Prospective 10-Year Evaluation of Hypobetalipoproteinemia in a Cohort of 772 Firefighters and Cross-Sectional Evaluation of Hypocholesterolemia in 1,479 Men in the National Health and Nutrition Examination Survey I

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Our specific aim in a 10-year prospective study of 772 Cincinnati firemen (predominantly aged 26 to 46 years) was to determine the prevalence, attributes, and etiology of persistent hypobetalipoproteinemia, defined by entry low-density lipoprotein cholesterol (LDLC) less than 75 mg/dL. A second specific aim was to cross-sectionally assess hypocholesterolemia (defined by total serum cholesterol [TC] <130 mg/dL) in 1,314 white and 165 black men aged 26 to 46 years in the National Health and Nutrition Examination Survey (NHANES I). The 141 black and 631 white firemen had 4,973 person-years of follow-up time (median, 7.1 yr/man). Of 772 men, 44 (5.7%) had entry LDL levels less than 75 mg/dL; they had a mean follow-up time of 7.3 yr/man. Of these 44 men, there were 12 (1.6% of the cohort) with entry LDLC less than 75 mg/dL, and at least 67% of their follow-up LDLC levels were less than 75. Their mean entry TC and LDLC levels were low (130 and 58 mg/dL), mean triglyceride (TG) was low (63 mg/dL), and mean high-density lipoprotein cholesterol (HDLC) was high (60 mg/dL). LDLC remained at less than 75 mg/dL in 81% of their follow-up samples. Their mean entry and follow-up cholesterol and LDLC did not differ ($P > .1$, 130 *v* 133 mg/dL and 58 *v* 63 mg/dL). Compared with 32 men with entry LDLC less than 75 mg/dL but with less than 67% of follow-up LDLC less than 75 mg/dL, the 12 men with persistently low LDLC had lower mean Quetelet indices and diastolic blood pressure at entry (2.36 *v* 2.58, $P = .056$; 73 *v* 80 mm Hg, $P = .03$) and on follow-up study (2.45 *v* 2.69, $P = .04$; 72 *v* 79 mm Hg, $P = .05$). Of 12 men with persistently low LDLC, two had truncated apolipoprotein (apo) B (familial hypobetalipoproteinemia), two had the apo E genotype 2/3, and two had acquired hypobetalipoproteinemia that antedated mortality from melanoma by 9 years and from alcoholism by 2 years. Comparable to white and black firemen aged 26 to 46 years, 2.9% and 3.6% of whom had entry serum TC less than 130 mg/dL, of 1,314 white and 165 black men in the NHANES I study (aged 26 to 46), 1.8% and 3.6% had hypocholesterolemia (entry TC < 130 mg/dL). Daily mean calorie, fat, and protein intake (grams per day) did not differ ($P > .05$) in men with entry TC less than 130 mg/dL compared with those with TC 130 to 230 or greater than 230 mg/dL. Hypocholesterolemia in white and black men in NHANES I could not be attributed to hypocaloric intake or to protein, fat, or carbohydrate undernutrition. There appear to be racial differences in the prevalence of hypocholesterolemia. Blacks comprised 18% of the firemen's cohort but 42% of those with persistent hypobetalipoproteinemia; among NHANES I subjects, 3.6% of blacks were hypocholesterolemic versus 1.8% of whites. Unless persistent hypobetalipoproteinemia reflects an underlying disease, alcoholism, etc., it is often heritable, and may be associated with a reduced likelihood of coronary heart disease (CHD) and with increased longevity.

IN NONINSTITUTIONALIZED, unselected population groups, one cause of hypocholesterolemia and hypobetalipoproteinemia is a common, highly penetrant, autosomal dominant trait, familial hypobetalipoproteinemia.[1-7] Hypocholesterolemia and hypobetalipoproteinemia in heterozygotes for familial hypobetalipoproteinemia are primarily caused by nonsense or frameshift mutations that lead to synthesis of a truncated species of apolipoprotein (apo) B, with apo B production rates approximately 30% of normals.[5-7] Familial hypobetalipoproteinemia is associated with a reduced risk of coronary heart disease (CHD) and prolongation of the life span,[1] probably because of low atherogenic low-density lipoprotein cholesterol (LDLC) and a low, antiatherogenic ratio of total cholesterol (TC) to high-density lipoprotein cholesterol (HDLC).[1-4]

Not all low TC and LDLC levels are advantageous (ie, associated with reduced CHD morbidity or mortality[1]), or familial.[1-7] Some[8,9] but not all[10] observational epidemiologic studies in Western, industrialized countries have shown increases in all-cause mortality associated with "low" serum TC (140 to 160 mg/dL). Hypocholesterolemia and anemia are useful indicators of protein-calorie undernutrition/malnutrition[11,12] and may also represent effects of alcoholism and liver disease,[8-10] thus in part explaining the increase in all-cause mortality associated with serum TC less than 140 to 160 mg/dL.[8,9] Hypocholesterolemia and hypobetalipoproteinemia have been linked to depression/suicide,[13] and this linkage is postulated as the basis of the association of low serum cholesterol with increased all-cause mortality.[8,9] However, recent studies suggest that depression causes undernutrition and hypocholesterolemia, and not vice versa.[14] Moreover, hypertriglyceridemia probably plays a more important role than hypocholesterolemia in the etiology of depression.[15] Clinically significant depression can often be ameliorated by reduction of triglyceride (TG) levels.[15] Finally, two major recent placebo-controlled cholesterol-lowering trials with simvastatin[16] and pravastatin[17] have shown 30% and 42% reductions in CHD morbidity and mortality, 30% and 21% reductions in all-cause mortality, and no increase in noncardiovascular mortality or suicide-homocide mortality.

