RELATION OF TRIGLYCERIDE LEVELS TO CORONARY ARTERY DISEASE: THE MILWAUKEE CARDIOVASCULAR DATA REGISTRY

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Freedman DS, Gruchow HW, Anderson AJ, Rimm AA, Barboriak JJ. Relation of triglyceride levels to coronary artery disease: The Milwaukee Cardiovascular Data Registry. American Journal of Epidemiology 127:1118-1130, 1988.

Abstract:
Although levels of triglycerides have consistently shown a strong association with cardiovascular disease In both case-control and cohort studies, it remains controversial whether this relation exists Independently of levels of cholesterol and other risk factors. The association of arteriographically documented coronary artery disease with plasma levels of triglycerides, total cholesterol, and high density lipoprotein (HDL) cholesterol was therefore examined in 5,216 white adults (81% were male) referred to two Milwaukee hospitals between 1972 and 1988. Elevated levels of triglycerides were related to the extent of coronary artery disease (estimated using the total number and severity of stenoses). In both sexes, this association existed independently of total cholesterol, age, obesity, hypertension, smoking, and alcohol consumption. In addition, the association between triglycerides and coronary artery occlusion was strongest at total cholesterol levels ≤250 mg/dl. However, both +stratified and regression analyses Indicated there was no residual association between triglyceride levels and occlusion after controlling for HDL cholesterol. (Levels of HDL cholesterol and triglycerides showed a moderate Inverse association: r = -0.39 to -0.51.) These results indicate that the association between coronary artery occlusion and levels of triglycerides is indirect, and that the disparate findings of earner studies may have resulted from not controlling for HDL cholesterol.
Keywords: cholesterol; coronary disease; lipoproteins, HDL; triglycerides

Article:
Much evidence supports an association between elevated levels of triglycerides and coronary heart disease. Diseases associated with high triglyceride levels (e.g., diabetes mellitus, obesity, chronic renal disease, and certain primary hyperlipoproteinemias) carry an increased risk of cardiovascular disease (1-3). Persons with angiographically-documented coronary artery disease (4-7) and survivors of myocardial infarctions (8-10) have consistently been found to have elevated levels of triglycerides. In addition, several prospective studies have found levels of triglycerides to be predictive of cardiovascular disease in at least some race-sex groups (11-18), and an experimental model for the possible atherogenic effects of hypertriglyceridemia has been pos*tulated* (19). Persons with mild hypertriglyceridemia (250-500 mg/dl) have approximately a twofold increased risk for cardiovascular *disease* (2).

Nevertheless, the independent relation of triglyceride levels to coronary heart disease remains controversial (20). Levels of triglycerides and high density lipoprotein (HDL) cholesterol are inversely related (with reported correlation coefficients ranging from -0.21 to -0.65 (21)), and low levels of HDL cholesterol have been related to cardiovascular disease in both clinical (22, 23) and prospective (24, 25) studies. The relation between triglyceride levels and cardiovascular disease may therefore be indirect, and has been eliminated by control-ling for HDL cholesterol (20, 24).

However, the inherent problems in controlling for closely related variables in regression analysis have been emphasized (26, 27), and recent analyses suggest that levels of triglycerides may be an independent risk factor

for coronary heart disease in men with HDL cholesterol levels below 40 mg/dl and in women (28). Results from the Paris Prospective Study also suggest an interaction between levels of cholesterol and triglycerides in men: triglycerides may be predictive of coronary heart disease only at low (<220 mg/dl) serum levels of cholesterol (18).

However, possible interactions between levels of triglycerides, total cholesterol, and HDL cholesterol with angiographically-documented coronary artery disease have not been examined. The objective of the current study, therefore, is to examine these interrelations (using both stratification and regression analyses) in a clinical database containing over 5,000 white adults.

MATERIALS AND METHODS

Population and disease status

Established in 1972, the Milwaukee Cardiovascular Data Registry is a clinical database consisting of patients referred to selected Milwaukee hospitals (St. Luke's and Wood Veterans Administration Hospital) for diagnostic coronary angiography. Indications for coronary angiography include 1) unstable angina pectoris, 2) moderate to severe stable angina, 3) previous myocardial infarction, and 4) recurrent chest pain of unknown origin. Current analyses are restricted to whites who underwent arteriography between 1972 and 1986; other groups (including blacks, Asians, American Indians, and Hispanics) represented less than 5 per cent (n = 312) of all patients. An additional 357 patients are excluded because either age (at time of catheterization) or race was not recorded Plasma levels of both total cholesterol and triglycerides were available for 7,529 patients. The extent of atherosclerotic disease in the main coronary arteries and branches was evaluated, without knowledge of risk factor data, by a radiologist and cardiologist experienced in the interpretation of arteriograms. Disagreements were resolved by consensus after consultation with a second cardiologist. Although possible variability in these readings was not assessed, others (29, 30) have reported a moderate degree of intra- and interobserver reproducibility.

Results were recorded according to a procedure suggested by Rowe et al. (31); however, the scale was inverted. The severity (per cent reduction in lumen diamet.er) of each occlusion in the three principal coronary arteries (right, left anterior descending, and left circumflex) was estimated. An (overall) occlusion score of 0 reflects no observed occlusion of any artery, while a maximum score of 300 represents total occlusion of the major vessels. Because the left main coronary artery supplies both the circumflex and anterior descending arteries, occlusions in this artery were doubled (e.g., a 50 per cent reduction received a score of 100). The number of diseased (>75 per cent reductions in lumen diameter) vessels was also recorded.

