CHOLESTEROL AND CORONARY ARTERY DISEASE: AGE AS AN EFFECT MODIFIER

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Abstract:
An elevation of serum cholesterol has been one of the more frequently cited risk factors for coronary heart disease, found in both case-control and cohort studies. As a result, this country has undertaken massive screening of adults older than 20 years of age in an attempt to identify those persons with cholesterol levels greater than 200 mg/dl, and follow up with an active approach for intervention. The suggested cutpoints for borderline (200-240 mg/dl), and definite (≥240 mg/dl) hypercholesterolemia have been applied to all age groups despite suggestions of a diminution of risk conferred by cholesterol in the elderly. This study of 2544 white men undergoing coronary angiography shows that for all men, aged 25-84 years, plasma cholesterol levels were associated with an increase in coronary artery occlusion ($r_s = 0.15$, $p < 0.01$). However, when stratified by age, this association held only for the younger men, the association diminishing to near zero in the oldest age group. The negative interaction between cholesterol levels and age in predicting coronary artery disease proved highly significant (p <0.00)) in multivariable linear regression analysis, suggesting that cholesterol levels are much less predictive of coronary artery disease in the elderly as compared to the young. These results point to the need for a more finely tuned set of criteria for the evaluation of hypercholesterolemia, one that takes into account the age of the screenee.
Key Words: Cholesterol, Coronary disease, Age factors, Risk factors, Coronary angiography, Cross-sectional studies

Article:
INTRODUCTION
Of the risk factors that increase the risk for coronary heart disease (CHD), serum cholesterol is among the most frequently cited in the literature. This relation has been shown in numerous case-control and cohort studies. As a result, this country has undertaken mass efforts to screen its population for persons with elevated lipid levels with hopes of preventing or delaying the onset of CHD [1]. To obtain these goals, it has been suggested that men and women at least 20 years of age who have total cholesterol levels of ≥200 mg/dl evaluated for risk of CHD. Further, for persons with cholesterol levels ≥240 mg/dl, an intensive intervention program should be initiated, involving a stepped approach starting with dietary interventions and progressing to drug therapy. While an admirable goal, the consequences of such programs have come into question [2]. The value of the suggested approach of predetermined cut-points for referral and therapy for men and women of all ages is especially questionable. While the relationship between total cholesterol and subsequent coronary events appears to hold for young to middle-aged men, there have been suggestions that this relationship may change in importance in different age groups.

The Framingham Study found that total cholesterol levels were less predictive of overt CHD in older men and women as compared to younger [3-7]. However, subfractions of serum cholesterol, in the high density lipoproteins (HDL) and low density lipoproteins (LDL), remained predictive for CHD events in both men and women over the age of 50. This diminution of risk has been found in other samples using CHD as an endpoint [9-11], and in studies of more restricted endpoints as well [12, 13]. Case—control studies have reported similar diminutions of risk imparted by total cholesterol levels [15, 16]. The timing of the measurement of cholesterol may be important but the age-related decrease in risk has been found in cross-sectional studies [14, 15] where cholesterol levels are measured at or near the time of the event as well as in studies measuring lipids 5 [5, 6, 13] to 10 or more years [10, 12, 16] previously.

However, not all studies have shown this attenuation of risk. Other observations have ranged from no association of cholesterol level with CHD [16], to consistent positive associations across age strata [17-20]. One further study noted that the crude association between total cholesterol and death from ischemic heart disease was not significant in men over the age of 65 [21]. However, after controlling for other risk factors, a one standard deviation increase in total cholesterol imparted a statistically significant 1.4-fold increase in risk for death from ischemic heart disease. These studies have all been based on 8-12 years of follow-up.

Because no firm conclusion concerning the relation between elevated cholesterol and the risk of CHD among older persons can be drawn from these studies, the efficacy of screening the elderly for elevated cholesterol levels remains questionable. One possible explanation for the mixed results is that these previous studies may have been limited due to their outcome measures of angina or mortality. These crude measures could have allowed for misclassification bias, either random (unbiased) or biased.