Our specific aim in a 10-year prospective study of 772 Cincinnati firemen[18] (predominantly aged 26 to 46 years) was to assess the prevalence, attributes, and etiology of persistent hypobetalipoproteinemia. A second specific aim was to cross-sectionally assess the attributes of hypocholesterolemia in 1,314

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white men and 165 black men (aged 26 to 46 years) in the National Health and Nutrition Examination Survey (NHANES I).[19]

SUBJECTS AND METHODS

Study Protocol

Firemen. Beginning in 1984, a prospective cohort study was initiated with enrollment of all Cincinnati firemen upon their 26th birthday.[18] Examinations for CHD risk factors included urinalysis, hematocrit, fasting blood sugar and lipid profile, electrocardiogram, and blood pressure measurement.[18] Beginning in March 1992, lipoprotein (a) [Lp(a)] level was measured. At entry, a medical history and physical examination were performed. Information was systematically obtained on cigarette smoking and family history of CHD in first-degree relatives aged 60 or less. Follow-up examinations were performed every 4 years for men less than age 40 and without major CHD risk factors, every 3 years for men aged 40 or older without CHD risk factors, and yearly for men with any major CHD risk factor.[18] At entry and on follow-up evaluation, studies were made to diagnose diabetes, and prescription drug use (if any) was recorded. Patients with diabetes were not excluded from follow-up study.

In 1996, we attempted to recall 12 men (1.6% of the cohort) with persistent hypobetalipoproteinemia, who had an entry LDLC level less than 75 mg/dL and at least two thirds of follow-up LDLC measurements less than 75. In seven (of 12) men who could be restudied, we determined apo B phenotypes and apo E genotypes, and did a variable number of tandem repeat (VNTR) analysis[20] to assess the etiology of the persistent hypobetalipoproteinemia.

NHANES I follow-up study group. NHANES I included a sample of the general noninstitutionalized population.[19] A prospective longitudinal assessment of 8,678 subjects began in 1971, continuing to 1975. A longitudinal follow-up evaluation, the NHANES I epidemiologic study, was performed in three waves (1982 to 1984, 1986, and 1987).[19] At entry in NHANES I, serum cholesterol level was measured. However, there was no follow-up determination of serum cholesterol.[19] NHANES I included a 24-hour dietary recall,[19] enabling an assessment of group dietary intake in subjects within various serum cholesterol categories (low [<130], middle [130 to 230], and high [>230 mg/dL]). NHANES I included determination of diabetes, which was not an exclusion for follow-up study.

In NHANES I, habitual physical activity and leisure time exercise levels were separately categorized by questionnaire as (1) little or none, (2) moderate, or (3) much.[19]

Laboratory Methods

In Cincinnati firemen,[18] fasting serum TC, LDLC, HDLC, and TG levels were measured enzymatically in our Lipid Research Clinics standardized laboratory.[21] In seven (of 12) patients with persistent hypobetalipoproteinemia, we determined apo B phenotypes and apo E genotypes and performed VNTR analysis following previously published methods.[20] Lp(a) was determined by immunoprecipitation analysis.[22]

Quetelet Index

The Quetelet index, a measure of relative ponderosity, was calculated following the Lipid Research Clinics formula, (weight [kg]/height [cm]^2) $\times$ 1,000.[23]

Statistical Analysis

Three major groups of firemen were arbitrarily categorized by varying levels of low entry-level LDLC (Table 1). For each fireman, we calculated mean values for follow-up visits and then calculated group means. Group I included 12 men with entry LDLC less than 75 mg/dL and at least two thirds of follow-up LDLC determinations less than 75 mg/dL (persistent hypobetalipoproteinemia) (Table 1 and Fig 1). Group II included 32 men with entry LDLC less than 75 mg/dL, but with less than two thirds of follow-up LDLC levels less than 75 mg/dL (Table 1 and Fig 1). Group III included 124 men with entry LDLC of at least 75 mg/dL but less than 100 mg/dL (Table 1 and Fig 2). The distribution of follow-up values for LDLC and TC were assessed in the 44 men with initial LDLC less than 75 mg/dL (Fig 3), as it was in all 168 men (groups I, II, and III together) with initial LDLC less than 100 mg/dL (Fig 4). The distribution of follow-up serum TC in 22 men with initial levels less than 130 mg/dL (Fig 5) and in 71 men with initial levels less than 150 mg/dL was also studied (Fig 5).

Within the three groups of firefighters categorized by entry LDLC (Table 1), entry and follow-up TC, LDLC, HDLC, and TG were compared using paired *t* tests or paired Wilcoxon tests, depending on whether the data were normally distributed[24] (Figs 1 and 2). Among the three groups of firemen, entry and follow-up values for Lp(a), TG, HDLC, Quetelet Index, fasting blood glucose, and systolic and diastolic blood pressure were compared (after adjusting for age) (Table 1). After covariance adjustment for age,[24] the three hypocholesterolemic groups (all with entry LDLC <100 mg/dL) were further compared with a fourth group (n = 604) with entry LDLC of at least 100 mg/dL (Fig 6).

To assess racial differences in lipid and lipoprotein cholesterol levels, we matched 141 black firemen with 141 white firemen by age and entry TC and then compared[24] LDLC, HDLC, and TG levels in the 141 pairs.

In 26- to 46-year-old subjects from NHANES I, the age group most comparable to the firemen, three serum cholesterol groups (low [<130 mg/dL], middle [130 to 230], and high [>230 mg/dL]) (Table 2) were selected for analysis and for comparison to the firemen. Among the three serum cholesterol groups in NHANES I men, the Quetelet Index and dietary calorie and protein, fat, and carbohydrate (grams per day) intake were compared using least-square means with covariance adjustment[24] for age (Table 2). Among the three NHANES I serum cholesterol groups (<130, 130 to 230, and >230 mg/dL), differences in the three habitual physical activity and leisure time exercise levels (little or none, moderate, or much) were assessed by chi-square and general linear model least-square means analyses with and without covariance adjustment[24] for age.

RESULTS

Firemen

There were 772 male Cincinnati firefighters (141 black and 631 white) with 4,973 person-years of follow-up study; the mean and median follow-up times were 6.4 and 7.0 years.[18] Of 772 men, 604 were aged 26 to 46 years. Twelve men, 1.6% of the cohort, were diabetic. For the entire cohort at entry, the mean TC (199 mg/dL), LDLC (127 mg/dL), and HDLC (48 mg/dL) were in a desirably low CHD-risk range,[25] as was mean TG[26] (127 mg/dL).

