and the trials were expressed as the decrease in the risk of ischaemic heart disease associated with a decrease in serum cholesterol concentration of 0·6 mmol/l; 0·6 mmol/l is about 10% of the average value in Western countries, was the approximate mean reduction in cholesterol concentration attained in the trials, and is a reduction attainable by a moderate reduction in dietary fat.[47,48]

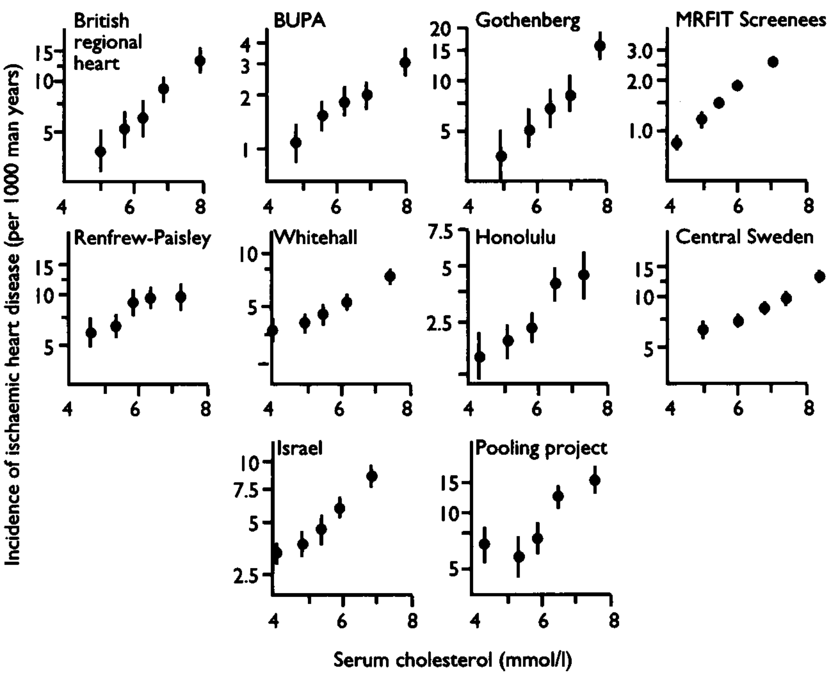

FIG 1—*Incidence of ischaemic heart disease, age adjusted with 95% confidence intervals, according to fifths of distribution of serum cholesterol concentration in 10 cohort studies*

Results

OBSERVATIONAL STUDIES—MEN

Cohort studies

Figure 1 shows the incidence (or mortality) of ischaemic heart disease in the fifths of the ranked cholesterol distribution plotted for each of the 10 cohort studies. The log-linear model for the relation between risk of ischaemic heart disease and serum cholesterol concentration fitted the data well, and in the large study of men screened for inclusion in the multiple risk factor intervention trial (MRFIT screenees) the association was almost perfectly described by a straight line (r=0·997). The magnitude of such a log-linear association can be expressed simply: a constant absolute difference in serum cholesterol concentration, say 0·6 mmol/l, from any point on the cholesterol distribution is associated with a constant percentage difference in the incidence of ischaemic heart disease.

Table I shows this result for each cohort study, unadjusted and adjusted for the two sources of underestimation. In table II the cohorts are subdivided when possible according to age at entry and the results are grouped into 10 year age bands according to the mean age of experiencing ischaemic heart disease events during follow up. The association between ischaemic

TABLE I—*Estimates from 10 cohort studies of percentage decrease in incidence of or mortality from ischaemic heart disease per 0·6 mmol/l (10%) decrease in serum cholesterol concentration*

Study	Period of recruitment	Average follow up period (years)	No of subjects	No of deaths from ischaemic heart disease	Estimated % decrease in ischaemic heart disease per 0·6 mmol/l decrease in serum cholesterol: Unadjusted	Adjusted for underestimation (95% confidence interval)
Men						
British regional heart[2]	1978-80	8	7 735	438*	22	33 (27 to 39)
BUPA[1] (England)	1975-82	13	21 515	538	17	27 (21 to 33)
Gothenberg (Sweden)	1974-7	7	6 897	360*	26	38 (31 to 44)
MRFIT screenees[4] (United States)	1973-5	12	361 662	6327	20	30 (28 to 32)
Renfrew-Paisley[5] (Scotland)	1972-6	15	7 000	878	11	17 (10 to 22)
Whitehall[6] (England)	1967-9	18	17 718	1542	12	18 (15 to 22)
Honolulu[7]	1965-8	19	7 961	371	22	33 (25 to 40)
Central Sweden[8]	1963-5	21	46 140	6626	12	19 (17 to 21)
Israel[9]	1963	23	9 902	1084	20	30 (25 to 34)
Pooling project[10] (United States)†	1950-60	9	8 274	647*	17	26 (21 to 31)
Women						
Renfrew-Paisley[5]	1972-6	15	8 262	490	12	‡
Central Sweden[8]	1963-5	21	46 570	3607	6	‡

*Deaths and non-fatal infarcts.
†Framingham and four other studies.
‡Appropriate estimates to adjust for underestimation in women are unavailable.

