Report of the Conference on Low Blood Cholesterol: Mortality Associations

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Background. **A National Heart, Lung, and Blood Institute (NHLBI) Conference was held October 9–10, 1990, to review and discuss existing data on U-shaped relations found between mortality rates and blood total cholesterol levels (TC) in some but not other studies. Presentations were given from 19 cohort studies from the United States, Europe, Israel, and Japan. A representative of each study presented its findings and also submitted tables of proportional hazards regression coefficients for entry TC levels in regard to death, and these were incorporated into a formal statistical overview adjusted for age, diastolic blood pressure, cigarette smoking, body mass index, and alcohol intake, as available.**

Methods and Results. **The U-shape for total mortality in men and the flat relation in women resulted largely from a positive relation of TC with coronary heart disease death and an inverse relation with deaths caused by some cancers (e.g., lung but not colon), respiratory disease, digestive disease, trauma, and residual deaths. Risk for combined noncardiovascular, noncancer causes of death decreased steadily across the range of TC. The conference considered possible explanations for the statistical associations found between low TC levels or active TC lowering and certain causes of death. One is that TC is lowered by some disease conditions themselves, such as wasting in chronic pulmonary disease or reduced production and secretion of cholesterol-bearing lipoproteins with liver disease. In this sort of situation, the TC: mortality association found in observational studies may be due to preexisting disease. This was addressed by excluding early deaths from the analysis, which did not change the results. The conference considered as well the biological function of cholesterol, which, if seriously deranged, might hypothetically cause a wide variety of diseases and dysfunction. The conference also considered the biological functions that might provide plausible mechanisms for the associations found.**

Conclusions. **Definitive interpretation of the associations observed was not possible, although most participants considered it likely that many of the statistical associations of low or lowered TC level are explainable by confounding in one form or another. The conference focused on the apparent existence and nature of these associations and on the need to understand their source rather than on any pertinence of the findings for public health policy. Further research is recommended to explain the observed associations of low TC levels (and TC lowering) with certain noncardiovascular diseases. This includes studies of the time course of TC change in disease, the relation of TC to morbidity, further studies of possible epidemiological confounding, monitoring of population trends in TC and mortality, further studies of the relations in women, auditing of noncardiovascular events in trials, studies of cell membrane, genetic and molecular links to cholesterol metabolism, TC level and disease, studies of disease manifestations in specific lipid disorders, and further study of the proposed causal mechanisms linking low TC and hemorrhagic stroke. (*Circulation* 1992;86:1046–1060)**

KEY WORDS • **cholesterol** • **mortality**

This National Heart, Lung, and Blood Institute (NHLBI) conference was organized to examine existing data on the relations of low blood total cholesterol (TC) level to risk of death and morbidity and to consider whether any relations found are causal. The issue was raised in 1971 by Japanese investigators

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who observed the ecological association of high rates of cerebral hemorrhage with low average blood cholesterol levels in their populations.[1] Later, they noted a decreasing trend in stroke incidence rates over the years as mean population TC levels rose and blood pressure levels fell.[2,3] Correlations were also found in individuals between low TC level and risk of cerebral hemorrhage in Japan,[4-7] Honolulu,[8,9] and Multiple Risk Factor Intervention Trial (MRFIT) screenee[10] cohorts. The issue was independently raised by observations of greater colon cancer risk in individuals having low TC levels within high-average TC societies in some studies[11-13] but not in others.[14-16] More recently, greater noncardiovascular disease (non-CVD) risk was observed in those having low TC levels.[17] In addition, the finding of excess non-CVD events and deaths among treated cohorts in several TC-lowering trials[18-25] but not in other single or multifactor intervention trials[26-30] has contributed to a renewed discussion about the possible health effects of low or of therapeutic lowering of TC levels. Finally, ecological studies suggest that populations having low average TC values (notably Japan) usually do not have excess cancer, non-CVD mortality, or total death rates, although they may have excess rates of hemorrhagic stroke.[31]

Public campaigns are now under way in industrialized countries to reduce elevated population mean levels of TC and low density lipoprotein (LDL) cholesterol, based on congruent evidence about their determining influence on both population and individual risk of atherosclerosis and epidemic coronary heart disease.[32,33] If these programs were to have any adverse effects, the nature and magnitude of such effects should be understood so that they can be avoided or minimized. Moreover, the scientific questions raised by the apparent non-CVD disease associations with low TC levels[34] could lead to new insights on general issues of diet and health and on the larger role of cholesterol in human biology.

Issues related to risks of elevated blood cholesterol and the costs and benefits of cholesterol lowering were addressed in other recent NHLBI conferences, on "Cholesterol and Heart Disease in Older Persons and Women"[35] and "Cost and Health Implications of Cholesterol Lowering".[36] The question of possible associations of low TC levels with cancer was addressed in a 1981 conference[37] sponsored by the NHLBI in which inconsistent evidence had led to concern of a possible increase in cancer risk at very low cholesterol levels (<180 mg/dl) in men.[38] Because the magnitude of this risk was generally modest when present, the panelists concluded that "the findings do not represent a public health challenge; however, they do present a scientific challenge."[37]

In the 1990 NHLBI conference, the investigators reported analyses on associations between low TC levels and disease in individual cohorts and in pooled data. Population (ecological) correlations were also presented along with a meta-analysis of clinical trials of TC lowering. Discussions were directed to the evidence about risk of specific diseases associated with low TC values including hemorrhagic stroke, cancers, and other diseases and with high TC values including coronary heart disease (CHD) and brain infarction. Potential mechanisms for the effects on disease or function of low blood or cell membrane cholesterol content were discussed, based on the metabolic and physiological roles of cholesterol. Effects of disease on blood cholesterol levels were also discussed, and the lack of information on lipoprotein subfractions was acknowledged. Finally, a panel recommended needs and opportunities for further research.

Methods

A summary analysis was carried out under the direction of Dr. Jacobs on data from 19 of 20 cohort studies invited to participate in the conference. A manuscript from the 20th study was shared with the study organizers.[39] Table 1 enumerates the studies and includes 11 from the United States,[8-10,16,40-57] one from southern Europe,[58] one from Israel,[59-61] two from Great Britain,[17,62-65] one from Scandinavia, and three from Japan.[1,2,5-7,66,67] The Scandinavian study (NORA) represents pooled data from five studies. Length of follow-up ranged from 9 to 30 years. Data were analyzed at each study center following a standard protocol developed at the University of Minnesota, where the pooled estimates were subsequently computed; data for individual participants were not available at the University of Minnesota. Data presented as part of the overview had not been published before conference presentation. The statistical overview itself had strengths and limitations that are reviewed in a later section herein.

Table 2 gives for each study, separately for men and women, the numbers at risk and numbers of total deaths, as well as deaths among those with TC level <160 mg/dl. Of a total of 68,406 deaths in all the studies, approximately 45% were coded to total cardiovascular causes (ICD 9, 390–459), 33% to total cancer causes (ICD 9, 140–239) and 22% to non-CVD, noncancer causes. The latter category included respiratory (ICD 9, 460–519), digestive (ICD 9, 520–579), traumatic (ICD 9, 800–999), and other causes (ICD 9, 1–139, 240–389, and 580–799), comprising 5%, 4%, 6%, and 7% of total mortality, respectively. The distribution of causes of death is not presented by sex because numbers of deaths were not separated for each cause for all studies in materials submitted for the overview.

