ELSEVIER

Atherosclerosis 165 (2002) 317–325

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Apolipoproteins and carotid artery atherosclerosis in an elderly multiethnic population: the Northern Manhattan stroke study

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Received 20 December 2001; received in revised form 2 April 2002; accepted 10 June 2002

Abstract

The association of apolipoproteins A-I and B (apo A-I and apo B) with cardiovascular disease has been studied in younger populations, but there is sparse information in the elderly. We determined whether apo A-I and apo B were associated with carotid artery atherosclerosis (CAA) in 507 stroke-free elderly community residents (mean age 70.1±11.7 years, 60% women, 41% Hispanics, 30% African American, 28% Caucasian). CAA severity was normal (no plaque or carotid stenosis) in 39%, mild (maximum plaque thickness $\leqslant$1.8 mm or carotid stenosis $<$40%) in 25%, and moderate/severe (maximum plaque thickness $>$1.8 mm or carotid stenosis $\geqslant$40%) in 36%. CAA severity increased with age in all race/ethnic groups ($P<0.01$). CAA was similar among African Americans and Caucasians, but less in Hispanics (age adjusted OR: 0.5, CI: 0.4–0.8). apo A-I $<$1.2 g/l (OR: 2.0, CI: 1.0–3.3) and apo B $\geqslant$1.4 g/l (OR: 2.0, CI: 1.1–3.6) were associated with moderate–severe CAA. An apo B/apo A-I ratio $\geqslant$1 was associated with moderate–severe CAA (OR: 2.4, CI: 1.3–4.4), and the association varied by race (Hispanics OR: 4.3, CI: 1.8–10; non-Hispanics, OR: 1.4, CI: 0.6–3.2). Total cholesterol, triglycerides and low density lipoprotein cholesterol were not associated with moderate–severe CAA, while high density lipoprotein cholesterol was protective (OR: 0.4, CI: 0.2–0.8). Thus, in an elderly population, apo A-I and B were determinants of moderate–severe CAA, and the degree of association varied by race/ethnicity

Keywords: Apolipoprotein; Atherosclerosis; Carotid arteries; Racial differences; Risk factors

1. Introduction

Extracranial carotid artery atherosclerosis (CAA) is a major cause of cerebral infarction and transient ischemic attacks, a disease primarily of the elderly. In population-based epidemiological studies, atherosclerotic risk factors such as age, hypertension, systolic blood pressure, diabetes mellitus, and smoking, but not lipids and lipoproteins, have been consistently associated with CAA [1–6]. It is notable that for coronary artery disease, although the magnitude of the association is progressively attenuated with age, the absolute risk attributable to blood lipids is greater among the elderly [7,8]. Further, intervention studies have shown that lowering of low density lipoprotein (LDL) cholesterol levels results in similar benefits in older and younger subjects, as well as in a reduction in cerebrovascular events [9]. The lack of a consistent association between lipids and CAA is therefore puzzling. In addition, most population-based studies of carotid atherosclerosis have so far been performed among Caucasians and in a few cases African Americans, but there is little information available for Hispanics. We recently demonstrated that Hispanics had significantly less carotid plaque than Caucasians or African Americans, and found a significant relationship between race/ethnicity, carotid plaque and LDL cholesterol, suggesting that the impact of lipid risk factors may vary across ethnicity [10].

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0021-9150/02/$ - see front matter
PII: S0021-9150(02)00246-0

Apolipoproteins A-I and B (apo A-I and B) are the major protein constituents of the high density lipoprotein (HDL) and LDL fractions, respectively. Previous studies addressing the association of apo A-I and apo B with cardiovascular disease have yielded mixed results. In some studies, although not universally found, apo B was reported to give better information than lipid levels, while in general, apo A-I levels have not been found to be independently predictive [11–13]. However, most of these studies were performed in younger and middle-aged populations. Among the elderly, although total cholesterol levels tend to decline, the HDL fraction of plasma cholesterol (HDL-C), and its ratio with total cholesterol (THR) remain important protective factors against CHD among the elderly [14]. Under the new National Cholesterol Education Program guidelines, a high proportion of the elderly are candidates for additional evaluation and possibly lipid-lowering interventions aimed at the primary or secondary prevention of coronary heart disease [15]. However, few studies have characterized the distributions of lipids and apolipoproteins in elderly populations, particularly among minority groups, and even fewer have studied the association of these parameters with measurements of atherosclerosis in this context. The aim of this study was therefore to investigate the association of apolipoproteins and lipids with carotid atherosclerosis in a multiethnic population-based sample of stroke-free subjects.