Therefore, to reduce the chance of these biases, information on the degree of coronary occlusion obtained from angiography studies of patients undergoing coronary arteriography was utilized to study age-specific cholesterol associations. With this more detailed and accurate assessment of the severity and extent of disease, further light is shed on the possible differences in the importance of plasma cholesterol levels for predicting coronary artery disease (CAD) among different age groups.

METHODS

Patient population

The study sample comprised 2544 white men entered in the Milwaukee Cardiovascular Data Registry from 1977 to 1986 following coronary angiography at St Luke's Hospital or Zablocki VA Medical Center in Milwaukee. The arteriography was performed as described by Sones and Shirey [22] or Judkins [23] and the films were reviewed independently by a cardiologist and radiologist. Their interpretations were made blind to knowledge of risk factors and were recorded on standardized forms. The degree of coronary occlusion was measured as suggested by Rowe *et al.* [24], except that the scale was inverted. Therefore, patients with no occlusion were assigned a score of 0, and patients with complete occlusion of the three main coronary arteries (right, left anterior descending, and circumflex) were assigned a score of 300.

Risk factor data

At the time of angiography, patients were requested to complete a comprehensive questionnaire detailing medical history and potential risk factors for CHD. Information collected included smoking history, history of hypertension or diabetes, alcohol consumption, and anthropometric measures including height and weight. In addition, fasting blood samples were drawn prior to angiography and analyzed for cholesterol and triglyceride content. Plasma levels of cholesterol and triglycerides were measured with automated procedures [25-27] in a laboratory that has been standardized and is monitored by the Centers for Disease Control. Smoking history, both past and present was combined into a 5-point scale taking into account both intensity and duration of the habit, with 1 representing no smoking and 5, two packs or more per day for at least 20 years [28].

Statistical analyses

Several statistical methods were employed to assess the relationship of independent risk factors with occlusion score for the entire study sample and within age strata. Descriptive statistics were calculated for variables within age-specific strata and for the entire study cohort. Spearman and Pearson correlations were calculated for risk factors with both age and occlusion score for the entire group; within each age-specific stratum, correlations were computed for each risk factor with occlusion score. Full-factorial analyses of variance were used to assess interactions between risk factors and age to predict occlusion, and between risk factors themselves while controlling for age. Risk factors that were measured on a continuous scale were coded into quintiles with cutpoints based on the entire study sample.

Multivariable linear regression models were constructed within each age-specific stratum to assess the importance of each risk factor in predicting occlusion score independent of other risks. Models were constructed with cholesterol levels and age coded as continuous variables and alternatively as indicator variables for quintiles or 10-year age groups. Similarly, other potential confounders were entered into the model as continuous variables or indicators for categories. A final model was constructed for the entire sample entering age, cholesterol, and the interaction between the two as continuous variables. Potential confounders of the cholesterol—occlusion relationship were similarly entered as continuous variables when possible. Within age-specific strata, similar models were constructed, with the exception of the addition of the interaction terms for age and cholesterol. These terms did not add significantly to the models within age strata. Because of the large sample size, alpha levels for statistical significance were set at $p < 0.01$ for analyses of the entire sample. Marginal significance was deemed to be $0.01 < p <$ **0.10.**

RESULTS

Characteristics of the study sample are shown in Table l. The average age of these men was 57 ± 9 years (mean ± SD). Occlusion scores for the sample ranged from 0 to 295 with a mean of 136 ± 82. Plasma cholesterol levels ranged from 95 to a high of 506 mg/dl with a mean of 223 ± 46 mg/dl. Stratifying by 5-year age groups, the mean occlusion score was generally higher in successively older age groups, ranging from 91 ± 81 in the 25-35-year-olds to 152 ± 80 in the men aged 66-70 years. Fifteen percent of the study sample had occlusion scores of 0, and the proportion generally decreased with age, 35% in the youngest group to 13% in the oldest. Cholesterol levels, on the other hand, increased from 223 ± 62 in the 25-35-year-olds to 237 ± 47 in the men aged 41-46 years and then decreased successively to 212 ± 48 mg/dl in men aged 71-84 years. The proportion of persons with diabetes and hypertension generally increased with age while body mass index (BMI) differed little among age groups.