Hypobetalipoproteinemia and hypocholesterolemia. The cutoff point arbitrarily used to identify "low" LDLC was less than 75 mg/dL. For the age group of the firemen, 75 mg/dL approximated the Lipid Research Clinics population prevalence study's fifth percentile for LDLC.[23] In a similar fashion, less than 130 mg/dL was used as a cutoff point for serum TC; this approximated the Lipid Research Clinics' fifth percentile for TC.[23] None of the firemen with low LDLC were taking lipid-lowering medications. There were 44 firemen whose initial LDLC was less than 75 mg/dL (5.7% of the population of 772 firemen with entry and follow-up LDLC) (Figs 1 and 3). These 44 men had 131 follow-up visits; 32% of these had mean LDLC levels less than 75 mg/dL and 34% had mean LDLC levels between 75 and 85 mg/dL (Fig 3). In this group of 44 men

Table 1. Entry and Follow-up Variables in Three Groups of Firemen, Two With Entry LDLC <75 and One With Entry LDLC <100 mg/dL

Variable	Group			Group Comparisons (*P*)*		
	I	II	III	I v II	I v III	II v III
No. of subjects	12	32	124			
Visits (n)	32	99	365			
Duration of follow-up (yr)	7.2 ± 3.3	7.3 ± 2.7	7.1 ± 2.7			
LDLC						
Entry	58 ± 12	64 ± 9	89 ± 7	NS	.0001	.0001
Follow-up	63 ± 9	93 ± 20	107 ± 22	.01	.0001	.05
TC						
Entry	130 ± 13	138 ± 28	160 ± 16	NS	.001	.0002
Follow-up	133 ± 12	163 ± 23	177 ± 22	.002	.0001	.01
TG						
Entry	63 ± 48	85 ± 60	100 ± 67	NS	.08	NS
Follow-up	61 ± 23	106 ± 57	113 ± 66	.04	.01	NS
HDLC						
Entry	60 ± 11	51 ± 11	51 ± 13	.02	.008	NS
Follow-up	58 ± 11	49 ± 10	49 ± 12	.02	.006	NS
Lp(a)	12 ± 13	21 ± 30	21 ± 24	NS	NS	NS
QI						
Entry	2.36 ± 0.3	2.58 ± 0.3	2.56 ± 0.3	.056	.07	NS
Follow-up	2.45 ± 0.3	2.69 ± 0.3	2.66 ± 0.3	.04	.05	NS
Glucose						
Entry	93 ± 31	94 ± 9	95 ± 8	NS	NS	NS
Follow-up	94 ± 9	95 ± 7	95 ± 12	NS	NS	NS
SBP						
Entry	124 ± 11	124 ± 15	122 ± 13	NS	NS	NS
Follow-up	124 ± 14	124 ± 14	122 ± 12	NS	NS	NS
DBP						
Entry	73 ± 6	80 ± 11	81 ± 8	.03	.01	NS
Follow-up	72 ± 6	79 ± 9	79 ± 7	.05	.03	NS
Age (yr)	32 ± 7	35 ± 9	35 ± 8	NS	NS	NS

NOTE. Group I, baseline LDLC <75 mg/dL, ≥two thirds of follow-up LDLC levels <75 mg/dL; group II, baseline LDLC <75 mg/dL, <two thirds of follow-up LDLC levels <75 mg/dL; group III, baseline LDLC ≥75 but <100 mg/dL. LDLC, TC, TG, HDLC, and fasting blood glucose are in mg/dL; systolic and diastolic blood pressure (SBP and DBP) are in mm Hg.

Abbreviation: QI, Quetelet Index.

*Group comparisons were made after adjusting for age (ANOVA).

with initial LDLC less than 75 mg/dL, 11.4% had serum TC less than 130 and 15.9% had values between 130 and 140 mg/dL at follow-up study (Fig 3).

The 44 men with entry LDLC less than 75 mg/dL were arbitrarily divided into two major groups, 12 who had at least two thirds of their follow-up LDLC values less than 75 mg/dL (persistent hypobetalipoproteinemia) and 32 who had less than two thirds of their follow-up LDLC levels less than 75 mg/dL (hypobetalipoproteinemia) (Fig 1 and Table 1). A third group of 124 firemen with entry LDLC of at least 75 but less than 100 mg/dL was also studied (Fig 2 and Table 1).

After matching 141 black and 141 white firemen by TC and age, black firemen had lower levels (mean ± SD) of TG (88 ± 50 *v* 99 ± 57 mg/dL, $P = .04$), comparable LDLC (117 ± 33 *v* 118 ± 31 mg/dL), and higher HDLC (52 ± 10 *v* 49 ± 11 mg/dL, $P = .03$).

Baseline LDLC <75 and two thirds of follow-up LDLC <75 mg/dL (persistent hypobetalipoproteinemia). These 12 men (1.6% of the cohort with baseline and follow-up LDLC) had 32 follow-up visits, 26 of which (81%) showed LDLC to be less than 75 mg/dL. These 12 men had low[23] mean TC at study entry (130 mg/dL), low mean LDLC (58 mg/dL),[23] low mean TG (63 mg/dL),[23] and relatively high HDLC (60 mg/dL) (Table 1 and Fig 1). In this group of 12 men, there were no significant changes ($P > 0.1$) between entry and follow-up mean lipid or lipoprotein cholesterol levels (Fig 1).

Of these 12 men with persistent hypobetalipoproteinemia, five were black and seven were white; the 18% of subjects who were black (141 of 772) in the cohort provided 42% (of 12) of the cases with persistent hypobetalipoproteinemia. Mean entry Lp(a) in these 12 men (12 ± 13 mg/dL) was lower ($P < .05$) than in the 604 men with entry LDLC greater than 100 mg/dL (28 ± 27 mg/dL) (Fig 6).

