

Is Relationship Between Serum Cholesterol and Risk of Premature Death From Coronary Heart Disease Continuous and Graded?

Findings in 356 222 Primary Screenees of the Multiple Risk Factor Intervention Trial (MRFIT)

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The 356 222 men aged 35 to 57 years, who were free of a history of hospitalization for myocardial infarction, screened by the Multiple Risk Factor Intervention Trial (MRFIT) in its recruitment effort, constitute the largest cohort with standardized serum cholesterol measurements and long-term mortality follow-up. For each five-year age group, the relationship between serum cholesterol and coronary heart disease (CHD) death rate was continuous, graded, and strong. For the entire group aged 35 to 57 years at entry, the age-adjusted risks of CHD death in cholesterol quintiles 2 through 5 (182 to 202, 203 to 220, 221 to 244, and ≥ 245 mg/dL [4.71 to 5.22, 5.25 to 5.69, 5.72 to 6.31, and ≥ 6.34 mmol/L]) relative to the lowest quintile were 1.29, 1.73, 2.21, and 3.42. Of all CHD deaths, 46% were estimated to be excess deaths attributable to serum cholesterol levels 180 mg/dL or greater (≥ 4.65 mmol/L), with almost half the excess deaths in serum cholesterol quintiles 2 through 4. The pattern of a continuous, graded, strong relationship between serum cholesterol and six-year age-adjusted CHD death rate prevailed for nonhypertensive nonsmokers, nonhypertensive smokers, hypertensive nonsmokers, and hypertensive smokers. These data of high precision show that the relationship between serum cholesterol and CHD is *not* a threshold one, with increased risk confined to the two highest quintiles, but rather is a continuously graded one that powerfully affects risk for the great majority of middle-aged American men.

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AN EXTENSIVE body of scientific knowledge exists demonstrating that serum cholesterol is etiologically related to risk of atherosclerotic disease, particularly coronary heart disease (CHD) in the prime of life. The findings supporting this conclusion come from more than twoscore prospec-

tive epidemiologic studies in many countries throughout the world, from clinical investigations such as angiographic studies, and from postmortem investigations; in addition, powerful concordant evidence is available from animal experimental research in several species, including nonhuman primates.¹⁻⁹ However, in recent years, a divergence of opinion has arisen as to whether the association between serum cholesterol and CHD risk is continuous and graded over the whole distribution

of this variable or whether it is a plateau-like relationship with no increase in CHD risk over the lower 10% to 60% of the distribution and with excess risk confined to persons with levels in the upper 40% of the distribution.^{10,11}

Recently available data in over 356 000 American men permit evaluation of this issue with a high degree of precision. These data are from the men screened for possible entry into the Multiple Risk Factor Intervention Trial (MRFIT) in a standardized way in 18 cities across the country in the early 1970s. This report presents the findings in this cohort of the relationship between baseline serum cholesterol levels and risk of fatal CHD.

METHODS

The data collection, screening, and follow-up methods used in this research have been published.¹² In brief, from November 1973 to November 1975, 361 662 men aged 35 to 57 years were screened in 18 US cities at 22 MRFIT clinical centers. Several methods of recruitment were used, including screening of employee, civic, and church groups, identification of men by house-to-house canvassing, and screening of respondents to mass media publicity.

Serum cholesterol levels were determined at one of 14 local laboratories using an automated system of chemical analysis (Auto Analyzer II), with standardization by the Lipid Standardiza-

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Table 1.—Quintiles of Serum Cholesterol and Six-Year CHD Mortality for 356 222 Primary Sscreenees of MRFIT*

