Published in final edited form as:
Neurology. 2006 January 24; 66(2): 223–227. doi:10.1212/01.wnl.0000194507.39504.17.

Cholesterol, *APOE* genotype, and Alzheimer disease:

An epidemiologic study of Nigerian Yoruba

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Abstract

Objective—To examine the relationship between cholesterol and other lipids, *APOE* genotype, and risk of Alzheimer disease (AD) in a population-based study of elderly Yoruba living in Ibadan, Nigeria.

Methods—Blood samples and clinical data were collected from Yoruba study participants aged 70 years and older (N = 1,075) as part of the Indianapolis-Ibadan Dementia Project, a longitudinal epidemiologic study of AD. Cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels were measured in fasting blood samples. DNA was extracted and *APOE* was genotyped. Diagnoses of AD were made by consensus using National Institute of Neurologic Disorders/Stroke-Alzheimer's Disease and Related Disorders Association criteria.

Results—Logistic regression models showed interaction after adjusting for age and gender between *APOE*-ε4 genotype and biomarkers in the risk of AD cholesterol*genotype ($p = 0.022$), LDL*genotype ($p = 0.018$), and triglyceride*genotype ($p = 0.036$). Increasing levels of cholesterol and LDL were associated with increased risk of AD in individuals without the *APOE*-ε4 allele, but not in those with *APOE*-ε4. There was no significant association between levels of triglycerides and AD risk in those without *APOE*-ε4.

Conclusions—There was a significant interaction between cholesterol, *APOE*-ε4, and the risk of Alzheimer disease (AD) in the Yoruba, a population that has lower cholesterol levels and lower incidence rates of AD compared to African Americans. *APOE* status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies.

The *APOE*-ε4 allele is a risk factor for Alzheimer disease (AD) in most populations.[1] The association between *APOE*-ε4 and AD for African Americans is less clear with some studies reporting no association[2] and others a weak association,[3] perhaps confined to the homozygous state.[4] We found no association between possession of the *APOE*-ε4 allele and AD in Yoruba residing in Nigeria.[5]

There is increasing evidence that cholesterol plays a role in AD pathology, perhaps through its effects on amyloid deposition.[6] We have previously reported a significant interaction between *APOE*-ε4, cholesterol, and AD in African Americans in whom increasing

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Disclosure: The authors report no conflicts of interest.

cholesterol levels increased the risk of AD in individuals without *APOE*-ε4 but not in individuals with the *APOE*-ε4 allele.[7]

We report on the interaction between *APOE*-ε4, cholesterol, and other lipids on the risk of AD in a population-based cohort of Yoruba who were evaluated as part of the Indianapolis-Ibadan Dementia Project.

Methods

Since 1992, we have been conducting a comparative, community-based epidemiologic study of prevalence rates, incidence rates, and risk factors for AD in populations of African origin, elderly African Americans in Indianapolis, IN, and Yoruba living in Ibadan, Nigeria. Study participants have been evaluated at approximately 36-month intervals; this report focuses on the Ibadan site, which is located in the southwestern part of Nigeria where the predominant ethnic group is the Yoruba.

In 2001, we conducted a two-stage study in which survivors of the 1992 cohort were interviewed and new participants were enrolled. A detailed description of the construction of the original cohort has been previously reported.[8]

The Ibadan study was conducted in a specific geographic area known as the Idikan wards. In 1992, a total population census was carried out door to door. Entry criteria at that time were age 65 and older and currently residing in Idikan. In 2001, 866 of the original cohort were seen. The geographic area was expanded in 2001, a census was conducted, and 1,939 new participants age 70 and older were enrolled.

Research design

The details of the research design and diagnostic process have been described elsewhere.[9] The 2001 wave of the study followed a two-stage design in which, during the first stage, all study participants had the Community Screening Interview for Dementia (CSI-D) that includes an interview with a close relative.[10,11] A fasting blood sample was drawn from participants who consented. Individuals were sampled for the second stage of the study on the basis of their performance on the screening interview. The second interview stage was a full in-home clinical assessment. Before each interview and blood draw, informed consent was obtained from participants and their informants. The institutional review boards at both universities approved the study.

