ARIC Manuscript Proposal # 973

PC Reviewed: 11/21/03	**Status: A**	**Priority: 2**
SC Reviewed: 11/24/03	**Status: A**	**Priority: 2**

1.a. Full Title: Apolipoprotein E polymorphism and cholelithiasis in a large, population-based cohort: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): ApoE and Gallbladder Disease

2. Writing Group (list individual with lead responsibility first):

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Writing Group: Aaron Folsom, Eric Boerwinkle, Molly Bray, others welcome

3. Timeline:

Analysis November 2003 – February 2004
Manuscript draft completed by March 2004
Journal submission by May 2004

4. Rationale:

Apolipoprotein E (apoE) has a major role in the intestinal absorption and formation of lipoprotein particles in the intestine and transport and uptake of these particles by the liver. In humans, the apoE protein is polymorphic with three common isoforms: E2, E3, and E4 (1). The E2 allele has been associated with higher concentrations of apoE and lower total serum cholesterol, while E4 has been associated with lower concentrations of apoE and higher total cholesterol (2,3). Since biliary cholesterol is mainly derived from the hepatic uptake of plasma lipoprotein cholesterol (4), and the cholesterol saturation of bile is believed to be a necessary condition for the development of cholesterol gallstones, it is plausible that apoE polymorphism modulates a predisposition to cholelithiasis.

Several small clinical studies have reported positive associations between the E4 allele and the presence of gallstones (5), the cholesterol content of gallstones (6), the recurrence of gallstones after shock-wave lithotripsy (7), and the incidence of cholelithiasis after bariatric surgery (8). A Finnish study of about 1,000 men and women utilized ultrasonography to detect gallstones in asymptomatic subjects and reported that the presence of gallstones was significantly lower in women carrying an E2 allele compared to those without an E2 allele (9). However, this study and another (5) failed to find any significant association between apoE polymorphism and gallstones in men. In a recently published report from Japan, no significant associations were found between the E4 allele and the individual constituents of

bile acid composition, and the prevalence of the E4 allele was similar in patients with and without cholesterol gallstones (10).

ApoE genotyping was conducted on the entire ARIC cohort and the cumulative incidence of symptomatic gallstones through 2000 can be ascertained using a combination of cohort surveillance and self-report (from both the Visit 4 medical history questionnaire and the comprehensive medical history questionnaire that was administered in conjunction with annual follow-up between 1994 and 1996). A preliminary examination of these data indicate that approximately 2,000 ARIC participants have had symptomatic cholelithiasis.

Previous ARIC work has demonstrated that white race, obesity, low HDL cholesterol, and elevated triglycerides and insulin, are pertinent risk factors for incident gallbladder disease in the cohort (11). While the E4 allele has been consistently associated with elevated total cholesterol, it is also inversely related with total plamsa triglycerides (12). Conversely, the E2 allele, while being associated with low total cholesterol, is associated with higher levels of triglycerides. In addition, both the E2 and E4 allele frequencies are higher in African-Americans, a race group known to have low rates of gallbladder disease. In light of previously determined risk factors for gallbladder disease in the ARIC cohort and the inconsistent results of studies of plasma lipids and gallstones, these known relations with apoE genotype give rise to competing hypotheses about the potential association between apoE genotype and gallbladder disease. An investigation of the association between apoE genotype and cholelithiasis in this large, population-based cohort with a wide variety of risk factor data would make an important contribution to the small body of existing clinic-based literature.

References:

(1) Mahley RW, Huang Y. Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond. *Curr Opin Lipidol* 1999; 10:207-210.

(2) Eichner JE, Dunn ST, Perveen G, Thompson DM., Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE Review. *Am J Epidemiol* 2002; 155:487-95.

(3) Boerwinkle E, Utermann G. Simultaneous effects of the apolipoprotein E polymorphism on apolipoprotein E, apolipoprotein B, and cholesterol metabolism. *Am J Hum Genet* 1988; 42(1):104-112.

(4) Zanlungo S, Nervi F. The molecular and metabolic basis of biliary cholesterol secretion in gallstone disease. *Front Biosci* 2003 8:s1166-74.

(5) Bertomeu A, Ros E, Zambon, et al. Apolipoprotein E polymorphism and gallstones. *Gastroenterol* 1996; 111(6):1603-1610.