Quintile	Serum Cholesterol, mg/dL (mmol/L)	CHD Mortality by Age Group, No. of CHD Deaths (6-y Death Rate per 1000)					
		35-39 y (n=74 077)	40-44 y (n=78 578)	45-49 y (n=84 319)	50-54 y (n=82 544)	55-57 y (n=36 704)	35-57 y (N=356 222)†
1	≤181 (≤4.68)	12 (0.59)	21 (1.28)	43 (2.95)	72 (5.39)	48 (8.31)	196 (3.23)
2	182-202 (4.71-5.22)	11 (0.67)	37 (2.29)	62 (3.72)	108 (6.92)	70 (9.97)	288 (4.18)
3	203-220 (5.25-5.69)	19 (1.37)	52 (3.37)	88 (5.28)	129 (7.73)	107 (14.50)	395 (5.60)
4	221-244 (5.72-6.31)	18 (1.44)	73 (4.72)	123 (6.97)	190 (10.59)	129 (16.05)	533 (7.14)
5	≥245 (≥6.34)	51 (4.57)	112 (7.41)	215 (11.46)	299 (15.78)	169 (19.91)	846 (11.06)
Total		111 (1.50)	295 (3.75)	531 (6.30)	798 (9.67)	523 (14.25)	2258 (6.34)

*CHD indicates coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial. Analysis is age specific and age standardized.

†Age-standardized six-year death rate per 1000.

Table 2.—Quintiles of Serum Cholesterol and Relative Risk of Six-Year CHD Mortality for 356 222 Primary Sscreenees of MRFIT*

Quintile	Serum Cholesterol, mg/dL (mmol/L)	Relative Risk of CHD Mortality by Age Group					
		35-39 y	40-44 y	45-49 y	50-54 y	55-57 y	35-57 y
1	≤181 (≤4.68)	1.00	1.00	1.00	1.00	1.00	1.00
2	182-202 (4.71-5.22)	1.14	1.79	1.26	1.28	1.20	1.29
3	203-220 (5.25-5.69)	2.32	2.63	1.79	1.43	1.74	1.73
4	221-244 (5.72-6.31)	2.44	3.69	2.36	1.96	1.93	2.21
5	≥245 (≥6.34)	7.75	5.79	3.88	2.93	2.40	3.42

*CHD indicates coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial. Analysis is age specific and age standardized.

tion Program, Centers for Disease Control, Public Health Service, Atlanta. Blood pressure was measured according to a standardized protocol by certified technicians, with first and fifth Korotkoff phases recorded as systolic and diastolic pressure, respectively. Three readings were taken with a standard stethoscope and mercury sphygmomanometer. The average of the second and third readings was used in this report. By means of a short questionnaire completed at the time of screening, number of cigarettes currently smoked each day and demographic characteristics were ascertained. Replies were also obtained concerning previous hospitalization of more than two weeks for "heart attack" as well as prescription of medication for diabetes.

Of the 361 662 screenees, 12 866 were eventually enrolled in the randomized clinical trial. The basis of this report, however, is the entire cohort of primary screenees. Vital status of these 361 662 men is being ascertained on an ongoing basis from data provided by the US Social Security System and the National Death Index. For decedents, death certificates are being obtained, abstracted, checked for correct match, and coded by one of two trained nosologists using the ninth revision of the *International Classification of Diseases*

Table 3.—Deciles of Serum Cholesterol and Six-Year CHD Mortality for 356 222 Primary Sscreenees of MRFIT*

Decile	Serum Cholesterol, mg/dL (mmol/L)	Mean Serum Cholesterol, mg/dL (mmol/L)	CHD Mortality		Relative Risk
			No. of Deaths	Rate per 1000	
1	≤167 (≤4.32)	153.2 (3.962)	95	3.16	1.00
2	168-181 (4.34-4.68)	175.0 (4.526)	101	3.32	1.05
3	182-192 (4.71-4.97)	187.1 (4.838)	139	4.15	1.31
4	193-202 (4.99-5.22)	197.6 (5.110)	149	4.21	1.33
5	203-212 (5.25-5.48)	207.5 (5.366)	203	5.43	1.72
6	213-220 (5.51-5.69)	216.1 (5.588)	192	5.81	1.84
7	221-231 (5.72-5.97)	225.9 (5.842)	261	6.94	2.20
8	232-244 (6.00-6.31)	237.7 (6.147)	272	7.35	2.33
9	245-263 (6.34-6.80)	253.4 (6.553)	352	9.10	2.88
10	≥264 (≥6.83)	289.5 (7.486)	494	13.05	4.13

*CHD indicates coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial. Analysis is age standardized.

