Associations of Lipoprotein Cholesterols, Apolipoproteins A-I and B, and Triglycerides With Carotid Atherosclerosis and Coronary Heart Disease

The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Previous research shows generally greater proportional elevation in apolipoprotein B (apoB) levels than in low-density lipoprotein cholesterol (LDL-C) in coronary heart disease (CHD) case subjects compared with control subjects. The Atherosclerosis Risk in Communities study provided general populations of 7261 men and women free of cardiovascular symptoms for evaluating the associations between intima-media thickening in extracranial carotid arteries measured using ultrasound imaging and fasting plasma LDL-C, high-density lipoprotein cholesterol (HDL-C), apoB, apolipoprotein A-I (apoA-I), triglycerides, and HDL density subfractions. A CHD group was selected for comparison. Lipid factors show approximately linear associations with carotid thickness: positive for LDL-C and plasma apoB and negative for HDL-C and apoA-I levels. Apolipoproteins and HDL density subfractions did not contribute to the association after accounting for LDL-C and HDL-C. Compared with control subjects, persons whose carotid thickness exceeded 0.9 mm had greater proportional elevations in LDL-C than in apoB, whereas HDL-C reductions were small. CHD case subjects showed greater proportional elevations of apoB than LDL-C. Although the lipid profiles associated with asymptomatic carotid wall thickening and stenotic coronary disease are similar, the differences found suggest that LDL-C is the most important lipid factor in earlier stages of atherogenesis, whereas the metabolism of triglyceride-rich lipoproteins and its effects on LDL and HDL may be more relevant to later atherothrombotic processes.

Key Words • atherosclerosis • carotid artery diseases • coronary artery disease • lipoproteins • apolipoproteins

Clearly, factors involved in different stages of atherogenesis may differ. For example, endotheliotropic agents and growth promoters may interact with plasma cholesterol levels in early lesions, whereas thrombosis is integral to complications leading to overt clinical disease. A tendency to thrombosis may be favored by abnormalities in triglyceride metabolism. Since impaired metabolism of triglyceride-rich lipoproteins also lowers HDL levels and affects LDL structure, lowering its ratio of cholesterol to apolipoprotein, we reasoned that subtle lipid profile differences may exist between persons with early atherosclerosis and those with later stenotic disease.

To test this hypothesis we studied the lipid profiles associated with both clinical CHD and asymptomatic intima-media carotid artery thickness. Since levels of each lipoprotein cholesterol are closely correlated with levels of the corresponding structural apolipoprotein (correlations of 0.7 to 0.8 for LDL-C with apoB and HDL-C with apolipoprotein A-I [apoA-I] in the population studied here), large populations are needed to study their individual relations with disease. The Atherosclerosis Risk in Communities (ARIC) study provided such a population with direct measurements of carotid arterial wall thickening by ultrasound imaging and standardized ascertainment of prevalent CHD.
Methods

Population

The ARIC study combines cardiovascular surveillance in all adults in four selected US communities with prospective study of cohorts aged 45 to 64 years selected to represent these communities. The communities are Forsyth County, North Carolina; Jackson, Miss; suburbs of Minneapolis, Minn; and Washington County, Maryland. Only blacks were selected in Jackson. The response rate, ie, the proportion of eligible subjects examined, was 46% in Jackson and 65% in each of the other communities.

ARIC cohort participants examined at baseline between November 1986 and February 1990 were eligible for the present study if they were taking no lipid-altering medications, were not diabetic or hypertriglyceridemic, and did not have any evidence of CHD. Of 15 800 examined, 446 (3%) were taking medications to reduce lipid levels; 3701 (23%) were taking β-blockers, α-blockers, or diuretics with known lipid-altering effects; and 1623 (10%) were women taking gonadal hormones. Fasting triglycerides were above 400 mg/dL (4.52 mmol/L) in 472 participants (3%); 1563 (10%) had diabetes (treated with drugs, diagnosed by a physician, or fasting blood glucose above 140 mg/dL [7.78 mmol/L]); and 1616 (10%) reported symptoms or a history or had electrocardiographic (ECG) evidence of CHD. Of the remaining participants, 1713 were excluded for lack of a fasting blood sample or for missing data on carotid arteries or lipid or confounding variables. Remaining for study were 7261 participants.