The proportional hazards regression model was used to study the relation of TC level to total mortality, total cardiovascular disease (CVD) mortality, total cancer mortality, and combined noncardiovascular, noncancer mortality for men and women separately, both unstratified and stratified by smoking or alcohol intake. Subcategories of cause of death—CHD, breast cancer, colon cancer, lung cancer, other cancers, respiratory disease, digestive disease, traumatic death, and all other causes—were studied separately for men and women. Separate regression coefficients for three TC classes (<160, 200–239, and ≥240 mg/dl) were computed for mortality risk relative to the class having TC levels 160–199 mg/dl. The category "TC<160 mg/dl" was studied because there was some evidence that such low levels, even though rarely found in middle-aged persons in U.S. and European studies, might be associated with excess mortality risk. The other categories were selected to study changes in the TC:mortality relation as cholesterol increased. It was convenient to study people with TC>200 mg/dl and those with TC>240 mg/dl because of the role these levels play in the National Cholesterol Education Program. Hazard rate ratios were computed as the exponential of each regression coefficient. Differences among these hazard rate ratios

TABLE 1. Description of Participating Studies

Study name	Age range (years)	Male (%)	Black (%)	Years of follow-up	Covariables available at baseline
1. MRFIT screening*	35–57	100	6.4	12	ACD
2. NORA (five studies)	35–64	55.6	0	≈9	ABCD
3. Kaiser Permanente Northern California	35–69	47.1	22.2	18.5	ABCDE
4. Honolulu	45–68	100	0	18.6	ABCDE
5. Puerto Rico	35–69	100	16	12	ABCDE
6. Tecumseh	35–69	49.8	0	21.3	ABCDE
7. Framingham	35–69	43.6	<0.1	30	ABCDE
8. NHEFS, NCHS	35–69	41.4	15.4	14.1	ABCDE
9. Yugoslavia	35–62	100	0	15	ABCDE
10. Paisley/Renfrew	45–64	45.8	<0.1	14.4	ABCD
11. Whitehall	40–64	100	≈0	21	ABCD
12. Akita	40–69	44.7	0	19.6	ABD
13. Osaka	40–69	33.8	0	8.9	ABCDE
14. Hiroshima/Nagasaki	35–69	36.5	0	14.7	ABCDE
15. Lipid Research Clinics	35–69	58.9	6.6	12.1	ABCDE
16. Chicago Peoples Gas	42–60	100	0	16.8	ABCDE†
17. Chicago Western Electric	41–57	100	0	20.8	ABCDE
18. Chicago Heart Association‡	35–69	53	0	14.3	ABCD
19. Israel	40–65	100	≈0	23	ABCD

A, age; B, body mass index; C, cigarette smoking; D, diastolic blood pressure; E, ethanol intake.
*Studies are referred to by their number in accompanying graphs.
†The Chicago Peoples' Gas study had information on alcohol only on problem drinkers.
‡Black participants in the Chicago Heart Association study were not included.

indicate curvature in the associated TC:mortality relations. A U shape would be indicated, for example, by the sequence of hazard rate ratios (for ascending TC level grouping) 1.2, 1.0, 1.0, 1.2, and a linear trend would be suggested by the sequence 1.1, 1.0, 0.9, 0.8. In separate analyses, relations of TC to mortality were analyzed with TC as a continuous variable. The resulting linear regression coefficients ignore curvature but indicate generally lower risk of death (for a negative coefficient) the higher the TC level, or generally higher risk of death (for a positive coefficient) the higher the TC level. To attempt to account for the potential effects of preexisting illness on the entry TC level and on subsequent disease relations, deaths occurring within 5 years of baseline were excluded except where noted. The regressions contained covariates of age, diastolic blood pressure, cigarette smoking (18 studies), body mass index (18 studies), and alcohol intake (12 studies). Data were excluded from individuals younger than 35 or older than 69 years at baseline or who had definite CHD at baseline according to each study's usual definition. The MRFIT also excluded men taking medication for diabetes. Regression coefficients were pooled inversely to their variances, including a component of variance for heterogeneity between studies, following the method of DerSimonian and Laird.[68] The MRFIT Screening Follow-up Study constitutes 67% of all men reported here and 38% of all deaths in men, and its data are therefore presented separately from the pooled regression coefficients. Not all studies submitted stratified and subcategory analyses, and some studies had insufficient numbers for analysis in specific TC cells.

Results

Tables 3–7 give pooled hazard rate ratios (a measure of relative risk) and their associated t values, comparing each of the TC categories, <160 mg/dl, 200–239 mg/dl, and ≥240 mg/dl, to the reference category, 160–199 mg/dl. The t values are the number of standard deviations that the estimated hazard rate ratio departs from 1. The pooled hazard rate ratios for grouped major causes of death are summarized graphically in Figure 1 and for the subcategories of noncardiovascular, noncancer causes in Figure 2. Also given in Tables 3–7 (with the label $n_{>1}/n$) is the number of studies showing increased risk compared with those with TC 160–199 mg/dl for each TC category and end point event, providing a measure of consistency across studies.

All-Causes Death

In men, risk for all-causes death occurring at least 5 years after baseline in relation to TC level was U-shaped in the pooled estimates and in the MRFIT, with risk 14–22% greater for those with TC<160 mg/dl or ≥240 mg/dl compared with those with TC 160–199 mg/dl (Table 3 and Figure 1). In women, the pooled estimate of risk for all causes-death was essentially flat across TC levels (Table 3 and Figure 1).

Total Cardiovascular Death

In men whose entry TC levels were greater than the reference TC class 160–199 mg/dl, the estimated risk for total CVD death increased systematically and consistently (deaths in the 5 years after baseline excluded: Table 3 and Figure 1). Risk for men with TC level <160 mg/dl, compared with those in the reference class, was

TABLE 2. Sample Size and Numbers of Deaths for the Entire Population and for Cases With Blood Cholesterol <160 mg/dl

	Total sample size	Total number of deaths	Crude death rate per 10^5 pers*yr	<160 mg/dl Sample size	<160 mg/dl Total deaths	<160 mg/dl non-CVD deaths
Men						
1. MRFIT screening	350,977	21,499	613	21,185	1,136	850
2. NORA (five studies)	42,156	2,404	570	639	36	27
3. Kaiser Permanente Northern California	41,109	8,259	2,009	1,151	175	109
4. Honolulu	7,642	2,055	2,689	364	139	105
5. Puerto Rico	9,061	1,394	1,538	1,235	232	151
6. Tecumseh	1,901	714	3,756	85	24	17
7. Framingham	2,046	1,211	5,919	56	34	24
8. NHEFS, NCHS	3,293	920	2,639	172	58	41
9. Yugoslavia	6,351	1,167	1,838	1,997	417	287
10. Paisley/Renfrew	6,707	1,902	2,836	188	78	48
11. Whitehall	17,597	4,022	2,286	2,189	489	271
12. Akita	1,012	309	3,053	604	180	106
13. Osaka	4,589	195	425	796	43	38
14. Hiroshima/Nagasaki	2,986	794	2,659	977	286	206
15. Lipid Research Clinics	3,486	346	993	174	15	3
16. Chicago Peoples Gas	1,210	469	3,876	44	15	7
17. Chicago Western Electric	1,903	691	3,631	40	14	8
18. Chicago Heart Association	12,292	1,753	1,426	721	87	51
19. Israel	9,358	3,032	3,240	898	234	139
Total	523,737	55,525		33,515	3,692	2,488
Women						
2. NORA (five studies)	33,677	755	224	592	11	9
3. Kaiser Permanente Northern California	46,081	6,051	1,313	1,359	107	88
6. Tecumseh	1,917	475	2,614	117	21	11
7. Framingham	2,647	1,180	4,458	50	13	7
8. NHEFS, NCHS	4,664	705	1,512	282	29	19
10. Paisley/Renfrew	8,044	1,396	1,735	77	15	8
12. Akita	1,250	254	2,032	666	109	55
13. Osaka	8,966	159	177	1,103	25	18
14. Hiroshima/Nagasaki	5,552	882	1,589	1,308	172	112
15. Lipid Research Clinics	2,937	241	821	157	6	3
18. Chicago Heart Association	9,179	783	853	453	27	23
Total	124,814	12,881		6,164	535	353

1.04 in the pooled data (ratio greater than 1 in 11 of 18 contributing studies) and was 0.89 in the MRFIT. In women, findings between studies were inconsistent; for example, total CVD death rate for those women having TC level ≥240 mg/dl was greater than for those having TC level 160–199 mg/dl in five of 11 studies (Table 3). The pooled estimated risk for total CVD death in women showed no trend across TC levels (Table 3 and Figure 1). In men, linear regression coefficients for TC and total CVD death were positive in the MRFIT and for 16 of 18 other studies (only Osaka and Hiroshima/Nagasaki had negative coefficients). In women, linear regression coefficients were positive in nine of 11 studies (only Tecumseh and Hiroshima/Nagasaki had negative coefficients).