The 12 men with persistent hypobetalipoproteinemia had higher mean entry HDLC (60 ± 11 mg/dL, $P < .001$) and lower TG (63 ± 48 mg/dL, $P < .05$) than the 604 men with entry LDLC greater than 100 mg/dL (HDLC, 48 ± 10; TG, 115 ± 58 mg/dL) (Fig 6).

Of the 12 men with persistent hypobetalipoproteinemia, at recall in August 1996, three were not available for resampling (patients no. 159, 221, and 761) and two were deceased (no. 204 [melanoma] and no. 370 [alcoholism]) (Table 3). In subject no. 204, persistent hypobetalipoproteinemia antedated death from melanoma by 9 years, and in subject no. 370, persistent hypobetalipoproteinemia antedated death from alcoholism by 2 years (Table 3). Two of seven persistently hypobetalipoprotein-

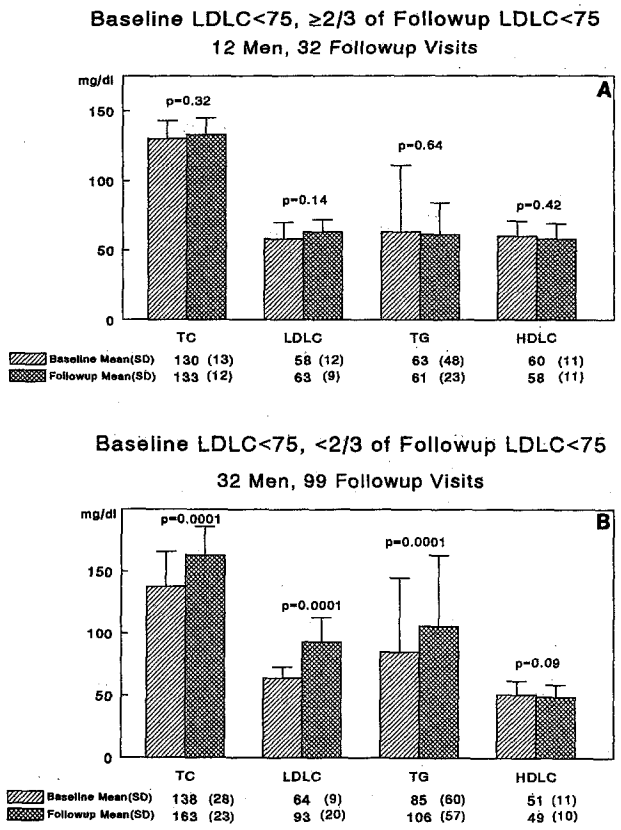


Fig 1. Comparison of baseline and follow-up (mean ± SD) TC, LDLC, TG, and HDLC (all mg/dL) for (A) 12 firemen whose baseline LDLC was < 75 mg/dL and who had ≥ two thirds of their follow-up LDLC levels < 75 mg/dL and (B) 32 firemen whose baseline LDLC was <75 mg/dL and who had < two thirds of their follow-up LDLC levels <75 mg/dL.

emic men (no. 664 and 778) had truncated apo B, with apo B phenotypes[20] B100,90 and B100,82, respectively; five of the men had normal, "wild-type" apo B phenotypes, B100,100 (Table 3). Two of the seven men (no. 609 and 778) were heterozygous for the mutant apo E2 allele (E2/3), three had normal, wild-type apo E3/3, and two were heterozygous for E3/4 (Table 3). Subject no. 778 had both truncated apo B

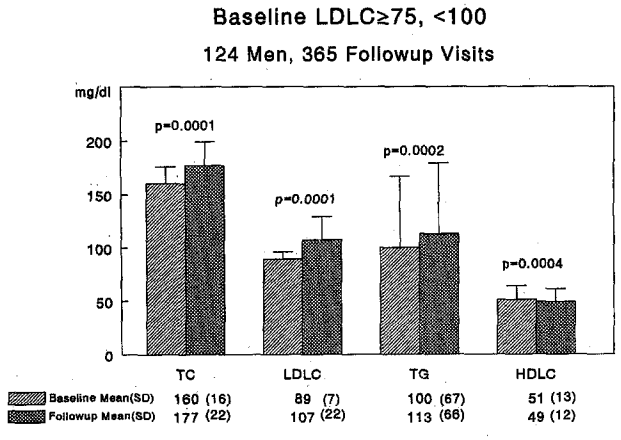
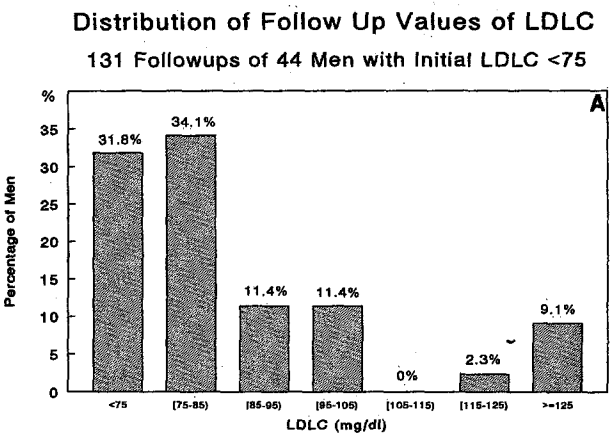


Fig 2. Comparison of baseline and follow-up (mean ± SD) TC, LDLC, TG, and HDLC (all mg/dL) for 124 firemen whose baseline LDLC was ≥75 but <100 mg/dL.



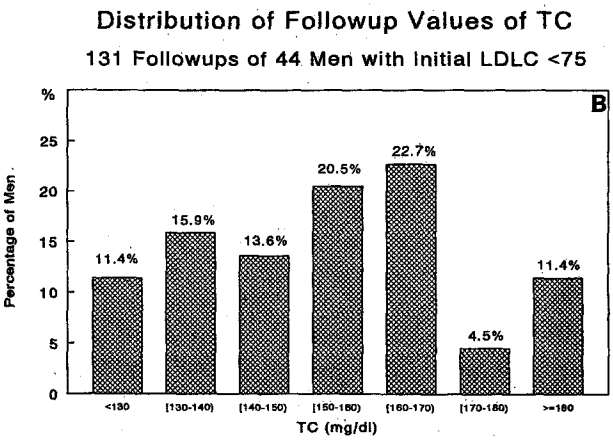


Fig 3. Distribution of follow-up values for (A) LDLC in 44 firemen with initial LDLC levels <75 mg/dL and (B) TC in 44 firemen with initial LDLC levels <75 mg/dL.