At baseline examination, 544 men met the following criteria for CHD: 63%, clinically recognized myocardial infarction; 3%, ECG evidence of transmural infarction without clinically recognized disease; 10%, coronary angioplasty or bypass surgery without infarction; and 24%, effort angina by Rose questionnaire without other evidence of disease.17 The diagnosis in women was based on Rose questionnaire angina alone in 75% of 497 CHD cases. Only 19% had clinical myocardial infarction, 3% had ECG evidence of myocardial infarction, and 3% had coronary angioplasty or bypass. A cohort group of similar size was obtained by selecting persons without CHD whose mean carotid intima-media thickness exceeded 0.89 mm in women or 0.98 mm in men. CHD and carotid case subjects were both compared with control subjects, defined as participants who met criteria for neither the CHD nor the carotid group. Mean thickness values in women were 1.07 mm in the carotid group, 0.75 mm in CHD case subjects, and 0.66 mm in control subjects. Corresponding values in men were 1.19, 0.88, and 0.73 mm, respectively. In analyses based on classifying subjects by disease, ie, CHD or carotid case subject or control subject, estimates of mean lipid values associated with the diseases are expected to be unbiased by differences in measurement precision. HDL subfractions, for example, are measured less precisely than total HDL. Thus, estimates of mean HDL-C in any case group are less precise than estimates of mean HDL-C. However, imprecision will not alter expected mean values.

Carotid Artery Measurements

Carotid artery wall thickness was measured from ultrasound images by methods that have been described.18,19 Briefly, the carotid arteries were scanned bilaterally at three sites prone to atherosclerosis: the distal 10 mm of the common carotid, the bifurcation, and the proximal 10 mm of the internal carotid. Sonographs were trained at the ARIC Ultrasound Reading Center and certified annually. Measurements were made from videotapes at the Reading Center without knowledge of any characteristics of the examinees. The current analysis uses the combined intima plus media thickness, defined as the distance between lumen-intima and media-adventitia interfaces and measured at 1-mm intervals along the longitudinal axis of the artery. The average of all measurements at all six arterial sites is used here to represent the total extent of carotid thickening. Only far-wall measurements (deep to the skin) are used, because they are more accurate. When inadequate imaging prevented measurements at any of the six sites, the average was derived using values imputed from measured to unmeasured sites by maximum likelihood methods using the EM algorithm.20 The imputation was based on relations observed in the population between thickness at various sites. Based on a random 800 examinations repeated by the sonographers, precision, estimated as the absolute difference between paired measurements, was 0.00 or 0.07 mm (compared with a mean carotid wall thickness of approximately 0.7 mm) in 54%, 36%, and 50% of the pairs for common carotid, bifurcation, and internal carotid arteries, respectively.18

Lipid Determinations

Lipid measurements were performed on plasma separated by centrifugation at 4°C from blood collected after a 12-hour fast into tubes containing EDTA. Aliquots were stored at each field center at −70°C and shipped weekly on dry ice to the ARIC Lipid Laboratory, where they were also stored at −70°C until analysis, usually within 6 weeks of receipt. Cholesterol and triglycerides were measured by enzymatic procedures21,22 with reagents supplied by Boehringer Mannheim Biochemical, adapted for analysis in the Cobas-Bio analyzer (Roche). Cholesterol was measured in total HDL and HDL-L, separated by the method of Warnick et al,23 as described recently.24 LDL-C was calculated using the Friedewald formula: LDL-C=total cholesterol−(triglycerides/5+HDL-C), where LDL-C and triglycerides are expressed in milligrams per deciliter.