Risk factor information

Medical records and questionnaires were used to obtain data concerning demographics, weight, height, alcohol consumption, smoking history, history of hypertension, previous myocardial infarction, angina, diabetes mellitus, and medication use. Persons were excluded from the current analyses if they reported use of thyroid or cholesterol-lowering medication, use of oral contraceptives or sex hormones, a history of diabetes mellitus, or hypo- or hyperthyroidism. These restrictions eliminated 1,649 persons; diabetics (n = 669) and persons using cholesterol-lowering drugs (n = 495) represented the majority of exclusions.

For the remaining 5,216 persons, height and weight were used to calculate Quetelet index (kg/m^2) (32). A five-point smoking scale, reflecting both frequency and duration of smoking (1: never smoked, 5: smoked two or more packs daily for 20 years or 1.5 packs daily for 30 years) was calculated as previously described (33). Alcohol intake (including beer, wine, and mixed drinks) was converted to ounces of absolute alcohol per week. Complete information on all covariates was available for 4,432 (85 per cent) persons.

Following an overnight fast, blood samples were collected before angiography. Plasma levels of total cholesterol and triglycerides were measured using automated procedures (34-36) in a laboratory that has been standardized by the Centers for Disease Control and is monitored by its surveillance program. Beginning in

1977, HDL cholesterol was measured using procedures employed by the Lipid Research Clinics (36); these levels were available for 1,123 persons.

Mild hypertriglyceridemia (250-500 mg/ dl) was present in 17 per cent of all males and 10 per cent of females; plasma triglyceride levels above 500 mg/dl were observed in 2 per cent of males and 1 per cent of females. Of persons with plume cholesterol levels below 250 mg/dl, mild hypertriglyceridemia was present in 12 per cent of males and 6 per cent of females.

Statistical analyses

Bivariate associations among coronary artery occlusion and various risk factors were assessed using Spearman correlations, and although several variables were not normally distributed, Pearson correlations yielded similar results. (Because of the numerous correlations examined and the large sample size, p values <0.001 were considered to be statistically significant in these analyses.) To examine the independent effects of triglycerides and cholesterol, mean occlusion scores were first calculated following a cross-classification of these two lipids. (Categories were chosen to yield roughly equivalent numbers of persons in each stratum.) Analysis of covariance was then used to examine main effects and possible interactions after controlling for age, Quetelet index, alcohol consumption, smoking history, and hypertension.

The interaction between plasma cholesterol and triglyceride levels was further examined in a series of regression models. A cholesterol level of 250 mg/dl was first used to dichotomize plasma cholesterol in the interaction term (0: ≤250 mg/dl; 1: >250 mg/dl). In addition, separate regression analyses were performed within the two cholesterol strata. Assumptions concerning normality and homoscedasticity (constant error variance) of residuals were verified in all regression analyses.

The independence of HDL cholesterol levels and triglycerides was further examined in persons with plasma total cholesterol levels ≤250 mg/dl. A series of multiple regression equations was again calculated, and the tolerance (37) of each regression coefficient was calculated. Tolerance is defined as $1 - R^2$ for a variable regressed on all other independent variables, and indicates the amount of variability that is "unexplained" by the other independent variables. (A low tolerance means that the independent variable is almost a linear combination of other independent variables.) Mean occlusion scores were also calculated after a cross-classification of plasma levels of total cholesterol, cholesterol, and triglycerides.

Persons with extreme occlusion scores (0 or >200) were used in an additional graphic analysis. After adjusting occlusion for the effects of other risk factors, disease status (low or high occlusion scores) was plotted against levels of triglycerides and HDL cholesterol. Mean values of these two plasma lipids were used to divide the data into four areas. The odds (38) of severe:minimal disease within each quadrant are shown, and odds ratios for severe disease were calculated.

RESULTS

Table 1 shows mean values of selected characteristics. The maximum coronary artery occlusion score was 295 in males and 285 in females, with approximately 18 per cent (n = 771) of males and 47 per cent (n = 455) of females having no observable occlusion. Although age and cholesterol levels showed no difference between the sexes, males had higher plasma levels (+38 mg/dl) of triglycerides and lower levels (-9 mg/dl) of HDL cholesterol. In addition, males tended to consume more alcohol and were heavier (past) smokers than were females. Male-female differences in the extent of occlusion were reduced by controlling for age, total and HDL cholesterol, triglycerides, Quetelet index, alcohol consumption, smoking history, and hypertension, but a higher occlusion score was still evident in males (122 vs. 89).

Spearman correlation coefficients are shown in table 2. Associations between risk factors and the occlusion score were generally stronger in females, although the ratio of total to HDL cholesterol showed the highest correlation with the extent of occlusion in both sexes. Levels of plasma cholesterol and triglycerides showed similar associations with occlusion (r = 0.16 and 0.14 in males, r = 0.32 and 0.30 in females). In addition, levels

of triglycerides were correlated positively with total cholesterol (r = 0.38 to 0.39) and inversely with HDL cholesterol (r = -0.39 to -0.51). In general, Quetelet index, hypertension, smoking history, and alcohol consumption were associated with levels of both triglycerides and HDL cholesterol.