Total Cancer Death

In men with TC level <160 mg/dl compared with 160–199 mg/dl, the risk ratio for total cancer deaths was greater than 1 in 15 of 18 studies; relative risk was 1.18 in the pooled studies and 1.23 in the MRFIT. The cancer risk ratio was close to 1 for classes of TC level >200 mg/dl (deaths in the 5 years after baseline excluded: Table 3 and Figure 1). In women, findings between studies were inconsistent; for example, total cancer death rate for those women having TC level <160 mg/dl was greater than for those having TC level 160–199 mg/dl in six of 11 studies (Table 3). In pooled data, there was little variation in women's risk for total cancer deaths across the four TC categories (Table 3 and Figure 1). In men, linear regression coefficients were negative in the MRFIT and in 14 of 18 other studies (only NORA, Tecumseh, Chicago Western Electric, and Whitehall had positive coefficients). In women, linear regression coefficients were negative in seven of 11 studies (only Tecumseh, NHEFS/NCHS, Akita, and Hiroshima/Nagasaki had positive coefficients).

Combined Non-CVD, Noncancer Death

Risk estimates for combined non-CVD, noncancer deaths in relation to TC level were similar from the

TABLE 3. Risk Ratios for Deaths Occurring ≥5 Years After Study Baseline

Blood cholesterol (mg/dl)	All causes			Total cardiovascular			Total cancer			Noncardiovascular, noncancer		
	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{<1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$
Pooled except MRFIT, men												
<160	1.17	3.6	14/18	1.04	0.8	11/18	1.18	2.3	15/18	1.32	5.3	16/17
160–199	1.00			1.00			1.00			1.00		
200–239	1.02	0.8	9/18	1.16	3.6	14/18	0.95	−1.8	8/18	0.89	−2.5	5/18
≥240	1.14	5.1	14/18	1.48	9.5	16/18	0.95	−1.2	8/18	0.87	−3.6	3/17
MRFIT men												
<160	1.17	4.0		0.89	−1.7		1.23	3.5		1.48	5.6	
160–199	1.00			1.00			1.00			1.00		
200–239	1.05	2.5		1.31	9.0		0.95	−1.7		0.87	−3.5	
≥240	1.22	10.0		1.86	20.7		0.91	−2.3		0.84	−3.4	
Pooled women												
<160	1.10	1.1	8/11	0.96	−0.3	6/11	1.05	0.5	6/11	1.41	2.0	7/11
160–199	1.00			1.00			1.00			1.00		
200–239	0.94	−1.4	3/11	0.95	−0.7	4/11	1.01	0.2	7/11	0.92	−1.2	5/11
≥240	0.97	−0.6	4/11	1.09	1.2	5/11	0.97	−0.6	5/10	0.82	−2.0	3/11

Adjusted proportional hazards model hazard rate ratios, relative to 1.0 for blood total cholesterol 160–199 mg/dl. Ages 35–69 at baseline, excluding people with coronary heart disease. Adjusted for age, diastolic blood pressure, cigarette smoking, body mass index and alcohol intake, where available. The hazard rate ratio is computed as e^{β}, t is the regression coefficient divided by its standard error, $n_{>1}/n$ is the number of studies with hazard rate ratio >1, of all contributing studies. n may vary from one comparison to another because some studies did not have enough observations at the total cholesterol level to make a proportional hazards estimate. t is the number of standard deviations that the estimated hazard rate ratio departs from 0. $|t| \geq 1.645$ corresponds to $p<0.10$, 1.96 to $p<0.05$, 2.56 to $p<0.01$, and 3.3 to $p<0.001$.

MRFIT men, from all other men pooled, and from all women pooled. In both men and women, risk was consistently greater, by about 40%, for those having low TC levels (<160 mg/dl) compared with the reference class (TC level, 160–199 mg/dl). Figure 3 summarizes the hazard rate ratios among those with TC levels <160 mg/dl compared with those with TC level 160–199 mg/dl for combined non-CVD, noncancer death for individual studies, with each study indicated by its identifying number given in Table 1. Consistency of excess risk in those with TC level <160 mg/dl is seen across studies, although most of the individual study estimates are not statistically significant. In both sexes, estimated risk was about 10% less than the reference class among those in TC class 200–239 mg/dl and was consistently less, by about 15%, in those men and women in the higher TC class ≥240 mg/dl (deaths in the 5 years after baseline excluded: Table 3 and Figure 1). In men, linear regression coefficients were negative in the MRFIT and in 15 of 18 other studies (only NORA, Framingham, and Chicago People's Gas had positive coefficients). In women, linear regression coefficients were negative in nine of 11 studies (only Akita and Osaka had positive coefficients).

Effect on Relative Risk of Including Deaths in the First 5 Years

Pooled estimated hazard rate ratios were calculated to include early deaths (those occurring in the 5 years after baseline). Gradients of pooled estimated risk between TC categories are generally a few percent steeper than those in Table 3.

Analyses Stratified by Alcohol Intake and Smoking

Pooled estimates of hazard rate ratios (deaths in the 5 years after baseline excluded) are presented for those with TC <160 and for those with TC ≥240 (each versus the reference class of 160–199 mg/dl), stratified on alcohol drinking status (Table 4) and smoking habit (Table 5). Not all studies provided these analyses. Puerto Rico and Yugoslavia estimates of hazard rate ratios for all drinkers combined were used in pooling data for both lighter and heavier drinkers. Stratification reduced the numbers at risk and rendered some estimates meaningless.

All causes, total CVD, total cancer and combined non-CVD, noncancer causes of death were studied. Relative risk for these four death outcomes were similar to the unstratified analysis of Table 3 for each stratum of drinking status (Table 4) and smoking status (Table 5) for both men and women. Note that there was very little information available concerning women who drank ≥30 ml/day of alcohol, particularly for TC<160 mg/dl.

Subcategory Causes of Death

Pooled estimates of rate ratios for men and for women and estimates for the MRFIT men separately are presented for nine subcategory causes of death in Tables 6 and 7 and Figure 2. Numbers of studies contributing information to the pooled estimates are indicated for each TC range. Some studies are omitted either because they did not provide these analyses or because a subcategory cause of death was rare.