2. Experimental procedure

2.1. Subjects

The Northern Manhattan Stroke Study (NOMASS), recruiting stroke subjects and controls, is a prospective community-based study designed to determine incidence rates, risk factors and outcome of stroke [16]. The cohort for the present study was derived from the stroke-free subjects enrolled in NOMASS. Stroke-free subjects $\geqslant 40$ years were randomly selected and recruited into this study through random digit dialing techniques [10]. After informed consent was obtained, sociodemographic characteristics, stroke risk factors, other medical conditions, diet, and functional status were evaluated, an electrocardiogram was obtained and an echocardiography was performed. Fasting blood specimens for glucose, lipids, lipoproteins and apolipoproteins were drawn. A neurological examination was completed. Approximately two thirds of the recruited stroke-free subjects were randomly selected to undergo carotid duplex ultrasonographic studies. In all, 507 stroke-free subjects, who had completed enrollment, including duplex ultrasonography and blood drawing, were included in this study.

2.2. Definitions of baseline variables

Race/ethnicity was categorized based on self-report, following definitions used in the US census of 1990, as Hispanic, Black but not of Hispanic heritage, non-Hispanic White, or others. Standardized questionnaires regarding sociodemographic characteristics, stroke risk factors and comorbid atherosclerotic diseases were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention [17]. Hypertension was defined as a systolic blood pressure recording $\geqslant 160$ mmHg or a diastolic blood pressure recording $\geqslant 95$ mmHg based on the mean of two blood pressure measurements, a patient's self-report of a history of hypertension, or use of antihypertensive therapy. Diabetes mellitus was defined by a patient's self-report of a history of diabetes mellitus, insulin use, oral hypoglycemic use, or fasting blood glucose $\geqslant 126$ mg/dl ($\geqslant 7.0$ mmol/l). Body mass index was calculated as weight (kilograms) divided by height (meters) squared, and obesity was defined as body mass index $\geqslant 27.8$ for men, and $\geqslant 27.3$ for women. Leisure–time/recreation physical activity was assessed by a questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics [18]. The questionnaire records the frequency and duration of 14 different recreational activities during the 2-week period before the interview. Leisure–time physical inactivity was defined as subjects with no leisure–time recreational physical activity. Cigarette smoking was characterized by amount (packs per day) and duration (number of years smoked). Smoking was categorized as no to mild smoking (none or any smoking for <20 years, or smoking <1 pack per day for 20–39 years), and heavy smoking (any smoking $\geqslant 40$ years, or smoking at least 1 pack per day for 20–39 years). Alcohol use was collected as drinks per day, week, or month. Comorbid conditions included coronary artery disease (myocardial infarction, angina) and peripheral vascular disease.

2.3. Measurement of serum lipids, lipoproteins and apolipoproteins

Plasma levels of cholesterol and triglycerides were determined by standardized enzymatic procedures (Boehringer Mannheim, Germany). HDL cholesterol levels were measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid and LDL cholesterol levels were calculated by the Friedewald formula. Serum levels of apo A-I and B were determined by commercially available immunonephelometric procedures. The interassay coefficients of variation for these measurements were 3–5% [19].

2.4. Category of CAA by duplex ultrasonography

CAA was assessed by a Siemens Quantum 2000 duplex ultrasound system with 7.5-MHz scanning frequency in B-mode and 5.0-MHz frequency in pulsed Doppler mode as described in detail elsewhere [10]. Briefly, with the subject lying in a supine position, the extracranial carotid arteries (including the common, internal, and external carotid arteries and the carotid bulb area) were imaged in the longitudinal and transverse planes. The presence, morphology and thickness of carotid plaques, defined as an area of focal hyperechoic wall thickening, and the extent of internal carotid artery stenosis were recorded. Based on maximum carotid plaque thickness and extent of internal carotid artery stenosis bilaterally, CAA was categorized as normal (no carotid plaque or internal carotid artery stenosis), mild (maximum carotid plaque thickness $\geqslant 1.8$ mm or maximum internal carotid artery stenosis $<40\%$) and moderate–severe (maximum carotid plaque thickness >1.8 mm or maximum internal carotid artery stenosis $\geqslant 40\%$). The use of a carotid plaque thickness of 1.8 mm to define the above groups was based on the CAA distribution in 1050 stroke-free subjects where the mean maximum plaque thickness was 1.31 mm (SD:1.32) and the 66.6% percentile was 1.8 mm [10]. Internal carotid artery stenosis $\geqslant 40\%$ was defined by standard criteria requiring a ratio of internal carotid artery: carotid artery velocities greater than 2, or peak internal carotid artery systolic flow velocity of $\geqslant 110$ cm/s. In previous studies at our center, the interrater reliability of the estimation of plaque morphology based on duplex Doppler sonography had a κ value of 0.05 for plaque surface structure, well below the value of 0.40 suggested for minimal reliability [20].