TABLE 1

Mean levels of selected variables: the Milwaukee Cardiovascular Data Registry, 1972–1986†

	Males (n = 4,251)	Females (n = 965)
	Mean ± standard deviation	
Occlusion score	131±86	73±86
No. of diseased vessels	1.2±1.0	0.6±0.9
Age (years)	55±9	56±10
TC (mg/dl)	234±50	236±52
TG (mg/dl)	189±124	151±89
HDL-C (mg/dl)‡	38±11	47±14
TC/HDL-C‡	6.0±1.8	5.2±1.8
Quetelet index (kg/m²)	26.6±3.5	25.9±5.0
Alcohol (oz/week)	5.7±7.1	2.3±4.5
Smoking history	3.4±1.4	2.2±1.4
Cigarette smoking	%	%
Never	19	47
Past	63	35
Current	18	18
Hypertensive	38	48
Angina	58	62
Myocardial infarction	47	30

† Abbreviations: TC, serum total cholesterol; TG, serum triglycerides; HDL-C, high density lipoprotein cholesterol.

‡ Restricted to the 883 males and 240 females with available information.

Associations between triglyceride levels and coronary artery occlusion were then examined within strata of other variables. Occlusion was more strongly related to plasma triglyceride levels in persons with-out a previous myocardial infarction than in those who reported a myocardial infarction (r = 0.18 vs. 0.07, males; r = 0.28 vs. 0.22, females). Although a stronger association between triglyceride levels and occlusion was also seen in males who did not use 0-blockers (r = 0.17 vs. 0.05), a comparable trend was not seen in females (r = 0.25 vs. 0.33). No differences in the magnitudes of the associations were seen across strata of smoking, alcohol consumption, and use of diuretics or antihypertensive agents.

TABLE 2

Associations† among the examined characteristics‡: the Milwaukee Cardiovascular Data Registry, 1972–1986

Characteristic	Occlusion score	Age	TC	TG	HDL-C§	TC/HDL-C§	Quetelet index	Hypertension	Alcohol consumption
Age									
Males	0.11*								
Females	0.24*								
TC									
Males	0.16*	−0.13*							
Females	0.32*	0.12*							
TG									
Males	0.14*	−0.12*	0.38*						
Females	0.30*	0.12*	0.39*						
HDL-C§									
Males	−0.20*	−0.01	0.21*	−0.39*					
Females	−0.27*	−0.01	0.08	−0.51*					
TC/HDL-C§									
Males	0.25*	−0.05	0.47*	0.56*	−0.72*				
Females	0.38*	0.05	0.52*	0.63*	−0.78*				
Quetelet index									
Males	−0.02	−0.03	0.04	0.23*	−0.19*	0.20*			
Females	0.05	0.04	0.14*	0.29*	−0.24*	0.27*			
Hypertension									
Males	0.04	0.08*	−0.03	0.10*	−0.07	0.05	0.11*		
Females	0.20*	0.13*	0.11*	0.20*	−0.26*	0.30*	0.19*		
Alcohol consumption									
Males	−0.09*	−0.08*	0.06*	0.07*	0.21*	−0.14*	0.03	0.02	
Females	−0.07	−0.10*	−0.02	−0.04	0.21*	−0.18	−0.10	−0.11*	
Smoking history									
Males	0.09*	−0.05*	0.06*	0.11*	0.01	0.02	0.06*	−0.03	0.11*
Females	0.16*	−0.10	0.04	0.16*	0.04	−0.08	−0.01	−0.12*	0.17*

* $p < 0.001$.

† Spearman correlation coefficients.

‡ Abbreviations: TC, serum total cholesterol; TG, serum triglycerides; HDL-C, high density lipoprotein cholesterol.

§ Correlations involving HDL-C are restricted to the 883 males and 240 females with available information.

Table 3 shows mean (unadjusted) occlusion scores after levels of total cholesterol and triglycerides were cross-classified. Main effects of both lipids were statistically significant ($p < 0.01$) in all four sex-age groups. However, negative interactions between levels of cholesterol and triglycerides were also observed. For example, in older males with plasma cholesterol levels ≤210 mg/dl, the *mean* occlusion score increased by 27 (from 116 to 143) as plasma triglyceride levels increased. However, at plasma cholesterol levels >250 mg/dl, the association between levels of triglycerides and occlusion was inconsistent. In addition, among young females who had plasma triglyceride levels >195 mg/dl, the highest mean occlusion score was seen at low levels of total cholesterol.

Various combinations of total cholesterol and triglycerides were then used in regression models to predict the extent of occlusion (table 4). Even after adjusting for the nonlipid risk factors, plasma levels of both cholesterol and triglycerides were significant predictors of coronary artery disease (modeb3 1 and 2). Furthermore, each lipid component was independently related to occlusion (model 3); the regression coefficient for triglycerides, however, was reduced after controlling for total cholesterol. (In model 3, standardized regression coefficients for males were 0.15 (cholesterol) and 0.06 (triglycerides); for females, 0.24 and 0.08.) The interaction between cholesterol and triglycerides was then assessed in model 4, and in males the association between triglyceride levels and occlusion was strongest at cholesterol levels ≤250 mg/dl. Although the negative, dichotomous interaction was not statistically significant in females ($p = 0.36$), a continuous interaction term (formed by multiplying levels of the two lipids together) approached statistical significance ($p = 0.07$, data not shown).