Coronary and Other Cardiovascular Death

CHD mortality rates increased consistently with increasing TC level in most studies (Table 6). The gradient of risk was steeper for the MRFIT than for the pooled estimates. Pooled estimates were slightly steeper for men than for women. Hemorrhagic stroke was not

TABLE 4. Risk Ratios for Deaths Occurring ≥5 Years After Study Baseline by Alcohol Stratum

Alcohol intake stratum (ml/day)	All causes			Total cardiovascular			Total cancer			Noncardiovascular, noncancer		
	Rate ratio	*t*	$n_{>1}/n$	Rate ratio	*t*	$n_{>1}/n$	Rate ratio	*t*	$n_{>1}/n$	Rate ratio	*t*	$n_{>1}/n$
Pooled except MRFIT, men												
					<160 vs. 160–199 mg/dl							
0	1.20	2.8	6/8	1.02	0.2	4/8	1.23	1.6	3/8	1.42	3.1	7/8
<30	1.22	2.6	7/9	1.20	1.5	5/9	1.14	0.8	7/9	1.45	3.8	9/9
≥30	1.32	3.2	8/9	1.27	2.1	5/8	1.40	1.9	7/9	1.49	3.8	9/9
					≥240 vs. 160–199 mg/dl							
0	1.04	0.4	4/9	1.30	2.4	5/9	1.03	0.3	3/9	0.85	−1.7	2/8
<30	1.10	2.5	7/9	1.49	5.5	7/8	0.85	−1.9	3/8	0.96	−0.5	5/9
≥30	1.02	0.5	4/9	1.20	1.9	5/9	0.94	−0.5	3/8	0.99	−0.1	3.8
MRFIT men (alcohol use not queried)												
Pooled women												
					<160 vs. 160–199 mg/dl							
0	1.23	2.0	6/6	1.11	0.5	3/6	1.31	1.0	5/6	1.80	3.6	4/5
<30	1.36	2.6	6/6	1.23	0.6	4/5	1.38	1.8	4/5	1.92	2.8	4/5
≥30	1.14	0.9	2/3	1.87	1.3	3/3	1.03	0.0	1/1	1.36	0.3	1/2
					≥240 vs. 160–199 mg/dl							
0	1.03	0.6	3/6	1.13	1.2	3/6	1.00	0.0	2/6	0.90	−1.0	3/6
<30	1.05	0.4	4/6	1.23	1.7	4/6	1.04	0.4	3/5	0.84	−0.7	2/5
≤30	0.88	−1.0	1/5	1.12	0.4	2/3	0.87	−0.7	1/5	0.77	−1.2	1/4

Adjusted proportional hazards model hazard rate ratios. Adjusted for age, diastolic blood pressure, cigarette smoking, and body mass index, where available (see Table 1). See notes Table 3.

$|t| \geq 1.645$ corresponds to $p<0.10$, 1.96 to $p<0.05$, 2.56 to $p<0.01$, and 3.3 to $p<0.001$.

considered in the overview analysis because it is a rare outcome in studies from the United States and northern Europe. In the MRFIT Screening Study, hemorrhagic stroke risk was inversely related to TC, and nonhemorrhagic stroke risk was positively related to TC.[10,69] The risk gradient for CHD in men and women across TC classes in Table 6 was steeper than that for total cardiovascular disease in Table 3. Therefore, the risk gradient across TC categories for non-CHD cardiovascular death was less steep than that for CHD death.

Cancer Death

Subcategory cancer deaths are considered in Table 6. There is little indication of a risk gradient across TC classes for breast (not shown) or colon cancer. The low relative risk estimate of 0.58 for colon cancer for women in the low TC class (<160 mg/dl) is based on only two studies. Pooled estimated risk of lung cancer death and of death from all other cancers combined was less with greater level of TC, suggesting a continuous downward gradient for cancer risk across TC levels. Data from the MRFIT suggest that some other subcategory cancers may also be elevated with low TC levels, notably liver, lymphatic, and hematopoietic cancers.[69]

Subcategories of Noncardiovascular, Noncancer Death

Death rates in subcategories of noncardiovascular, noncancer causes of death tended to be higher the lower the TC level, excluding deaths within 5 years (Table 7 and Figure 2). Pooled and MRFIT estimates of hazard rate ratios for respiratory disease death were >1 for those with TC<160 mg/dl and were progressively higher with lower TC level among the four categories considered here, suggesting a continuously negative graded risk. Digestive disease death rates showed a pattern of elevation at low TC levels and reduction at high TC levels, also suggesting a continuously graded risk. Death from trauma and from all residual causes showed excess estimated hazard rate ratios for men (pooled and MRFIT) and women with low TC (<160 mg/dl) but were little different from 1 at higher TC levels. The pooled estimated hazard rate ratio for traumatic death for women with TC<160 mg/dl was similar to that for men but had a higher variance and therefore a lower *t* value.

Consistency of Findings Across Studies

The extent of consistency of findings across the range of TC levels found in these studies is noteworthy in the similarity of findings for such disparate populations as Japan, the United States, and Europe, covering a wide range of average population TC levels and cultures. For example, noncardiovascular, noncancer mortality rates in men were elevated for those with TC<160 mg/dl compared with those with TC 160–199 mg/dl in 13 of 14 U.S. and European studies (all except the Lipid Research Clinics study) as well as in the Osaka, Akita, and Hiroshima/Nagasaki studies in men (studies 12, 13, and 14 in Figure 3). In U.S. and European women, the Framingham and Paisley/Renfrew studies were the only two to show lower noncardiovascular, noncancer mortality rates at TC levels

TABLE 5. Risk Ratios for Deaths Occurring ≥5 Years After Study Baseline by Smoking Stratum

Smoking stratum	All causes			Total cardiovascular			Total cancer			Noncardiovascular, noncancer		
	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$
Pooled except MRFIT, men												
					<160 vs. 160–199 mg/dl							
Nonsmoker	1.14	2.6	11/13	1.06	0.8	8/13	1.12	1.2	9/13	1.33	3.1	9/13
Smoker	1.14	2.3	10/13	1.04	0.5	6/13	1.14	1.7	11/13	1.30	3.8	10/13
					≥240 vs. 160–199 mg/dl							
Nonsmoker	1.09	1.7	8/13	1.39	4.9	9/12	0.92	−1.0	6/12	0.88	−2.1	1/12
Smoker	1.13	4.6	11/13	1.47	8.4	13/13	0.98	−0.3	7/13	0.88	−2.3	4/13
MRFIT men												
					<160 vs. 160–199 mg/dl							
Nonsmoker	1.25	4.0		0.96	−0.4		1.29	3.0		1.59	4.4	
Smoker	1.11	2.0		0.82	−1.9		1.17	2.0		1.37	3.2	
					≥240 vs. 160–199 mg/dl							
Nonsmoker	1.32	8.7		1.87	12.7		0.98	−0.3		1.03	0.4	
Smoker	1.18	5.7		1.86	13.7		0.89	−2.4		0.73	−4.7	
Pooled women												
					<160 vs. 160–199 mg/dl							
Nonsmoker	1.22	1.7	6/8	1.18	0.8	6/8	1.05	0.3	4/7	1.70	3.4	6/8
Smoker	1.24	2.0	6/8	1.30	1.2	5/6	1.14	0.7	4/7	1.82	3.0	5/6
					≥240 vs. 160–199 mg/dl							
Nonsmoker	0.94	−0.8	3/8	1.03	0.4	3/8	0.98	−0.3	5/8	0.81	−1.5	3/8
Smoker	1.02	0.3	4/8	1.24	2.3	5/8	1.00	0.0	3/7	0.82	−1.7	2/8

Adjusted proportional hazards model hazard rate ratios. Adjusted for age, diastolic blood pressure, body mass index, and alcohol intake, where available (see Table 1). See notes Table 3.

$|t| \geq 1.645$ corresponds to $p<0.10$, 1.96 to $p<0.05$, 2.56 to $p<0.01$, and 3.3 to $p<0.001$.