2.5. Statistical analysis

Distribution of mild and moderate–severe CAA was evaluated and stratified by different age ranges. ANOVA was used to compare mean age in the different groups of CAA in all and among each race-ethnic subgroup. The association of sociodemographic parameters, risk factors and comorbid conditions with mild CAA and moderate–severe CAA were compared separately using those with absent CAA as a reference. The odds ratios (OR), 95% confidence intervals (CI) and significance were judged based on the χ^2 test for categorical variables. Multivariate analyses were performed using a logistic regression model to identify independent factors. Variables were selected for entry if probability value was less than 0.10 after univariate testing. Modeling was done using the selected variables as the independent variables and CAA as the dependent variable. Odds ratios and 95% CI were calculated. Because of the co-linearity of various lipid parameters, models were developed by separately adding lipid parameters to a model containing other sociodemographic and risk factors variables. Statistical interactions were evaluated in the final models.

3. Results

The mean age of the study group was 70.1 ± 11.7 years (median age 71 years; range 40–99 years); 40% were men and 60% were women. The race-ethnic distribution was 41% Hispanic ($n=206$), 28% non-Hispanic whites ($n=141$), 30% non-Hispanic blacks ($n=153$) and 1% others ($n=7$). Of the subjects, 196 (39%) had no detectable CAA, while 128 subjects (25%) had mild CAA (maximum carotid plaque thickness $\leqslant 1.8$ mm or maximum internal carotid artery stenosis $<40\%$), and 183 subjects (36%) showed signs of moderate–severe CAA (maximum carotid plaque thickness >1.8 mm or maximum internal carotid artery stenosis $\geqslant 40\%$). Sociodemographics, atherosclerotic risk factors and comorbid atherosclerotic diseases for each of the CAA categories are shown in Table 1. The frequency of diabetes mellitus, hypertension, heavy smoking and presence of coronary artery disease or peripheral vascular disease was greater in the group with moderate–severe CAA compared to no CAA. The group with mild CAA had intermediate frequencies of these parameters between the other two groups. Among the race/ethnicity groups, the proportion of African Americans and Caucasians were higher among moderate–severe CAA compared to no CAA, while the relative frequency of Hispanics decreased with increasing CAA.

For all subjects, CAA severity increased with age. Thus, while any form of CAA was present in only 14% of the subjects between 40–54 years, this proportion increased to 80% of the subjects $\geqslant 75$ years of age (data not shown). This increase was most prominent among subjects with moderate–severe CAA, which increased from 3% of the youngest cohort to 51% of the oldest cohort. Concomitantly, the proportion of subjects with no detectable CAA decreased sequentially from 86% of the subjects between 40 and 54 years to 20% of subjects $\geqslant 75$ years. When dichotomizing age at 65 years, there was a significant association with presence of CAA, with OR of 3.7 for mild CAA and 6.0 for moderate–severe CAA (Table 2). When analyzing the three race/ethnicity groups separately, CAA severity increased with age in all groups ($P<0.001$) (data not shown).