(6) Juvonen T, Kervinen K, Kairaluoma MI, et al. Gallstone cholesterol content is related to apolipoprotein E polymorphism. *Gastoenterol* 1993; 104(6):1806-1813.

(7) Portincasa P, van Erpecum KJ, van De Meeberg PC, et al. Apolipoprotein E4 genotype and gallbladder motility infulence speed of gallstone clearance and risk of recurrence after extracorporeal shock-wave lithotripsy. *Hepatol* 1996; 24(3):580-587.

(8) Abeid SA, Szold A, Gavert N, et al. Apolipoprotein E genotype and the risk of developing cholelithiasis following bariatric surgery: a clue to prevention of routine prophylactic cholecystectomy. *Obes Surg* 2002; 12:354-357.

(9) Niemi M, Kervinen K, Rantala A, et al. The role of apolipoprotein E and glucose intolerance in gallstone disease in middle aged subjects. *Gut* 1999; 44(4):557-62.

(10) Hasegawa K, Terada S, Kubota K, et al. Effect of apolipoprotein E polymorphism on bile lipid composition and the formation of cholesterol gallstone. *Am J Gastroenterol* 2003; 98:1605-1609.

(11) Boland LL, Folsom AR, Rosamond WD. Hyperinsulinemia, dyslipidemia, and obesity as risk factors for hospitalized gallbladder diease: a prospective study. *Ann Epidemiol* 2002; 12:131-140.

(12) Mahley RW, Rall SC. Apolipoprotein E: Far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000; 01:507-537.

5. Main Hypothesis/Study Questions:

1. Does the presence of an E2 or E4 allele confer excess risk for symptomatic cholelithiasis?

   And if so,

   a.) is the association independent of other known risk factors? (confounding)

   b.) is the association independent of plasma lipid levels? (causal pathway)

   c.) does the association vary by gender? race? plasma lipid levels? obesity status?

6. Data (variables, time window, source, inclusions/exclusions):

Determination of symptomatic cholelithiasis: Cohort surveillance files through 2000 will be used to identify any cases of cholelithiasis that occurred during ARIC follow-up. Information from the comprehensive medical history questionnaire administered by telephone from 1994-1996 (AMHA) and the medical history questionnaire from the Visit 4 clinic examination (MHQA) will be used to identify self-reported cases of gallstones that may have occurred prior to enrollment in ARIC. Because abdominal ultrasound was not performed as part of ARIC, careful consideration will be given to instances in which gallstones may have been detected by ultrasound inadvertently. We have no specific hypothesis *per se* about apoE genotype being associated only with gallstones that become symptomatic, but restricting to cases that are symptomatic might help to minimize misclassification.

Other variables and Visit 1 covariates: ApoE genotype, gender, race, age, field center, body-mass index, waist-to-hip ratio, smoking status, lipids levels, diabetes status and insulin level, and hypertension.

Exclusions: Exclude those who are not white or African-American, those with missing apoE genotype data, those who have indicated they do not want their DNA used for any type of analysis, and those who have not given consent for non-CVD related genetic research.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __X__ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __X__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___**X**___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MS#732 (Boerwinkle) ApoE genotype and stroke – *no overlap*
MS#794 (Bray) Dietary fat modulates the ApoE-CVD risk factors association – *no overlap*
MS#924 (Blair) ApoE genotype and cognitive function. – *no overlap*
MS#104 (Boerwinkle) ApoE polymorphism influences postprandial retinyl palmitate, but not triglycerides – *no overlap*
MS#104A (de Andrade) ApoE genotype predicts atherosclerosis – *no overlap*
MS#188 (Brown) ApoE genotype and glucose, insulin, and triglycerides – *withdrawn*
MS#202 (Surguchov) ApoE genotype and plasma lipid transport – *no overlap*
MS#346A (Ellsworth) ApoE gene predicts incident CHD in whites – *no overlap*
MS#346B (Ellsworth) ApoE gene predicts incident CHD in African-Americans – *no overlap*
MS#944 (Wong) ApoE polymorphism and retinal disease – *no overlap*
MS#675 (Boland) Risk factors for incident gallbladder disease – *no overlap; did not look at ApoE genotype*

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.