<160 mg/dl, whereas the NORA and NHEFS/NCHS studies showed no difference in noncardiovascular, noncancer mortality rates in women at TC levels <160 versus 160–199 mg/dl. Elevated noncardiovascular, noncancer mortality rates were seen in the low TC class of two of three studies of Japanese women (Figure 3). This pattern was repeated in separate analyses of respiratory, digestive, traumatic, and all other deaths and was found more consistently in men than in women. Mortality rates were elevated for these

TABLE 6. Risk Ratios for Deaths Occurring ≥5 Years After Study Baseline: Coronary Heart Disease and Subcategories of Cancer

Blood cholesterol (mg/dl)	Coronary heart disease			Colon cancer			Lung cancer			Other cancer		
	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$
Pooled except MRFIT, men												
<160	0.92	−1.2	3/12	1.00	0.0	5/9	1.20	1.2	6/12	1.19	1.8	10/12
160–199	1.00			1.00			1.00			1.00		
200–239	1.23	5.7	10/13	0.82	−1.7	3/11	0.93	−1.1	4/11	0.92	−2.1	6/12
≥240	1.69	10.6	11/12	0.92	−0.7	3/9	0.90	−1.2	6/11	0.91	−1.6	5/11
MRFIT men												
<160	0.78	−2.6		1.07	0.4		1.27	2.5		Analysis not done		
160–199	1.00			1.00			1.00					
200–239	1.48	9.7		1.21	2.0		0.86	−2.6				
≥240	2.20	19.7		1.13	1.1		0.83	−2.9				
Pooled women												
<160	1.02	0.1	4/8	0.58	−0.9	0/2	2.79	1.4	4/5	1.36	2.1	5/8
160–199	1.00			1.00			1.00			1.00		
200–239	1.12	1.3	6/8	1.16	0.6	5/8	1.15	1.0	5/7	1.04	0.4	4/8
≥240	1.56	3.5	8/9	1.13	0.6	3/6	0.99	−0.1	4/6	0.98	−0.2	3/7

Adjusted proportional hazards model hazard rate ratios. Adjusted for age, diastolic blood pressure, cigarette smoking, and body mass index, where available (see Table 1). See notes Table 3.

$|t| \geq 1.645$ corresponds to $p<0.10$, 1.96 to $p<0.05$, 2.56 to $p<0.01$, and 3.3 to $p<0.001$.

TABLE 7. Risk Ratios for Deaths Occurring ≥5 Years After Study Baseline: Subcategories of Noncardiovascular, Noncancers

Blood cholesterol (mg/dl)	Respiratory			Digestive			Trauma			Residual		
	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$	Rate ratio	t	$n_{>1}/n$
Pooled except MRFIT, men												
<160	1.11	1.0	8/12	1.41	2.6	10/12	1.40	3.0	12/14	1.43	3.2	10/13
160–199	1.00			1.00			1.00			1.00		
200–239	0.89	−1.3	7/13	0.74	−3.1	2/13	0.98	−0.2	6/13	1.02	0.2	5/13
≥240	0.75	−2.9	2/10	0.72	−2.0	3/11	0.91	−1.1	5/12	1.03	0.5	8/12
MRFIT men												
<160	1.21	1.1		1.70	3.4		1.27	1.9		1.84	4.4	
160–199	1.00			1.00			1.00			1.00		
200–239	0.68	−3.9		0.81	−2.0		0.90	−1.5		1.06	0.7	
≥240	0.58	−4.8		0.78	−2.2		0.92	−1.0		1.06	0.6	
Pooled women												
<160	1.85	2.4	4/6	2.01	3.0	6/7	1.26	0.5	4/6	1.53	2.2	5/7
160–199	1.00			1.00			1.00			1.00		
200–239	0.91	−0.6	1/8	0.85	−2.8	2/7	0.98	−0.1	4/8	0.97	−0.2	5/9
≥240	0.76	−1.9	3/8	0.69	−2.2	1/8	0.95	−0.3	4/9	0.99	−0.1	3/8

Adjusted proportional hazards model hazard rate ratios. Adjusted for age, diastolic blood pressure, cigarette smoking, and body mass index, where available (see Table 1). See notes Table 3.

$|t| \geq 1.645$ corresponds to $p<0.10$, 1.96 to $p<0.05$, 2.56 to $p<0.01$, and 3.3 to $p<0.001$.

four death subcategories at low TC level for at least two of the three Japanese studies except for trauma in women, where the Akita study had insufficient information to contribute to the analysis. A finding of elevated mortality due to liver cancer, chronic hepatitis, cirrhosis, and nonmedical deaths at low TC levels has also been reported in a Chinese study of more than 9,000 Shanghai residents followed for 8–13 years,[39] with mean TC level ≈160 mg/dl, with analyses of men and women combined, with regression dilution bias removed, and with adjustment for age, sex, diastolic blood pressure, cigarette smoking, and alcohol drinking status.

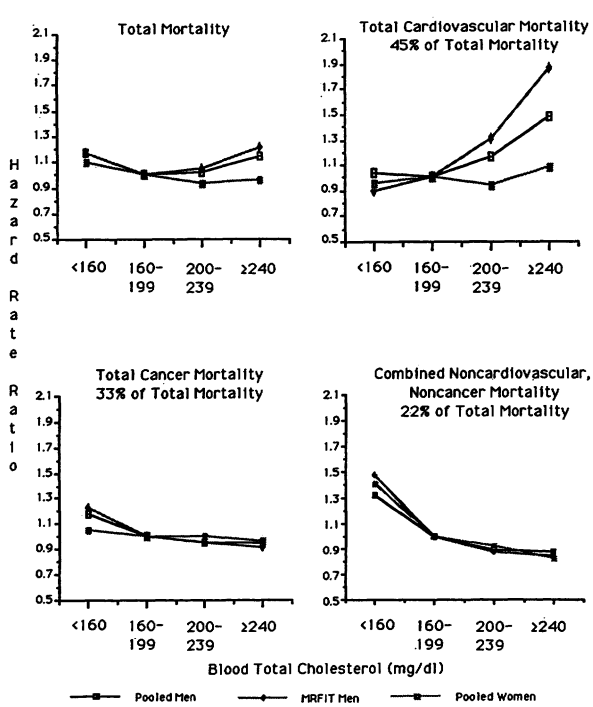

FIGURE 1. *Graphs of pooled and Multiple Risk Factor Intervention Trial (MRFIT) estimates of adjusted hazard rate ratios in deaths occurring at least 5 years after baseline in men and women aged 35–69 years without coronary heart disease at baseline.*

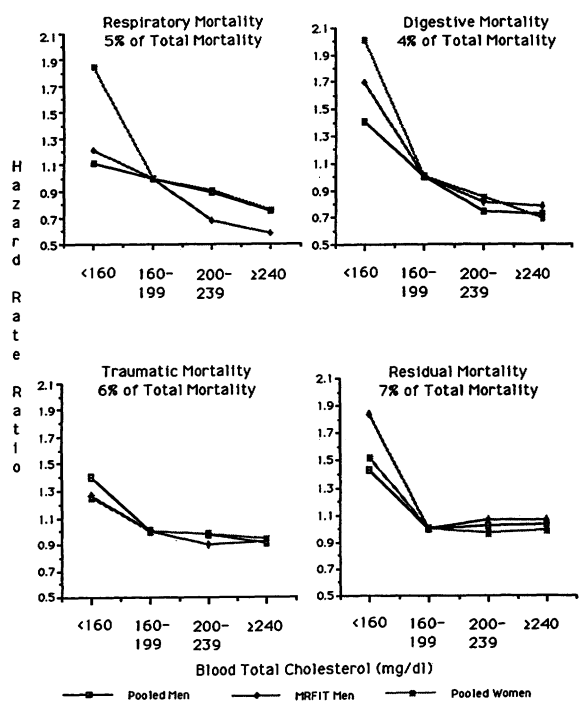

FIGURE 2. *Graphs of pooled and Multiple Risk Factor Intervention Trial (MRFIT) estimates of adjusted hazard rate ratios in deaths occurring at least 5 years after baseline in men and women aged 35–69 years without coronary heart disease at baseline.*