ApoA-I was determined by a modified radioimmunoassay.26,27 We have previously shown the assay to be specific for apoA-I, accurate in recovery experiments and in comparison with a consensus value, and reliable in frozen plasma specimens.28 The apoB radioimmunoassay of Schonfeld et al29 was used with minor modifications. LDL standard and tracer were prepared by zonal ultracentrifugation.30 ApoB levels are well preserved using our sample processing methods but are lowered 7% by freezing.31

For measurement of plasma cholesterol, triglycerides, and HDL-C, plasma pools from the US Centers for Disease Control and Prevention (CDC) were used as internal quality control material, following Lipid Research Clinics protocols.32 External control of successful participation in the CDC’s Lipid Standardization Program. The laboratory prepared in-house pools for quality control for HDL-C, HDL-L, apoA-I, and apoB. For external quality control, aliquots from a subset of samples were stored at field centers for an additional week. Analysis of these “blind” replicates provides a measure of variability that includes storage, shipping, and sample processing effects and transcription errors in field centers and laboratory. Blind-duplicate coefficients of variation (SD for a pair divided by its mean) for total cholesterol, LDL-C, triglycerides, HDL-C, HDL-L, apoB, and apoA-I were 5%, 10%, 7%, 5%, 12%, 16%, and 14%, respectively.

Statistical Methods

Carotid thickness was studied in relation to proportions above or below sex-specific population means for each lipid. This method, for example, compares carotid thickness in persons with LDL-C 30% above the population mean with thickness in persons with apoB 30% above the mean, thereby providing an evaluation of lipoprotein composition differences. For example, if 30% apoB elevations and 30% LDL-C elevations are associated with different thickness values, this suggests that carotid thickening is associated with an LDL composition difference, a difference in moles of cholesterol per mole of apoB. The method also permits comparison with the literature on CHD, which has suggested that case subjects...
Results

Table 1 shows carotid thickness and lipid values by sex. Mean carotid intima-media thickness was 0.68 mm in women and 0.77 mm in men. Women had higher HDL-C, HDL subfractions, and apoA-I values than men; men had higher triglycerides. Twenty-four percent of women and 19% of men were nonwhites. Mean systolic blood pressure was 118 mm Hg in women and 120 mm Hg in men. Women smoked less.

Fig 1 shows sex-specific, race- and age-adjusted mean carotid thickness by LDL-C. Fig 2 shows HDL-C relations. The associations are approximately linear across a wide range of lipoprotein concentrations, with greater carotid thickness at greater LDL-C levels and at lower HDL-C levels. Similar associations were seen between thickness and the apolipoproteins, positive for apoB and negative for apoA-I (data not shown). The impression of linearity is supported by the finding that none of the eight quadratic terms tested (for LDL-C, HDL-C, apoB, and apoA-I, in women and men) were statistically significant.

Separate linear regressions were used to estimate associations of each lipid with carotid thickness while controlling for age and race. Table 2 shows carotid thickness differences predicted from 30% increases in each lipid. In both sexes, higher levels of LDL-C, apoB, and triglycerides and lower levels of HDL-C, apoA-I, and both HDL subfractions were significantly associated with thicker carotid walls. In both sexes, 30% LDL-C differences were associated with greater carotid thickness differences than were 30% apoB differences. Differences in triglycerides or HDL subfractions were associated with smaller thickness differences than were similar differences in LDL-C or HDL-C. LDL-C values were associated with the largest thickness differences in each sex.

TABLE 2. Differences (±SE) in Carotid Artery Intima-Media Thickness Predicted From 30% Increases in Lipoprotein and Apolipoprotein Levels, According to Sex, Adjusted by Multiple Linear Regression for Age and Race*

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>0.0290±0.0027</td>
<td>0.0255±0.0034</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.0225±0.0025</td>
<td>0.0171±0.0031</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.0169±0.0028</td>
<td>-0.0179±0.0030</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>-0.0147±0.0036</td>
<td>-0.0226±0.0041</td>
</tr>
<tr>
<td>HDL subfraction 1</td>
<td>-0.0082±0.0015</td>
<td>-0.0081±0.0015</td>
</tr>
<tr>
<td>HDL subfraction 2</td>
<td>-0.0145±0.0031</td>
<td>-0.0146±0.0031</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.0083±0.0016</td>
<td>0.0095±0.0017</td>
</tr>
</tbody>
</table>

*Each lipid factor, entered in a separate linear model, was associated with carotid thickness at a significance level of P<.001.
Table 3. Differences in Carotid Artery Intima-Media Thickness Predicted by Multiple Linear Regression Models From 10 mg/dL Greater Lipoprotein and Apolipoprotein Levels and Specified Risk Factor Differences, According to Sex

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>0.0770†</td>
<td>0.0896†</td>
</tr>
<tr>
<td>White race</td>
<td>-0.0248†</td>
<td>-0.0276†</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.0060†</td>
<td>...</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>0.0022</td>
<td>...</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>...</td>
<td>-0.0108†</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>...</td>
<td>0.0008</td>
</tr>
<tr>
<td>HDL2 cholesterol</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>HDL3 cholesterol</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>...</td>
<td>0.0002</td>
</tr>
<tr>
<td>Smoking (10 pack-years)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SBP (10 mm Hg)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; and SBP, systolic blood pressure. Differences in carotid artery intima-media thickness are expressed in millimeters.

†P<.001. ‡P<.05. §P<.01.

Table 3 shows the results from six regression models, using carotid thickness as the dependent variable and age, race, and various combinations of lipids as independent variables: (1) LDL-C and apoB; (2) HDL-C and apoA-I; (3) LDL-C, HDL-C, and triglycerides; (4) LDL-C, HDL2-C, HDL3-C, and triglycerides; (5) LDL-C, HDL-C, triglycerides, apoB, and apoA-I; and (6) LDL-C, HDL-C, and triglycerides, with smoking and systolic blood pressure.

Models with only a lipoprotein cholesterol and its associated apolipoprotein (models 1 and 2) consistently showed statistically significant coefficients for lipoprotein cholesterol and smaller insignificant coefficients for the apolipoproteins. Age, race, LDL-C, HDL-C, and triglycerides (model 3) explained 14% of variance in women and 12% of variance in men. Addition of apolipoproteins (model 5) increased the proportion of variance explained by only 1.3% in men (from .1215 to .1231) and 0.2% in women. Substitution of HDL subfractions for total HDL-C (model 4) increased variance explained by less than 0.1%. Adding smoking and blood pressure (model 6) increased the percentage of variance explained but did not reduce coefficients for the lipoproteins.

Table 4 compares persons with CHD and those with increased carotid thickness. Since CHD and carotid groups were older than control subjects (55, 57, and 53 years, respectively, for women; 57, 58, and 54 years, respectively, for men) and there were differences in the percentage of blacks (26%, 29%, and 26%, respectively, for women; 13%, 17%, and 21%, respectively, for men), all comparisons were age and race adjusted. Data are shown both for the entire population not taking lipid-lowering drugs and separately for those who were also not taking any medications that may secondarily alter lipids.

Among men a lipid profile difference between the diseases emerged: relative to control subjects, apoB was elevated more than LDL-C for CHD case subjects, whereas for carotid case subjects LDL-C was elevated.
TABLE 4. Percent Difference in Lipoprotein and Apolipoprotein Levels Between Persons With Coronary Heart Disease or Carotid Intima-Media Thickness and Persons With Neither Condition, According to Sex*

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean In Controls</td>
<td>CHD</td>
</tr>
<tr>
<td>No. of persons</td>
<td>6021</td>
<td>497</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.46</td>
<td>5.5†</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>0.90</td>
<td>6.2‡</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.52</td>
<td>-7.4†</td>
</tr>
<tr>
<td>Apolipoprotein A-I, g/L</td>
<td>1.44</td>
<td>-4.8†</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.29</td>
<td>10.6†</td>
</tr>
</tbody>
</table>

Persons not taking lipid-altering medications

<table>
<thead>
<tr>
<th>No. of persons</th>
<th>Control</th>
<th>CHD</th>
<th>Carotid</th>
<th>Control</th>
<th>CHD</th>
<th>Carotid</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.47</td>
<td>1.8</td>
<td>9.8†</td>
<td>3.56</td>
<td>6.8‡</td>
<td>6.5†</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>0.89</td>
<td>1.5</td>
<td>9.4†</td>
<td>0.94</td>
<td>7.6†</td>
<td>3.6†</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.52</td>
<td>-6.0†</td>
<td>-7.3†</td>
<td>1.19</td>
<td>-8.9†</td>
<td>-5.5†</td>
</tr>
<tr>
<td>Apolipoprotein A-I, g/L</td>
<td>1.42</td>
<td>-3.7†</td>
<td>-3.3†</td>
<td>1.24</td>
<td>-6.8†</td>
<td>-5.0†</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.21</td>
<td>8.1†</td>
<td>10.5†</td>
<td>1.41</td>
<td>13.6†</td>
<td>8.4†</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

*Adjusted for age and race by ANCOVA.
†P<.001 compared with control subjects.
‡P<.01 compared with control subjects.
§/β-Blockers, α-blockers, diuretics, or (for women) gonadal hormones.
||P<.05 compared with control subjects.

more than apoB. This difference was tested using the ratio of LDL-C to apoB, which was greater in carotid than CHD case subjects (P=.001). Triglycerides were higher in CHD than carotid case subjects. Excluding persons taking lipid-altering medications did not alter the findings. Similar trends were seen for women, but CHD-carotid differences were smaller and not significant. In both disease groups, HDL-C was reduced more than apoA-I.

Discussion

This study presents associations between blood lipid levels and preclinical atherosclerotic arterial wall thickening in adult residents of four US communities who received ARIC examinations and were free of medications or medical conditions that might affect study results. Since atherosclerosis was measured noninvasively in asymptomatic populations, these results are free of the clinical and other specific selection biases that may occur in autopsy or angiography studies. The population is large enough to provide statistically reliable estimates of separate effects of closely correlated lipid factors. We report that lipoprotein levels have consistent associations with carotid atherosclerosis and provide evidence of a subtle difference between the lipid profiles associated with carotid atherosclerosis and prevalent CHD.

The carotid intima-media thickness differences reported here are small. For example, 30% lipid differences are associated with thickness differences of only 0.01 to 0.03 mm. Although highly statistically significant, these differences represent less than 5% of the average thickness of approximately 0.7 mm. However, they are believed to reflect changes located almost exclusively in the intima, which may be only an endothelial cell thickness in the absence of atherosclerosis. In general, our findings relate to early stages of atherogenesis, which predominate in this free-living middle-aged population. Even in the group with thicker carotid arteries selected for comparison with CHD case subjects, only 7% had a mean intima-media thickness exceeding 1.5 mm, none exceeded 2.3 mm, and only 6% had carotid stenosis, defined as any lumen narrower than 2 mm.

This study demonstrates consistent associations of intima-media thickness of the extracranial carotid arteries with lipid factors: positive with LDL-C and apoB and negative with HDL-C and apoA-I levels. The relations are approximately linear. LDL-C, for example, shows no point below which effects are clearly absent or reduced. The LDL-C associations with carotid atherosclerosis in the ARIC populations are much stronger than the HDL-C associations. LDL-C coefficients (Table 3, model 3) standardized for population standard deviations (Table 1) are 1.7 and 2.9 times as large in men and women, respectively, as those for HDL-C.

The positive associations of LDL and negative associations of HDL with carotid thickness mirror the results of a vast literature on CHD, as expected. The validity of the intima-media carotid thickness measured in ARIC as an index of atherosclerosis is evidenced by its strong association with known risk factors for atherosclerosis. Furthermore, since atherosclerosis in all arterial sites is similar pathologically, it is expected to be associated with a similar lipid pattern. In fact, lipid associations with atherosclerosis of major intracranial arteries are similar to those with coronary arteries and
are clearly established with extracranial carotid arteries.37

Our study shows that carotid thickening is associated with slightly greater proportional elevations in LDL-C than apoB. This differs from the pattern reported for CHD. CHD, except when it occurs with familial hypercholesterolemia, is often associated with small, dense LDL, with a low ratio of cholesterol to apoB.38 Kwiterovich39 found hyperapobetalipoproteinemia in association with CHD. Studies we reviewed with at least 50 case subjects and 50 control subjects show that CHD case subjects compared with control subjects tend to have greater proportional elevations of apoB than LDL-C. This pattern was seen in five post–myocardial infarction studies42-44; only one study showed a greater proportional elevation in LDL-C.45 The pattern was similar for coronary angiographic studies: seven showed consistently greater proportional elevation of apoB5-44,46 four showed inconsistent results in subgroups47-50, and none showed consistently greater elevation of LDL-C.

Thus, ARIC LDL-C and apoB results for carotid atherosclerosis differ from expectations based on more than 10 years of reports on CHD. They also differ from the CHD findings reported here. This difference might be affected by cross-sectional bias, since associations reported in this study are based on lipids and disease status assessed at the same examination. Without prospective study one cannot know with certainty whether the CHD associations are causal or reflect, in part, lipid changes subsequent to the disease or its treatment. We attempted to reduce potential bias by excluding case subjects who were taking lipid-altering medications. Still, other drugs, lifestyle changes, weight change, or selective survival may have influenced the lipid pattern seen, both in ARIC and in previous CHD case-control studies. Prospective studies, which avoid this bias, certainly show weaker triglyceride associations with CHD than case-control studies.1 However, if confirmed by prospective CHD studies, the subtle difference found in this study between the lipid profiles associated with early carotid thickening and more advanced, stenotic disease in the coronary arteries could have etiologic relevance. It may relate to thrombosis, which though clearly a factor in coronary ischemic states,10 is of uncertain importance in early atherosclerosis. Thrombosis may result from impaired fibrinolysis or factor VII activation, both of which are associated with elevated blood triglycerides, particularly in the postprandial state.11,12 The fibrinolytic defect may be mediated by triglyceride-induced plasminogen activator inhibitor–1 elevation.14 Our hypothesis suggests that CHD may be related to greater apoB than LDL-C elevations because higher triglyceride levels, which favor thrombosis, also alter LDL composition,81 lowering its ratio of cholesterol to apoB,15 and raise total plasma apoB because of the apoB in very-low-density lipoprotein. The hypothesis that triglyceride elevation contributes more to CHD than carotid disease, together with its known effect of lowering plasma HDL-C levels, would also explain why we and others52 found less HDL reduction with early carotid atherosclerosis than is usually reported with CHD.

Results reported here in terms of mean lipoprotein levels might miss subpopulations with hyperapobeta-

poproteinemia (with low ratios of LDL-C to apoB) or familial hypercholesterolemia (with high ratios). However, the distribution of ratios of LDL-C to apoB in CHD case subjects, carotid case subjects, and control subjects (data not shown) did not indicate that these conditions were frequently found in association with either disease in the ARIC populations. Our findings included an unexpected sex difference: the lipid profile differences between CHD and carotid case subjects found in men were reduced and not significant in women. This difference may be an artifact of diagnostic imprecision due to the known lower specificity of Rose questionnaire angina in women.

Acknowledgments

The ARIC study is carried out as a collaborative study supported by contracts N01-HC55015, N01-HC55016, N01-HC55018, N01-HC55019, N01-HC55020, N01-HC55021, and N01-HC55022 from the National Heart, Lung, and Blood Institute, Bethesda, Md. We are indebted to Valerie Stinson, Pam Pile, Hoang Pham, and Teri Trevino for sample preparation; to Dingyi Zhao, John Crouch, Debbie Rubin-Williams, and Yi-Hsin Yang for assistance in the preparation of the manuscript; and to Royanne Bar, Jeannette Bensen, Faye Blackburn, Marilyn Bowers, Carol Christman, Amy Haire, Sonny Harrell, Joel Hill, Byrna Lester, Gail Murton, Catherine Paton, Delilah Posey, Rajam Radhakrishnan, Seshadri Raju, and Virginia Wym for their unfailing help.

References


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*Arterioscler Thromb Vasc Biol.* 1994;14:1098-1104
doi: 10.1161/01.ATV.14.7.1098

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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