Assessing possible hazards of reducing serum cholesterol

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Abstract

***Objective*—To assess whether low serum cholesterol concentration increases mortality from any cause.**

***Design*—Systematic review of published data on mortality from causes other than ischaemic heart disease derived from the 10 largest cohort studies, two international studies, and 28 randomised trials, supplemented by unpublished data on causes of death obtained when necessary.**

***Main outcome measures*—Excess cause specific mortality associated with low or lowered serum cholesterol concentration.**

***Results*—The only cause of death attributable to low serum cholesterol concentration was haemorrhagic stroke. The excess risk was associated only with concentrations below about 5 mmol/l (relative risk 1·9, 95% confidence interval 1·4 to 2·5), affecting about 6% of people in Western populations. For non-circulatory causes of death there was a pronounced difference between cohort studies of employed men, likely to be healthy at recruitment, and cohort studies of subjects in community settings, necessarily including some with existing disease. The employed cohorts showed no excess mortality. The community cohorts showed associations between low cholesterol concentration and lung cancer, haemopoietic cancers, suicide, chronic bronchitis, and chronic liver and bowel diseases; these were most satisfactorily explained by early disease or by factors that cause the disease lowering serum cholesterol concentration (depression causes suicide and lowers cholesterol concentration, for example). In the randomised trials nine deaths (from a total of 687 deaths not due to ischaemic heart disease in treated subjects) were attributed to known adverse effects of the specific treatments, but otherwise there was no evidence of an increased mortality from any cause arising from reduction in cholesterol concentration.**

***Conclusions*—There is no evidence that low or reduced serum cholesterol concentration increases mortality from any cause other than haemorrhagic stroke. This risk affects only those people with a very low concentration and even in these will be outweighed by the benefits from the low risk of ischaemic heart disease.**

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Introduction

In our previous analysis we quantified the benefit of reducing serum cholesterol concentration in terms of risk of ischaemic heart disease.[1] There remains uncertainty over possible harmful effects of cholesterol reduction,[2-7] and in this paper we analyse data on mortality from causes other than ischaemic heart disease to assess the strength and consistency of the evidence for harmful effects.

Methods

We analysed the same observational studies and randomised trials used in our analysis of cholesterol and ischaemic heart disease.[1 8-21] We divided the deaths from causes other than ischaemic heart disease into four categories; circulatory diseases other than ischaemic heart disease, cancer, accidents and suicide, and other causes (mainly chronic respiratory, digestive, and neurological diseases). Within these categories we examined cause specific mortality data, particularly causes of death previously linked to low cholesterol concentration (haemorrhagic stroke, lung cancer, suicide, and chronic respiratory disease[2]). We also examined other relevant information, including smaller cohort studies.

OBSERVATIONAL STUDIES

Mortality in men in the four categories was available from the 10 cohort studies examined in our previous paper,[1 8-12] though from only two of the five component studies of the United States pooling project (the two Chicago studies[9]). In cohort studies associations between low cholesterol concentration and disease may arise because serum cholesterol is lowered by certain conditions that cause disease (for example, alcoholism) or by the presence of early disease (for example, cancer). To minimise the effect of such associations we divided the cohort studies into two groups as previously suggested,[2] the four that recruited men who were employed and so likely to have been healthy at recruitment and the six that recruited from the general population (community cohorts), which necessarily included some people with chronic diseases. We also examined the effect of omitting deaths occurring in the earlier years of follow up.

The study cohorts were divided into subgroups (usually fifths) according to ranked cholesterol concentration and for each study we expressed the excess mortality as the ratio of the death rate in the subgroup with the lowest cholesterol concentrations of each study (below about 5 mmol/l) to that in the remainder of the cohort (see footnote to table II). Continuous models did not fit the data well since any excess mortality was concentrated in the subgroup with the lowest cholesterol concentrations. Authors of seven of the original reports provided unpublished data to allow an analysis based on almost complete data on mortality from causes other than ischaemic heart disease from the 10 cohort studies. Mortality from causes other than ischaemic heart disease were available for two of the three international studies described in our previous paper.[1 13-15] We expressed their results in the same way as the cohort studies, the ratio of the mortality in communities with mean serum cholesterol concentrations below and above 5 mmol/l.

RANDOMISED CONTROLLED TRIALS

Data on mortality from causes other than ischaemic heart disease (both sexes combined) were available from the 28 trials included in our analysis.[1 16-21] As before, we analysed the results on an intention to treat basis (all deaths irrespective of adherence to treatment). With unpublished data from authors of 12 of the trials, vital status at the end of the trial was known for 99·5% of the total of 52 350 subjects randomised. Table I summarises the data. As in our previous analysis[1] we used logistic regression analysis to combine the odds ratios from each trial to obtain a summary odds ratio for the effect of cholesterol reduction on each of the four specified categories of deaths. We weighted the

odds ratio from each trial by its reduction in cholesterol concentration since a greater change in cholesterol concentration should produce a greater change in mortality from any disease causally related to serum cholesterol concentration. The results of an unweighted analysis were similar, however.