(B100,82) and the apo E2/3 genotype. VNTR studies showed that none of the seven men with persistent hypobetalipoproteinemia came from the same family (no founder effect) (Table 3).

Hypobetalipoproteinemia. There were 32 hypobetalipoproteinemic men with entry LDLC less than 75 mg/dL who had less

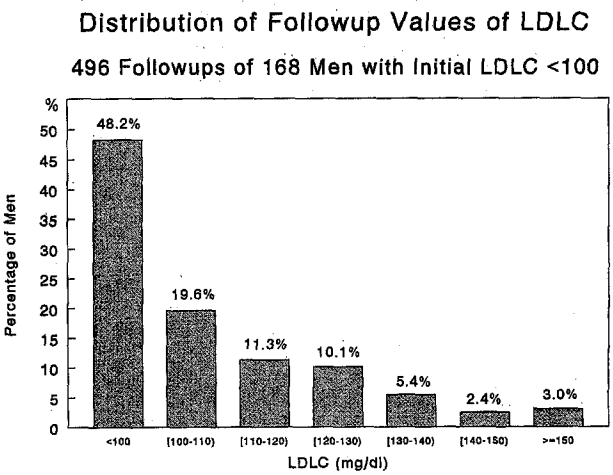


Fig 4. Distribution of follow-up values for LDLC in 168 firemen with initial LDLC <100 mg/dL.

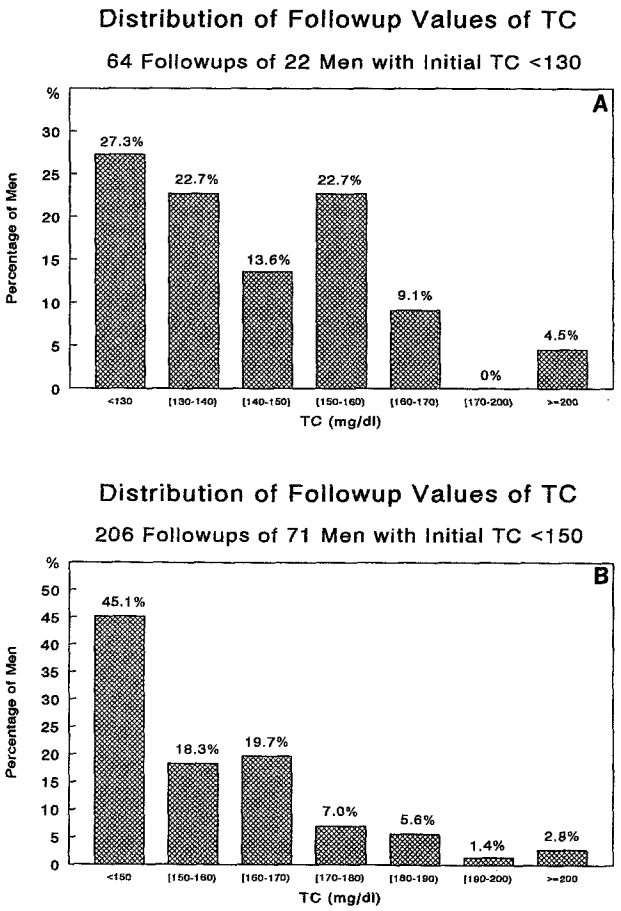


Fig 5. Distribution of follow-up values for TC in (A) 22 firemen with initial TC levels <130 mg/dL and (B) 71 firemen with initial TC levels <150 mg/dL.

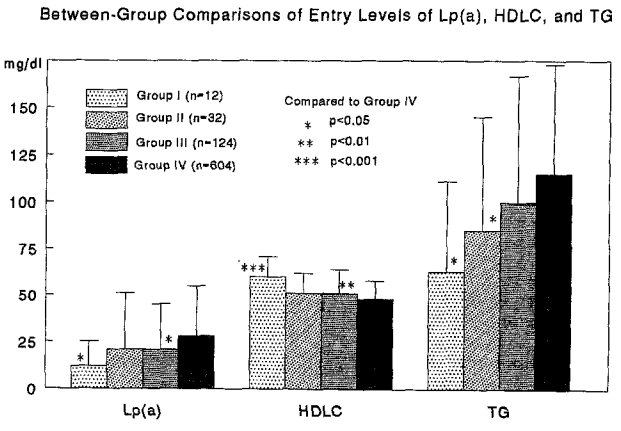


Fig 6. Entry levels (mean ± SD) of Lp(a), HDLC, and TG (all mg/dL) in 3 groups of firemen with varying degrees of entry and follow-up hypobetalipoproteinemia *v* 604 firemen with entry LDLC ≥100 mg/dL. *P* values are from least-square means after adjusting for age. Group I, baseline LDLC <75 mg/dL, ≥ two thirds of follow-up LDLC levels <75 mg/dL (n = 12); group II, baseline LDLC <75 mg/dL, < two thirds of follow-up LDLC levels <75 mg/dL (n = 32); group III, baseline LDLC ≥75, but <100 mg/dL (n = 124); group IV, baseline LDLC ≥100 mg/dL (n = 604).