We next analyzed univariate associations for sociodemographic factors, atherosclerotic risk factors and comorbid atherosclerotic diseases with the presence of CAA. As seen in Table 2, mild CAA was less common among African Americans than Caucasians and both mild and moderate–severe CAA was seen less frequently among Hispanics compared to Caucasians. No differ-

Table 1
Frequencies of sociodemographics, atherosclerotic risk factors and comorbid atherosclerotic diseases in cohort

	No CAA ($n = 196$)	Mild CAA ($n = 128$)	Moderate–severe CAA ($n = 183$)
Sociodemographics			
Age ($\geqslant 65$)	101 (52)	102 (80)	158 (86)
Gender (men)	89 (45)	50 (39)	78 (43)
Education ($\geqslant$ high school)	99 (50)	73 (57)	103 (56)
Medicaid (yes)	46 (23)	34 (27)	53 (29)
Race			
African American	53 (27)	32 (25)	68 (37)
Caucasian	35 (18)	47 (37)	59 (32)
Hispanic	106 (54)	48 (38)	52 (28)
Risk factors			
Hypertension	78 (40)	62 (48)	97 (53)
Diabetes mellitus	24 (12)	22 (17)	35 (19)
Obesity	96 (49)	48 (38)	71 (39)
Leisure-time physical inactivity	57 (29)	31 (24)	50 (27)
Smoking			
Light smoking	36 (18)	12 (9)	11 (6)
Heavy smoking	56 (29)	56 (44)	96 (52)
Alcohol use			
>0 and $\leqslant 2$ drinks per day	63 (32)	35 (27)	49 (27)
>2 drinks per day	42 (21)	17 (13)	22 (12)
Comorbid conditions			
Coronary artery disease	18 (9)	19 (15)	31 (17)
Peripheral vascular disease	19 (10)	13 (10)	30 (16)

Values are number (percentage).

ence was seen in sociodemographic factors other than age and race/ethnicity (gender, education and Medicaid status) for subjects with and without CAA. Other variables, such as obesity, physical inactivity and alcohol drinking were not associated with the presence of CAA. Among atherosclerotic risk factors, there was no significant difference between subjects with mild CAA compared to subjects without CAA, except for heavy smoking. More prominent differences were found for subjects with moderate–severe CAA, where hypertension, diabetes mellitus, and heavy smoking were significantly associated with presence of CAA (Table 2). Further, history of coronary artery disease or peripheral vascular disease was significantly associated with moderate–severe CAA.

The frequency distribution of apo A-I, apo B and the apo B/apo A-I ratio in the study cohort is shown in Fig. 1. As seen in the figure, the apo A-I distribution was somewhat skewed with a tail towards higher levels, while the apo B distribution had a more Gaussian pattern. Levels of apo A-I were higher among women than men, and higher among African Americans than Caucasians or Hispanics in agreement with previous population studies (Table 3). No differences in apo B levels were found between these groups. Further, apo B levels increased gradually with increasing CAA, while a decreasing trend was seen for apo A-I levels. These differences were reflected in the apo B/apo A-I ratio, which increased significantly with increasing severity of CAA. Of the ethnic groups, Hispanics had the highest apo B/apo A-I ratio, resulting from slightly higher mean apo B and slightly lower mean apo A-I levels compared to Caucasians, while African Americans had the lowest ratio, largely due to the higher apo A-I levels.

Categorical univariate analysis of lipids, lipoproteins and apolipoproteins for subjects with moderate–severe CAA compared to no CAA are displayed in Table 4. The levels for dichotomization were chosen to represent clinically relevant cut-off levels. As seen in the table, a total cholesterol/HDL-C ratio $\geqslant 5$, apo A-I levels <1.2 g/l and apo B/apo A-I ratio $\geqslant 1$ were significantly associated with moderate–severe CAA levels. In contrast, no association with moderate–severe CAA was found for total cholesterol levels $\geqslant 5.92$ mmol/l ($\geqslant 240$ mg/dl), triglyceride levels $\geqslant 2.03$ mmol/l ($\geqslant 200$ mg/dl) and LDL cholesterol levels $\geqslant 3.95$ mmol/l ($\geqslant 160$ mg/dl). In univariate analysis, apo B levels $\geqslant 1.4$ g/l showed a borderline association with moderate–severe CAA.

As gender and race/ethnicity influenced apolipoprotein levels, a multiple logistic regression model was used to assess which apolipoprotein and lipid variables were independently associated with CAA. As seen in Table 4, low apo A-I levels (<1.2 g/l), and an apo B/apo A-I ratio $\geqslant 1$ remained significantly associated with moderate–severe CAA after adjustment for age, hypertension, diabetes mellitus, heavy smoking and race-

Table 2
Univariate odds ratio and 95% CI For variables associated with mild and moderate–severe CAA