The sampling method for selection of individuals for full clinical assessment used the scores from the screening interview to stratify participants into performance groups (good, intermediate, and poor) using cut points established in pilot studies and confirmed in successive waves of the study.[10] For individuals in the original baseline cohort, we tracked changes in scores over each successive screening interview and categorized the decline in scores as “poor performance” (7% with most decline), “intermediate performance” (8 to 14% decline group), and “good performance” (stable scores, improvement, or minimal decline). This resulted in 75% in the good performance group, approximately 13% in the intermediate group, and 12% in the poor performance group. Because the poor performance group represents those with a high probability of dementia, all the individuals in the poor performance group were invited to have a clinical assessment. The intermediate performance group includes borderline scores with an intermediate probability of having dementia, 75% of this group were given clinical assessments to maximize the number of clinically diagnosed AD subjects within our clinical resources. The scores in the good performance group indicate normal cognition with the lowest probability of having dementia. From this group, a random sample of 2.5% were given a full clinical assessment

in order to ascertain true normal subjects from the entire spectrum of cognitive performance in this large group.

For the survivors of the original prevalence study, the 2001 wave of the study was the third incidence wave. For the newly enrolled enrichment cohort, the 2001 wave of the study was a baseline prevalence study in which existing cases of AD were identified.

Screening instrument

The CSI-D was developed by our group specifically for use in comparative epidemiologic studies of dementia in disparate populations.[11,12] A close relative (informant) is also interviewed. The study participant is asked to identify a close relative or friend who knows them well in the following hierarchy: spouse, adult offspring, or other close relative residing in the same familial or adjacent compound. Relatives younger than the age of 20 are excluded because they may not be able to assess current functioning in comparison to functioning in midlife.

Clinical assessment

Clinical assessments were conducted in a home visit by a physician and research nurse. The assessment includes the following: 1) cognitive assessment using an adaptation of the Consortium to Establish a Registry for AD (CERAD),[13] 2) physical and neurologic examination and functional status review, 3) blood sample, if not previously drawn, 4) semistructured informant interview, 5) neuroimaging as clinically indicated.

Diagnosis

A consensus diagnostic conference was held to review all clinical assessment data and to agree on a diagnosis. Local normative values were used to guide interpretation of the CERAD scores.[14] Indianapolis clinicians also made a consensus diagnosis for the Ibadan clinical assessments. For cases in which there was disagreement about diagnoses between sites, a consensus conference was held in which both clinical teams determined the final consensus diagnosis in a telephone conference or a site visit. Clinically assessed participants were diagnosed as normal, cognitively impaired not demented (CIND), or as having dementia, with dementia further subtyped (see next section). Individuals diagnosed with CIND are excluded from the analyses reported here.

Diagnostic criteria

For a diagnosis of dementia, both the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R)[15] and International Classification of Diseases, 10th Revision (ICD-10)[16] criteria had to be satisfied. Dementia subtyping followed the National Institute for Neurologic and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA)[17] criteria for probable and possible AD, and ICD-10 criteria[18] for vascular dementia and other secondary dementias (e.g., alcohol dementia, Parkinson dementia).

Blood samples

Fasting blood samples were drawn in 10-mL purple top (EDTA) Vacutainer tubes. The specimens were transported on ice from the field to the laboratory at Ibadan University College Hospital. In the laboratory, red blood cells, buffy coat, and plasma were separated. After labeling the plasma and buffy coat tubes with a unique bar code for each subject, the samples were stored in a −70°C freezer. Samples were shipped to Indiana University in approved blood shipping containers with dry ice, and arrived usually within 3 days. Buffy

coat samples were used for DNA extraction and biochemical analyses were carried out on the plasma.

APOE analyses

DNA was extracted from blood samples using standard protocols and *APOE* genotypes were determined by Hhal digestion of amplified products.[19]

Biomarker analyses

Cholesterol, triglycerides, and high-density lipoprotein (HDL) levels were determined using commercial kits from Roche Diagnostics (Indianapolis, IN). Low-density lipoprotein (LDL) levels were calculated from the Friedewald equation.