Results and discussion

GENERAL

There was an important difference between the results from the employed and community cohorts. The four employed cohorts showed no overall excess mortality from causes other than ischaemic heart disease associated with low serum cholesterol concentration: the overall relative risk among men in the subgroups with the lowest cholesterol concentrations compared with the remainder of the cohorts was 1·00 (see table II). In contrast there was a highly significant excess in mortality from all causes other than ischaemic heart disease in the subgroups with the lowest cholesterol concentrations in the six community cohorts (relative risk 1·20, $P<0·001$). The difference between the two types of study was highly significant ($p<0·001$) and supported by the other smaller published cohort studies of employed men, which also showed no excess mortality from causes other than ischaemic heart disease,[22-27] and by other community cohorts which did.[2] This difference indicates that in the community cohorts illness that was present on entry to the study lowered serum cholesterol and caused the excess mortality.

The randomised trials (table I) combined showed no significant excess in mortality from all causes other than ischaemic heart disease (relative odds 1·07 per 0·6 mmol/l (10%) reduction in cholesterol concentration, 95% confidence interval 0·97 to 1·18, P=0·16). Randomised trials are of limited value in assessing hazard in this context for three reasons. Firstly, they recorded too few deaths from causes other than ischaemic heart disease to be sensitive to any cause specific hazard. Secondly, their duration was short (mean 4·6 years) with deaths occurring on average only two or three years from the start of treatment, much less time, for example, than the latent interval normally required for a carcinogen to exert its effect. Finally, the treated subjects did not have low enough cholesterol concentrations to confirm or refute the excess mortality occurring at concentrations below about 5 mmol/l in the community cohorts.

In examining the four specified categories of death from causes other than ischaemic heart disease in turn we have sought to reach a conclusion based on all the evidence and to reconcile any apparent inconsistencies.

CIRCULATORY DISEASES OTHER THAN ISCHAEMIC HEART DISEASE (TABLE II)

There was no significant excess mortality from circulatory diseases other than ischaemic heart disease taken as a whole in either the cohort studies of employed men (relative risk 0·92) or the community cohorts (relative risk 1·12). But only two cohort studies (MRFIT screenees and Honolulu) distinguished deaths from haemorrhagic and thrombotic stroke.[10 11 28] Both studies showed an excess risk of haemorrhagic stroke in the subgroup with the lowest cholesterol concentration with relative risks of 1·60 (27 deaths) and 2·28 (21 deaths) respectively, yielding a combined estimate of 1·86 (1·37 to 2·53, $P<0·001$). The excess was not apparent in the broader category of all circulatory diseases other than ischaemic heart disease because mortality from thrombotic stroke and other

TABLE I—*Numbers of deaths by category in randomised controlled trials of reduction in serum cholesterol concentration, both sexes combined (only references additional to those in table IV in previous paper[1] are cited)*

Trial*	No of subjects		Vital status known at end of trial (%)	No of deaths during trials†										Deaths from cancer during observation after trial	
				Ischaemic heart disease		Other circulatory diseases		Cancer		Accidents and suicide		Other diseases			
	Treated	Control		Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control
Drug trials															
Subjects without known ischaemic heart disease:															
Helsinki[16]	2051	2030	>99	14	19	8	4	11	11	9	5	2	4		
WHO‡	5331	5296	>99	76	69	22	18	72	54	24	24	21	6	131	142
Lipid Research Clinics[17]	1906	1900	>99	32	44	5	3	16	15	11	4	4	5	30	29
Subjects with ischaemic heart disease:															
Helsinki	311	317	>99	8	17	1	1	0	2	1	1	0	0		
Newcastle[18]‡	244	253	70	27	48	1	0	2	2	0	0	1	2		
Scottish[18]	350	367	>99	34	38	3	2	3	5	1	1	1	2		
Coronary Drug Project:															
Clofibrate	1103	2789	>99	240	632	19	28	11	27	5	15	7	16	26	97
Niacin	1119			238		12		14		8		5		31	
Veterans Administration drug-lipid‡	145	284	97	42	69	1	3	0	2	0	1	1	6		
Stockholm	279	276	>99	47	73	7	2	4	6	0	1	3	0		
Gross	23	29	89	1	0	0	1	0	1	0	0	0	0		
Subjects with or without ischaemic heart disease:															
Upjohn§‡	1149	1129	97	19	31	5	6	4	5	2	1	4	2		
EXCEL§‡	6582	1663	>99	28	3	4	0	0	0	0	0	1	0		
Dietary trials															
Subjects without known ischaemic heart disease:															
Minnesota	4541	4516	>99	61	54	44	47	23	20	33	28	108	99		
Los Angeles[19]	424	422	>99	41	50	9	21	33	20	‖		59	62	8	10
Subjects with ischaemic heart disease:															
Medical Research Council[20]‡	199	194	>99	25	26	2	0	1	6	0	0	1	0	0	4
Oslo[21]	229	229	>99	37	50	1	2	1	3	0	0	1	0	6	2
Sydney‡	221	237	>99	37	24	1	2	1	1	0	1	0	0		
DART‡	1018	1015	>99	97	97	5	5	4	6	1	1	4	4		
Surgery trial															
Subjects with ischaemic heart disease:															
POSCH	421	417	>99	32	44	3	5	8	8	3	3	3	1		

