Lipids and Risk of Coronary Heart Disease
The Framingham Study

William P. Castelli, MD, Keaven Anderson, PhD, Peter W. F. Wilson, MD, and Daniel Levy, MD

Total cholesterol level is significantly related to risk of coronary heart disease (CHD), adjusting for other risk factors in women 50 to 79 years old and in men aged 50 to 64 years, at P < .001. Determining the levels of lipoproteins such as low-density-lipoprotein (LDL) cholesterol and high-density-lipoprotein (HDL) cholesterol improves the prediction of risk. Triglycerides are independently related in women at all ages but miss statistical significance in the multivariate studies in men. The total cholesterol–HDL cholesterol ratio is another powerful predictor at all ages in women and is the only lipid predictor independently related to CHD in men 65 to 80 years old. Inspection of the age-specific association of cholesterol with risk in men and women also reveals that the absolute rates of disease worsen with age. Ann Epidemiol 1992;2:23–28.

KEY WORDS: *Total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol–HDL ratio, coronary heart disease.*

INTRODUCTION

The Framingham Study was started in 1948 to obtain prospective measures on a cohort of healthy, free-living Americans to understand their relationship to the subsequent development of atherosclerotic vascular disease, particularly coronary heart disease (CHD), stroke, and peripheral vascular disease. The purpose of this article is to examine the most recent evidence relating measures of the blood lipids to the development of CHD. The population is currently passing through the older ages, with the youngest cohort at entry in Framingham arriving at the mid to late 70s. This provides much more data on the impact of the various blood fat levels in the older age groups. Total cholesterol levels, which in earlier publications (1) did not appear to predict risk of CHD over the age of 50, started to do so some 10 years later with more followup (2). This article extends these observations and, as in the other articles, not only explores the risk attributable to total cholesterol level but also expands the view to look at the way in which total cholesterol is carried in the blood, namely, in the lipoproteins, which turn out to be much better predictors of CHD risk at any age but particularly in the elderly.

METHODS

The Framingham Study has followed a cohort of 5209 men and women who were selected largely through a process of random allocation from 10,000 men and women residents in the town in 1948 and who were between the ages of 30 and 62. Of these

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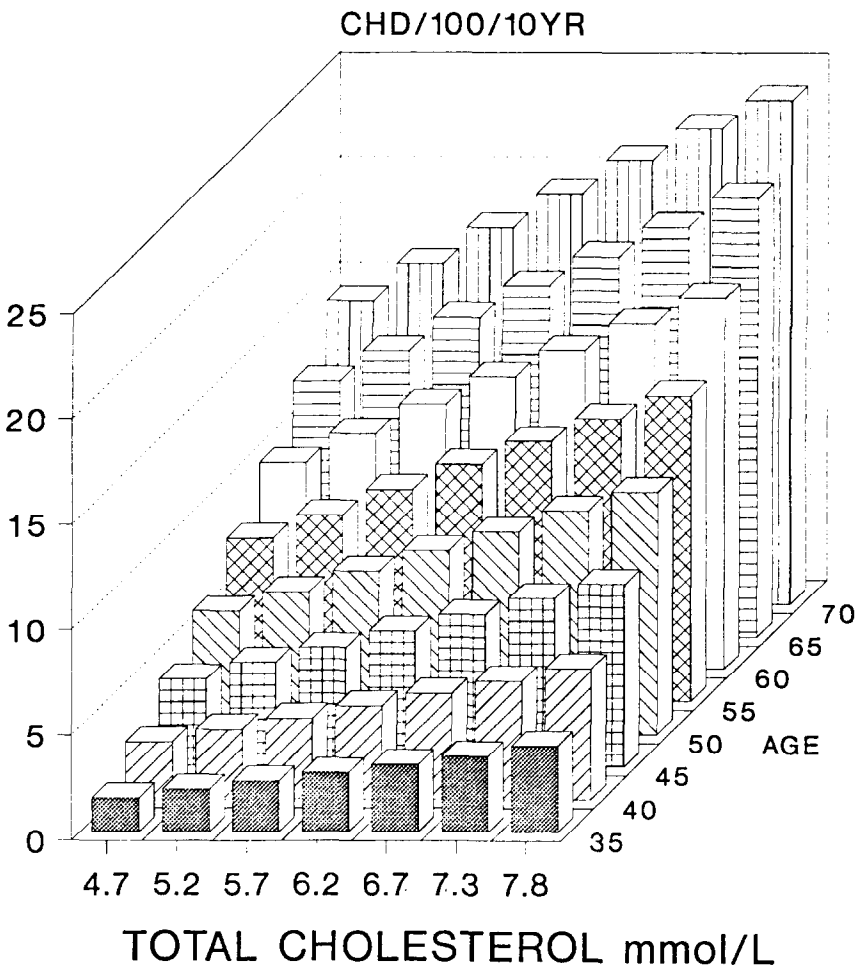

FIGURE 1 The rate of coronary heart disease in 10 years, according to age and level of total serum cholesterol in men with the major risk factors low (5).