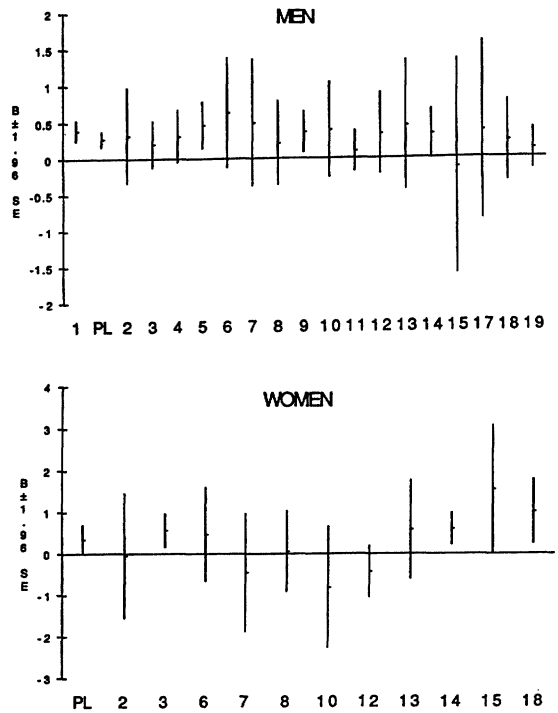

FIGURE 3. *Graphs of noncardiovascular, noncancer deaths (adjusted proportional hazards regression coefficients) in deaths at least 5 years after baseline for blood cholesterol comparison <160 vs. 160–199 mg/dl. PL, pooled studies. B±1.96 SE stands for the regression coefficient ±1.96 times its standard error.*

Strengths and Limitations of Overview Analysis

The broad perspective of the overview of observational studies presented here suggested statistical associations of low TC level with a variety of noncardiovascular causes and subcategories of death, particularly lung cancer, respiratory disease, digestive disease, trauma (less reliably in women than in men), and a residual of noncardiovascular, noncancer, nonrespiratory, nondigestive, and nontraumatic causes. The overview provided a "first level investigation" of confounding by adjusting for age, diastolic blood pressure, cigarette smoking, body mass index, and (where available) usual alcohol intake. It stratified on cigarette smoking and alcohol with end points of major causes of death.

Further research is needed on the possible confounding effects of lifestyle factors such as socioeconomic status, alcohol, smoking, and age. Law and Thompson[70] reported a 15% greater estimated risk in men for total cancer (mortality and incidence) at low levels of TC in 35 studies pooled but found no TC:cancer relations within four study populations from the highest socioeconomic stratum. Similarly, Smith et al[65] pointed to factors such as employment grade and marital status in suggesting that inverse TC:death rate associations were generally stronger in population samples that contain sick individuals than in samples in which the "healthy worker effect" would operate. Chen et al[39] suggested that endemic hepatitis in Asian populations is the true cause of excess mortality at low levels of TC associated with liver disease. Lifetime alcohol exposure is difficult to measure with self-report measures, and heavy exposure is known to cause liver disease, which may both lower TC and ultimately cause death. Smith et al[65] suggested that excess risk of cancer death at low TC levels is restricted to smoking-related cancers; the MRFIT Screening Study[69] similarly found excess risk associated with low TC for death caused by lung cancer or chronic obstructive lung disease to be concentrated in smokers. Whether the excess mortality risk at low TC levels is seen in younger as well as in older people was not resolved at the conference.

The overview of observational studies eliminated the first 5 years of deaths, which would most likely be the ones in which TC was low as a result of preexisting disease. There is, in fact, little information about the time course of TC level in many diseases. Smith et al[65] reported a cross-sectional inverse association between respiratory capacity and symptoms and TC at baseline in participants of the Whitehall study. A classic example of a low TC:death association is found in cancer deaths within several years of a TC measurement, where a low TC value is almost certainly a consequence of disease.[14,71–74] It is documented that people with acute and chronic inflammatory diseases have low total and high-density lipoprotein (HDL) cholesterol. Cytokines such as tumor necrosis factor and IL-6 have been found to lower TC levels when injected into animals.[75,76] Furthermore, cytokines are elevated in patients with chronic diseases including congestive heart failure.[76,77] Chronic inflammation leads to the release of cytokines, which may subsequently decrease hepatic secretion of lipoproteins.[76] Cytokines may be released due to inflammation in chronic obstructive pulmonary disease. Low TC is associated with a wide variety of anemias.[78,79] Leukemic cells (especially in acute nonlymphocytic leukemia) show exceptional elevations of high-affinity, LDL receptor–mediated cholesterol degradation, and the rate of degradation is inversely related to plasma TC levels.[71] There is also evidence that among leukemia patients in remission after therapy, TC levels rise significantly.[80] Dietary sources of fat and cholesterol strongly influence serum TC levels, and malabsorption syndromes are accompanied by low TC levels. Alcohol secreted in the lung may alter membrane integrity and cell function by inducing lipid changes and impairing surfactant secretion.[81] Nevertheless, some studies[69,82] found that elevated mortality at low levels of TC persisted even after the first 10 or more years of deaths were removed from analysis.

Because TC is measured with uncertainty due to both laboratory variation and true day-to-day biological variation, observed associations found between TC and deaths may be flatter than the true associations.[83] Correction for regression dilution bias caused by within-person error would be expected to result in steeper positive slope estimates, such as that for TC versus atherosclerotic disease deaths,[84] and steeper negative slope estimates, such as that found in the overview for TC versus some other causes of death. The influence on the observation of TC:mortality relations of within-person error in TC and in covariates should be studied further.

There was considerable conference discussion of the meaning of the overview analysis. An asset of the overview was considered to be the identification of

consistencies and inconsistencies between studies in low TC:mortality relations, including Japanese as well as U.S. and European studies. Identification of consistencies through examination of quantitative estimates of the magnitude of the statistical relations was thought to be particularly important in the study of low TC:mortality relations, where typical individual studies have low power.

Despite these contributions, the overview was hampered in several respects. For logistic reasons, namely that only two analysis requests could be filled (the second not by all the studies) before the conference, all desirable analyses could not be done, and, specifically, the underlying assumptions of the proportional hazards model could not be checked thoroughly. The major potential deviation from these assumptions would be failure of the proportionality assumption, for example, if the excess risk at low TC levels disappeared after a sufficiently long period after baseline. A second important potential deviation from underlying assumptions of the proportional hazards model would be interaction of low TC level and mortality with a third factor, such as alcohol abuse, dietary intake, age, or genetic factors. A variation of this problem is the possibility that the statistical associations are based on different mechanisms in different populations. A third possibility for bias in the overview analysis is the lack of data from all studies having pertinent data. An ideal, if logistically difficult, method would have been to create a list of all extant studies having a minimum number of observations of the relation of low TC level and death, and to then analyze all such studies. However, many conference participants thought it unlikely that such results would differ from those reported here because of the extensive nature of the 19 studies included here. It would have been preferable to analyze more specific causes of death, particularly in the analyses stratified by smoking and alcohol intake, which were restricted to major causes of death.