NHLBI=National Heart, Lung and Blood Institute, EXCEL=expanded clinical evaluation of lovastatin, DART=Diet and reinfarction trial, POSCH=program on surgical control of the hyperlipidemias; CLAS=cholesterol-lowering atherosclerosis study, FATS=familial atherosclerosis treatment study, STARS=St Thomas's atherosclerosis regression study.
*In nine additional trials all deaths were from ischaemic heart disease or from ischaemic heart disease and one other cause (treated/control): CLAS 0/1, FATS 1/0, St Mary's 5/4, STARS‡ 1/3, London hospitals‡ 21/26, Begg 4/9 (and other circulatory 0/1), NHLBI‡ 5/6 (and other diseases 0/1), Sahni 1/3 (and all non-cardiac 3/4, McCaughan‡ 2/2 (and cancer 0/1).
†Six trials recorded deaths from unknown causes as follows (treated/control): WHO 1/0, Coronary drug project 6/0/5, Upjohn 3/3, Los Angeles 32/25, Oslo 8/10, POSCH 0/1.
‡Unpublished data supplied by authors.
§Authors supplied separate data for those with and without ischaemic heart disease.
‖Not available separately, combined with other diseases.

TABLE II—*Association of low serum cholesterol concentration with mortality from causes other than ischaemic heart disease. Numbers for cohort studies are relative risk (number of deaths) in the subgroup with lowest cholesterol concentrations† (compared with rest of cohort); for international studies are relative risk (number of deaths) in communities with mean cholesterol concentration below 5 mmol/l (compared with >5 mmol/l); and for randomised trials are estimated reduction in risk for reduction in cholesterol concentration of 0·6 mmol/l (total number of deaths). (Only references additional to those in table I in previous paper[1] are cited)*

Detail of study	Circulatory diseases except ischaemic heart disease	Cancer	Accidents and suicides	Other diseases	All causes except ischaemic heart disease
Cohorts of employed men:					
BUPA‡	0·79 (25)	0·89 (99)	0·84 (12)	0·92 (30)	0·88 (166)
Whitehall‡[9]	1·01 (107)	1·03 (236)	0·91 (16)	1·27 (126)*	1·07 (485)
Israeli‡	0·84 (94)	1·06 (147)	1·05 (21)	0·99 (186)	0·98 (448)
Chicago[9]	0·95 (13)	0·89 (31)	§	1·04 (24)	0·91 (68)
All studies	0·92 (239)	1·00 (513)	0·95 (49)	1·08 (366)	1·00 (1167)
95% Confidence interval	0·80 to 1·05	0·91 to 1·10	0·70 to 1·30	0·97 to 1·21	0·94 to 1·06
Cohorts from community settings:					
British regional heart‡	1·60 (18)	1·06 (48)	1·64 (7)	2·01 (31) **	1·36 (104) **
MRFIT screenees trial[10]	0·99 (113)	1.30 (499)***	1·28 (127)**	1·82 (224)***	1·34 (963)***
Renfrew-Paisley‡	1·18 (77)	1·27 (191)**	2·61 (10) *	1·51 (108)***	1·35 (543)***
Honolulu[11]	1·28 (34)¶	1·41 (138)***	1·16 (16)	1·27 (111)*	1·33 (299)***
Gothenberg‡	1·11 (7)	0·98 (29)	1·37 (9)	1·37 (26)	1·20 (71)
Central Sweden[12]	NA	1·14 (667)**	1·19 (107)	NA	1·07 (1923)**
All studies	1·12 (249)	1·23 (1572)***	1·29 (276)***	1·62 (500)***	1·20 (3715)***
95% Confidence interval	0·98 to 1·28	1·17 to 1·30	1·13 to 1·47	1·47 to 1·78	1·15 to 1·24
International studies:					
Seven Countries[13,14]	1·85 (126)***¶	0·98 (176)	0·87 (28)	NA	1·16 (262) *
International comparison[15]	1·37	0·88	0·63	0·92	0·98
Randomised trials:					
All trials (table I)	1·00 (304)	1·07 (403)	1·17 (184)	1·07 (436)	1·07 (1330)
95% Confidence interval	0·82 to 1·21	0·90 to 1·26	0·90 to 1·52	0·92 to 1·26	0·97 to 1·18

*<0·05, **P<0·01, ***P<0·001.
†Lowest cholesterol group was 6% of cohort for multiple risk factor intervention trial screenees, 14% for Honolulu, 20% for others.
‡Unpublished data supplied by authors.
§Combined with other diseases.
¶Stroke mortality only.
NA=not available.

circulatory diseases decreased with decreasing serum cholesterol concentration.[10,11,28] Data from smaller cohort studies that recorded haemorrhagic stroke showed an association with low serum cholesterol concentration in three cohorts in which average blood pressure was fairly high[29-31] but not in two cohorts with lower blood pressure,[32,33] indicating an interaction with blood pressure. Within cohorts also, the excess of haemorrhagic stroke at low serum cholesterol concentrations was apparent only in those subjects with relatively high blood pressure.[28,29]