	CAA	
	Mild	Moderate/severe
Sociodemographics		
Age (⩾ 65 years vs < 65 years)	3.7 (2.2, 6.2)*	6.0 (3.6, 9.9)*
Gender (men vs women)	0.8 (0.5, 1.2)	0.9 (0.6, 1.3)
Education (⩾ high school vs < high school)	1.3 (0.8, 2.0)	1.3 (0.8, 1.9)
Medicaid (yes vs no)	1.2 (0.7, 2.0)	1.3 (0.8, 2.1)
Race		
African American vs Caucasian	0.5 (0.2, 0.8)**	0.8 (0.4, 1.3)
Hispanic vs Caucasian	0.3 (0.2, 0.6)*	0.3 (0.2, 0.5)*
Hispanic vs African American	0.8 (0.4, 1.3)	0.4 (0.2, 0.6)*
Risk factors		
Hypertension (yes vs no)	1.4 (0.9, 2.2)	1.7 (1.1, 2.6)**
Diabetes mellitus (yes vs no)	1.5 (0.8, 2.8)	1.7 (1.0, 3.0)**
Obesity (yes vs no)	0.6 (0.4, 1.0)	0.7 (0.4, 1.0)
Physical inactivity (yes vs no)	1.3 (0.8, 2.1)	1.1 (0.7, 1.7)
Heavy smoking vs non-smoking	1.7 (1.1, 2.8)**	2.3 (1.5, 3.7)*
Alcohol use		
⩽ 2 drinks per day vs none	0.7 (0.4, 1.3)	0.9 (0.5, 1.6)
> 2 drinks per day vs none	0.5 (0.2, 1.1)	0.6 (0.3, 1.2)
Comorbid conditions		
Coronary artery disease (yes vs no)	1.5 (1.0, 2.3)	1.9 (1.3, 2.9)*
Peripheral vascular disease (yes vs no)	1.2 (0.7, 1.9)	2.0 (1.2, 3.2)*

Values are OR (95% CI). *$P < 0.005$; **$P < 0.05$ subjects with CAA compared to subjects without CAA.

ethnicity (Hispanics versus non-Hispanics). In addition, apo B levels ⩾1.4 g/l were associated with moderate–severe CAA. In contrast, higher total cholesterol, triglyceride and LDL cholesterol levels were not associated with moderate–severe CAA, while a higher HDL cholesterol level was protective (OR: 0.4, CI: 0.2–0.8). In addition, a total/HDL cholesterol ratio ⩾5 was associated with moderate–severe CAA. This ratio correlated significantly with the apo B/apo A-I ratio ($r = 0.56$, $P = 0.02$). Of note, the association between the apo B/apo A-I ratio and moderate–severe carotid atherosclerosis remained significant also when the total/HDL cholesterol ratio was included in the multiple regression model (OR 2.1, CI: 1.3–4.4). A significant interaction was detected between the apo B/apo A-I ratio and Hispanic race-ethnicity, but not among African Americans and Caucasians (Hispanics, OR: 4.3, CI:1.8–10; non-Hispanics, OR:1.4, CI:0.6–3.2). No interaction between HDL cholesterol and Hispanic race-ethnicity was detected.

Of the lipid or apolipoprotein parameters, only the apo B/apo A-I ratio differed significantly between the groups with mild CAA versus no CAA using a multiple logistic regression model. An apo B/apo A-I ratio ⩾1 significantly predicted mild carotid atherosclerosis (OR: 3.2, CI: 1.04–10.0). Also age ⩾65 years (OR: 3.3, CI: 1.9–5.6) and heavy smoking (OR: 1.6, CI: 1.0–2.7) were predictors of mild CAA, while Hispanics were less prevalent than non-Hispanics (OR: 0.6, CI: 0.3–0.9).