Table 2. Clinical Characteristics of 1,314 White Men and 165 Black Men Aged 26 to 46 at Entry Into NHANES I

Cholesterol Group	White Men (n = 1,314) No.	White Men Mean ± SD	Black Men (n = 165) No.	Black Men Mean ± SD
Protein				
<130	24	118 ± 64	6	89 ± 59
130-230	929	104 ± 54	113	100 ± 51
>230	361	102 ± 48	46	79 ± 38
Fat				
<130	24	123 ± 55	6	115 ± 90
130-230	929	112 ± 62	113	110 ± 68
>230	361	110 ± 54	46	74 ± 34
Carbohydrate				
<130	24	302 ± 142	6	274 ± 233
130-230	929	287 ± 129	113	276 ± 118
>230	361	264 ± 116	46	207 ± 85
Calories				
<130	24	2,892 ± 1,139	6	2,629 ± 2,052
130-230	929	2,703 ± 1,144	113	2,680 ± 1,272
>230	361	2,579 ± 1,004	46	2,046 ± 794
Quetelet Index				
<130	24	2.48 ± .35	6	2.55 ± .52
130-230	925	2.52 ± .38	111	2.45 ± .44
>230	361	2.65 ± .36*	45	2.60 ± .39
Serum cholesterol				
<130	24	121 ± 6	6	123 ± 6
130-230	929	189 ± 24	113	183 ± 25
>230	361	259 ± 26	46	268 ± 40
Habitual physical activity				
<130	24	2.29 ± 0.75	6	2.17 ± 0.41
130-230	929	2.44 ± 0.65	113	2.55 ± 0.60
>230	361	2.32 ± 0.69†	46	2.59 ± 0.62
Leisure time exercise				
<130	24	2.13 ± 0.80	6	1.67 ± 0.52
130-230	929	2.04 ± 0.76	113	1.82 ± 0.79
>230	361	1.95 ± 0.77‡	46	1.85 ± 0.79

*$P \leq .025$, low cholesterol (<130 mg/dL) *v* high cholesterol (>230).
†$P = .003$, cholesterol 130-230 mg/dL *v* high cholesterol (>230).
‡$P = .046$, cholesterol 130-230 mg/dL *v* high cholesterol (>230).

than two thirds of their follow-up LDLC levels less than 75 mg/dL (Table 1 and Fig 1). This group of 32 men had low mean TC and LDLC (138 and 64 mg/dL) and TG (85 mg/dL) at entry (Table 1). However, there were significant increases (all $P = .0001$) in TC, LDLC, and TG levels on follow-up study to 163, 93, and 106 mg/dL (Table 1 and Fig 1).

Of these 32 men, nine were black and 23 were white. The mean entry TG level for these 32 men (85 ± 60) was lower ($P < .05$) than the level (115 ± 58) in 604 men with entry LDLC of at least 100 mg/dL (Fig 6).

There were 124 men with baseline LDLC of at least 75 but less than 100 mg/dL (Table 1 and Fig 2). On follow-up study, their TC increased from a mean of 160 to 177 mg/dL ($P = .0001$), LDLC increased from a mean of 89 to 107 mg/dL ($P = .0001$), TG increased from 100 to 113 mg/dL, and HDLC decreased from 51 to 49 mg/dL (Fig 2). Of these 124 men, 30 were black and 94 were white. They had lower entry Lp(a) (21 ± 24 mg/dL, $P < .05$) and higher HDLC (51 ± 13 mg/dL, $P < .01$) than the 604 men with entry LDLC of at least 100 mg/dL (Lp(a), 28 ± 27; HDLC, 48 ± 10 mg/dL) (Fig 6).

Table 3. Mean Entry and Follow-up LDL, HDL, TC, TG (all mg/dL), Apo B Phenotype, VNTR, and Apo E Genotype in 12 Men with Persistent Hypobetalipoproteinemia

Patient No.	Race/ Age (yr)	LDL		HDL		TC		TG		Apo B Phenotype	VNTR	Apo E Genotype
		Entry	Follow-up	Entry	Follow-up	Entry	Follow-up	Entry	Follow-up			
159	W/36	47	68	87	73	145	159	53	86	—	—	—
204*	B/39	45	64	53	56	140	138	208	90	—	—	—
221	B/23	54	59	61	64	123	131	39	41	—	—	—
370†	W/48	68	58	59	70	139	134	62	30	—	—	—
609	W/41	53	71	64	51	126	134	45	62	100/100	38/58	2/3
664	B/32	67	68	45	50	119	125	37	40	100/90	37/47	3/4
699	W/32	71	58	46	39	123	117	29	99	100/100	37/40	3/4
730	W/26	63	70	66	64	137	145	40	55	100/100	37/51	3/3
761	B/26	68	70	59	44	145	130	83	83	—	—	—
778	W/28	51	69	48	47	111	126	61	47	100/82	40/54	2/3
840	W/29	71	63	64	67	144	140	43	50	100/100	36/43	3/3
851	B/29	35	39	63	67	109	115	55	47	100/100	38/44	3/3

*Persistent hypobetalipoproteinemia anteceded death from melanoma by 9 years.
†Persistent hypobetalipoproteinemia anteceded death from alcoholism by 2 years.

We assessed the distribution of follow-up values for LDLC in all 168 firemen with initial LDLC less than 100 mg/dL (22% of 772 firemen who had entry and follow-up LDLC levels) (Fig 4). Of these 168 firemen, 48.2% had mean follow-up LDLC levels less than 100 and an additional 30.9% had follow-up LDLC less than 120 mg/dL (Fig 4).

Follow-up study of subjects with low entry TC (<130 and <150 mg/dL). Twenty-two firemen had initial TC less than 130 mg/dL; they had 64 follow-up visits (Fig 5). On follow-up study, mean TC remained less than 130 mg/dL in 27% of these men, and was 130 to 140 in 23% and 140 to 150 in 14% (Fig 5). Thus, 64% of these firefighters with initial plasma TC less than 130 mg/dL retained levels less than 150 mg/dL on follow-up study (Fig 5).

There were 71 men who had initial TC less than 150 mg/dL with 206 follow-up visits (Fig 5). Nearly half of them (45.1%) retained a TC level of less than 150 on follow-up evaluation, and another 18% had mean TC levels between 150 and 160 mg/dL (Fig 5).