TABLE 3

Mean levels of coronary artery occlusion according to plasma levels of total cholesterol and triglycerides (mg/dl), by sex and age group: the Milwaukee Cardiovascular Data Registry, 1972–1986

Plasma total cholesterol	Age group					
	≤55 years			>55 years		
	Plasma triglycerides			Plasma triglycerides		
	≤130	131–195	>195	≤130	131–195	>195
Males						
≤210	86 ± 86† (292)	121 ± 86 (188)	117 ± 83 (123)	116 ± 92 (398)	120 ± 83 (251)	143 ± 79 (143)
211–250	106 ± 85 (205)	129 ± 86 (219)	127 ± 83 (268)	129 ± 88 (269)	154 ± 79 (279)	156 ± 78 (208)
>250	123 ± 85 (108)	134 ± 84 (248)	148 ± 79 (420)	149 ± 88 (129)	155 ± 82 (217)	149 ± 79 (286)
Females						
≤210	16 ± 47 (116)	22 ± 42 (35)	112 ± 105 (12)	35 ± 61 (93)	84 ± 81 (47)	101 ± 100 (16)
211–250	53 ± 73 (59)	65 ± 85 (43)	82 ± 92 (26)	81 ± 84 (82)	73 ± 84 (63)	123 ± 92 (33)
>250	75 ± 85 (48)	68 ± 77 (43)	95 ± 86 (45)	94 ± 86 (65)	117 ± 95 (72)	132 ± 90 (67)

† Values are mean ± standard deviation; sample sizes are in parentheses.

Regression analyses, stratifying by sex and total cholesterol, confirmed that a negative interaction existed between total cholesterol and triglycerides. At low levels (≤250 mg/dl) of total cholesterol, regression coefficients for triglycerides were 0.08 (males) and 0.16 (females); $p < 0.001$ for both values. In contrast, at total cholesterol levels >250 mg/dl, the corresponding regression coefficients for triglycerides were 0.03 (males) and 0.01 (females).

To assess the independent relations of triglycerides and HDL cholesterol levels with coronary artery disease, an analogous set of analyses were then performed in normocholesterolemic persons (plasma total cholesterol ≤250 mg/dl) who had HDL cholesterol measurements (table 5). In these persons, levels of triglycerides and total cholesterol were each independently related to occlusion in males, whereas (possibly because of the smaller sample size) only triglycerides were a significant predictor of occlusion in females. However, triglyceride levels were no longer related to occlusion in either sex after controlling for HDL cholesterol (model 4).

TABLE 4

Multiple linear regression analyses predicting occlusion score by plasma levels of total cholesterol and triglycerides: the Milwaukee Cardiovascular Data Registry, 1972–1986

Model§	Independent variables					
	Males (n = 3,630)†			Females (n = 802)†		
	Cholesterol (mg/dl)	Triglyceride (mg/dl)	Interaction‡	Cholesterol (mg/dl)	Triglyceride (mg/dl)	Interaction‡
1	0.29¶ (0.24, 0.35)			0.44 (0.34, 0.55)		
2		0.08 (0.05, 0.10)			0.16 (0.10, 0.23)	
3	0.26 (0.20, 0.32)	0.04 (0.02, 0.06)		0.40 (0.29, 0.51)	0.08 (0.01, 0.15)	
4	0.33 (0.25, 0.40)	0.07 (0.04, 0.10)	−0.05 (−0.08, −0.02)	0.44 (0.30, 0.58)	0.10 (0.02, 0.18)	−0.04 (−0.12, 0.04)

† Restricted to persons with complete information for all covariates.

‡ Interaction between cholesterol and triglycerides. Value is 0 if plasma cholesterol ≤ 250 mg/dl; value is equal to triglyceride level if cholesterol > 250 mg/dl.

§ All models include age, Quetelet index, smoking history, hypertension, and alcohol consumption as covariates.

¶ Value is regression coefficient; 95 per cent confidence limits are given in parentheses.

TABLE 5

Multiple linear regression analyses predicting occlusion score by plasma levels of total cholesterol, triglycerides, and HDL cholesterol in normocholesterolemic† patients: the Milwaukee Cardiovascular Data Registry, 1972–1986

Model	Independent variables (mg/dl)					
	Males (n = 622)‡			Females (n = 168)‡		
	Total cholesterol	Triglyceride	HDL cholesterol	Total cholesterol	Triglyceride	HDL cholesterol
1	0.48§ (0.27, 0.69)			0.34 (−0.06, 0.73)		
2		0.12 (0.04, 0.21)			0.19 (0.04, 0.34)	
3	0.43 (0.22, 0.65)	0.09 (0.0, 0.18)		0.27 (−0.13, 0.67)	0.18 (0.03, 0.33)	
4	0.66 (0.44, 0.88)	−0.06 (−0.16, 0.04)	−2.16 (−2.83, −1.49)	0.42 (0.01, 0.83)	0.07 (−0.10, 0.24)	−1.34 (−2.37, −0.31)

† Plasma total cholesterol ≤ 250 mg/dl.