4. Discussion

4.1. Difference of CAA by race-ethnicity

A number of studies, including our own, have shown that the prevalence of CAA and atherosclerotic risk factors as well as the mortality rates of cardiovascular diseases differ significantly among Hispanics, non-Hispanic whites and non-Hispanic blacks [9,21–24]. Although stroke incidence rates were higher among Hispanics than among Caucasians in NOMASS, the severity of CAA was less in stroke-free Hispanics than Caucasians and African Americans [10]. The race–ethnic differences in CAA became more prominent in advanced (moderate–severe) atherosclerosis. Our previous study also showed the age-adjusted maximal plaque thickness was less in Hispanics than Caucasians and African Americans [10]. These findings are concordant with The Insulin Resistance Atherosclerosis Study which revealed that Hispanics have significantly less CCA intima-media thickness than Caucasians after adjustment for conventional cardiovascular risk factors and insulin sensitivity [22]. Other population-based studies of racial differences in CAA, especially the Cardiovascular Health Study and Atherosclerotic Risk in Communities study [3,4], have mainly focused on African Americans and Caucasians and rarely on Hispanics. According to the findings from the Third National Health and Nutrition Examination Survey, the prevalences of cardiovascular risk factors, including systolic blood pressure, body-mass-index, physical inactivity and diabetes, are greater in Hispanic and African American women than in Caucasian women [23]. However, the United States vital statistics analysis showed the mortality rates of coronary artery disease and stroke were lower among Hispanics than among Caucasians [24]. Heterogeneity in Hispanic populations could explain some of these differences, and genetic and other environmental risk factors not measured in this study could also contribute to these race-ethnic disparities [24].

4.2. Relation of apo B and apo A-I to CAA

The total apo B plasma concentration comprise the total amount of apo B in triglyceride-rich lipoproteins (including very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL)) as well as in