5209 men and women, 5127 were free of cardiovascular disease at entry. These people have been seen every 2 years to determine whether they had developed cardiovascular disease in the interim. During the study period, many new measures were introduced to study their association with subsequent development of cardiovascular disease, always beginning with the 2-year format. CHD, as used in this article, is the sum of different end points related to coronary disease. These end points include two death end points, sudden death and nonsudden death from CHD. Three morbid end points, angina pectoris, coronary insufficiency, and myocardial infarction, have also been identified. The diagnoses are made using the evidence obtained every 2 years at a comprehensive medical examination, as well as medical reports from hospitalizations, physician office visits, and interrogation of family members. A panel of three physicians reviews all the data to assess which end point is achieved, using standard criteria that are updated and described periodically (3). Cholesterol levels were measured using the

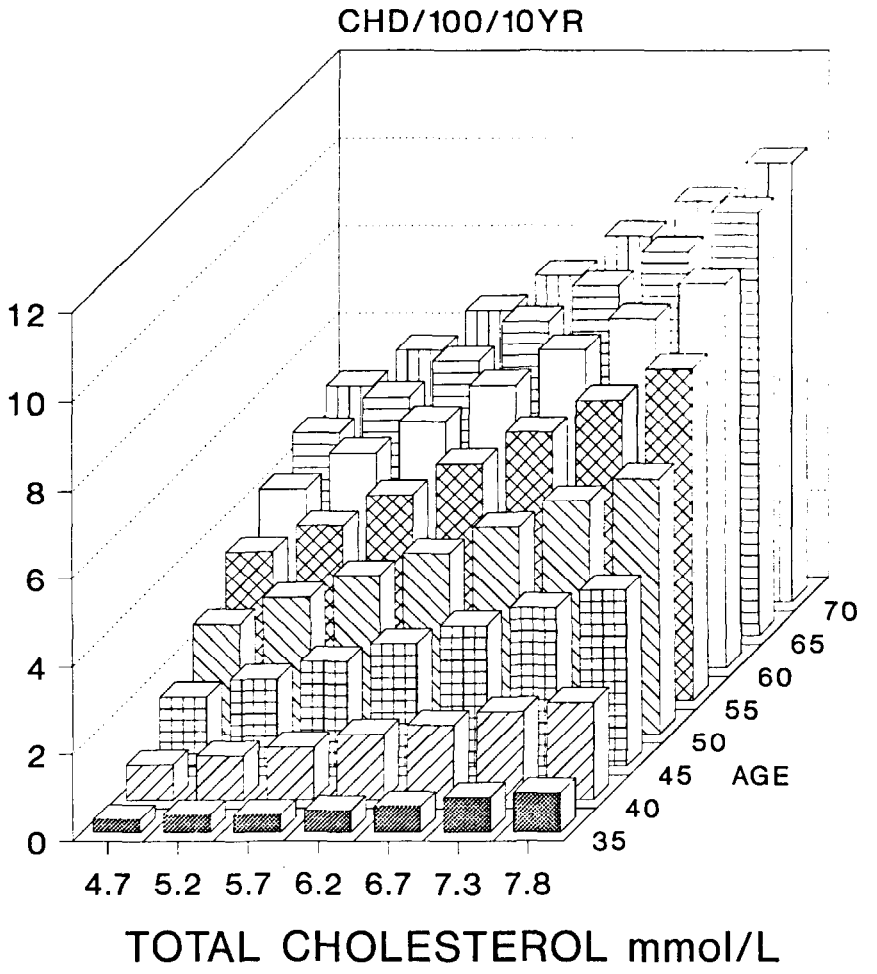

FIGURE 2 The rate of coronary heart disease in 10 years, according to age and level of total serum cholesterol in women with the major risk factors low (5).