The international studies did not distinguish haemorrhagic and thrombotic stroke but showed a significant excess in mortality from all stroke in communities with mean serum cholesterol concentrations below 5 mmol/l, probably due to haemorrhagic stroke as it is more common with low serum cholesterol concentration.[10,11] Data from the seven countries study showed that the excess did not arise through confounding with higher blood pressure in communities with low cholesterol concentrations.[13,14] Mortality from stroke was on average similar in treated and control subjects in the randomised trials, but the trials were uninformative as few of their subjects had low serum cholesterol concentrations (<5 mmol/l). Further evidence comes from an association over time between rising serum cholesterol concentration and falling rates of stroke in Japan, after adjustment for changes in other determinants of stroke mortality.[34,35] Experiments in hypertensive rats and other data have suggested that very low serum cholesterol concentrations may weaken the endothelium of intracerebral arteries.[2,28,36]

The excess mortality from haemorrhagic stroke at cholesterol concentrations lower than about 5 mmol/l among people with fairly high blood pressure is consistent across studies and the evidence indicates that it is cause and effect. Confounding is improbable: it is unlikely that some unknown cause of haemorrhagic stroke should be associated with high blood pressure and low cholesterol concentration. The most likely explanation is that in groups at high risk of haemorrhagic stroke through higher blood pressure a very low serum cholesterol concentration exacerbates the risk, possibly through weakening arterial walls. At very low cholesterol concentrations, however, the increased mortality from haemorrhagic stroke is small compared with the lower mortality from ischaemic heart disease. In the largest study (MRFIT screenees), for example, a comparison of mortality in the group with the lowest cholesterol concentrations (<4·14 mmol/l) and in the next lowest group (4·14-5·15 mmol/l) showed that mortality from haemorrhagic stroke in the lowest group was 0·3 per 10 000 man years higher but mortality from ischaemic heart disease was 3·3 per 10 000 man years lower.[10] Mortality from thrombotic stroke was also lower. The balance of benefit is clear.

CANCER (TABLES II AND III, FIGURE)

The cohorts of employed men showed no excess mortality from cancer (relative risk 1·00). The community cohorts showed an excess in the subgroup with the lowest cholesterol concentrations (relative risk 1·23, P<0·001). The difference between the employed and community cohorts was again highly significant (P<0·001) and reinforced by the smaller published studies of employed cohorts, which also showed no excess in mortality from cancer[22-27] and by other community cohorts which did.[2,37] In the community cohorts the excess mortality from cancer that was apparent for several sites (for example, colon cancer) was limited to deaths occurring within a few years of the cholesterol measurement and so attributable to preclinical cancer lowering serum cholesterol concentration.[37] This effect is not apparent for other cancers in table III because the early excess is diluted with longer follow up. In an analysis of all published cohort studies we have previously shown that the association was present on a long term basis only for lung and other smoking related cancers and lymphatic and haemopoietic cancers,[37] confirming the site specific data from the four community cohort studies in table III. The association with lymphatic and haemopoietic cancers occurs because the cancers lower the cholesterol concentration, the effect persisting for several years because patients with these cancers may have their survival prolonged by treatment. Serum cholesterol concentration increases when chemotherapy induces

TABLE III—*Site specific data relating to excess mortality from cancer in four community cohort studies. Numbers are relative risk (number of deaths) in subgroup with lowest cholesterol concentration compared with remainder of each cohort*

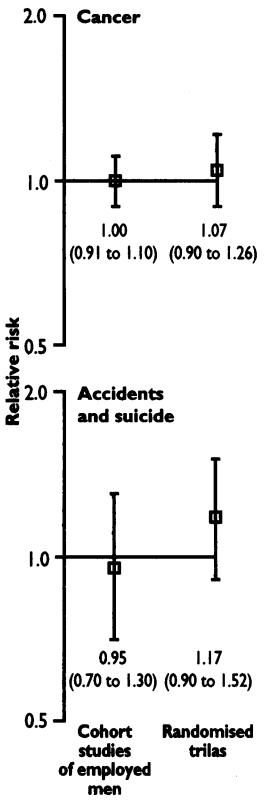
Detail of study	Lung cancer	Other cancers related to smoking‡	Lymphatic and haemopoietic cancers (ICD-9 200-208)	All other cancers
Cohorts from community settings:				
British regional heart†	1·60 (22)	NA	2·68 (7)	0·68 (19)
MRFIT screenees	1·30 (167)***	1·35 (45)*	2·07 (77)***	1·14 (210)
Renfrew-Paisley†	1·35 (89)*	1·48 (39)*	0·47 (3)	1·09 (60)
Honolulu	1·58 (40)**	NA	NA	NA
All studies	1·36 (318)***	1·41 (84)**	2·05 (87)***	1·10 (289)
95% Confidence interval	1·21 to 1·53	1·11 to 1·77	1·63 to 2·56	0·97 to 1·24

*P<0·05, **P<0·01, ***P<0·001.
†Unpublished data supplied by authors.
‡ICD-9 140-50, 157, 160, 161, 188, 189 (150 and 157 only in MRFIT screenees.
NA=not available.