Statistical analysis

Demographic variables and medical histories were compared between individuals with and without blood samples using two-sample *t* tests for continuous variables and χ^2 tests for categorical variables. Demographic variables, medical histories, and lipid profiles were also compared between normal individuals and those with AD for the ε4 group and the no ε4 group, separately, using two-sample *t* tests for continuous variables and χ^2 tests for categorical variables. The logistic regression model was conducted separately for each biomarker with AD as a response variable. Each model included one biomarker, *APOE* genotype, biomarker-*APOE* genotype interaction as well as adjusting for age and gender. Due to the small number of individuals with AD, the variables of education, body mass index (BMI), and self-reported vascular disease history such as hypertension, heart attack or angina, stroke, and diabetes were included univariately in the model to determine whether these variables are significantly related to the risk of AD. Education level was dichotomized as those having any formal education vs no formal education because the majority of participants had no education at all. *APOE*-ε4 homozygous and heterozygous groups were combined into one group of individuals with an *APOE*-ε4 allele for comparison to the group with no *APOE*-ε4 allele. In order to better interpret the *APOE*-ε4 genotype effects, we also centered each biomarker measure by subtracting its sample mean. Wald's χ^2 statistics were used to test the significance of odds ratios from each logistic regression model. A p value <0.05 was defined as significant difference in the analysis.

Results

In the 2001 study wave, 2,438 individuals were evaluated. This analysis includes participants who gave blood samples for *APOE* genotyping and biomarker analysis. There is no significant difference between individuals in this analysis and those who did not give blood samples in age at screening phase, gender, education, percentage of AD, percentage with at least one ε4 allele, mean BMI, and percentages of individuals with heart disease, stroke, diabetes, and hypertension. A total of 1,075 Yoruba study participants were included in this analysis. Of these, 29 were diagnosed with AD, 132 were clinically diagnosed as normal, and the remaining 914 were in the good performance group on the screening interview. For this analysis, the clinically diagnosed normal group is combined with the good performance group for comparison to the AD group to include additional subjects with biomarkers.

Table 1 shows the demographic characteristics, mean lipid levels, and the proportions of self-reported vascular diseases for the AD group and the normal subjects by *APOE* genotype. The mean age at screening phase for the AD group was older compared to the normal group for both genotype groups (without *APOE*-ε4 allele, $p = 0.001$, and with the *APOE*-ε4 allele, $p = 0.030$). Within the AD group, there were no differences in age for the

APOE-ε4 group compared to those without ε4 ($p = 0.3107$). The proportions of women ($p = 0.024$) and those with heart disease ($p = 0.011$) were higher in the AD group than in the normal groups for individuals without *APOE*-ε4, but not for individuals with *APOE*-ε4. Other characteristics such as education, mean BMI, diabetes, hypertension, and stroke were not significantly different between the AD and the normal groups for either genotype. The mean cholesterol and LDL for the AD groups were higher than the normal groups for individuals without *APOE*-ε4 (cholesterol $p = 0.041$, LDL $p = 0.035$), but not for individuals with *APOE*-ε4. A rather different trend was seen for the mean triglycerides. The mean triglycerides for the AD groups was lower compared to the normal groups for individuals with *APOE*-ε4 ($p < 0.001$), but not for individuals without *APOE*-ε4. There was no difference for the mean HDL between the AD and the normal groups, with or without *APOE*-ε4.

Logistic regression results showed interaction between *APOE*-ε4 genotype and biomarkers on the risk of AD for cholesterol ($p = 0.022$), LDL ($p = 0.018$) and triglycerides ($p = 0.036$), but not for HDL ($p = 0.66$) (table 2), after adjusting for age and gender. Education, BMI, and history of vascular disease were excluded from the logistic regression models because they were not significant in the models. For individuals without ε4, increasing level of cholesterol and LDL was associated with increased risk of AD (cholesterol odds ratio [OR] 1.015, $p = 0.025$ and LDL OR = 1.017, $p = 0.023$). With each 20-point increase in cholesterol in the no ε4 group, the OR for AD would be 1.35. For individuals with *APOE*-ε4, increasing level of cholesterol and LDL was not associated with AD risk (cholesterol OR = 0.992, $p = 0.283$ and LDL OR = 0.988, $p = 0.228$). The interaction effect between cholesterol and *APOE*-ε4 is demonstrated in the figure.