Abell-Kendall method; triglycerides levels, using the Kessler-Lederer technique; and lipoprotein measures, by methods described in the manual of operations of the Lipid Research Clinics Program (4). The population used for the calculations in the 50- to 79-year age group included 922 men and 1295 women free of cardiovascular disease and cancer (other than basal cell carcinoma) at the time lipoprotein fractions were measured, between 1968 and 1973. Men and women were studied separately, as were those below younger than 65 and those 65 and older, at baseline examination. Subjects were divided into groups using tertiles of the measurements of interest. Direct age-adjusted incidence rates were computed from age-specific Kaplan-Meier survival curves within 5-year age groups. Tests for any difference and trend between groups were performed using log-rank tests, stratifying by 5-year age groups. Tests for associations between the continuous lipoprotein measurements and incidence were carried out using the score test from the Cox proportional hazards survival model, again stratifying

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TABLE 1 Lipids and coronary heart disease (CHD). Multivariate regression coefficients, excluding prevalent CHD, blocked by 5-year age groups, controlling for systolic blood pressure, glucose, and cigarette smoking

	Men		Women	
	50–64 y	65–79 y	50–64 y	65–79 y
Total cholesterol	.67	.27	2.51[a]	.98
LDL cholesterol	.66[b]	.25	2.19[a]	1.13[b]
HDL cholesterol	−93[c]	−.18	−1.05[c]	−1.11[b]
Triglycerides	.24	−.18	.48[b]	− .69[b]

[a] $P < .001$.
[b] $P < .05$.
[c] $P < .01$.

by 5-year age group. For other models presented in this article, a parametric regression model was used for risk estimation of probabilities of disease given different risk factor levels, as recently described in an updated coronary risk profile (5).

RESULTS

Based on the new regression model, the rate of CHD according to total cholesterol is described in Figures 1 and 2, in men and women who have a low-risk profile, that is, low systolic blood pressure and blood glucose concentration, average values of HDL cholesterol, no left ventricular hypertrophy, and no current smoking history. These figures allow one to look at age-specific rates of CHD according to levels of total cholesterol. One can see a rise in the absolute rate of CHD with a rise in age and level of cholesterol. A slightly different view is seen if one simply uses the raw data and looks at all men and women followed for 30 years, grouped according to their total cholesterol level and age. These people have much higher absolute rates of CHD than do the groups represented in Figures 1 and 2, but with more numbers the association of total cholesterol level adjusted by the other major risk factors reaches a $P < .001$ for women 50 to 79 years old and for men under the age of 65. For men 65 and older, the relationship of total cholesterol level to CHD gives a P value of .068(6).

Using the 16-year follow-up of lipoprotein measures collected in the late 60s, one can see (Table 1) the statistical association of total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels in men and women, 50 to 79 years old. These represent multivariate logistic coefficients adjusted for systolic blood pressure, cigarette smoking, glucose levels, and the fractions reported, blocked by 5-year age groups, excluding prevalent CHD. In this analysis with fewer subjects, it is apparent that lipoprotein measures, including triglyceride levels, predict CHD in women between 50 and 79 years old. The lipoprotein levels, except the triglycerides, predict CHD in men under age 65 but not those 65 or older.

A series of Kaplan-Meier curves used to portray the duration of survival without CHD over a period of 15 years are portrayed in Figures 3 and 4. These figures show the survival time for tertiles of the total cholesterol–HDL cholesterol ratio in men and women 65 and older. As shown, the total cholesterol–HDL cholesterol ratio is the only lipid attribute that discriminates in a statistically significant way CHD-free survival time in men 65 or older. This measure is the most powerful lipid predictor in men and women, both 65 and older and under the age of 65.