TABLE IV—*Details of excess mortality from accidents and suicide in two community cohort studies. Numbers are relative risk (number of deaths) in subgroup with lowest cholesterol concentrations compared with remainder of each cohort*

Detail of study	Suicide			Accidents and homicide
	All	Years 0-6	Years ⩾7	
Cohorts from community settings:				
MRFIT screenees	1·52 (48)**	1·96 (24)**	1·24 (24)	1·14 (79)
Central Sweden	1·43 (47)*	2·35 (21)**†	1·08 (26)	1·05 (60)
All studies	1·48 (95)***	2·10 (45)***	1·16 (50)	1·10 (139)
95% Confidence interval	1·18 to 1·85	1·50 to 2·95	0·86 to 1·58	0·92 to 1·32

*P<0·05, **P<0·01, ***P<0·001.
†Years 0-6, ⩾7.



Association between serum cholesterol concentration and mortality from cancer and from accidents and suicide. Relative risks (95% confidence intervals) in cohort studies of employed men compare subgroups (fifths) with lowest cholesterol concentration with remainder of cohort and in randomised trials show estimated effect of reduction in cholesterol of 0·6 mmol/l (10%)

remission of disease, indicating that it is the cancers that lower the cholesterol concentration rather than the reverse.[37]

The association with lung and other smoking related cancers cannot be explained in this way. The two international studies, however, showed no association between low serum cholesterol concentration and cancer of all sites or lung cancer[13 15]; nor did an analysis of death rates from 65 Chinese counties.[38] Data on food consumption in different countries showed an association between high dietary fat and death rates from lung cancer and cancer of all sites.[39 40] Most important, the cohorts of employed people together showed no excess mortality from lung cancer. The link with lung cancer rests entirely on the community cohorts and has been shown to be heterogeneous among these, being most evident in cohorts of men in low socioeconomic groups.[37] The restriction of the association to certain groups in this way favours confounding—that is, a factor linked to both low serum cholesterol concentration and a high risk of lung cancer.

Cigarette smoking lowers the concentration of high density lipoprotein cholesterol[37 41] and so may partly explain the confounding, but smoking is not associated with low total serum cholesterol concentration; the reduced concentration of high density lipoprotein cholesterol is usually balanced by raised concentration of low density lipoprotein cholesterol because smokers eat more saturated fat.[37] This overall balance, however, could conceal a high risk subgroup in which the effect of lowering high density lipoprotein cholesterol is greater than the effect of raising low density lipoprotein cholesterol. The poorest people in a community, for example, may have the lowest serum cholesterol concentration[41] and are likely to smoke each cigarette more intensely. Such an explanation for the confounding requires confirmation, but the restriction of the association to certain studies indicates that confounding is involved.

The randomised trials showed no overall excess of mortality from cancer (P>0·2, table II). Two trials raised concern over an excess of deaths from cancer in treated subjects (72 *v* 54 deaths in the World Health Organisation clofibrate trial (P=0·12) and 33 *v* 20 in the Los Angeles dietary trial (P=0·08; table I). The remaining trials, with 224 deaths from cancer, showed no excess. These results could have arisen by chance (neither was significant), and there was no significant site specific excess in either. Data available from the Los Angeles trial showed that the excess mortality occurred mainly among men who did not adhere to their allocated diet and so was not due to the diet (10 *v* 2 deaths among men who did not eat the allocated diet and 13 *v* 11 among men who did so for more than half of their meals). Also the duration of the two trials, like the others, was shorter than the interval normally required for a carcinogen to exert its effect. Data after the trial period (table I), available for six of the trials (including the two that originally raised concern), provides information on the risk of cancer five to 10 years after reduction in cholesterol concentration: the overall relative odds estimate was 0·88 with a comparatively narrow confidence interval (0·74 to 1·05), which provides evidence against a low cholesterol concentration being a cause of cancer.

ACCIDENTS AND SUICIDE (TABLES II AND IV, FIGURE)

There was again a striking difference between the four employed cohorts and six community cohorts. In the community cohorts a significant excess arose, due to a higher rate of suicide in the subgroup with the lowest cholesterol concentrations (relative risk 1·48, P<0·001). Among the employed men and in the international data there was no association between low cholesterol concentration and deaths from accidents and suicide nor from suicide alone. Depression is the major psychiatric illness that predisposes to suicide, so given the association with suicide it is not surprising that an association between low cholesterol concentration and depression has been observed.[42 43] There are only two possible explanations: either low serum cholesterol concentration causes depression (and thereby suicide) or is a consequence of depression. The evidence refutes the causal explanation and supports the consequential one: lowering cholesterol concentration does not lead to depression but depression lowers cholesterol concentration. In support of the latter are the observations that anorexia is a common feature of depression[43] and that treating depression leads to an increase in serum cholesterol concentration.[44] Two trials in which serum cholesterol concentration was lowered substantially (by more than 20%) indicate that lowering serum cholesterol does not affect mood. The Air Force coronary atherosclerosis prevention study (AFCAPS) found no difference between treated and control subjects in emotional wellbeing.[46] In the expanded clinical evaluation of lovastatin (EXCEL) trial[47] the incidence of depression was 1·4% in 6582 treated patients and 1·7% in 1663 patients taking placebo, and serious depression (leading to discontinuation in the trial), anxiety, insomnia, dizziness, and other symptoms were all equally common in the two groups (J Tobert, personal communication).