A hypothesis that could not be addressed in analyses generated for this conference was that it may not be the absolute level of TC that matters but the position in the TC distribution. For example, genetic abnormalities of cell membranes (linked with their cholesterol content) might predominate in those who have a low cholesterol for their culture independent of absolute level of TC. Another interpretive difficulty, which follows from the fact that the observational studies were designed with hypotheses about CVD in mind, is the general absence of cohort data on morbidity and of data on factors that might confound the relations of low TC and noncardiovascular disease. Another possible problem is lack of comparability of TC measurements among studies. The pooled analysis gives estimates of TC–end point event relations within each study, before pooling, so that, for example, those with measured TC <160 mg/dl are compared with people in the same study with measured TC level between 160 and 199 mg/dl. If comparability of TC between studies were poor, the comparison of actual TC levels might be offset, for example, to <150 to 150–189 mg/dl in one study, and <180 to 180–219 mg/dl in another.

For these reasons, there was general agreement among conference participants that the overview analyses were insufficient to indicate that the relations found of low TC and excess mortality were causal but were nevertheless important as guides for research.

Relation of Low TC to Death in Women

Many findings for women were discrepant from those for men. Of particular importance in women was considered to be the essentially flat relation of TC to total mortality, total CVD, and total cancer. Despite the lack of relation of TC to total CVD in women, it was noted that the relation of TC to CHD death was strong and positive in both sexes, in agreement with the findings of a previous meta-analysis.[35] However, women are less studied than men, and when findings for women were concordant with findings for men, they were at times more likely due to chance (e.g., for the relation of low TC to traumatic death). The conferees considered that biological differences between men and women might account for some of the sex differences in the associations. However, some of the ambiguities might be attributed to lack of power caused by the absence of a large cohort study in women analogous to the MRFIT Screening Study in men. It was suggested that studies should include women up to age 79 years to achieve comparable age-specific death rates to those in men, where studies used an age cutoff of 69 years. Further, the study of associations of disease with lipoprotein subfractions, not possible in this conference, is particularly pertinent in women because their HDL subfraction tends to be a relatively greater proportion of total lipoprotein than is the case in men.

Findings From Clinical Trials

Three studies[85–87] with angiographic end points and several meta-analyses[18,23,24] of randomized clinical trials show that TC lowering reduces the incidence of CHD. On the other hand, non-CVD death appears to be increased in those treated to lower TC, largely in single-factor primary prevention trials that used drug treatments. In contrast to these single-factor primary cholesterol-lowering trials, an excess in non-CHD deaths has been seen in only one of four multifactor intervention trials,[25,27–30] and no excess was seen in several trials of secondary prevention.[88,89]

At the conference, Yusuf presented an extension of an earlier meta-analysis of clinical trials of TC lowering.[90] This extension involved 32 randomized clinical trials of TC lowering in over 42,000 individuals in which TC lowering reduced CHD incidence and mortality ($p<0.001$). The reduction in CHD was related to the "strength of the intervention" defined as degree of cholesterol lowering times duration of the study, with benefit seen in both dietary and drug trials and in primary and secondary prevention studies. On the other hand, in this meta-analysis of clinical trials, there was an excess of noncardiac deaths in treated compared with control groups. Yusuf noted that this excess was of borderline statistical significance, was spread over a number of causes, and was not related to the strength of the intervention. Yusuf interpreted these findings as biologically implausible and probably due to chance; specific methodology and details of this meta-analysis were not available for this report. Whether the excess in noncardiac deaths in some clinical trials is real or due to chance remains to be determined.[91,92]

TABLE 8. Ecological Correlations Between Fatty Acids in the Diet in 1979–81 and Mortality in 1987, Ages 35–74, 31 Countries

Cause of death (1987)	Fatty acids (1979–1981)					
	Saturated		Monounsaturated		Polyunsaturated	
	Men	Women	Men	Women	Men	Women
Total mortality	−0.02	−0.14	−0.26	−0.36	−0.15	−0.18
Total cardiovascular	−0.02	−0.31	−0.42	−0.53	−0.31	−0.28
Coronary heart	0.25	−0.02	−0.22	−0.24	−0.49	−0.27
Stroke	−0.63	−0.62	−0.54	−0.51	−0.15	−0.14
Total cancer	0.29	0.51	0.34	0.18	−0.10	−0.17
Colon cancer	0.48	0.56	0.32	0.30	0.10	−0.03
Colorectal cancer	0.48	0.49	0.22	0.07	0.00	−0.20
Lung cancer	0.29	0.48	0.40	0.16	−0.10	−0.15
Breast cancer	...	0.66	...	0.50	...	0.12
Stomach cancer	−0.55	−0.58	−0.54	−0.51	−0.19	−0.06
Combined noncardiovascular, noncancer	−0.35	−0.12	−0.26	−0.14	0.02	0.02
Digestive	−0.55	−0.46	−0.15	−0.19	0.21	0.17
Respiratory	−0.10	−0.03	−0.19	−0.29	−0.12	−0.14
Trauma	−0.14	−0.00	−0.14	−0.10	−0.11	−0.07

Fatty acids expressed as grams of intake per day.

The conference participants noted important differences in meaning between the findings in clinical trials of TC lowering and those of observational studies. The TC lowering of clinical trials occurred over a relatively short period during midlife and rarely reached values of interest in the analyses of observational studies (i.e., TC<160 mg/dl), whereas the low TC values in observational studies probably represent long-standing low levels. Clinical trial participants also tend to have higher CVD risk and higher average entry TC levels than the populations from which they derive and tend to be more select volunteers than are participants in observational studies. Therefore, the mechanisms by which active TC lowering might influence end point events are likely to be different from those by which a customarily low TC level might influence risk.

Findings From International Studies and Ecological Associations

Average population TC versus deaths rates. Average TC levels obtained systematically for whole populations were only available from 15 centers of the World Health Organization–sponsored MONICA Project,[93,94] whereas available total and cause-specific death rates were for whole countries. Ecological correlations computed from these data for TC levels and various causes of death are therefore not presented here.

Nutrients versus death rates. Average population nutrient intake was examined because of other evidence that diet determines the average TC level of populations (Table 8). Associations of dietary components with subcategory causes of death among countries were based on per capita food disappearance data supplied by the United Nations Food and Agriculture Organization.[31,95–100] Ecological correlations with CHD death were positive for saturated fatty acids in men only and negative for monounsaturated fatty acids in both sexes. Ecological correlations between saturated or monounsaturated fatty acid intake and cancer death rates were positive in men and women except for stomach cancer, which was negative in both sexes. Stamler's analysis of data on nutrient intake from 20 countries is in agreement with findings in Table 8 for breast, colon, and stomach cancer.[101,102] Both saturated and monounsaturated fatty acids were strongly inversely correlated with total stroke death and less strongly inversely correlated with noncardiovascular, noncancer causes of death. Ecological correlations with polyunsaturated fatty acid intake were generally small except for negative correlations with CHD death in both men and women.

Biological Plausibility of Low TC as a Cause of Death

The conferees considered possible biological mechanisms whereby the low TC state might be causally related to disease. It was postulated that either an excess or deficiency in functions related to cholesterol metabolism could lead to disease risk. There is wide evidence that cholesterol is essential to and intimately involved with many aspects of cellular structure and function.[103,104] For example, it affects the fluidity of cell membranes, membrane permeability, transmembrane exchange, signal transmission, and other cell properties. Cholesterol is a precursor for five major classes of steroid hormones. It affects gluconeogenesis and immune function; its transport forms, the lipoproteins, also serve as vehicles for fat-soluble vitamins, antioxidants, drugs, and toxins. Thus, cholesterol plays general, fundamental, and highly specific roles in the economy of the body.