‡ Restricted to persons with complete information on all independent variables. All models include age, Quetelet index, smoking history, hypertension, and alcohol consumption as covariates.

§ Value is regression coefficient; 95 per cent confidence limits are given in parentheses.

Mean occlusion scores (adjusted for total cholesterol and nonlipid risk factors) are shown for ea.ch sex in table 6, according to plasma levels of triglycerides, total cholesterol, and HDL cholesterol. Although several of the cell sizes were small, coronary artery occlusion was inversely related to HDL cholesterol in nine of the 10 possible comparisons. (The one exception was ob-served in males with low levels of total cholesterol, but high levels of triglycerides.) In contrast, the association between levels of triglycerides and occlusion was less consistent; no association was seen in males who had low levels of total and HDL cholesterol, or in females with high levels of total cholesterol. The five females with high total cholesterol levels, but low levels of both HDL cholesterol and triglycerides, all had occlusion scores above 171, emphasizing the relative importance of HDL cholesterol.

Persons with either severe (>90th percentile, males; >80th percentile, females) or minimal (<10th percentile, males; <20th percentile, females) coronary artery disease were then included in an additional analysis. These extreme occlusion scores were first adjusted for total cholesterol and other risk factors, and then plotted according to plasma levels of both HDL cholesterol and triglycerides (figure 1). (This analysis would not reveal possible interactions with total cholesterol.) Mean levels of triglycerides and HDL cholesterol were used to divide the figure into four areas, and the odds of severe:minimal disease are shown for persons in each quadrant.

TABLE 6

Adjusted† mean levels of coronary artery occlusion in normocholesterolemic‡ persons, according to levels of plasma triglycerides, total cholesterol, and HDL cholesterol: the Milwaukee Cardiovascular Data Registry, 1972–1986

Sex	Triglycerides (mg/dl)	Total cholesterol (mg/dl)			
		≤210 mg/dl		211–250 mg/dl	
		HDL cholesterol (mg/dl)		HDL cholesterol (mg/dl)	
		≤40	>40	≤40	>40
Males	≤130	124 ± 91§ (70)	89 ± 89 (77)	126 ± 75 (23)	98 ± 99 (53)
	131–195	129 ± 76 (97)	106 ± 84 (30)	143 ± 70 (58)	132 ± 71 (37)
	>195	124 ± 81 (78)	139 ± 99 (9)	149 ± 76 (70)	111 ± 72 (20)
Females	≤130	69 ± 99 (6)	38 ± 62 (37)	212 ± 37 (5)	63 ± 63 (33)
	>130	86 ± 73 (24)	52 ± 58 (14)	100 ± 92 (25)	70 ± 85 (24)

† Values have been adjusted for age, Quetelet index, smoking history, hypertension, and alcohol consumption.
‡ Plasma total cholesterol ≤ 250 mg/dl.
§ Values are mean ± standard deviation; sample sizes are in parentheses.

As compared with triglycerides, levels of HDL cholesterol showed a stronger association with disease status. For example, in males with low plasma triglyceride levels, the odds of severe disease in persons with low (≤38 mg/dl) levels of HDL cholesterol was 3.3 (1.47/0.44) times the odds in persons with high levels of HDL cholesterol. (A similar odds ratio, 3.4 (2.70/0.80), was seen between low levels of HDL cholesterol and severe disease in males with high triglyceride levels.) In contrast, high (vs. low) triglyceride levels were associated with an odds ratio of 1.8. Females showed similar associations between low HDL cholesterol and severe disease (odds ratios of 2.7 and 4.4), whereas odds ratios between triglyceride levels and occlusion were 1.6 and 1.0.

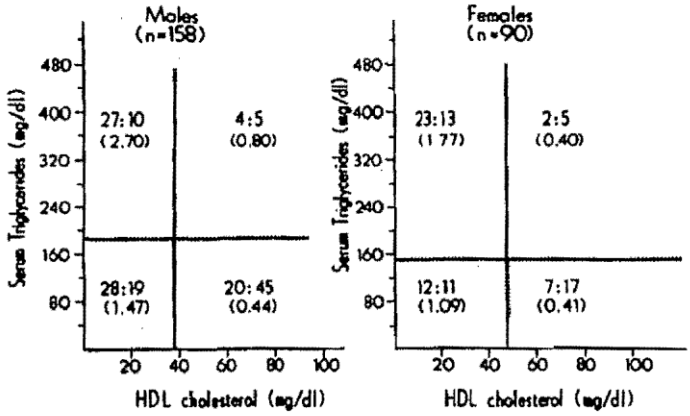

FIGURE 1. Odds of severe:minimal coronary artery disease according to levels of triglycerides and HDL cholesterol. Within each sex, occlusion scores were first adjusted for the effects of total cholesterol, hypertension, Quetelet index, age, smoking history, and alcohol consumption. Persons with extreme occlusion scores (<10th percentile vs. >90th percentile, males; <20th percentile vs. >80th percentile, females) were then plotted according to levels of both HDL cholesterol and triglycerides. (All nondiseased males had an occlusion score of 0, while diseased males had occlusion scores above 200; corresponding cutpoints in females were 50 and 150.) Dashed lines represent mean levels, and the odds of severe:minimal disease are shown for each quadrant.