TABLE II—*Estimates (adjusted for underestimation) from 10 cohort studies of percentage decrease in risk of ischaemic heart disease in men per 0·6 mmol/l decrease in serum cholesterol concentration, according to age at death*

Study	Estimated % reduction in risk of ischaemic heart disease (95% confidence interval) for age at death (years): 35-44	45-54	55-64	65-74	75-84
British regional heart			33 (27 to 39)		
BUPA		44 (31 to 55)	26 (16 to 36)	19 (10 to 28)	
Gothenberg			38 (31 to 44)		
MRFIT screenees	54 (45 to 62)	38 (33 to 42)	27 (25 to 29)		
Renfrew-Paisley*			17 (5 to 28)	17 (8 to 25)	
Whitehall*		28 (10 to 43)	21 (16 to 26)	16 (11 to 20)	
Honolulu				33 (25 to 40)	
Central Sweden					19 (17 to 21)
Israel*			32 (26 to 37)	22 (13 to 29)	
Pooling project		40 (30 to 49)	23 (16 to 30)	13 (0 to 25)	
Summary estimate	54	39	27	20	19

*Unpublished data supplied by authors.

TABLE III—*Estimates from international studies of the percentage decrease in incidence of or mortality from ischaemic heart disease per 0·6 mmol/l decrease in serum cholesterol concentration*

Study	No of subjects	No of deaths from ischaemic heart disease	Estimated % decrease in ischaemic heart disease per 0·6 mmol/l serum cholesterol decrease (95% confidence interval): Men	Women
Seven countries[12 13]	11 579	413	36 (23 to 47)	NA
Ni-Hon-San[14]	11 594	90*	45 (24 to 60)	NA
International comparison[11]	NA	NA	37 (31 to 43)	31 (20 to 40)
All studies			38 (33 to 42)	31 (20 to 40)

*Deaths and non-fatal infarcts.
NA=not applicable.

heart disease and serum cholesterol concentration decreases with age. A weighted quadratic regression fitted this relation with age well and yielded estimates that a decrease in cholesterol concentration of 0·6 mmol/l (10%) was associated with a decrease in risk of ischaemic heart disease by 54% at age 40, 39% at age 50, 27% at age 60, 20% at age 70, and 19% at age 80 (table II). A simple combination of the results of the studies in each 10 year age group, weighted inversely by variance, gave almost identical results.

International studies

The three international studies showed similar associations between serum cholesterol concentration and ischaemic heart disease (fig 2, table III). On average a difference in cholesterol concentration of 0·6 mmol/l was associated with a difference in mortality from ischaemic heart disease of 38% (95% confidence interval 33% to 42%) in men. The mean age at death was in the range 55-64 years for all three studies. Differences in serum cholesterol concentration explained over 80% of the international variation in mortality from ischaemic heart disease ($r^2 > 0·80$).

RANDOMISED CONTROLLED TRIALS—MEN

Table IV displays the data from each trial. There was a dose response association, with trials that achieved a greater reduction in serum cholesterol concentration on average showing a greater reduction in ischaemic heart disease ($P < 0·001$). Table V shows the summary estimates from all the trials combined for a 0·6 mmol/l reduction in cholesterol concentration according to duration of reduction. The reduction in ischaemic heart disease increased with increasing duration of the reduction in cholesterol concentration as follows (for all the trials): within 2 years by 7% (0 to 14%, P=0·06), from 2·1-5 years by 22% (15% to 28%, P<0·001) and from 5·1-12 years by 25% (15% to 35%, P<0·001), all per 0·6 mmol/l reduction in concentration. There was no significant heterogeneity between the estimates from the different trials within each category of duration (P=0·11). Summary estimates by duration were similar for subgroup analyses of data from the drug and dietary trials and for trials in men with and without known ischaemic heart disease on entry (table V). The overall average reduction was 18% (13% to 22%, P<0·001). The mean range of age at death was 55-64 years in almost all the trials.