Quetelet Index, fasting blood glucose, and systolic and diastolic blood pressure for varying degrees of entry and follow-up hypobetalipoproteinemia. At study entry, the group of 12 firemen with persistent hypobetalipoproteinemia was the thinnest of the three hypobetalipoproteinemic groups and remained the thinnest on follow-up study (Table 1). Although the three LDLC groups did not differ by virtue of fasting blood glucose and systolic blood pressure at entry and on follow-up study, diastolic blood pressure at entry and on follow-up study was lower in the 12 firemen with persistent hypobetalipoproteinemia (Table 1).

Overall, the men with low entry LDLC and persistently low LDLC appeared to be further protected against CHD by virtue of being relatively thin and having low Lp(a), high HDLC, low TG, and low diastolic blood pressure (Table 1 and Fig 6).

Hypocholesterolemia in NHANES I Men

Of 1,314 white men in NHANES I, one (.08%) was diabetic; none of 165 black men were diabetic. None of the NHANES I men with low serum TC were taking lipid-lowering drugs.

In the same age range as the firemen (26 to 46 years), 24 of 1,314 (1.8%) white NHANES I men had serum TC less than 130 mg/dL, as did six of 165 (3.6%) black men (Table 2). Of 468 white firemen ages 26 to 46, 14 (3%) had serum TC less than 130 mg/dL, as did six of 136 (4.4%) 26- to 46-year-old black firemen. Within race groups, the percentage of the firemen and men from NHANES I with TC less than 130 mg/dL did not differ ($\chi^2 = 2.24$, $P = .13$ for whites; $\chi^2 = .005$, $P = .9$ for blacks).

In 24 white NHANES I men aged 26 to 46 with serum TC less than 130 mg/dL, serum cholesterol was 121 ± 6 mg/dL (Table 2). The hypocholesterolemia was not due to calorie undernutrition, with the mean intake in these 24 men being 2,892 ± 1,139 cal/d, not significantly different ($P > .05$) from that of 929 white men who had entry serum TC between 130 and 230 mg/dL, whose mean daily caloric intake was 2,703 ± 1,144 (Table 2). Moreover, in 361 white men whose serum cholesterol was greater than 230 mg/dL, mean daily caloric intake was 2,579 ± 1,004, also not different from the 24 men with serum cholesterol less than 130 mg/dL (Table 2). White NHANES I men with entry serum cholesterol less than 130 mg/dL had mean protein, fat, and carbohydrate intakes of 118, 123, and 302 g/d; intakes were 104, 112, and 287 g/d for those with cholesterol levels of 130 to 230 mg/dl, and 102, 110, and 264 g/d for those with the highest serum cholesterol (>230 mg/dL) ($P > .05$ for all comparisons; Table 2). The 24 white men with serum TC less than 130 mg/dL were thinner ($P \leq .025$) (Quetelet Index, 2.48 ± .35) than the 361 with TC greater than 230 mg/dL (2.65 ± .36).

In 1,314 NHANES I white men, the distribution of habitual physical activity was significantly different among the three serum cholesterol categories (<130, 130 to 230, and >230 mg/dL) ($\chi^2 = 10.1$ [4*df*], $P = .04$), with higher habitual physical activity for subjects with serum cholesterol levels of 130 to 230 mg/dL versus greater than 230 mg/dL ($\chi^2 = 8.9$ [2*df*], $P = .012$). The percentage of white men in the habitual physical activity categories little-none, moderate, and much in the group with serum cholesterol levels of 130 to 230 mg/dL was 8.7%, 38.2%, and 53.1%, versus 12.5%, 42.9%, and 44.6% for greater than 230 mg/dL cholesterol ($\chi^2 = 8.9$ [2*df*], $P = .012$). Without age adjustment, the mean habitual activity scores were also

higher (2.44 ± 0.65) for serum cholesterol 130 to 230 mg/dL than for greater than 230 mg/dL (2.32 ± 0.69, $P = .003$) (Table 2), with similar results for age-adjusted habitual activity ($P < .05$). Mean unadjusted leisure time exercise scores were also higher (2.04 ± 0.76) for serum cholesterol 130 to 230 mg/dL than for greater than 230 mg/dL (1.95 ± 0.77, $P = .046$) (Table 2). The highest mean leisure time exercise score (2.13 ± 0.80) was found for white men in the lowest serum cholesterol group (<130 mg/dL) (Table 2).

There were six black men with serum TC less than 130 mg/dL, 3.6% of 165 black men aged 26 to 46 (Table 2). Compared with 113 black men with serum TC of 130 to 230 mg/dL and 46 with serum TC greater than 230 mg/dL, mean daily caloric intake and carbohydrate, fat, and protein intake were the lowest in men with the highest cholesterol levels (Table 2). As was the case in white men, black men with the highest serum cholesterol levels had the highest scores on the Quetelet Index (Table 2). Similar to findings in white men, neither protein, fat, carbohydrate, nor caloric undernutrition could account for the hypocholesterolemia in six black NHANES I men with entry TC less than 130 mg/dL (Table 2).

In 165 black men, the distribution of habitual physical activity and leisure time exercise, as well as the mean levels of physical activity and leisure time exercise, did not differ ($P > .1$) among the three serum cholesterol groups (Table 2).

DISCUSSION

The association between hypocholesterolemia and increased all-cause mortality previously reported in some[8,9] but not all[10] observational epidemiologic investigations probably reflects underlying secondary hypocholesterolemia,[11,12,27-35] caused by variegated diseases, substance abuse, and alcoholism, all of which would be expected to increase all-cause mortality. Causes of acquired hypocholesterolemia and hypobetalipoproteinemia include nonspecific chronic illness and undernutrition or malnutrition (often alcoholic),[8,9,36] severe infection,[30] HIV infection,[27] malabsorption,[28] cancers, adenomas, and leukemias,[29,31,32,35] repetitive plasmapheresis,[33] and hyperthyroidism. Within this frame of reference, of 12 persistently hypobetalipoproteinemic men in the current study, two (17%) had acquired hypobetalipoproteinemia that anteceded death from melanoma by 9 years and death from alcoholism by 2 years. Low serum cholesterol concentrations in noninstitutionalized subjects generally do not reflect inadequate caloric or nutrient intake,[37] a finding replicated in NHANES I men in the current study.