DISCUSSION

Despite the possibility of various biases in studies of persons undergoing arteriography, associations between risk factors and anatomically documented coronary artery disease have generally confirmed associations seen in prospective studies (39). The current results indicate that although the relation of triglycerides with coronary artery disease exists independently of serum total cholesterol in normocholesterolemic persons, there is little residual association after controlling for HDL cholesterol. Although levels of HDL cholesterol and triglycerides

are inversely correlated, the extent of coronary artery occlusion is primarily related to decreased levels of HDL cholesterol, rather than to increased triglycerides.

Bivariate associations between levels of triglycerides and cardiovascular disease have been reported 'in numerous prospective and retrospective studies (4-18), and even after controlling for total (or low-density lipoprotein) cholesterol, associations have persisted in some (5, 8, 12, 13, 16-18), but not all studies. However, the relation of triglycerides to cardiovascular disease may vary according to the clinical endpoint (myocardial infarction, cerebral stroke, or cardiovascular mortality) studied (12, 13, 16, 16), and it is also possible that triglyceride levels are predictive of coronary heart disease in women but not in men (11, 14).

Based on results of the Paris Prospective Study, Cambien et al. (18) suggested that these different findings may be partly due to a stronger association of triglycerides with cardiovascular disease at low (vs. high) levels of total cholesterol. Results of the current analyses, along with studies of myocardial infarction survivors (9, 10), an autopsy study of adolescents (40), and a recent report from the Lipid Research Clinics (41) also emphasize the importance of triglycerides at low levels of total cholesterol. However, a recent prospective study of normocholesterolemic men (42) found that mild hypertriglyceridemia was not predictive of cardiovascular disease mortality. (Hypertriglyceridemia was approximately three times more prevalent in the current study.) The use of different clinical end-points may also contribute to the disparate results. The relation of cholesterol to sudden cardiac death may be weaker than its association with myocardial infarction (43), and analogous differences may exist for triglycerides. Therefore, the atherogenic effects of triglycerides may be best assessed using angiographically defined coronary artery disease as an endpoint.

Hulley et al. (20) have suggested that controlling for levels of HDL cholesterol might eliminate any residual association between triglyceride levels and cardiovascular disease, and the current results support this hypothesis. However, the problems in controlling for a closely related variable in regression have been emphasized (26, 27), and alternative methods have been suggested. Abbott and Carroll (26) have proposed that the relation between a predictor (triglycerides) and dependent variable might be more accurately represented by its projected slope, which controls for only the nonredundant information in the covariate (HDL cholesterol). However, only a moderate correlation exists between levels of triglycerides and HDL cholesterol, with over 65 per cent of the variability in plasma triglyceride levels unexplained by HDL cholesterol and other variables in the current study. Furthermore, after controlling for HDL cholesterol by stratification in the current study, triglycerides showed little residual association with occlusion, similar to results of the Cooperative Lipoprotein Phenotyping Study (8).

Several methodological questions arise in angiographic studies of coronary artery disease. Because deaths (either sudden or due to myocardial infarction) occur, enrolled cases may not be representative of all per-sons with coronary artery disease, and the resulting distributioru3 of lipids and coronary artery disease may be attenuated. In addition, since elevated levels of cholesterol or triglycerides may influence the decision to perform diagnostic angiography, persons presenting with angina pectoris but without coronary artery disease may have elevated lipid levels.

The inherent limitations of arteriograms in assessing atherosclerotic lesions should also be considered. Variability exists in their interpretation, with interobserver agreement reported to be as low as 63 per cent for lesions in the left anterior descending artery (29, 30). In addition, as compared with histologic findings, angiography tends to systematically underestimate the amount of disease (44). However, possible selection and misclassification biases in the current study would have resulted in a similar underestimation of the *actual* relation of coronary artery disease to levels of both triglycerides and HDL cholesterol. It is interesting that the association between triglycerides and occlusion was strongest in persons without a previous myocardial infarction; the occurrence of clinical disease may have led to lifestyle changes which altered triglyceride levels.

Nevertheless, many of the observed associations correspond closely to those observed in population-based studies, arguing against marked biases. Male-female differences in levels of plasma triglycerides and HDL

cholesterol, and interrelations among plasma levels of triglycerides, total cholesterol, and HDL cholesterol were com-parable to associations seen in more representative samples (45, 46). Positive associations of triglyceride levels with both Quetelet index and cigarette smoking were observed, and HDL cholesterol was *associated* with both Quetelet index (negatively) and alcohol consumption (positively). Data from the Framingham Study (47) also suggest that levels of triglycerides and HDL cholesterol may be more predictive of subsequent coronary heart disease in women than in men. The stronger cross-sectional associations observed with coronary artery occlusion among women in the current study were not due to the large proportion of females with occlusion scores of 0; analyses excluding nondiseased subjects yielded comparable male-female differences (data not shown).

Even if not directly related to cardiovascular disease, it has been suggested that elevated levels of triglycerides may be a marker for certain forms of hyperlipoproteinemias (2). Although hypertriglyceridemics typically have decreased levels of HDL cholesterol, this association is not strong enough to be clinically useful (48). In addition, apolipoprotein A-I, which may be a better predictor of cardiovascular disease than is HDL cholesterol, is only weakly associated with triglycerides (49), and hypertriglyceridemics with normal levels of apolipoprotein B have minimal coronary artery disease (50). Because the prevalence of hypertriglyceridemia in normocholesterolemic persons is likely to be less than 5 per cent (42), measurement of triglyceride levels in the general population may yield little additional information concerning cardiovascular disease risk.