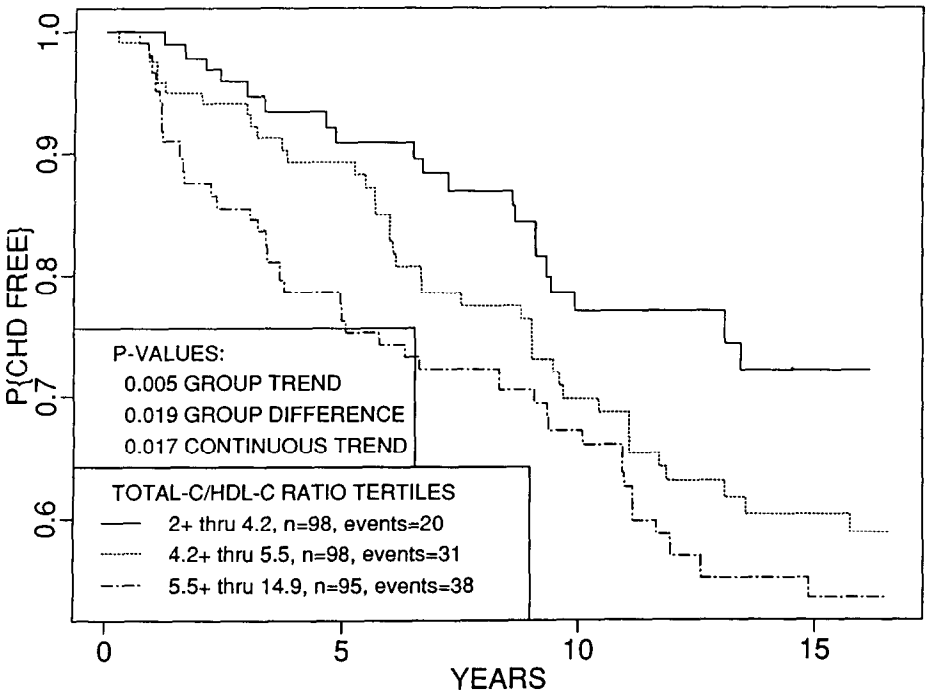

FIGURE 3 Kaplan-Meier curves of survival time without CHD by tertile of the total cholesterol–HDL cholesterol ratio in men, over a 15-year period.

DISCUSSION

These data demonstrate that lipids, portrayed primarily by lipoprotein measures, contribute to the incidence of CHD up to the age of 80 in men and women. Whereas LDL cholesterol, HDL cholesterol, and triglyceride levels and the total cholesterol–HDL cholesterol ratio play this role in women between 50 and 79 years old, it is only the total cholesterol–HDL cholesterol ratio that reaches statistical significance in men 65 and older. However, for men and women up to the age of 65, many lipid measures predict the risk of subsequent CHD. The weakest of these lipid measures to predict risk is total cholesterol level and yet most who dispute a role of lipids in people over the age of 50 have only used arguments supported by analyses that never go beyond looking at the total cholesterol level (7).

The contribution of the lipoprotein analyses to knowledge of risk should not be understated. Lipoprotein levels become especially important when one considers that the average person who develops CHD in our society has a cholesterol level of about 5.8 mmol/L (225 mg/dL). The average person at the same age who does not develop CHD has only a slightly lower total cholesterol level. Most of the heart attacks in our society occur in people who have a total cholesterol level between 5.2 mmol/L (200 mg/dL) and 6.2 mmol/L (240 mg/dL). LDL cholesterol is a better predictor in these ranges than is total cholesterol, but both HDL cholesterol and the ratio of total cholesterol to HDL cholesterol are much more powerful predictors than is LDL cholesterol. The ratio of total cholesterol to HDL cholesterol eventually wins out as the only lipid predictor of CHD in men aged 65 to 79 years.

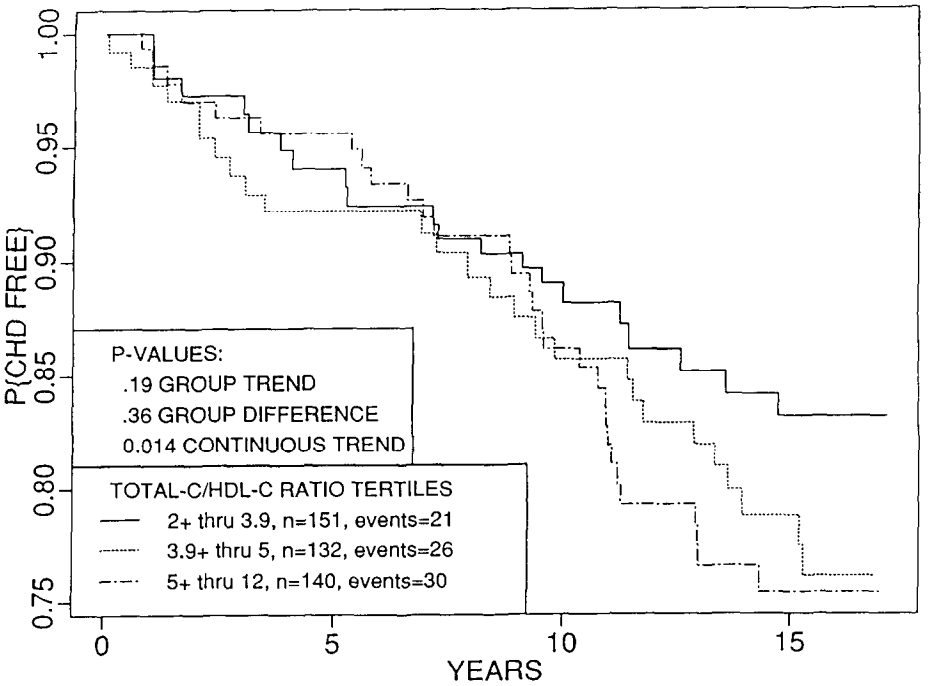

FIGURE 4 Kaplan-Meier curves of survival time without CHD by tertile of the total cholesterol–HDL choleserol ratio in women, over a 15-years period.

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