In all the trials combined there were highly significant reductions in both fatal ischaemic heart disease and non-fatal myocardial infarction of 10% (3% to 16%, P=0·004) and 21% (15% to 27%, P<0·001) respectively, per 0·6 mmol/l reduction in cholesterol concentration (separate data classified by duration of treatment were not available). The difference between fatal and non-fatal events was significant (P=0·01), but the inference that the risk of non-fatal infarction is reversed more rapidly than that of risk of death from ischaemic heart disease is not justified because the comparison is subject to bias. The analysis of fatal

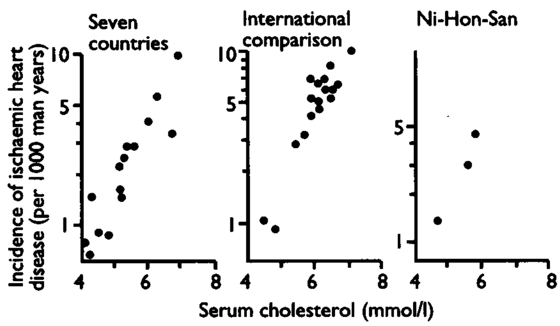

FIG 2—*Incidence of ischaemic heart disease according to mean serum cholesterol concentration of different communities in three international studies. (In the seven countries study one community in which only one man died is omitted)*

TABLE IV—*Randomised controlled trials of reduction in serum cholesterol concentration. Numbers of men with ischaemic heart disease events (deaths or non-fatal infarcts) by time period*

Trial	Method of cholesterol reduction	Mean reduction in serum cholesterol concentration (mmol/l)*	No of men		No of men with ischaemic heart disease event by time period since entry to trial					
					≤2 Years		2·1-5 Years		5·1-12 Years	
			Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls
Drug trials										
Men without known ischaemic heart disease:										
Helsinki[15]	Gemfibrozil	0·7	2051	2030	27	28	28	53	1	3
World Health Organisation[16,17]†	Clofibrate	0·6	5331	5296	52	56	75	91	46	63
Begg[18]	Clofibrate	0·7	76	79	4	8	3	11	NA	
Lipid Research Clinic[19]†	Cholestyramine	0·7	1906	1900	46	51	51	66	58	70
Men with ischaemic heart disease:										
Helsinki[20]†	Gemfibrozil	0·8	311	317	10	14	25	10	NA	
Newcastle[21]	Clofibrate	0·6	192	208	‡		49	73	NA	
Scottish[22]	Clofibrate	0·6	288	305	‡		51	64	NA	
Coronary drug project[23,24]†	Clofibrate	0·4	1103	2789	135	359	128	372	46	108
	Niacin	0·7	1119		129		126		32	
Veterans Administration drug-lipid[25,26]†	Niacin	0·6	145	284	28 (years 0-3)	48	14	21	NA	
Stockholm[27,28]§	Clofibrate, niacin	0·8	279	276	37	41	36	60	NA	
CLAS[29]	Colestipol, niacin	1·3	94	94	1	5	NA		NA	
Gross[30]§	Colestipol	0·6	23	29	1	0	NA		NA	
NHLBI[31]†	Cholestyramine	0·9	57	59	3	3	2	7	0	1
FATS[32]	Three drugs	1·5	94	52	2	0	NA		NA	
Sahni[33]	Lovastatin	0·7	79	78	3	4	NA		NA	
Men with or without ischaemic heart disease‖:										
Upjohn[34]†‖	Colestipol	0·5	548	546	13	25	6	5	NA	
EXCEL[35]†‖	Lovastatin	1·1	6582	1663	62	20	NA		NA	
McCaughan[36]	Probucol	0·7	88	30	2	2	NA		NA	
Dietary trials										
Men without known ischaemic heart disease:										
Minnesota[37]	High polyunsaturated low saturated fat diet	0·7	2197	2196	55	57	14	17	NA	
Los Angeles[38]	High polyunsaturated low saturated fat diet	0·9	424	422	18	22	23	27	11	16
Men with ischaemic heart disease:										
Medical Research Council[39]†	High polyunsaturated low saturated fat diet	1·0	199	194	23	29	22	20	0	3
Oslo[40]	High polyunsaturated low saturated fat diet	1·1	229	229	28	34	33	47	NA	
Sydney[41]†	High polyunsaturated low saturated fat diet	0·3	221	237	25	15	12	9	NA	
St Mary's[42]§	Corn oil	0·6	28	52	8	11	NA		NA	
STARS[43]†¶	Low fat diet	1·1	60	30	1	4	2	1	NA	
DART[44]†¶	Low fat diet	0·3	1018	1015	132	144	NA		NA	
London Hospitals[45]†	Low fat diet	0·6	130	134	39	35	8	15	NA	
Surgery trial										
Men with ischaemic heart disease:										
POSCH[46]†§	Ileal bypass	1·5	421	417	36	31	15	42	30	53