The relative importance of levels of HDL cholesterol (vs. triglycerides) is also in agreement with most of the experimental evidence concerning atherosclerosis. Although Zilversmit (19) has suggested that the formation of chylomicron remnants may be atherogenic, triglycerides exhibit little sclerogenic activity (51) and cholesterol-rich lipoprotein particles are more likely to penetrate the arterial wall (62). In contrast, many studies implicate HDL cholesterol in atherosclerosis (53), possibly by facilitating the efflux of intracellular cholesterol (54). Disparate findings of earlier epidemiologic studies concerning triglyceride levels are likely to have resulted from a failure to control for levels of HDL cholesterol.

REFERENCES

1. Tzagournis M. Triglycerides in clinical medicine: a review. Am J Clin Nutr 1978;31:1437-52.
2. National Heart, Lung, and Blood Institute Consensus Development Panel. Treatment of hypertriglyceridemia. JAMA 1984;251:1196-1200.
3. Grundy SM. Hypertriglyceridemia: mechanisms, clinical significance, and treatment. Med Clin N Am 1982;66:519-35.
4. Barboriak JJ, Rimm AA, Anderson AJ, et al. Coronary artery occlusion and blood lipids. Am Heart J 1974;87:716-21.
5. Cohn PF, Gabbay SI, Weglicki WB. Serum lipid levels in angiographically defined coronary artery disease. Ann Intern Med 1976;84:241-5.
6. Gotto AM, Gorry GA, Thompson JR, et al. Relationship between plasma lipid concentrations and coronary artery disease in 496 patients. Circulation 1977;56:875-.93.
7. Holmes DR, Elveback LR, Frye RL, et al. Association of risk factor variables and coronary artery disease documented with angiography. Circula-tion 1981;63:293-9.
8. Castelli WP, Doyle JT, Gordon T, et al. HDL cholesterol and other lipids in coronary heart disease. The Cooperative Lipoprotein Phenotyping Study. Circulation 1977;55:767-72.
9. Brunner D, Altman S, Lowbel K, et al. Serum cholesterol and triglycerides in patients suffering from ischemic heart disease and in healthy subjects. Atherosclerosis 1977; 28: 197-204
10. Kameda K, Matsuzawa Y, Kubo M, et al. Increased frequency of lipoprotein disorders similar to type III hyperlipoproteinemia in survivors of myocardial infarction in Japan. Atherosclerosis 1984; 51: 241-9
11. Kannel WB, Castelli WP, Gordon T, et al. Serum cholesterol, lipoproteins and the risk of coronary heart disease. Ann Intern Med 1971; 74: 1-12
12. Pelkonen R, Nikkilä E, Koskinen S, et al. Association of serum lipids and obesity with cardiovascular mortality. Br Med J 1977; 2: 1185-7.

13. Carlson LA, Böttiger LE, Ahfeldt PE. Risk factors for myocardial infarction in the Stockholm Prospective Study. Acta Med Scand 1979; 206: 351-60.
14. Heyden S, Heiss G, Hames CG, et al. Fasting triglycerides as predictors of total and CHD mortality in Evans County, Georgia. J Chronic Dis 1980; 33: 275-82.
15. Salonen JT, Puska P., Relation of serum cholesterol and triglycerides to the risk of acute myocardial infarction, cerebral stroke and death in eastern Finnish male population. Int J Epidemiol 1983; 12: 26-31.
16. Petersson B, Trell E, Hood B. Premature death and associated risk factors in urban middle-aged men. Am J Med 1984; 77: 418-26.
17. Åberg H, Lithell H, Selinus I, et al. Serum triglycerides are a risk factor for myocardial infarction but not for angina pectoris. Results from a 10-year follow-up of Uppsala Primary Preventive Study. Atherosclerosis 1985; 54: 89-97.
18. Cambien F, Jacqueson A, Richard JL, et al. Is the level of serum triglyceride a significant predictor of coronary death in "normocholesterolemic" subjects? The Paris Prospective Study. Am J Epidmiol 1986; 124: 624-32.
19. Zilversmit DB. A proposal linking atherogenesis to the interaction of endothelial lipoproteins lipase with triglyceride-rich lipoproteins. Circ Res 1973; 33: 633-8.
20. Hulley SB, Rosenman RH, Bawol RD, et al. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. N Engl H Med 1980; 302: 1383-9.
21. Davis CE, Gordon D, LaRosa J, et al. Correlations of plasma high-density lipoprotein cholesterol levels with other plasma lipid and lipoproteins concentrations. The Lipid Research Clinics Program Prevalence Study. Circulation 1980; 62(suppl IV): IV-24-30.
22. Pearson TA, Bulkley BH, Achuff SC, et al. The association of low levels of HDL cholesterol and arteriographically defined coronary artery disease. Am J Epidemiol 1979; 109: 285-95.
23. Barboriak JJ, Anderson AJ, Rimm AA, et al. High density lipoprotein cholesterol and coronary artery occlusion. Metabolism 1979; 28: 735-8.
24. Rosenman RH, Brand RJ, Sholtz RI, et al. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol 1976; 37: 903-10.
25. Castelli WP, Garrison RJ, Wilson PWF, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986; 256: 2835-8.
26. Abbott RD, Carroll RJ, Interviewing multiple logistic regression coefficients in prospective observational studies. Am J Epidemiol 1984; 119: 830-6.
27. McGee D, Reed D, Yano K. The results of logistic analyses when the variables are highly correlated: an empirical example using diet and CHD incidence. J Chronic Dis 1984; 37: 713-19.
28. Castelli WP, The triglyceride issue: a view from Framingham. Am Heart J 1986; 112: 432-7.
29. Detre KM, Wright E, Murphy ML, et al. Observer agreement in evaluating coronary angiograms. Circulation 1975; 52: 979-86.
30. Zir LM, Miller SW, Dinsmore RE, et al. Interobserver variability in coronary angiography. Circulation 1976; 53: 627-32.
31. Rowe GG, Thomsen JH, Sternlund RR, et al. A study of hemodynamics and coronary blood flow in man with coronary artery disease. Circulation 1969; 39: 139-48.
32. Keys A, Fidanza F, Karvonen MJ, et al. Indices of relative weight and obesity. J Chronic Dis 1972; 25: 329-43.
33. Barboriak JJ, Rimm AA, Anderson AJ, et al. Coronary artery occlusion and alcohol intake. Br Heart J 1977; 39: 289-93.
34. Block WD, Jarrett KJ Jr, Levine JB. Use of single color regent to improve the automated determination of serum total cholesterol. In: Skeggs LT Jr, ed. Automation in analytical chemistry. New York: Mediad, Inc, 1966: 345-7.
35. Kessler G, Lederer H. Flurometric measurement of triglycerides. In: Skeggs LT Jr, ed. Automation in analytical chemistry. New York: Mediad, Inc, 1966: 341-4.
36. Manual of Laboratory Operations, Lipid Research Clinics Program. Vol. 1. Bethesda, MD: National Institutes of Health, 1974. (DHEW Publ no. (NIH) 75-628.)
37. Norusis MJ. SPSS-X advanced statistics guide. New York: McGraw-Hill Books Co, 1985; 40-58.

38. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley and Sons, 1981:61-4.
39. Pearson TA. Coronary arteriography in the study of the epidemiology of coronary artery disease. Epidemiol Rev 1984; 6: 140-66.
40. Newman WP, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atheroschlerosis. The Bogalusa Heart Study. N Engl J Med 1986; 314: 138-44.
41. Criqui MH, Heiss G, Cohn R, et al. Triglycerides and coronary heart disease mortality. The Lipid Research Clinics Prevalence Study. Paper presented at the 27th annual conference on cardiovascular disease epidemiology. Charleston, SC. March 1987.
42. Barrett-Connor E, Khaw KT. Borderline fasting hypertriglyceridemia: Absence of excess risk of all-cause and cardiovascular disease moratlity in healthy men with hypercholesterolemia. Prev Med 1987; 16: 1-8.
43. Oliver MF. Serum cholesterol – the knave of hearts and the joker. Lancet 1981; 2: 1090-5.
44. Pujadas G. Coronary angiography in the medical and surgical treatment of ischemic heart disease. New York: McGraw-Hill Book Co, 1980; 274-304.
45. Cowan LD, Wilcosky T, Criqui MH, et al. Demographic, behavioral, biochemical, and dietary correlates of plasma triglycerides. Lipid Research Clinics Program Prevalence Study. Arteriosclerosis 1985; 5: 466-80.
46. Taylor KG, Carter TJ, Valente AJ, et al. Sex differences in the relationships between obesity, alcohol consumption and cigarette smoking and serum lipid and apolipoprotein concentrations in a normal population. Atherosclerosis 1981; 38: 11-18.
47. Lerner DJ, Kannel WB, Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986; 111: 383-90.
48. Philippi T, Barrett-Connor E. Fasting plasma glucose, uric acid, and triglycerides as predictors of the ratio of total cholesterol to HDL-C. Am J Clin Pathol 1984; 82: 329-32.
49. Freedman DS, Srinivasan SR, Webber LS, et al. Divergent levels of HDL cholesterol and apolipoprotein A-I in children. The Bogalusa Heart Study. Arteriosclerosis 1987; 7: 347-53.
50. Sniderman AD, Wolfson C, Teng B, et al. Association of hyperapobetalipoproteinemia with endogenous hypertriglyceridemia and atherosclerosis. Ann Intern Med 1982; 97: 833-8.
51. Adams CWM. Atheroma lipids. J Atherosclerosis Res 1967; 7: 117-19.
52. Klimov An, Nagomev VA. Mechanism of lipoprotein penetration into the arterial wall leading to development if atherosclerosis. Atherosclerosis Rev 1983; 11: 107-17.
53. Heiss G, Johnson NJ, Reiland S, et al. The epidemiology of plasma high-density lipoprotein cholesterol levels. The Lipid Research Clinics Program Prevalence Study. Summary. Circulation 1980; 62(suppl IV): IV-116-136.
54. Miller GJ, Miller NE. Plasma high-density lipoprotein concentration and development of ischaemic heart-disease. Lancet 1975; 1: 16-19.