(ICD 9). Six-year CHD mortality data (ICD 9 codes 410-414) are given in this report for men aged 35 to 39, 40 to 44, 45 to 49, 50 to 54, and 55 to 57 years at screening, as well as for the entire cohort aged 35 to 57 years, and were stratified by baseline cigarette use and diastolic blood pressure (DBP) status. For the purposes of this article, which focuses on serum cholesterol, these latter two variables were dichotomized

as follows: cigarette smoking as no or yes and DBP as less than 90 mm Hg or greater than or equal to 90 mm Hg. Other reports deal in greater detail with the relation of these two variables to risk of CHD mortality in this cohort.^{13,14} For calculation of CHD death rates for men aged 35 to 57 years, the direct method of standardization was used to adjust for differences in age distribution of subgroups.

Table 4.—Quintiles of Serum Cholesterol, DBP, Smoking Status, and Six-Year CHD Death Rate per 1000 for 356 222 Primary Screeners of MRFIT*

Quintile	Serum Cholesterol, mg/dL (mmol/L)	DBP <90 mm Hg			DBP >90 mm Hg			Total		
		No. of Deaths	No. of Men	Rate per 1000	No. of Deaths	No. of Men	Rate per 1000	No. of Deaths	No. of Men	Rate per 1000
Nonsmokers										
1	≤181 (≤4.68)	47	35 741	1.6	36	9612	3.7	83	45 353	2.1
2	182-202 (4.71-5.22)	82	34 553	2.5	51	11 599	4.0	133	46 152	2.9
3	203-220 (5.25-5.69)	87	31 939	2.7	80	12 839	5.6	167	44 778	3.5
4	221-244 (5.72-6.31)	126	30 431	3.8	94	14 500	5.6	220	44 931	4.4
5	≥245 (≥6.34)	188	26 996	6.4	200	16 930	10.7	388	43 926	8.0
Total		530	159 660	3.3	461	65 480	6.4	991	225 140	4.3
Smokers										
1	≤181 (≤4.68)	82	20 017	5.2	31	5002	6.3	113	25 019	5.4
2	182-202 (4.71-5.22)	95	19 675	5.5	60	5977	10.0	155	25 652	6.7
3	203-220 (5.25-5.69)	128	18 812	7.3	100	6397	15.5	228	25 209	9.5
4	221-244 (5.72-6.31)	186	19 119	10.2	127	7533	16.6	313	26 652	12.1
5	≥245 (≥6.34)	250	18 907	13.3	208	9643	21.4	458	28 550	16.0
Total		741	96 530	8.4	526	34 552	15.1	1267	131 082	10.3
All Men										
1	≤181 (≤4.68)	129	55 758	2.8	67	14 614	4.6	196	70 372	3.2
2	182-202 (4.71-5.22)	177	54 228	3.5	111	17 576	6.0	288	71 804	4.2
3	203-220 (5.25-5.69)	215	50 751	4.3	180	19 236	8.8	395	69 987	5.6
4	221-244 (5.72-6.31)	312	49 550	6.2	221	22 033	9.2	533	71 583	7.1
5	≥245 (≥6.34)	438	45 903	9.1	408	26 573	14.4	846	72 476	11.1
Total		1271	256 190	5.2	987	100 032	9.3	2258	356 222	6.3

*DBP indicates diastolic blood pressure; CHD, coronary heart disease; and MRFIT, Multiple Risk Factor Intervention Trial. Analysis is age standardized.

Rates were standardized to the age distribution of the total group of 361 662 screeners.

Mortality rates are presented by quintile and decile of serum cholesterol levels for the 356 222 men free of a history of hospitalization for myocardial infarction. Approximate quintiles and deciles of serum cholesterol levels were determined with use of the entire screened population (361 662 men) and are presented from lowest (quintile 1) to highest (quintile 5 or decile 10). Elevated blood pressure was defined as a mean diastolic reading equal to or greater than 90 mm Hg. Smoking was defined as any use of cigarettes.