Further evidence confirms the conclusion that the association between low serum cholesterol concentration and suicide is due to a common link with depression. Low serum cholesterol concentration is strongly associated with suicide in the first five years after the cholesterol measurement (P<0·001), but there is no significant association thereafter (table IV). Cholesterol tracks throughout life sufficiently to predict death from ischaemic heart disease 30-40 years later[24] and should do the same if it were a cause of suicide. Since it does not the association must be a short term consequence of depression not a cause of it. In a similar way alcoholism, itself associated with depression and other mental illness and also a direct cause of death from accidents and suicide, leads to a low serum cholesterol concentration.[48]

The randomised trials showed no significant excess

in the broad category of deaths due to accidents and suicide ($P>0.2$; table II). Two of the trials raised concern over excess risk from accidents and suicide in treated subjects (9 *v* 5 deaths in the Helsinki gemfibrozil trial ($P=0.29$) and 11 *v* 4 in the Lipid Research Clinics cholestyramine trial ($P=0.07$)). Neither result was significant, and the remaining trials, with 155 deaths, did not suggest an excess.

In the two trials combined (20 *v* 9 deaths) compliance data showed that the extra deaths occurred predominantly among men who took no medication at all (8 *v* 2) or fewer than half (3 *v* 0), leaving an excess of only two deaths (9 *v* 7) among those who took at least half the medication.[16] In the Lipid Research Clinics trial information on psychiatric illness was recorded at entry; all the excess mortality from accidents and suicide lay in patients with psychiatric illness on entry,[16] confirming that the difference was due to the chance allocation of more psychiatric patients to the active group than the placebo.

It is coincidental that there was a link between accidents and suicides and low serum cholesterol concentration in both cohort studies and trials. The evidence indicates that it was produced in the cohort studies by depression lowering cholesterol concentration and predisposing to suicide, and in the trials by chance.

OTHER DISEASES (DEATHS NOT DUE TO CIRCULATORY DISEASES, CANCER, OR ACCIDENTS AND SUICIDE) (TABLE II)

In the employed cohorts there was an excess mortality from other diseases (relative risk 1·08), which, though not significant, included a significant increase from chronic respiratory disease in the Whitehall study (relative risk 1·49, $P<0.01$). There was no indication of any other excess mortality. This result differed significantly ($P<0.001$) from the result in the community cohorts, in which there was an overall excess risk from other diseases (relative risk 1·62, $P<0.001$). This excess was non-specific, including several chronic diseases, but was mainly due to excess mortality from chronic respiratory, liver, and bowel diseases. Other community cohort studies confirmed these associations,[2 33] but the international data showed no excess.

Such an association of low cholesterol concentration with increased mortality in some observational studies is predictable since many diseases or their causes can lower serum cholesterol concentration. Even non-specific illness may lower cholesterol (a survey of 1636 British adults showed lower cholesterol in people who reported any illness over the previous week (n=264) than in those who did not, by 0·23 mmol/l on average ($P<0.001$), whether or not eating was affected by the illness[41]). Chronic digestive diseases can cause malabsorption of fat and will thereby lower serum cholesterol concentration. Alcoholism and hepatitis B infection are associated with low serum cholesterol[48 49] and cause chronic liver disease. Patients with chronic bronchitis may have low serum cholesterol because they are thin, because they develop respiratory infections (which lower cholesterol[50 51]), and perhaps because of the effect of smoking that we proposed for lung cancer (the association with low cholesterol concentration was more pronounced in smokers[10]). The effect of early disease lowering cholesterol concentrations cannot be avoided by censoring the deaths occurring in the first few years after recruitment because the clinical progression of these chronic diseases is slow and often delayed by treatment.

The randomised trials showed no significant overall excess mortality from other diseases ($P>0.2$). Cause specific mortality data showed no significant excess except for seven deaths related to treatment, two from complications of ileal bypass surgery in the program on surgical control of the hyperlipidemias (POSCH) trial and five from complications of surgery for gall stones in treated subjects (none in controls) in trials of the drug clofibrate (known to cause gall stones). There were also two deaths in treated patients from pancreatitis, which may have followed impaction of gall stones in the pancreatic duct (a particularly lethal form of pancreatitis). Only one trial showed an excess mortality from other diseases (the WHO clofibrate trial, 21 *v* 6 deaths, $P=0.006$, table I); it was partly due to an excess mortality related to gall stones (6 *v* 0, $P=0.03$) attributable to the drug, but among the remaining deaths (15 *v* 6, $P=0.08$) there was no significant cause specific excess. The other trials taken together showed no significant excess in mortality from any specific disease.

Previous analyses of randomised trials

Four recent meta-analyses of the randomised trials have used total (all cause) mortality as the critical outcome measure, and all four produced conclusions different from our own. Ravnskov concluded that lowering cholesterol concentration did not reduce total mortality and was unlikely even to prevent ischaemic heart disease.[4] Muldoon *et al*, in an analysis restricted to men without ischaemic heart disease on entry to the trials, concluded that there was a reduction in mortality from ischaemic heart disease but not in total mortality and were reluctant to recommend reduction in cholesterol concentration.[5] Davey Smith *et al* concluded that the only benefit was in high risk subjects and that it was cholesterol lowering drugs, not diets, that were hazardous.[6 7] These conclusions, identifying hazard either in all people or in subgroups, differ from our own for the following reasons.

USE OF TOTAL MORTALITY AS ARBITER

Total mortality is not an informative arbiter in the available data, though of course the ultimate one. Even with all the studies combined total mortality is too insensitive in monitoring the effects of an intervention that reduces mortality from only one cause, even one as common as ischaemic heart disease. The observed reduction in mortality from ischaemic heart disease in all the trials combined (2618 deaths) was 10% per 0·6 mmol/l reduction in cholesterol concentration ($P=0.004$, see table V). With 1330 deaths from causes other than ischaemic heart disease and 94 from unknown causes (see table V) this 10% reduction in ischaemic heart disease is equivalent to an expected overall reduction in total mortality of 6% per 0·6 mmol/l reduction in cholesterol concentration if lowering cholesterol had no effect on mortality from causes other than ischaemic heart disease. The observed reduction in total mortality of 4% (95% confidence interval 10% reduction, 2% increase) is not significant yet is reasonably close to, and statistically consistent with, the 6% expected reduction. The results on total mortality therefore lack the statistical power to conclude either that reduction in serum cholesterol concentration carries no hazard at all or that there is a hazard large enough to cancel the benefit from the reduced mortality from ischaemic heart disease. The limited statistical power reflects the small expected reduction in total mortality (6% per 0·6 mmol/l reduction in cholesterol concentration), which in turn reflects the short duration of the trials: about half the deaths from ischaemic heart disease occurred in the first two years when there was little reduction.[1]

SELECTION OF TRIALS IN DIFFERENT ANALYSES

Different analyses included different sets of trials. Ravnskov omitted 13 trials (mostly small) that we included but added seven others,[4] Davey Smith *et al*

added four.[6] The trials excluded from our analysis but included by others fall into three categories: firstly, multiple risk factor intervention trials which did not test cholesterol reduction alone (five trials); secondly, trials in which the treatment had major effects on risk of ischaemic heart disease other than through cholesterol reduction (oestrogen or thyroxine, three trials and three arms of a fourth trial); and, thirdly, one non-randomised trial.

The inclusion or exclusion of different groups of trials has relatively little effect on the overall estimate provided that the reduction in ischaemic heart disease is related to the magnitude of the reduction in serum cholesterol concentration in each trial. Ravnskov's analysis showed a mean reduction of 10% in non-fatal ischaemic heart disease ($P<0.01$) and 6% in fatal ischaemic heart disease ($P=0.06$). His analysis gave equal weight to each trial irrespective of the reduction in cholesterol concentration attained and included large trials with only a small reduction (1-2%). Our estimate of the reduction in mortality from ischaemic heart disease (10% per 0·6 mmol/l reduction in cholesterol concentration), when adjusted for the smaller overall mean reduction of 0·4 mmol/l in Ravnskov's analysis yields a 7% reduction, similar to his estimate of 6%. His analysis failed to show a dose-response association between reduction in ischaemic heart disease and either duration or reduction in cholesterol concentration across the trials. This cannot be replicated because he did not specify his methods, but our analysis of more comprehensive data showed highly significant effects of both duration and extent of reduction in cholesterol concentration.

DISCREPANCIES BETWEEN RESULTS FOR SUBJECTS WITH AND WITHOUT ISCHAEMIC HEART DISEASE AND TRIALS OF DRUGS OR DIET

Table V shows that the trials of men without ischaemic heart disease on entry suggest an excess in mortality from causes other than ischaemic heart disease ($P=0.07$), but the trials of men with ischaemic heart disease on entry do not; and the drug trials show an excess ($P=0.02$) but the dietary trials do not. These differences arise because of the way in which four trials are categorised: the Los Angeles dietary and WHO clofibrate trials, which raised the concern over cancer (and other diseases in the WHO trial) and the Helsinki gemfibrozil and Lipid Research Clinics cholestyramine trials, which raised the concern over accidents and suicide (table I). These four trials all recruited men without ischaemic heart disease on entry and three of them used drugs, so raising concern in these two categories. But, as reasoned above, the evidence indicates that apart from the six deaths from gall stone disease in the WHO trial that were attributable to the drug clofibrate, the higher mortality in treated men in these four trials was spurious: it was concentrated among men who did not take the treatment, was associated with disease present on entry, was not significant in any trial, and there was no significant cause specific excess. Subset analyses of trials of people without ischaemic heart disease on entry, people at low risk of ischaemic heart disease or trials of drugs will include these trials and are liable to show a spurious significant excess mortality. This explains, firstly, the analysis of Muldoon *et al*, which was restricted to trials of men without ischaemic heart disease on entry and showed no reduction in total mortality;[5] secondly, the analysis of Davey Smith *et al*, which concluded that total mortality was increased in trials of men with a low risk of ischaemic heart disease; and, thirdly, the analysis of Davey Smith and Pekkanen restricted to eight trials that concluded that drugs that lower cholesterol concentration were hazardous.[7]

TABLE V—*Combined results from randomised trials of reduction of serum cholesterol concentration; relative odds of death in treated/control groups per 0·6 mmol/l (10%) reduction in cholesterol according to type of trial*

Cause of death	No of trials	No of deaths	Odds of death in treated/control groups (95% confidence interval)	P value
Ischaemic heart disease	28	2618	0·90 (0·84 to 0·97)	0·004
All causes other than ischaemic heart disease:*				
All trials	28	1330	1·07 (0·97 to 1·18)	0·16
Drug trials	18	636	1·20 (1·02 to 1·40)	0·02
Dietary trials	9	660	1·01 (0·88 to 1·15)	>0·2
Surgery trial	1	34	0·99 (0·50 to 1·97)	>0·2
Subjects without ischaemic heart disease†	8	990	1·11 (0·99 to 1·24)	0·07
Subjects with known ischaemic heart disease	21	339	0·99 (0·83 to 1·18)	>0·2
All cause mortality‡:				
All trials	28	4042	0·96 (0·90 to 1·02)	0·17
Drug trials	18	2537	0·97 (0·89 to 1·05)	>0·2
Dietary trials	9	1394	0·97 (0·88 to 1·07)	>0·2
Surgery trial	1	111	0·75 (0·50 to 1·13)	>0·2
Subjects without ischaemic heart disease†	8	1555	1·06 (0·97 to 1·17)	>0·2
Subjects with ischaemic heart disease	21	2482	0·90 (0·84 to 0·97)	0·008

*Five trials recorded no deaths other than from ischaemic heart disease.
†One trial, with one death from cause other than ischaemic heart disease and four deaths from ischaemic heart disease could not be classified.
‡Includes 94 deaths of unknown cause.

Public health implications

- There is an excess risk of haemorrhagic stroke at very low serum cholesterol concentrations (the lowest 6% in Western countries), but this is outweighed by the low risk of ischaemic heart disease and is not a practical public health concern
- Detailed analysis of cause specific mortality data in the major observational studies and all the randomised trials provides strong evidence for the safety of lowering serum cholesterol; there is no evidence that serum cholesterol reduction increases the risk of death from any cause except haemorrhagic stroke
- Reports that deaths from cancer or from accidents and suicide are related to low serum cholesterol can be readily explained by certain diseases lowering cholesterol or by simple chance
- Certain drugs may have side effects—for example, clofibrate causes gall stones—but analysis of cause specific mortality did not indicate any other hazard

Conclusions

There is an excess risk of haemorrhagic stroke in people with very low serum cholesterol concentrations (below about 5 mmol/l) that in Western communities is outweighed by a deficit of deaths from ischaemic heart disease. Otherwise there is no evidence that a low serum cholesterol concentration is harmful. Observational associations of low cholesterol concentrations with lung cancer, suicide, chronic bronchitis, and digestive diseases can be explained by factors that cause these diseases or by early disease lowering serum cholesterol concentration. In the randomised trials nine deaths were attributable to complications of specific treatments but otherwise there was no increase in mortality from any specific cause that was significant, consistent between trials, or present in men who complied with cholesterol lowering treatment. The evidence is clear. The need is not to repeat research that has already been performed but to disseminate the results, their interpretation, and the conclusions so that preventive action can be taken to confer the substantial health benefit of lowering average serum cholesterol concentrations in Western populations.

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ONE HUNDRED YEARS AGO

THE HEALTH OF FLORENCE.

The preference which the Queen has shown for Florence as a place of spring residence, and the benefit which Her Majesty is understood to have derived from her sojourns there, will serve to increase the popularity of the beautiful Tuscan city, with the large and growing class who follow the wise custom of taking an early spring holiday. The sanitary deficiencies of most Italian cities are well known, and are freely admitted by those Italians who have given special attention to the study of hygiene; much has been done to improve them, and in Florence itself the municipality has shown a good deal of activity. At the same time much remains to be done, especially in the direction of better domestic sanitary appliances. The drainage and internal fittings of even the best houses, hotels, and villas, are not such as would be sanctioned in this country. So much is this the case that we understand that when the Queen decided to go to Florence this year, no house was available of sufficient size and where the sanitary arrangements were satisfactory. The Villa Fabbricotti was selected on account of its situation and capacity; and Her Majesty's advisers—in opposition to local advice—found the drainage on such an antiquated and dangerous system (although the villa is comparatively modern) that they felt bound to recommend that it should be completely renewed. This was carried out under the inspection of the firm of English sanitary engineers who have supervised, with such satisfactory results, the drainage of Cannes. From the official *Bolletino di Statistica*, of the city of Florence, for the year 1893, it appears that the death-rate was 24·3 per mille, or excluding stillborn, 23·2 per mille. The population of the city is given as 186,015 at the end of 1892; the number of deaths from typhoid fever was 88, and from diphtheria and croup 129.

(*BMJ* 1894;i:1094.)