Little evidence was presented at the conference, however, that the low serum cholesterol levels examined in the overview studies (<160 mg/dl) would be sufficient to cause cellular dysfunction. The conference considered the exceedingly rare condition of homozygous abetalipoproteinemia in which there are low circulating levels of TC (<50 mg/dl).[105] Intestinal malabsorption of fat, progressive degeneration of the central nervous system, retinal pigmentary degeneration, abnormal red

blood cells, and cardiomyopathy probably involve a functional disturbance of delivery of cholesterol to peripheral tissues and is partly correctable by administration of large doses of vitamin E and water-soluble vitamin A and vitamin K.[105] Because the defects would not be corrected simply by raising TC, hypocholesterolism is not analogous to hypothyroidism. It was considered difficult to relate directly these multiple manifestations of a genetic disorder to the multiple noncardiovascular, noncancer causes of death among older adults having low TC levels.

Considerable work has been done on the possible biological role of low TC in hemorrhagic stroke patients. The inverse relation between TC level and the risk of hemorrhagic stroke suggests that low TC, possibly exacerbated by hypertension, may predispose with these conditions over those with either hypertension or low TC level alone.[8,10,69] Cerebral hemorrhage occurs mostly from intraparenchymal small arterioles in the basal ganglia of the brain. Angionecrosis, the basic pathological finding, is not a proliferative disorder of the intima like atherosclerosis but rather involves the disappearance of medial smooth muscle cells, which may ultimately lead to burst microaneurysms. The presence or absence of dietary factors that exert deleterious or protective effects on endothelial and medial elements of the vessels is seen as important. Low cholesterol content of endothelial cell membranes may play a role in intracerebral hemorrhage,[106–111] although one study found no relation of cell membrane microviscosity to TC.[112] Brown et al[113] and Goldstein et al[114] emphasize the powerful homeostatic mechanisms controlling cellular content of unesterified cholesterol.

This fragmentary evidence of a possible causal relation between low TC level and hemorrhagic stroke was considered inconclusive because the chain of events associating low TC to loss of medial smooth muscle cells is unknown. It was suggested that the chain of events could relate to nutritional factors that contribute both to high blood pressure and low TC, whereas low TC per se might play no role in loss of smooth muscle cells.

Recommended Research for Study of Relations Between Low Blood Cholesterol Level and Disease

Time course of TC change in disease. Little is known about the time course of TC change in disease, apart from some cancers. Is TC already low in those who will develop disease (consistent with causality)? Does TC drop gradually throughout stages of developing disease or rather precipitously at a given stage? These questions should be examined in cohorts having repeat TC measurements, along with concomitantly collected lifestyle and diet data, to ascertain the chain of events leading to low TC and to disease.

Epidemiological confounding. Central to issues of confounding is further research about the role of alcoholism, nutritional status, socioeconomic factors, evidence of preexisting disease including liver dysfunction, and other potential confounders of associations found between low TC level and death. Further study is warranted of factors considered in the overview, including age, sex, alcohol intake, cigarette smoking, body fatness, and blood pressure level. Study should also focus on characteristics of population subgroups with low TC levels compared with other TC strata.

Population monitoring. Studies of time trends in TC levels, in parallel with other risk factor levels, lifestyle trends, treatment trends, and disease and death rates, are recommended to evaluate ecological relations. Are trends of population TC levels (down or up) related to trends of disease rates?

TC:mortality relations in women. To obtain more precise information about TC:mortality associations in women, a screening and mortality follow-up study should be undertaken, comparable in size to the MRFIT Screening Study. Such a study should measure HDL cholesterol as well as TC and should include older women, for example, up to age 79 years.

Active TC lowering. Further exploration is needed on whether the active lowering of TC by various means has deleterious effects in some persons or situations, and, if so, what is the "trade-off" with the well-demonstrated beneficial effects from lowering the risk and severity of atherosclerotic diseases. Studies are needed from existing randomized clinical trials of the internal consistency and validity of relations found between non-CVD events and TC lowering in treated groups, including case audits.[115] There should be further study whether any observed association of disease risk with low TC level, or of experimental lowering of TC level, is a graded one.[116]

Long-term follow-up studies among cohorts of the experimental and control subjects of cholesterol-lowering trials are recommended to examine a broad set of CVD and non-CVD disease end points according to 1) type of intervention on cholesterol lowering (diet, classes of drugs, primary or secondary surgery, single or multifactorial intervention), 2) duration and magnitude of TC change, and 3) toxic or beneficial effects of drugs (by comparing placebo and drug groups for the association between TC change and risk).

Mechanisms

Questions should be pursued about biological mechanisms that might help explain low TC:disease associations.

Studies of cell mechanisms. Cell mechanisms of low cholesterol effects require studies along several lines. 1) Is change in membrane lipid composition and function of nucleated cells (such as endothelial cells, pulmonary cells, or intestinal cells) associated with change in serum TC level in the physiological range of interest? 2) How much variation in membrane lipid regulation is there between individuals and between cellular beds, and does this variation relate to TC level? 3) Vessel endothelium and small intracranial vessels should be studied by electron microscopy in subjects having low TC level (e.g., in spontaneously hypertensive rats). 3) Is lipoprotein transport to site of action of substances such as antioxidants or toxins affected by changes in serum TC level in the range of interest? 4) What is the effect of nutrition and TC level on small artery integrity, on angiogenesis, and on maintenance of normal structure and function of the fully differentiated artery? 5) How are blood and cell cholesterol related to immune response in neoplasia and inflammation and to the roles of cytokines in inflammation and cell-cell communication?

Diseases possibly related to specific lipid disorders. Studies are recommended of the long-term risk and nature of CVD and of non-CVD, according to lipoprotein

levels and change in lipoprotein levels, in individuals having specific lipid disorders including both genetic hypocholesterolemias and those caused by gastrointestinal surgery such as ileojejunal bypass or gastrectomy. Systematic investigation is recommended of possible links between cholesterol metabolism and specific cancers or other disease processes that may be associated with low TC level. This includes, for example, potential pathways by which intermediate products in cholesterol biosynthesis influence the activation of oncogenes, processes under genetic control, markers for which may soon be available.

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Appendix

Participants in the Conference on Low Cholesterol: Mortality Associations

MRFIT screenee Follow-up: James Neaton, Deborah Wentworth, David Jacobs, Lewis Kuller, Jeremiah Stamler, Roger Sherwin, Duck-Joo Lee, Joanna Shih, Henry Blackburn.

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Tecumseh: Millicent Higgins, Jake Keller.

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Paisley/Renfrew: David Hole, Christopher Isles, Charles Gillis, Victor Hawthorne.

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Osaka and Akita: Hiroyasu Iso, Yoshio Komachi, Masamitsu Konishi, Takashi Shimamoto, Minoru Iida.

Hiroshima/Nagasaki: Hideo Sasaki, Kazunori Kodama, Fumiyoshi Kasagi.

Lipid Research Clinics Prevalence Study Follow-up: Jacques Rossouw, Basil Rifkind, Shrikant Bangdiwala.

Chicago: Alan Dyer, Jeremiah Stamler, Richard Shekelle.

Israel: Jack Medalie, Uri Goldbourt, Stephen Zyzanski, Shlomit Yaari.

Other conference presenters: Frederick Epstein, John Farquhar, David Gordon, Antonio Gotto, Peter Greenwald, William Harlan, A.S. Hoffman, Malcolm Law, Gardner MacMillan, Henry McGill, Paul Meier, James Nelson, Thomas Pearson, John Potter, Ross Prentice, Thomas Price, Ernst Schaefer, Thomas Thom, Herman Tyroler, Knut Westlund, Philip Wolf, Salim Yusuf.

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