Table 1. Characteristic of study sample by age group (mean and standard deviation)

	Risk factor								
	n	Occlusion score	Plasma TC (mg/dl)	Plasma TG (mg/dl)	BMI (kg/m^2)	Alcohol (oz/wk)	Smk score	Htn	Dbt
Total sample	2544	136 (82)	223 (46)	184 (115)	26.9 (3.7)	5.4 (7.3)	3.3 (1.4)	42	10
25–35	37	91 (81)	223 (62)	166 (89)	26.8 (3.6)	5.3 (8.9)	3.2 (1.1)	32	3
36–40	71	105 (91)	228 (49)	169 (76)	26.7 (4.2)	5.5 (7.5)	3.1 (1.3)	44	3
41–45	157	119 (87)	237 (47)	188 (86)	27.0 (2.9)	6.1 (6.7)	3.5 (1.3)	34	4
46–50	290	127 (80)	224 (46)	199 (140)	27.0 (3.7)	6.4 (8.6)	3.4 (1.4)	36	7
51–55	456	133 (79)	228 (46)	198 (126)	27.0 (3.5)	6.4 (9.2)	3.6 (1.4)	39	9
56–60	580	139 (79)	224 (49)	189 (140)	21.2 (3.9)	5.2 (6.1)	3.3 (1.4)	46	12
61–65	481	148 (80)	222 (44)	175 (84)	26.9 (3.9)	4.7 (6.4)	3.3 (1.4)	47	12
66–70	312	152 (80)	212 (42)	169 (94)	26.4 (3.6)	3.9 (5.4)	3.0 (1.4)	43	15
71–84	160	127 (87)	212 (48)	164 (85)	26.7 (3.6)	5.2 (7.5)	3.2 (1.4)	49	5

TC—total cholesterol; TG—triglyceride; BMI—body mass index; Smk Score—smoking history score (1–5); Htn—report of hypertension; Dbt—report of diabetes.

Table 2 presents the bivariate associations of risk factors with occlusion score. For brevity, only the Spearman correlations are presented as not all associations measured could be assumed to come from a bivariate normal distribution, and Pearson correlations yielded similar results.

Table 2. Association of risk factors with coronary occlusion and age [Spearman correlation coefficients (*n*)]

	Occlusion	Age
Plasma cholesterol	0.15** (2544)	−0.11** (2544)
Plasma triglycerides	0.13** (2544)	−0.09** (2544)
BMI	−0.01 (2446)	−0.04 (2446)
Alcohol consumption	−0.07** (2359)	−0.10** (2359)
Smoking history	0.09** (2467)	−0.07** (2467)
Report of hypertension	0.06** (2544)	0.08** (2544)
Report of diabetes	0.11** (2544)	0.07** (2544)
Age	0.10** (2544)	1.00 (2544)

*$p < 0.05$; **$p < 0.01$.

For the entire sample, the strongest association with occlusion lies with cholesterol levels with a Spearman correlation coefficient of 0.15 ($p < 0.01$). Smoking history, triglyceride levels, and report of hypertension or diabetes were all significantly associated with occlusion, whereas BMI showed no association. Alcohol intake was inversely associated with occlusion ($p < 0.01$).

Table 3. Association between risk factors and occlusion by 5-year age groups (Spearman correlation coefficients)

	Age category								
	−35	−40	−45	−50	−55	−60	−65	−70	−80
TC	0.42**	0.36**	0.38**	0.20**	0.18**	0.18**	0.09*	0.07	0.01
TG	0.40*	0.32*	0.16*	0.21**	0.16**	0.14**	0.14**	0.00	0.06
BMI	0.05	0.23	−0.16	−0.05	−0.00	0.02	0.03	−0.03	−0.06
ALCOHO	0.12	0.02	−0.05*	0.00	−0.07	−0.08	−0.04	−0.14*	−0.08
SMOKE	0.26	0.18	0.27**	0.08	0.11*	0.04	0.13**	−0.01	0.06
HYPERT	0.05	0.24*	−0.02	0.03	0.05	0.08	0.07	−0.03	0.08
DIABET	0.08	0.01	0.11	0.09	0.11*	0.09*	0.11*	0.09	0.10

*$p < 0.05$; **$p < 0.01$; TC—plasma cholesterol; TG—plasma triglycerides; BMI—body mass index; ALCOHO—alcohol intake; SMOKE—smoking index; HYPERT—hypertension (yes/no); DIABET—diabetes (yes/no).

The age-specific correlations are presented in Table 3. For both total cholesterol and triglyceride levels, the association with occlusion is weaker in older age groups. Cholesterol levels are highly correlated with occlusion in the youngest age group (r_s = 0.42, $p < 0.01$). This association is diminished in the 511-55-year-olds (r_s = 0.18, $p < 0.01$), and falls to a non-significant 0.01 in men aged 70-84 years. The association between triglycerides and occlusion shows a similar pattern, with a correlation of 0.40 ($p < 0.05$) in the 26-35-year-olds, 0.16 in the 51-55-year-olds and 0.05 in the 70-84-year-olds. BMI showed no clear pattern of association with occlusion across age strata, while the report of diabetes showed fairly consistent associations with occlusion.

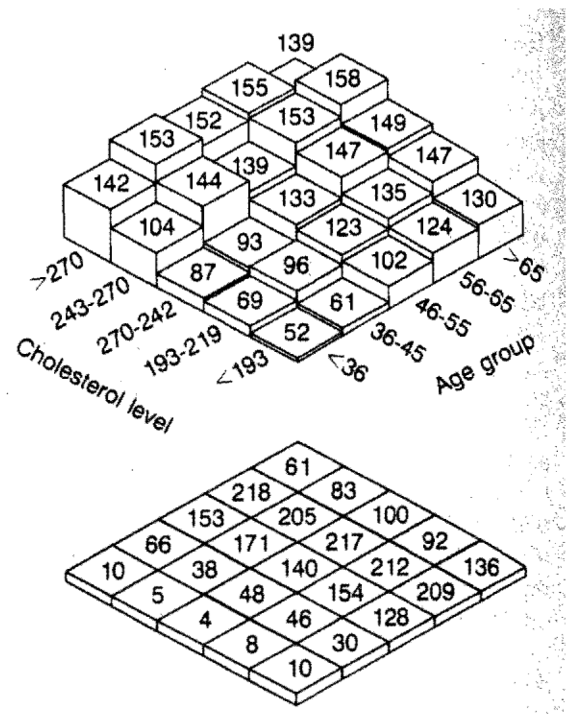

Fig. 1. Stereogram of occlusion score stratified by age group and cholesterol levels. Mean occlusion score by age and cholesterol level. Occlusion score represented by height of cell and given in upper diagram. Sample sizes given within cells of lower diagram. Interaction term by analysis of variance statistically significant ($F = 1.76$, $p < 0.03$).

In examining the relationship between age, cholesterol, and occlusion score jointly, the interaction between age and cholesterol level was found to be marginally significant by analysis of variance (F = 1.76, $p < 0.03$), with age blocked in 10-year age groups and cholesterol levels in quintiles. The stereogram in Fig. 1 depicts this changing relationship across the five age- and cholesterol level- specific strata. In general, occlusion increases with age and with cholesterol level. However, in the older age groups, the relationship between cholesterol and occlusion is attenuated.

Table 4. Regression models of occlusion on plasma cholesterol score (CR) stratified by age

	Unadjusted coefficient	Adjusted coefficient	R^2	ΔR^2	n
Overall*					
No interaction	0.267	0.242	0.088	0.016	2198
With interaction		0.964	0.092	0.210†	2198
Age-specific strata					
25–40	0.611	0.204	0.136	0.009	34
40–50	0.659	0.525	0.174	0.066	202
50–60	0.296	0.236	0.068	0.016	658
60–70	0.258	0.224	0.049	0.014	904
70–83	0.115	0.098	0.071	0.003	400

Unadjusted coefficient: Bivariate relationship.
Adjusted: for triglycerides, BMI, alcohol intake, smoking history, year of catheterization, age, age^2, and report of hypertension or diabetes.
R^2 multiple coefficient of determination for entire model.
ΔR^2 change in multiple coefficient of determination due to cholesterol level.
*See text for explanation.
†Change due to cholesterol level and its interaction with age.

This can be seen again in the multivariable analysis presented in Table 4. For the entire study sample, the unadjusted regression coefficient for plasma cholesterol in predicting occlusion score is 0.267. Adjusting the model for triglyceride level, BMI, alcohol intake, smoking history, year of catheterization, age, age^2, and report of diabetes or hypertension modifies the coefficient slightly to 0.242. The model explains 8.8% of the variation in occlusion for the sample. When the interaction between age and cholesterol level is added, the multiple coefficient of determination increases to 0.092, of which 23% can be attributed to the addition of cholesterol and its interaction with age to the model. The interaction term for age and cholesterol proved highly significant (b = —0.0127, $p < 0.001$) and must be included in interpreting the adjusted coefficient for the entire sample. For example, at the mean age of 57.3 years, the effective coefficient for cholesterol level, including the interaction term, becomes 0.24. At age 40, the coefficient is 0.46; at age 70, 0.076.

When stratified by age, the changing association is quite evident. The coefficient for cholesterol is the largest in the 40-50-year-olds for both the crude bivariate association and after adjustment for other risk factors. In successively older age groups, a unit increase in cholesterol level is predictive of smaller increases in occlusion score. The adjusted coefficient ranges from 0.525 in the 40-50-year-olds, to 0.098 in the men aged 70-83 years. Similarly, cholesterol levels become less predictive of occlusion score in successively older age groups. In the 40-50-yearolds, the entire model has a multiple coefficient of determination of 0.174, of which 0.066 is contributed by the addition of cholesterol to the model. The magnitude of change in R^2 diminishes in older age groups, to 0.014 in the 60-70- year-olds and to 0.003 (4.2% of the entire model) in the oldest age group.

DISCUSSION

The present study demonstrates clearly that .the cross-sectional relationship between total cholesterol and coronary occlusion diminishes With age. There is less occlusion per unit in crease in cholesterol levels in successively older age groups. Further, assuming a linear model, the strength of the association between cholesterol and occlusion also diminishes. That is to say, cholesterol becomes less predictive of occlusion in older age groups. This change in relationship, however, must be explored further so as to ascertain its importance.

The results of this study are not unlike those observed in other studies. The Framingham, Busselton, and Los Angeles studies all found that cholesterol levels were less predictive of CHD in older as compared to younger age groups [3-10]. However, these results differed from some other studies that found either no relation [16], an increase in risk conferred by cholesterol levels in older age groups [17-20], or a slight decrease in risk [21]. These discrepant findings could be due to imprecise outcome measures used. CHD is usually a continuous developmental process of atherosclerosis and/or thrombosis, as opposed to a simple dichotomy. In studies based on outcomes of CHD mortality or clinical manifestations, there may be room for noise to enter statistical models [29]. The present study allows for the examination of the role of plasma cholesterol levels with a potentially direct measure of the continuous process of atherosclerotic heart disease. This measure, however, is not without problems owing to the possibility of remodelling in diseased and collateral vessels.

Although the results of this investigation provide strong evidence for a modification of the relationship between cholesterol levels and occlusion owing to age, the etiologic importance of this effect can be debated. It has been suggested that the change may not be due to a change in the biological effect of cholesterol in the disease process, but may be artifact owing to the cumulative effect of other factors in the aged [30], with cholesterol being one component cause of several sufficient causes of CAD [31]. If the number of sufficient causes lacking cholesterol as a component increased with age, cholesterol would appear to lose strength as a causative agent. Another alternative explanation is that the observed change in relationship may reflect a "harvesting effect". Men who are prone to elevated cholesterol levels and subsequently overt CHD may be dying sooner than others. As a consequence, the surviving men in the older age groups may not be representative of all men initially at risk in this and other studies. That is to say that there may be another form of hypercholesterolemia that is not associated with CAD. It may be that the coronary arteries in the aged are less susceptible to the atherogenic effects of cholesterol. Conversely, the composition of lipoproteins may be different among the aged secondary to dietary or metabolic changes; these lipoproteins may be less atherogenic. As men who have the atherogenic form may succumb to their disease early, the remaining men are not at the same risk of death from CHD. Further, the surviving men are at greater risk of death due to other causes compared to younger men and thus may be removed from subsequent followup due to competing risks. Alternatively, the non-atherogenic hypercholesterolemia may be of late-onset and may not be identifiable at younger ages. As this study is based on cross-sectional data, we cannot determine whether or not the elevated cholesterol levels represent a lifelong pattern, or a late-onset form of abnormality. Simply put, the observed change of effect in this study may be due to a selection artifact in the population rather than physiological change. In addition, because there is more disease among the aged (i.e. higher occlusion scores) any association may appear to be decreased for arithmetic reasons secondary to less variability in occlusion score. This could also play a role in the diminished association between triglycerides and occlusion score among the older age groups as well.

Another factor that must be taken into account when interpreting these results is that this study sample is probably not representative of the general population [29]. The study sample is drawn from patients referred to two medical centers for cardiac catheterization and imaging. Preferential referral of certain patients could result in a distortion of the measure of effect. Young men may have been more likely to have been referred for catheterization if they had elevated cholesterol as compared to older men with otherwise similar indications. This could result in an inflation of the correlation coefficients in the younger age groups, but should not impact the functional relationship (regression coefficients) between cholesterol levels and CAD. In these regards, cholesterol levels, in this study sample generally decreased across groups with advancing age, in direct opposition to population trends [32]. The mean cholesterol level for the youngest age groups fell near the eightieth percentile of the white males screened in the Lipid Research Clinics Prevalence Study, while successively older age groups neared the median. However, this sample did show some characteristics that would be expected in the general population. In general, the proportion of patients reporting hypertension or diabetes increased with age. Similarly, the amount of CAD as measured by occlusion score increased with age. It should be noted that cholesterol levels were positively associated with disease for all patients and within age strata as in population-based studies. Further, for the subset of men having had the HDL subfraction measured, the inverse relationship between HDL-cholesterol levels and occlusion remained predictive for all age strata as in previous studies [6, 10] (data not shown). Therefore, it does not appear that the men in this study were atypical with respect to relationships between total cholesterol and CHD.

Barrett-Connor has suggested the possibility of a shift in risk factor distribution in recent years, such that persons with high levels of risk factors are no longer weeded out through selective mortality by age 50 or 65 [21]. The evidence presented herein would contradict this conclusion. There is a definite decrease in importance of total cholesterol levels in predicting coronary occlusion. Further, there was no interaction between year of catheterization and cholesterol level in predicting occlusion (data not shown). That is to say that the age-specific relationships between cholesterol levels and coronary occlusion did not change within the time frame of this study.

If the weight of evidence presented herein and from other studies is accepted to indicate a decrease in relative risk of CAD for a given level of plasma cholesterol in older age groups, this attenuated risk should be taken into account for individual patients in determining intervention strategies. Perhaps, it may be more appropriate to evaluate patients for elevated levels of cholesterol in terms of relative cutpoints [2], based on age-specific lipid levels, rather than the current absolute cutpoints across all age groups. However, it should also be remembered that a smaller increase in relative risk in the elderly could still represent a substantial increase in absolute risk as the incidence of CHD is so great. Further, as noted by Epstein, while predictive power may be lost with total cholesterol levels, a greater good may be achieved through the possibility of disease regression [33] with appropriate interventions.

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