For triglycerides, there was no significant association between triglycerides and AD in individuals without ε4. For individuals with *APOE*-ε4, there was an inverse relationship between fasting triglyceride levels and risk of AD (see table 2).

We also used logistic regression model with the smaller group of clinically diagnosed normal subjects and the AD group and found similar interaction between *APOE* genotype and cholesterol level ($p = 0.004$), *APOE* and LDL ($p = 0.004$), *APOE* and triglycerides ($p = 0.012$), but not for HDL ($p = 0.66$) adjusting for age, gender, education, and BMI. The pattern of interaction was similar to what is presented in the figure.

Discussion

In this study, there was a significant interaction between cholesterol, *APOE*-ε4, and the risk of AD, which is very similar to our previously published report on African Americans.[7] Increasing levels of cholesterol were associated with an increased risk of AD, but only for individuals without the ε4 allele. A similar interaction with ε4 and AD risk was seen for LDL where increasing levels of LDL were also associated with an increased risk of AD. There was also a significant interaction between triglycerides, *APOE*, and AD risk. Increased levels of triglycerides were not associated with an increase in the risk of AD for individuals without the ε4 allele.

There are several unique features of the study. The Yoruba have a lower incidence of AD than the African Americans. The age-standardized annual incidence rate for AD in the Yoruba was 1.15% (95% CI: 0.96% to 1.35%) and for the African Americans was 2.52% (95% CI: 1.40% to 3.64%).[9] Previously, when we investigated the risk of AD in the absence of biomarker data, we reported that the possession of the ε4 allele did not confer an overall increase in risk of AD in Yoruba. Cholesterol levels are lower in Yoruba than in African Americans.[20] Indeed, in this study, mean cholesterol levels (and levels of LDL and

triglycerides) in Yoruba are lower than recommended levels for reducing the risk of heart disease.[21] The mean lipid levels observed in this study are very similar to those reported in another Nigerian sample.[22] There was also no reported use of statins in this population.

The *APOE* and lipid interaction is being explored as an explanation to understand the risk of AD. This is not surprising because *APOE* plays a central role in cholesterol uptake and transport in the brain and is necessary for amyloid deposition in transgenic mice.[23] In addition, cholesterol has been shown to affect amyloid production,[24,25] and increased levels have been associated with an increased risk of AD. Some studies have reported a significant interaction between *APOE* and cholesterol in determining the risk of AD.[26-28] One of these studies suggested that cholesterol, in fact, mediates some of the effects of *APOE*-ε4 on AD.[28] However, the reports on cholesterol levels and AD risk have not always been consistent. Some studies have failed to find a relationship between cholesterol and AD risk[29-31] or an interaction between *APOE*, cholesterol, and AD.[32]

The precise mechanisms by which *APOE* isoforms and lipids are involved in the pathogenesis of AD still remain unclear. Each *APOE* isoform has shown to have different lipoprotein affinity. Also, *APOE* affinity for Aβ seems to be affected not only by isoform type but also by whether it is associated with lipids. Lipid associated *APOE* proteins have a higher Aβ binding affinity than the delipidated isoforms.[33] In one study, the *APOE*-ε3 molecules that contained lipid associated particles (native state) had a two- to threefold higher Aβ binding affinity than *APOE*-ε4.[33] Thus, the higher the lipid level is, the more *APOE*/lipid complexes are formed, increasing the interaction with Aβ. Perhaps, once a high threshold of lipid levels has been reached, it does not matter which *APOE* isoform is present; they all will interact with Aβ. Whether this *APOE*-lipid-Aβ interaction affects metabolism, clearance, or deposition has yet to be resolved. One recent study suggested that AD disease progression was influenced by an *APOE*-ε4 cholesterol interaction.[34] That study suggested that high cholesterol levels might increase *APOE*-ε3 expression to a greater extent than *APOE*-ε4, leading to increased Aβ deposition in individuals with *APOE*-ε3.