Although hypocholesterolemia and hypobetalipoproteinemia[27-36] are commonly acquired, they can also often reflect a common, highly penetrant, autosomal dominant trait,[1-7,20,38-42] familial hypobetalipoproteinemia, which is characterized by longevity and relative freedom from CHD morbidity and mortality and is not associated with increased all-cause mortality.[1] Of 772 firemen studied, two (0.26% of the cohort, 17% of those with persistent hypobetalipoproteinemia) had this beneficial[1] inherited trait. Most commonly, familial hypobetalipoproteinemia is discerned during population screening.[1-4,38,40,41] Although the prevalence of familial hypobetalipoproteinemia has been estimated to be approximately 0.5%,[1-5,38,40] its appearance (particularly in healthy subjects) is often associated with surprise or consternation.[41]

Using the Lipid Research Clinics population prevalence study's fifth percentile for LDLC (≤75 mg/dL) and TC (≤130 mg/dL),[23] there were 44 firemen whose initial LDLC was less than 75 mg/dL (5.7% of the cohort of firemen studied). Of 772 firemen with entry and follow-up LDLC levels, there were 12 (1.6%) with persistent low LDLC. Two of the 12 with persistent hypobetalipoproteinemia had truncated apo B, indicating familial hypobetalipoproteinemia[20,42] (.26% of the cohort, 17% of those with persistent hypobetalipoproteinemia). As summarized by Schonfeld,[42] "... some forms of familial hypobetalipoproteinemia (FHBL) are genetically linked to various truncation-producing mutations of the gene. To date, approximately 30 deletion, insertion, or non-sense mutations have been identified resulting in apoB truncations ranging in size from apoB-9 to apoB-89." Two of 12 firemen with persistent hypobetalipoproteinemia were heterozygous for the mutant apo E2 allelle (E2/3) associated with low LDLC levels.[43,44] Apo E2–containing lipoproteins bind poorly to LDL receptors, with resultant upregulation of the number/activity of the receptors and a reduction in LDLC.[43,44] One of 12 subjects with persistent hypobetalipoproteinemia had two heritable causes of low LDL, truncated apo B and the E2/3 genotype.[42-44] Four of 12 with persistent hypobetalipoproteinemia had neither truncated apo B nor the E2 genotype to account for the low LDL. We postulate that their persistently low LDL was associated with hypoabsorption of dietary cholesterol,[45] or was possibly because they were faithful vegetarians.

The 12 men with persistent hypobetalipoproteinemia had mean entry LDLC of 58 mg/dL and follow-up LDLC of 63 mg/dL. Unlike the other two groups of firemen with less persistent hypobetalipoproteinemia, mean follow-up LDLC in these 12 men remained unchanged from entry levels. On the other hand, LDLC increased 18 to 29 mg/dL in the other two groups of men with less persistent hypobetalipoproteinemia, reflecting regression toward the mean, where, on repeated measurement, values at the tails of the distribution tend to migrate toward the group mean.[46] At study entry, the 12-man group with persistent hypobetalipoproteinemia was the thinnest of three hypobetalipoproteinemic groups and remained the thinnest on follow-up study. Moreover, their diastolic blood pressure at baseline and follow-up evaluation was lower than in the other hypobetalipoproteinemic groups. As a group, these men also had low Lp(a), high HDLC, and low TG accompanying their low LDLC. However, Averna et al[6] have recently shown that patients heterozygous for familial hypobetalipoproteinemia do not have low Lp(a) levels. Beyond their low LDLC, firemen with persistent hypobetalipoproteinemia (1.6% of the cohort) appeared to be further protected against CHD by being relatively thin and having low Lp(a), high HDLC, low TG, and low diastolic blood pressure.

In the age range 26 to 46 years (comparable to that of the firefighters), 1.8% of white NHANES I men had TC less than 130 mg/dL, as did 3.6% of the black men. The prevalence of hypocholesterolemia in NHANES I men did not differ from that in firemen. In NHANES I men aged 26 to 46 with TC less than 130 mg/dL, hypocholesterolemia was not due to protein, fat, carbohydrate, or calorie undernutrition, which did not differ in men with entry-level cholesterol less than 130, 130 to 230, or greater than 230 mg/dL in agreement with findings by Goichot

et al.[37] In NHANES I, white men in the lowest serum cholesterol group (<130 mg/dL) were thinner than those in the highest cholesterol group (>230 mg/dL) but their mean caloric intake was higher (2,892 *v* 2,579 cal/d). In NHANES I and speculatively elsewhere, the paradox that men who weigh the least and have the lowest serum cholesterol levels (<130 and 130 to 230 mg/dL) ingest the most calories is probably accounted for by higher levels of habitual physical activity and leisure time exercise. In white men in NHANES I, the distribution of habitual physical activity was shifted toward higher levels for serum cholesterol values of 130 to 230 mg/dL versus greater than 230 mg/dL. Mean habitual physical activity and leisure time exercise levels were also higher in men with serum cholesterol levels of 130 to 230 mg/dL versus greater than 230 mg/dL.

There appear to be racial differences in the prevalence of hypocholesterolemia. Black men comprised 18% of the firemen cohort but 42% of those with persistent hypobetalipoproteinemia; among NHANES I subjects, 3.6% of black men were hypocholesterolemic, versus 1.8% of white men.

Decreasing LDLC by simvastatin and pravastatin, respectively, in the recent blinded, placebo-controlled 4S and Western Scotland studies[16,17] produced a reduction in all-cause mortality and no increase in suicide or homicide mortality. In epidemiologic studies, unless persistent hypobetalipoproteinemia reflects an underlying disease, alcoholism, undernutrition, malnutrition, etc., it is often heritable, and may be associated with a reduced likelihood of CHD, an increased longevity,[1] and, speculatively, a decrease in all-cause mortality.

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