RESULTS

Serum Cholesterol Quintiles

Mean serum cholesterol levels for the five serum cholesterol quintiles were 163.7, 192.4, 211.5, 231.7, and 271.2 mg/dL (4.23, 4.98, 5.47, 5.99, and 7.01 mmol/L), respectively. For each of the five age groups (35 to 39 years, 40 to 44 years, 45 to 49 years, 50 to 54 years, and 55 to 57 years), six-year risk of fatal CHD was progressively higher for quintiles 2 through 5 of the serum cholesterol level, compared with quintile 1 (Tables 1 and 2). Range of

relative risk was greater for younger than for older men, eg, 7.75 for men aged 35 to 39 years and 2.40 for men aged 55 to 57 years. However, absolute excess risk, ie, difference in risk between a higher quintile of serum cholesterol level and quintile 1, tended to increase with age. For quintile 5, for example, there was an absolute excess risk at ages 35 to 39 years of 3.98 deaths per 1000 in six years, compared with 11.60 for the age stratum 55 to 57 years.

For the entire cohort of 356 222 men, six-year CHD mortality rates were higher by 29%, 73%, 121%, and 242% for serum cholesterol quintiles 2, 3, 4, and 5, respectively, compared with quintile 1 (Tables 1 and 2). For these five quintiles, the 95% confidence intervals¹⁵ for the age-standardized six-year CHD mortality rates were as follows: quintile 1, 2.8 to 3.7; quintile 2, 3.7 to 4.7; quintile 3, 5.0 to 6.2; quintile 4, 6.5 to 7.7; and quintile 5, 10.3 to 11.9.

Serum Cholesterol Deciles

Age-standardized risk of six-year CHD mortality was also continuous and graded over the range of the deciles of serum cholesterol levels (Ta-

ble 3). The first decile, serum cholesterol level less than or equal to 167 mg/dL (≤4.32 mmol/L), had the lowest death rate (3.16 per 1000); the tenth decile, serum cholesterol equal to or greater than 264 mg/dL (≥6.83 mmol/L), had the highest rate (13.05 per 1000), a rate more than four times higher. Rates were similar for men in the first and second deciles; for men in the third decile (range, 182 to 192 mg/dL [4.71 to 4.97 mmol/L]), the rate was 31% higher than for those in the first decile and was progressively higher for each subsequent decile.

Serum Cholesterol Quintiles Stratified by Cigarette Use and DBP

In each of the nine analyses (Table 4), six-year age-standardized CHD death rates were continuously and progressively higher for men in serum cholesterol quintiles 2 through 5, compared with those in quintile 1. This was the finding for nonsmokers with DBP less than 90 mm Hg and greater than or equal to 90 mm Hg, for smokers with DBP less than 90 mm Hg and greater than or equal to 90 mm Hg, for all nonsmokers and all smokers, and for all men with DBP less than

90 mm Hg and greater than or equal to 90 mm Hg. For the large group of nonsmokers with DBP less than 90 mm Hg (159 660 men, or 45% of the cohort), relative risks for serum cholesterol quintiles 2, 3, 4, and 5 were 1.56, 1.69, 2.38, and 4.00, respectively. These data underscore the key role of serum cholesterol levels above optimal in the causation of premature CHD.

With multiple logistic regression analysis,¹⁶ including age, DBP, cigarette use, and diabetic status, the coefficient for serum cholesterol level and six-year CHD mortality was .0078. This parameter estimate indicates that a higher serum cholesterol level of 20 mg/dL (0.52 mmol/L) is associated with a relative risk of 1.17 (95% confidence interval, 1.15 to 1.19). Since the mean serum cholesterol level for the entire cohort was 214.6 mg/dL (5.55 mmol/L),¹² this translates into an estimate that a 9% higher serum cholesterol level was associated with a 17% greater CHD death rate—that is, a 1% higher serum cholesterol level was associated with an almost 2% higher CHD risk. This is almost certainly an underestimate, since with use of a single serum cholesterol measurement there is bound to be some misclassification due to both intraindividual variability and laboratory error. This estimate is similar to that derived statistically years ago from prospective studies¹⁶ and recently from the intervention experience of the Lipid Research Clinics Coronary Primary Prevention Trial.¹⁷

The age-specific CHD death rates (Table 1) were used to estimate the number of excess CHD deaths in quintiles 2 through 5, based on the estimated number of CHD deaths that would have occurred if all men of each age group had had the age-specific rate of quintile 1. For all 356 222 men, CHD deaths would have numbered 1143, rather than the observed 2258. Based on their higher rates, estimated numbers of excess CHD deaths for the men aged 35 to 57 years at screening in quintiles 2, 3, 4, and 5 are 66, 167, 290, and 592, totaling 1115 excess CHD deaths in quintiles 2 through 5. Of this total of excess CHD deaths, 6% were in quintile 2, 15% were in quintile 3, 26% were in quintile 4, and 53% were in quintile 5. With a total of 2258 CHD deaths, the estimate is that 49% (1115/2258) are excess deaths attributable to serum cholesterol levels equal to or greater than 182 mg/dL (≥ 4.71 mmol/L). With control for age, DBP, cigarette use, and diabetes, the estimate of population attributable risk from the multiple logistic analysis is similar—46% of

all CHD deaths in this cohort were excess deaths attributable to serum cholesterol levels equal to or greater than 180 mg/dL (≥ 4.65 mmol/L).

For men in each of the five quintiles of serum cholesterol levels, CHD mortality was higher for cigarette smokers than for nonsmokers, without or with high blood pressure. Most risk ratios for smokers compared with nonsmokers were greater than 2.0—overall, 2.4 (Table 4, last column, 10.3/4.3). Similarly, for men in each of the five quintiles of serum cholesterol levels, whether nonsmokers or smokers, CHD mortality was higher for those with DBP greater than or equal to 90 mm Hg compared with those with DBP less than 90 mm Hg, with risk ratios in the range of 1.2 to 2.3 or 1.8 overall (Table 4, last row, 9.3/5.2). The extremes of risk based on the three factors, as stratified in Table 4, ranged from 21.4 per 1000 to 1.6, the former being 13.4 times greater than the latter. Only 35 741 men (10%) of the entire cohort of 356 222 were in the lowest risk group, ie, had a serum cholesterol level equal to or less than 181 mg/dL (≤ 4.68 mmol/L), had a DBP less than 90 mm Hg, and were not cigarette smokers. If their six-year age-standardized CHD mortality rate of only 1.6 per 1000 had prevailed for the whole cohort, the estimate is that CHD deaths would have numbered 560 instead of the total 2258. The estimated number of excess deaths attributable to serum cholesterol levels equal to or greater than 182 mg/dL (≥ 4.71 mmol/L), cigarette smoking, and elevated blood pressure in various combinations is 1698, which is 75% of all CHD deaths.

An additional estimate of excess CHD mortality in this cohort was made based on the following five criteria for optimal risk: serum cholesterol level equal to or less than 181 mg/dL (≤ 4.68 mmol/L), systolic pressure less than 120 mm Hg, DBP less than 76 mm Hg, no cigarette smoking, and no history of diabetes. A DBP of less than 76 mm Hg was used since this was the cut point for the lowest quintile of DBP; for the men in this quintile, six-year age-adjusted CHD death rate was lower than that for men in the four other DBP quintiles. Of the entire cohort of 356 222 men, only 7948 (2.2%) met all five of these criteria. Among these 7948 men, CHD deaths numbered only six, and the six-year age-adjusted CHD mortality rate was only 0.8 per 1000. If the entire cohort of 356 222 men had had a rate of 0.8 per 1000, there would have been only 285 CHD deaths, rather than the 2258 observed. Thus, based on this estimate, 1973 CHD deaths (87%

of the total) were excess deaths attributable to above optimal levels of the five established major CHD risk factors, prevalent in various combinations among 98% of the cohort.

COMMENT

The data of this large prospective study clearly demonstrate that for American men aged 35 to 57 years in 1973 to 1975, the relationship between serum cholesterol and six-year risk of CHD death was continuous, graded (dose-related), and strong over the entire range of the distribution of this variable. In age-specific analyses for men aged 35 to 39, 40 to 44, 45 to 49, 50 to 54, and 55 to 57 years at screening and in age-standardized analyses with stratification based on cigarette use and DBP, risk of CHD rose steadily for men in the second, third, fourth, and fifth quintiles, compared with the first quintile; this was the consistent finding without exception. Overall, based on the data for the entire cohort of 356 222 men, for men in quintile 2 with serum cholesterol levels of 182 to 202 mg/dL (4.71 to 5.22 mmol/L) and for men in quintile 3 with serum cholesterol levels of 203 to 220 mg/dL (5.25 to 5.69 mmol/L), six-year age-standardized death rates were 29% and 73% higher, respectively, than for men in quintile 1. With CHD deaths numbering 288 and 395 for quintiles 2 and 3, respectively, and 196 for quintile 1, these estimates of relative risk have a high degree of precision. Thus, they lend powerful support—along with the data from the other quintile analyses and the decile analysis and data from other studies^{1-9,11}—to the conclusion that the relationship of serum cholesterol to CHD in the US population is a *graded one* and *not* a threshold (plateau-like) one. That is, the great majority of adults in the United States are at increased CHD risk because of their status in regard to this trait, and not only those in the highest or the two highest quintiles of the distribution. Specifically, serum cholesterol levels of about 180 mg/dL (4.65 mmol/L) and above are associated with increased risk for middle-aged American men, and not only levels equal to or greater than 220 or 240 mg/dL (5.69 or 6.21 mmol/L).

Quantitative estimates, based on these data, of the distribution of excess CHD risk across serum cholesterol quintiles 2 through 5 lend further weight to the importance of the foregoing conclusion. Thus, while 53% of the estimated excess CHD deaths attributable to serum cholesterol levels above optimal were derived from quintile 5,

about 21% were distributed across quintiles 2 and 3 and another 26% were in quintile 4. Therefore, a high-risk-only strategy—based on the idea of a threshold relationship, hence dealing only with severe hypercholesterolemia—has only a limited potential to have an impact on the totality of excess risk. This is the case, for example, when hypercholesterolemia requiring treatment is defined solely as 2 SD above the mean (2.5% of the population), or the cut point used is the 95th or 90th percentile (5% or 10% of the population) or a level equal to or greater than 265 mg/dL (≥ 6.85 mmol/L) (approximately the tenth decile cut point for the MRFIT cohort) or a level equal to or greater than 240 or 245 mg/dL (6.21 or 6.34 mmol/L) (approximately the fifth quintile cut point here). Even with this last cut point, 47% of the estimated excess risk, distributed across quintiles 2 through 4, would be neglected.

Since the first American Heart

Association statement on diet and CHD in 1961,^{7,18} the emphasis of recommendations by expert groups for coronary prevention in the United States has been on a two-pronged strategy, involving advice for improved eating habits for the whole population, to shift the serum cholesterol distribution of the whole population downward, plus special approaches for individuals and families at higher risk.^{1-7,9} This is also the strategy set down in the Report of the World Health Organization Expert Committee on the Prevention of Coronary Heart Disease⁸ and in the several reports on public policy emanating from other industrialized countries concerned with the epidemic of premature CHD.^{3,19-23}

It is a reasonable inference that the steady and marked decline in CHD mortality in the United States since the late 1960s—greater than for any other country in the world (many countries have been steady in their rates, and others have registered rising

rates)—is related to the improvements in nutrition and serum cholesterol distribution, as well as in other major risk factors (eg, cigarette use, blood pressure).^{3,5,16,23-26}

The US Department of Health and Human Services, in a recent report, *Health United States 1983—and Prevention Profile*, set the goal for 1990 of a further nutrition-related decline in mean serum cholesterol levels for American adults, to less than 200 mg/dL (<5.17 mmol/L).²⁷ Correspondingly, the National Heart, Lung, and Blood Institute, in accordance with the recommendations of two recent major reports,^{3,9,27,29} has launched a National Cholesterol Education Program. The massive data set reported herein is yet another scientific underpinning for these goals and endeavors.

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