Triglyceride levels for subjects without ε4 were not associated with an increased risk of AD. Other studies have also found no association between triglyceride levels and AD risk but did not stratify for *APOE*.[35-41] Triglycerides are associated with an increased risk of coronary artery disease, particularly in women and patients with diabetes.[41,42] However, the association between triglycerides and risk of coronary artery disease has been difficult to demonstrate because there is a larger daily variation in fasting triglycerides (20 to 30%) and not all triglyceride-rich lipoproteins are atherogenic. Hence, larger samples of AD cases with multiple measures may be needed to demonstrate that triglycerides are a risk factor for AD.

Similar to cholesterol, we did observe an interaction between triglycerides and *APOE* genotype. At low levels of triglycerides, possession of a ε4 allele was associated with an increased risk of AD. This interaction has not been demonstrated in Western societies.[35] *APOE*-ε4 may be a “thrifty” allele.[40] Low serum triglycerides may reflect a hypocaloric diet or high carbohydrate diet. This diet-gene interaction may lead to altered fatty acid delivery to neurons and dysfunctional processing of amyloid.[43]

The study sample had a small number of AD cases (29 subjects) and will require confirmation once a larger number of subjects become available. Most of the attrition of the 1992 cohort was due to death, raising the possibility of survivor bias. However, the possession of the *APOE*-ε4 allele was not associated with mortality risk in this cohort.[44] For this analysis, the clinically assessed normal group was combined with the good performance group in order to use more of the biomarker data in the analysis. It is possible that there may

have been undiagnosed cases of mild cognitive impairment or dementia in this group; however, analysis using just the clinically diagnosed normal group for comparison to the AD group revealed similar and significant cholesterol and *APOE* interaction. The analysis for this report is cross-sectional and longitudinal analysis would be important. The follow-up study is currently under way. Nevertheless, it provides more information suggesting that cholesterol, a potentially modifiable risk factor, is associated with increased risk of AD even in a population with relatively low levels of cholesterol.

Acknowledgments

The authors thank the elders of Idikan, Ibadan for their participation.

Supported by grant RO1AGO9956-14, The Indianapolis-Ibadan Dementia Project from the National Institute on Aging.

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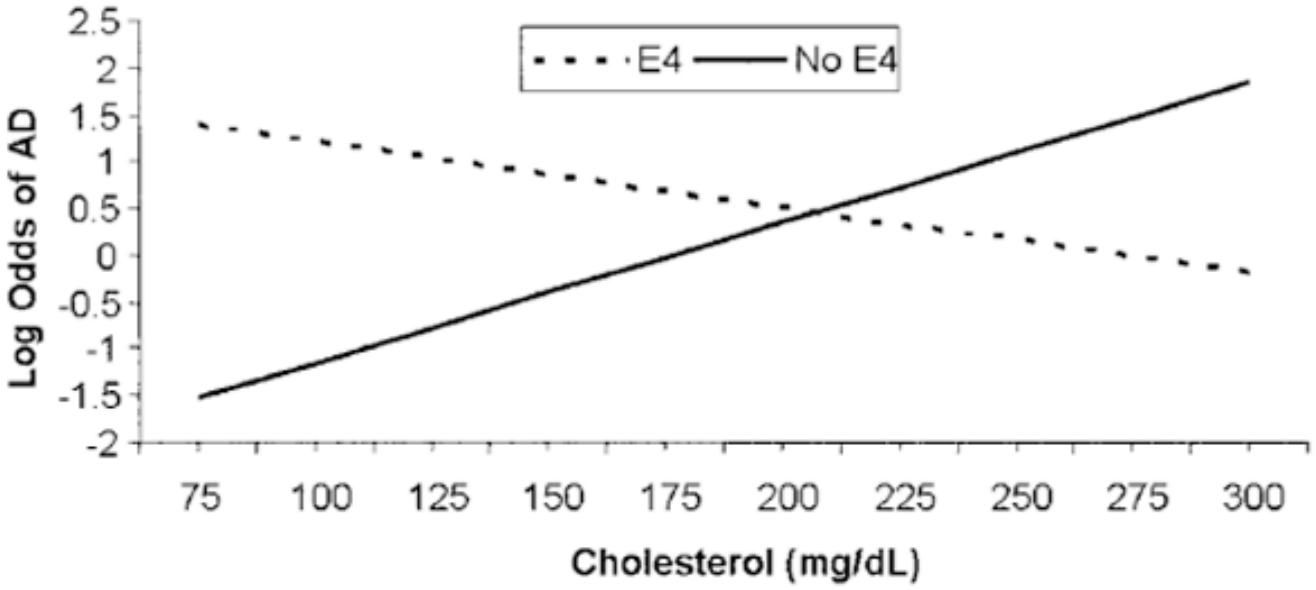