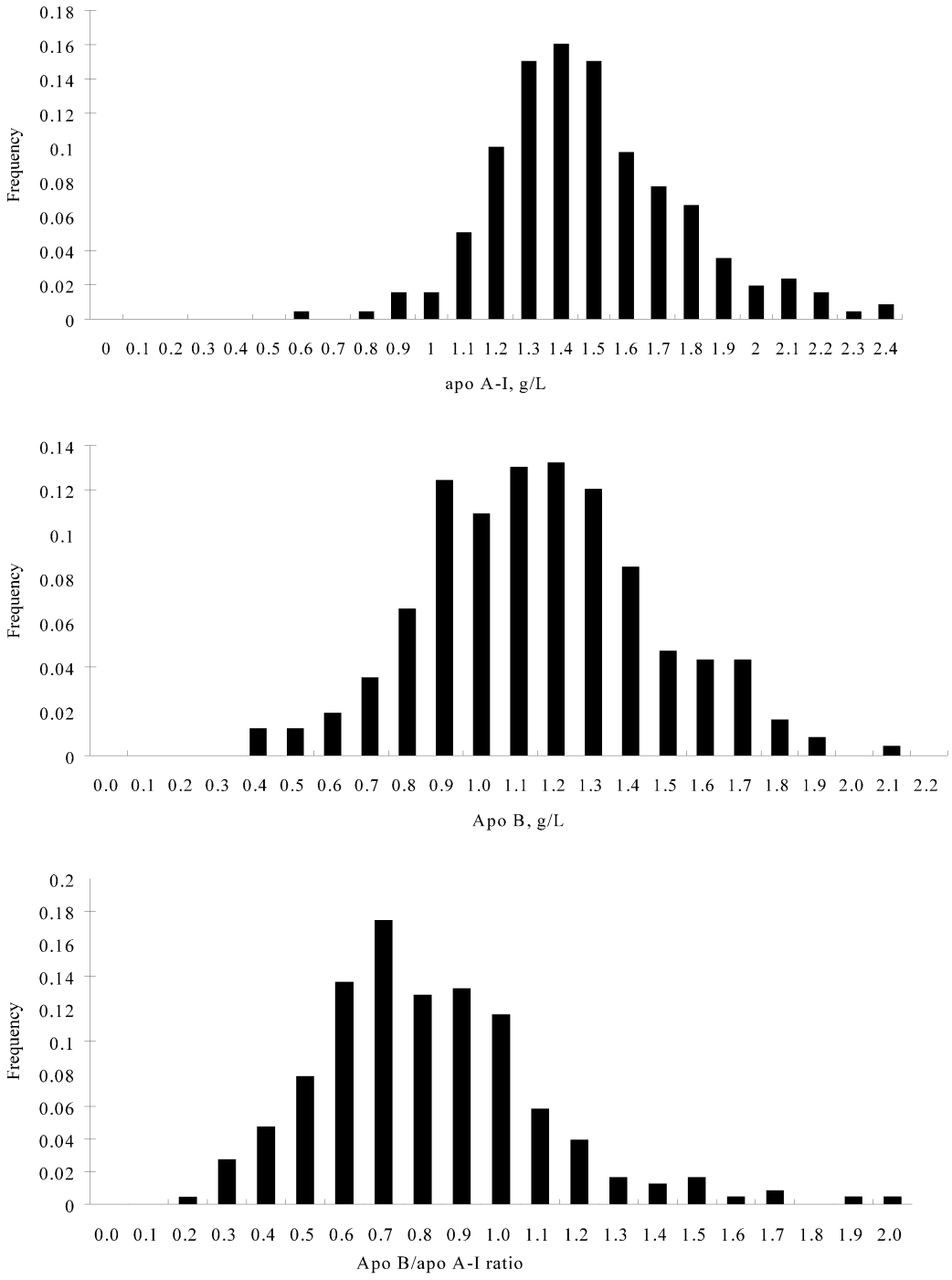

Fig. 1. Relative frequency of apo A-I levels (top), apo B levels (middle) and the apo A-I/apo B ratio (bottom) in the studied population ($n = 507$). Results for apo A-I and apo B are given as g/l.

cholesterol-rich particles (mainly LDLs) [25]. Recent studies have disclosed that triglyceride-rich apo B-containing lipoproteins, primarily VLDL remnants and IDL are significantly related to ischemic heart disease [25,26]. Lately, it has been hypothesized that preferentially smaller particles within the triglyceride-rich lipoprotein range, with a higher apo B: lipid ratio, may be associated with cardiovascular disease [11]. Also within the LDL spectrum there is particle heterogeneity, and smaller, dense LDL particles with a high apo B:cholesterol ratio have been suggested to be particularly atherogenic [25]. Studies have shown that hyperapobetalipoproteinemia is an important risk factor for patients with ischemic heart disease [26] as well as for young adults with a parental history of premature coronary heart disease [27]. So far, only a few studies

Table 3
Mean apolipoprotein levels (±SD) by age, gender, race-ethnicity and degree of carotid atherosclerosis

	apo B	apo A-I	apo B/apo A-I
Men	1.12±0.29	1.37±0.26	0.86±0.32
Women	1.17±0.30	1.56±0.28	0.78±0.25
P-value	NS	0.0001	0.001
African Americans	1.13±0.30	1.57±0.31	0.76±0.27
Caucasians	1.14±0.28	1.45±0.26	0.81±0.24
Hispanics	1.17±0.31	1.43±0.27	0.86±0.32
P-value	NS	0.0001	<0.01
$\leqslant$ 54 years	1.11±0.29	1.44±0.31	0.83±0.40
55–64 years	1.21±0.31	1.49±0.33	0.85±0.28
65–74 years	1.16±0.30	1.47±0.27	0.82±0.28
$\geqslant$ 75 years	1.12±0.29	1.48±0.26	0.78±0.25
P-value	NS	NS	NS
No CAA	1.10±0.30	1.51±0.30	0.76±0.29
Mild CAA $\leqslant$ 1.8 mm	1.17±0.27	1.47±0.26	0.83±0.26
Moderate–severe CAA $>$ 1.8 mm	1.18±0.31	1.45±0.27	0.85±0.29
P-value	0.022	NS	<0.01

Results for apo A-I and apo B levels are given as g/l.

have addressed the important role of apo B on CAA, and there is virtually no information in elderly [12,13]. Our study clearly showed that an apo B concentration $\geqslant$1.4 g/l and an apo B/apo A-I ratio $\geqslant$1 were significantly related to moderate–severe CAA, even after controlling for traditional risk factors. These result suggest that the plasma concentration of apo B, broadly mirroring the number of potentially atherogenic particles, was a better determinant of CAA than total cholesterol and LDL cholesterol in our elderly population. This concept is supported by previous findings, such as the Systolic Hypertension in the Elderly Program study, where a high apo B concentration was significantly related to carotid stenosis [6]. The association between apo B levels and carotid atherosclerosis is not limited to elderly subjects, as apo B was found to be a significant indicator of CAA also in middle-aged men and women in the Bruneck Ischemic Heart Disease and Stroke Prevention Study [28]. Interestingly, we found an interaction among apolipoproteins, Hispanic (versus non-Hispanic) race-ethnicity, and CAA, as the association between apolipoprotein levels and CAA was particularly pronounced among Hispanics. It is noteworthy that a high apo B level is a characteristic of the metabolic syndrome, present in a comparatively high frequency in Hispanics. Our previous study showed an interaction among Hispanic (versus non-Hispanic) race-ethnicity, LDL cholesterol and maximal ICA plaque thickness [10]. However, in the present analysis, LDL cholesterol was not associated with CAA and there was no interaction between LDL cholesterol and race-ethnicity. Although the methods of estimating CAA applied to these two studies were not identical, it is suggested that apo B may be more powerful than LDL-C in determination of CAA for Hispanics.

Both apo A-I and HDL cholesterol were similarly and significantly negatively associated with moderate–severe CAA in the present study. We have previously demonstrated that HDL cholesterol has significantly protective properties in ischemic stroke [29]. In the Physicians' Health Study, there was little predictive value of apo A-I for myocardial infarction after considering conventional risk factors including HDL cholesterol and the total/HDL cholesterol ratio [30]. Our study results revealed that apo A-I and HDL cholesterol had similar protective effects for CAA among the elderly. Further, the ratio of apo B to apo A-I was a significant determinant of moderate–severe CAA, underscoring that analysis of these apolipoprotein levels may provide important information in risk prevention among elderly. Notably, the apo B/apo A-I ratio remained significantly asso-

Table 4
Association of lipids and lipoproteins with moderate–severe CAA in univariate and multivariate models

Lipids, lipoproteins and apolipoproteins	Overall No (%)	OR (95% CI)	
		Moderate–severe CAA	
		Univariate	Multivariate
Total cholesterol $\geqslant$ 5.92 mmol/l	92 (18)	1.3 (0.8, 2.2)	1.1 (0.6, 2.1)
Triglyceride $\geqslant$ 2.03 mmol/l	98 (19)	1.2 (0.7, 1.9)	1.3 (0.7, 2.4)
HDL cholesterol $\geqslant$ 0.93 mmol/l	419 (83)	0.7 (0.4, 1.2)	0.4 (0.2, 0.8)*
LDL cholesterol $\geqslant$ 3.95 mmol/l	88 (17)	1.5 (0.9, 2.6)	1.5 (0.8, 2.8)
Total/HDL cholesterol ratio $\geqslant$ 5	186 (37)	1.5 (1.0, 2.3)**	2.4 (1.4–4.1)**
apo A-I $<$ 1.2 g/l	435 (86)	0.6 (0.3, 1.0)**	2.0 (1.0–3.3)**
apo B $\geqslant$ 1.4 g/l	98 (19)	1.6 (1.0, 2.7)	2.0 (1.1–3.6)**
apo B/apo A-I ratio $\geqslant$ 1	113 (22)	1.7 (1.0, 2.7)**	2.4 (1.3, 4.4)*

In the multivariate model, adjustments were made for age, hypertension, diabetes mellitus, heavy smoking and race-ethnicity (Hispanics versus non-Hispanics).

* $P<0.01$.

** $P<0.05$.

ciated with moderate–severe carotid atherosclerosis when the total/HDL cholesterol ratio was included in the regression model.

4.3. Limitations of the present study

Although the present study is the first study to demonstrate an association of apolipoproteins and CAA across ethnicity, it has several limitations. First, this study had a cross-sectional design limiting our possibilities to draw inferences about a causal pathway. Although age, hypertension, diabetes, smoking, HDL cholesterol, apo A-I and apo B were independently related to CAA, we cannot with certainty establish whether these factors predict development of CAA. In addition, it is likely that there are complex interactions among these risk factors. Second, our stroke-free subjects were sampled from northern Manhattan and may be not representative of race-ethnicity variations in other areas of United States. As mentioned above, stroke incidence and mortality rates vary in different Hispanic areas. The Hispanic residents in northern Manhattan are mainly from the Dominican Republic and other Caribbean islands and differ in several aspects from Mexican Americans. On the other hand, the setting of the study also had offered important strengths. Subjects were recruited using random digit dialing, helping to insure that the sample was population based and race-ethnic comparisons were made using subgroups drawn from the same underlying community to minimize sociodemographic differences.

In conclusion, Hispanics had less significant CAA than blacks and whites from the Northern Manhattan community. Age, hypertension, diabetes, smoking, race-ethnicity, HDL cholesterol and apolipoprotein A-I and B levels were independently related to moderate–severe CAA. Apolipoproteins, in particular the apo B/apo A-I ratio, may be a useful determinant of moderate–severe CAA.

Acknowledgements

This study was supported by grants NS 9993, HL 62705, RR 00645 from the NIH. J.S.J. is a recipient of a research fellowship from the Department of Neurology, National Taiwan University, Taipei, Taiwan.

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