NA=not applicable.
NHLBI=National Heart, Lung and Blood Institute, CLAS=cholesterol-lowering atherosclerosis study, FATS=familial atherosclerosis treatment study, EXCEL=expanded clinical evaluation of lovestatin, STARS=St Thomas's atherosclerosis regression study, DART=diet and reinfarction trial, POSCH=program on surgical control of the hyperlipidemias.

*Difference in mean cholesterol concentration between treated and control subjects throughout trial.
†Unpublished data supplied by authors.
‡Data for years 0-2 not separately available and are combined with years 2·1-5 years.
§Minority of subjects are women, sex specific data being unavailable.
‖Authors supplied separate data.
¶Some treated patients also took drug cholestyramine.

events must have diluted the true magnitude of the effect by including people who did not adhere to their allocated treatment (intention to treat analysis). The analysis of non-fatal events, on the other hand, will have overestimated the true effect through not including such non-compliers. They are typically high risk patients, and since more treated than control patients did not comply, the exclusion of non-compliers will leave the remaining treated patients at lower risk as a group than the remaining control patients. The true effect of reduction of cholesterol concentration is likely to lie between the two estimates for fatal and non-fatal events and is reasonably estimated by our main analysis of a combination of fatal and non-fatal events. In observational studies the strength of the association with serum cholesterol concentration was similar for fatal and non-fatal events.[2,3,10]

We excluded from our main analysis four trials that used oestrogen and two trials that used thyroxine[24-26,50-54] to lower serum cholesterol concentration because these two agents have major effects on the risk of ischaemic heart disease that are not mediated through reduction in concentration. Oestrogen produced only a small reduction in serum cholesterol (mean 0·15 mmol/l) and has complex effects on mortality from ischaemic heart disease, reducing it in lower doses but increasing it at higher doses.[51,55] Thyroxine simulates thyrotoxicosis and so can precipitate myocardial infarction and death from ischaemic heart disease.[56] Inclusion of these six trials in the overall analysis changed the estimate of the reduction in ischaemic heart disease per 0·6 mmol/l reduction in cholesterol concentration from 18% ($P<0·001$) to 14% ($P<0·001$) but introduced a high degree of heterogeneity between trials ($P<0·001$), indicating statistical incompatibility between the results of trials that use these two agents and trials that used other regimens to lower cholesterol concentration. Inclusion of four multiple risk factor intervention trials[57-60] changed the overall result from 18% to 19%.

RESULTS FOR WOMEN

The international estimate was similar for women and men (table III). Three randomised trials with separate data on women showed a significant reduction in ischaemic heart disease similar in size to that observed in men in the same trials.[21,22,46] A fourth trial suggested no effect in women, but most of the ischaemic heart disease events occurred within the first few months after reduction of cholesterol concentration.[37] Some cohort studies produced smaller estimates of the cholesterol-ischaemic heart disease association in women than in men recruited in the same study,[8,61,62] but this can be explained by greater regression dilution bias in women. Serum cholesterol concentration increases steadily in women between the ages of about 35 and 60 years but remains fairly constant in men.[11,63] The increase in women would be expected to affect different women to a different extent, so the rank position of individual women in the distribution of cholesterol concentrations would change more than in men during the follow up period of the study and regression dilution bias would be greater than in men. Studies with shorter follow up, in which this effect should be less pronounced, recorded similar associations in women and men.[61]

Discussion

Our results show a striking consistency between the different categories of data. The cohort studies show the effect of age—a decrease in low density lipoprotein (and total) cholesterol concentration of 0·6 mmol/l in men is associated with a decrease in the risk of ischaemic heart disease of about 50% at the age of 40, 40% at 50, 30% at 60, and 20% at 70 and over (table II). The results of the international studies and randomised trials apply to the age group 55-64 years, and for this age group the estimates from the three types of study can be compared. The cohort study estimate of 27% is lower than the estimate of 38% from the international studies, but the variation in serum cholesterol concentration between countries reflects differences in total dietary fat, reduction of which also favourably alters factor VII activity and coagulation and hence risk of myocardial infarction.[64] (Between individual people (the cohort studies) genetic factors are important determinants of the variation in serum cholesterol.)

The trials show that little reduction in risk of ischaemic heart disease occurs in the first two years after lowering cholesterol, but the summary estimate for the reduction in incidence of ischaemic heart disease five or more years after reduction of cholesterol concentration (25%) is close to that from the cohort studies (27%), showing that the full reduction in risk of ischaemic heart disease is achieved within five years. This is consistent with radiographic measurements of the regression of coronary artery atheroma in trials on lowering cholesterol concentration.[29,31,32,43,46] A man of 35 who reduces his serum cholesterol concentration by 0·6 mmol/l would therefore halve his risk of ischaemic heart disease by the age of 40.

The more limited data available for women indicate that a decrease in serum cholesterol concentration is associated with a similar proportionate reduction in risk of ischaemic heart disease as in men.

The observational data show that in Western societies there is no threshold below which a lower serum cholesterol concentration is not associated with a lower risk of ischaemic heart disease. In the two largest cohort studies the 95% confidence limits of the mortality from ischaemic heart disease in the successive fifths of the cholesterol distribution do not overlap (MRFIT screenees and central Sweden,[4,8] fig 1), confirming a continuous relation which, as Chinese data have shown,[65] extends to cholesterol values below 4 mmol/l. The international studies show that differences in serum cholesterol concentration (and hence in dietary saturated fat) are the most important determinant of the differences in mortality from ischaemic heart disease between countries, accounting for over 80% of the total variation.

An individual person may have difficulty in lowering serum cholesterol concentration by more than about 0·3 mmol/l through dietary change[41,44,66]; the availability of palatable low fat food may be limited when other members of the family or community do not alter their diet. In high risk patients (those with ischaemic heart disease) cholesterol lowering drugs are justified; they can reduce serum cholesterol by 1·2 mmol/l (20%),[35,66] while the dietary changes needed to achieve such a reduction are impractical for an individual person (lowering total dietary fat to about 27% of total energy intake or saturated fat to about 8%).[47-49] This 20% reduction in cholesterol would reduce mortality from ischaemic heart disease by half in people aged 55-64 years. On a community basis a reduction in serum concentrations of total and low density lipoprotein cholesterol through dietary change of 0·6 mmol/l (about 10% for total and 15% for low density lipoprotein cholesterol), reducing mortality from ischaemic heart disease by 25-30% in people aged 55-64 years, is a realistic target. It would require a reduction in total dietary fat from about 42% to 35% of total energy intake or a reduction in saturated fat from about 20% to 13%.[47,48] Reduction in concentration of 0·6 mmol/l in entire communities has occurred through dietary change over periods of a few years[11,67,68] and was attained in seven of the nine dietary trials listed in table IV.

Action needs to be taken to reach this target. This includes wider public education, labelling of foods sold in supermarkets, and provision of information on the content of restaurant meals. Most important, though more difficult, is to implement national and international policies on food subsidies that are linked to health priorities.

TABLE V—*Randomised controlled trials of percentage reduction in serum cholesterol concentration: summary estimates of reduction in ischaemic heart disease in men per 0·6 mmol/l (10%) reduction in serum cholesterol concentration according to time period since entry to trial*

	Time since entry to trial		
Trial	≤2 years	2·1-5 years	5·1-12 years
All drug trials	10	21	22
All dietary trials	9	14	37
Trials of men without known ischaemic heart disease	11	25	24
Trials of men with ischaemic heart disease	6	20	26
All trials (95% confidence interval)	7 (0 to 14)	22 (15 to 28)	25 (15 to 35)

Public health implications

- The combined evidence from the 10 largest cohort studies, three international (ecological) studies, and 28 randomised trials shows conclusively that lowering a person's serum cholesterol concentration results in substantial protection from ischaemic heart disease
- The benefits of serum cholesterol reduction are related to age; a 10% reduction in serum cholesterol concentration produces a reduction in ischaemic heart disease of 50% at age 40, 40% at age 50, 30% at age 60, and 20% at age 70
- The benefit can be realised quickly—the greater part after two years and the full benefit after five years
- Lowering serum cholesterol concentrations in a population is critical in reducing mortality from ischaemic heart disease
- Appropriate action is needed, including wider health education, labelling of foods, and policies on food subsidies that are linked to health priorities

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Blacket,[41] G F Watts,[43] M L Burr,[44] D Sharland,[45] and H Buchwald.[46]

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