Figure. Predicted log ORs of AD risk vs cholesterol level by APOE-ε4 group. This graph shows an interaction between cholesterol and APOE. For individuals without ε4, there was an increased risk of AD with higher cholesterol levels

Table 1

Demographics, self-reported vascular history, and lipid measures in AD and normal participants by APOE genotype

	AD		Normal	
	ε4, n = 14	**No ε4, n = 15**	**ε4, n = 416**	**No ε4, n = 630**
% Female	71.4% (10.0)	93.3% (14.0)	64.9 (270.0)	65.6 (413.0)
% Educated	14.2% (2.0)	6.7% (1.0)	13.2 (55.0)	15.6 (98.0)
Mean age, y (SD)	79.7 (6.3)	82.8 (8.6)	75.9 (4.8)	76.4 (5.2)
Mean BMI (SD)	19.7 (3.7)	21.3 (3.9)	21.7 (4.6)	22.1 (4.8)
% Diabetes	0.0% (0.0)	0.0% (0.0)	1.0% (4.0)	2.0% (12.0)
% Heart attack	7.1% (1.0)	20.0% (3.0)	9.0% (38.0)	5.0% (32)
% Hypertension	7.1% (1.0)	31% (4.0)	27.0% (110.0)	25.0% (150.0)
% Stroke	7.1% (1.0)	0.0% (0.0)	1.4% (6.0)	1.8% (11.0)
Mean cholesterol (SD)	173.2 (39.9)	192.2 (36.0)	179.2 (39.7)	170.9 (36.0)
Mean HDL (SD)	54.2 (13.5)	52.9 (12.2)	50.0 (13.7)	50.0 (13.4)
Mean LDL (SD)	104.8 (31.1)	121.4 (33.8)	110.9 (31.8)	103.2 (33.0)
Mean triglycerides (SD)	71.5 (11.4)	89.8 (37.0)	91.3 (36.3)	89.2 (37.0)

Values represent % (n) or mean (SD).

AD = Alzheimer disease; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2

Logistic regression results for the effects of lipids biomarkers and APOE on AD risk controlling for age and gender

Model	Regression coefficient	SE	Odds ratio	*p* Value
Cholesterol	0.015	0.007	1.015	0.025
Genotype (ε4 vs no ε4)	0.674	0.410	1.962	0.100
Cholesterol*genotype	−0.022	0.010	0.978	0.022
LDL	0.017	0.007	1.017	0.023
Genotype (ε4 vs no ε4)	0.627	0.408	1.872	0.124
LDL*genotype	−0.029	0.012	0.971	0.018
HDL	0.014	0.019	1.014	0.457
Genotype (ε4 vs no ε4)	0.536	0.402	1.709	0.182
HDL*genotype	−0.0003	0.027	0.999	0.991
Triglyceride	0.002	0.007	1.002	0.788
Genotype (ε4 vs no ε4)	0.407	0.436	1.502	0.351
Triglyceride*genotype	−0.033	0.016	0.968	0.036

AD = Alzheimer disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein.