Apolipoprotein E Polymorphism Modulates the Association Between Obesity and Dyslipidemias During Young Adulthood: The Bogalusa Heart Study

Sathanur R. Srinivasan, Christian Ehnholm, Abdalla Elkasabany, and Gerald S. Berenson

To elucidate to what extent apolipoprotein (apo) E polymorphism modulates obesity-induced dyslipidemias during young adulthood, longitudinal data on 759 individuals (72% white/28% black; initial and follow-up mean age, 25.9 and 32.7 years) were examined. Among both races and the total sample, the apo E2 group (with E2/2 or E2/3 phenotype) had significantly lower and the apo E4 (with E4/4 or E3/4 phenotype) group higher low-density lipoprotein (LDL) cholesterol than the apo E3 (with E3/3 phenotype) group at both examinations. In addition, the apo E2 group displayed higher high-density lipoprotein (HDL) cholesterol in the total sample. No allele-specific effect was noted for the longitudinal changes (Δ). An increase in Δ adiposity, measured as Δ body mass index (BMI), was accompanied by higher increase in ΔLDL cholesterol in the e4 carriers than the e2 carriers among the whites ($P < .05$) and the total sample ($P < .01$); an increase in Δ triglycerides and decrease in Δ HDL cholesterol in the e2 carriers than the e4 carriers among all the groups ($P < .05$ to $.001$). Among the apo E phenotype groups, the incidence of high (>75th percentile specific for race and sex) LDL cholesterol at follow-up was in the order E4 > E3 > E2 both in the obese (BMI > 30; P for trend = .033) and the nonobese (BMI < 25; P for trend = .035) groups. Although the increase of low (<25th percentile specific for race and sex) HDL cholesterol or high triglycerides showed no apo E phenotype-specific trend, the incidence of high triglycerides without high LDL cholesterol was in the order E2 > E3 > E4 only in the obese group (P for trend = .025). The prevalence trend for dyslipidemias at follow-up among the persistently obese and nonobese groups also gave similar results. Thus, apo E gene locus influences not only the levels of certain lipoprotein variables during young adulthood, but also modulates the association between obesity and dyslipidemias.

APOLIPOPROTEIN (apo) E alleles are genetic markers for dyslipidemias and coronary artery disease.[1-3] The apo E gene locus is polymorphic; 3 alleles, termed e2, e3, and e4, produce 6 phenotypes: E2/2, E2/3, E2/4, E3/3, E3/4, and E4/4.[4,5] The apo E isoforms encoded by the 3 alleles differ in terms of their influence on binding to cell surface receptors (apo E, apo B/E receptors) and their ligands, catabolism of apo B-containing lipoproteins, conversion of very–low-density lipoproteins (VLDL) to low-density lipoproteins (LDL), and intestinal absorption of dietary cholesterol, mechanisms that are thought to mediate levels of lipoproteins.[6-14]

Population studies have shown that compared with the e3 allele, the e2 allele lowers and the e4 allele raises total cholesterol and LDL cholesterol.[15-21] In addition, both the e2 and e4 alleles are found to be associated with higher triglyceride levels in some, but not all studies.[1,2,15,17,20-25] That this allele effect on lipoprotein variables, especially LDL cholesterol, occurs in populations around the world, despite variations in genetic background and environment, underscores the direct role of the apo E gene in determining lipoprotein levels and consequently dyslipidemias.

The association between obesity and dyslipidemias is well recognized.[26-29] Earlier studies, including our own in children, have found that the apo E polymorphism alters the relation of body fat mass and distribution to lipoprotein levels.[30-37] However, most of the studies were cross-sectional in nature. Moreover, to what extent apo E polymorphism modulates obesity-induced dyslipidemias in young adult populations unselected for dyslipidemias is not clear. The present study examines this aspect with the use of longitudinal data from the ongoing Bogalusa Heart Study, a community-based investigation of early natural history of cardiovascular disease.[38]

SUBJECTS AND METHODS

Population

In 1988 to 1991, 1,930 young adults aged 20 to 32 years, residing in the biracial (65% white, 35% black) community of Bogalusa, LA, were examined (baseline). Seven hundred fifty-nine of these subjects who had apo E phenotyped at baseline and participated later in the 1995 to 1996 survey (follow-up) were considered for this analysis. Mean ± SD baseline age, follow-up age, and follow-up period were 25.9 ± 3.1 years, 32.7 ± 3.1 years, and 6.8 ± 0.8 years, respectively. The study cohort consisted of 72% whites, 28% blacks, 40% males, and 60% females.

General Examination

Essentially the same protocols were used in all surveys. All participants were instructed to fast for 12 hours before venipuncture, with compliance ascertained by an interview. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, to calculate the body mass index (BMI, kg/m^2).

Serum Lipid and Lipoprotein Analyses

Cholesterol and triglyceride levels were measured enzymatically in an Abbott VP instrument (Abbott Laboratories, North Chicago, IL). Serum lipoprotein cholesterol was measured by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedure.[39] The laboratory is monitored for accuracy of measurements of total cholesterol, triglycerides, and HDL cholesterol concentration by a

From the Tulane Center for Cardiovascular Health and Departments of Epidemiology and Biostatistics, Tulane School of Public Health and Tropical Medicine, New Orleans, LA; and the National Public Health Institute, Helsinki, Finland.

Submitted August 11, 2000; accepted December 12, 2000.

Supported by Grants No. HL-38844 from the National Heart, Lung, and Blood Institute and AG-16592 from the Institute on Aging.

Address reprint requests to Gerald S. Berenson, MD, Tulane Center for Cardiovascular Health, 1440 Canal St, Suite 2140, New Orleans, LA 70112.

0026-0495/01/5006-0011$35.00/0

doi:10.1053/meta.2001.23299

surveillance program of the Centers for Disease Control and Prevention, Atlanta, GA.

Apo E Phenotyping

Serum samples that were kept frozen at -70°C after lipid and lipoprotein analyses were sent to Helsinki, Finland (Dr Ehnholm) for apo E phenotyping. Phenotyping was performed directly in serum using a modification[40] of the method of Havekes et al,[41] which is based on isoelectric focusing of delipidated serum followed by immunoblotting using rabbit antihuman apo E antiserum. Based on 147 pairs of blind duplicate analysis, there was 95% concordance in apo E phenotype assignment. Although DNA genotyping is considered more accurate and increasingly being used for determining apo E polymorphism, results from the Framingham Offspring Study showed that both methods gave similar apo E allele frequencies and allelic effects on lipoprotein variables.[42]

Statistical Analysis

Because the sample size of homozygous phenotypes E2/2 and E4/4 in the study cohort was too small, individuals were classified into the following 3 phenotype groups as in previous studies[33,35]: (1) apo E2 group (n = 92) carrying either the E2/2 or the E3/2 phenotype; (2) apo E3 group (n = 446) carrying the most frequent E3/3 phenotype; and (3) apo E4 group (n = 200) carrying either the E4/3 or the E4/4 phenotype. Individuals with E4/2 phenotype (n = 21) were not included, because they carry an allele that is common to either the apo E2 group or the apo E4 group.

Statistical analysis was performed using the SAS software package (SAS Institute, Cary, NC). The gene-counting method was used for estimating apo E allele frequency within each race-sex group. Individual χ^2 tests of independence were used to determine significance of both race and sex differences in the distribution of allele frequency.

Analysis of covariance to adjust for age and race/sex as applicable was performed to test whether mean levels of lipoprotein variables were homogeneous among the 3 apo E phenotype groups. Post hoc comparison of lipoprotein variables and their changes over time between the phenotype groups were determined by the least significant difference (LSD) test. To avoid the problem of multiple comparisons, the LSD test was used only if the F-value for the apo E phenotype effect was found significant.

The average effect of the e2 or the e4 allele versus the e3 allele on lipoprotein variables was estimated using a regression approach described by Templeton.[43]

The effect of interaction between changes in BMI over time and the e2 allele or the e4 allele on changes in lipoprotein variables was measured in terms of multiple linear regression coefficients using a regression parameterization procedure for longitudinal data described by Gueguen et al.[30] In addition to the 2 interaction terms (Δ BMI and number of e2 or e4 alleles), the regression model included age and BMI at baseline, time interval between examinations, and race/sex as applicable.

The incidence of specific dyslipidemia at follow-up was determined according to the obesity status at baseline and apo E phenotype group. Mantel-Haenzel χ^2 test for trend was used to examine the effect of apo E phenotype on the incidence of dyslipidemia in obese and nonobese groups. Similar analysis was performed to determine the prevalence of dyslipidemia at follow-up by apo E phenotype group among those who were persistently obese or nonobese at baseline and follow-up. Dyslipidemias were defined as race- and sex-specific values above the 75th percentile for high LDL cholesterol or high triglycerides and below the 25th percentile for low HDL cholesterol. Individuals with BMI above 30 were classified as obese; below 25 as nonobese.

RESULTS

The relative frequency of the e2, e3, and e4 alleles in the study cohort by race (0.068, 0.792, and 0.140 for whites *v* 0.103, 0.702, and 0.195 for blacks) was similar to that reported earlier in the Bogalusa young adult population at large.[44] Blacks versus whites displayed a lower frequency of the e3 allele and higher frequencies of both the e2 and e4 alleles ($P < .001$).

Mean levels of serum LDL cholesterol, HDL cholesterol, and triglycerides at baseline and follow-up and their changes over time in whites, blacks, and the total sample are presented in Tables 1 through 3 by apo E phenotype group. There was no evidence of race or sex by apo E phenotype interaction for any of these lipoprotein variables. Levels of LDL cholesterol varied significantly among the 3 phenotype groups both at baseline and follow-up, regardless of race. Compared with the apo E3 group, the apo E2 group had lower and the apo E4 group higher LDL choleterol at both periods. Levels of HDL cholesterol by the apo E phenotype group varied significantly in the total sample, with the apo E2 group versus the apo E3 showing higher values at both examinations. Whites and blacks tended to show a similar, but nonsignificant trend. Serum triglyceride levels at both examinations did not vary by the apo E phenotype group in whites, blacks, or the total sample. There were no significant apo E phenotype-specific differences in change over time of these 3 lipoprotein variables.

With respect to significant allele-specific effects on lipoprotein variables in the total sample, the average effect of the e2 allele versus the e3 allele was to lower LDL cholesterol by 16.9 mg/dL at baseline ($P < .001$) and 20.1 mg/dL at follow-up ($P < .001$) and to raise HDL cholesterol by 3.0 mg/dL at baseline ($P < .01$) and 2.8 mg/dL at follow-up ($P < .01$). On the other hand, the average effect of the e4 allele versus the e3 allele was to raise LDL cholesterol by 6.2 mg/dL at baseline ($P < .01$) and 5.3 mg/dL at follow-up ($P < .01$).

Table 1. Levels of Serum LDL Cholesterol at Baseline and Follow-up and Change Over Time in Young Adult Cohort by apo E Phenotype Group

	Mean ± SD, mg/dL		
LDL Cholesterol	E2	E3	E4
Baseline			
Whites[b]	100 ± 29[y] (60)*	116 ± 32 (343)	123 ± 31[y] (136)
Blacks[a]	103 ± 30[x] (32)	111 ± 31 (103)	122 ± 33[x] (44)
All[b]	101 ± 25[y] (92)	115 ± 32 (446)	123 ± 32[y] (200)
Follow-up			
Whites[b]	110 ± 30[y]	127 ± 34	134 ± 32[x]
Blacks[b]	107 ± 31[x]	120 ± 37	129 ± 32[x]
All[b]	109 ± 30[y]	126 ± 35	133 ± 32[y]
Change†			
Whites	10 ± 24	11 ± 30	11 ± 23
Blacks	3 ± 25	8 ± 27	7 ± 27
All	8 ± 25	11 ± 29	10 ± 25

* Sample size at baseline and follow-up.

† Follow-up value − baseline value.

[a,b] Variation among phenotype groups, a: $P < .05$; b: $P < .001$ (age- and race-/sex-adjusted).

[x,y] Different from E3 group, x: $P < .05$; y: $P < .001$ (age-, and sex-/race-adjusted).

Table 2. Levels of Serum HDL Cholesterol at Baseline and Follow-up and Change Over Time in Young Adult Cohort by apo E Phenotype Group

	Mean ± SD, mg/dL		
HDL Cholesterol	E2	E3	E4
Baseline			
Whites	52 ± 13 (60)*	49 ± 11 (343)	49 ± 10 (136)
Blacks	59 ± 14 (32)	56 ± 16 (103)	57 ± 13 (44)
All[a]	54 ± 14[x] (92)	51 ± 12 (446)	52 ± 12 (200)
Follow-up			
Whites	51 ± 14	48 ± 12	48 ± 13
Blacks	55 ± 15	53 ± 17	53 ± 15
All[a]	52 ± 14[x]	49 ± 14	49 ± 13
Change†			
Whites	−1 ± 10	−1 ± 9	−1 ± 10
Blacks	−5 ± 20	−3 ± 14	−4 ± 12
All	−3 ± 14	−2 ± 10	−2 ± 11

* Sample size at baseline and follow-up.

† Follow-up value − baseline value.

[a] Variation among phenotype groups, a: $P < .05$; b: $P < .001$ (age- and race-/sex-adjusted).

[x] Different from E3 group, $P < .05$ (age- and race-/sex-adjusted).

The effect of interaction between the apo E alleles and the longitudinal change (Δ) in BMI on Δ LDL cholesterol, Δ HDL cholesterol, and Δ triglycerides adjusted for initial age and BMI, age interval between examinations, and sex/race is shown in Fig 1 for whites, blacks, and total sample. Regarding Δ LDL cholesterol, the interaction effect was significant in whites and the total sample, with an increase in Δ BMI accompanied by greater increase in Δ LDL cholesterol in the e4 carriers than the e2 carriers. The interaction effect was significant for Δ HDL cholesterol and Δ triglycerides in whites, blacks, and the total sample. An increase in Δ BMI lowered Δ HDL cholesterol and raised Δ triglycerides to a larger extent in the e2 carriers than the e4 carriers.

The incidence and prevalence of dyslipidemias by obesity status and apo E phenotype were examined in the total sample because of inadequate sample size of each racial group when categorized according to dyslipidemia, obesity, and apo E phenotype. The relationship of baseline obesity status (BMI above 30 or below 25) to the incidence of specific dyslipidemia (above the race- and sex-specific 75th percentile for LDL cholesterol and triglycerides and below the 25th percentile for HDL cholesterol) at follow-up by apo E phenotype group is given in Table 4. Among the apo E groups, the proportion of subjects who developed high LDL cholesterol at follow-up was in the order E4 > E3 > E2, both in the obese (P for trend = .033) and the nonobese (P for trend = .035) groups. The incidence of low HDL cholesterol or high triglycerides showed no significant pattern among the 3 apo E groups either in the obese or the nonobese group. However, the obese apo E4 group and the obese apo E2 group displayed the highest incidence of low HDL cholesterol and high triglycerides, respectively. Although the incidence of high triglycerides showed no significant apo E phenotype-specific trend either in the obese or the nonobese groups, the proportion of subjects who developed high triglycerides without concomitant rise in LDL cholesterol at follow-up was in the order E2 > E3 > E4 only in the obese group (P for trend = .025), with the apo E2 group showing 8.6-fold higher incidence than the nonobese apo E2 group ($P < .01$).

The prevalence of dyslipidemias at follow-up among those who were persistently obese or nonobese at both examinations are given in Table 5 by apo E phenotype group. The prevalence trend of any particular dyslipidemia across the apo E2, E3, and E4 phenotype groups was essentially similar to that of the incidence trend described above in obese, as well as nonobese groups. The prevalence of high LDL cholesterol was highest in the obese apo E4 group, while the prevalence of hypertriglyceridemia without high LDL cholesterol was highest in the obese apo E2 group. Further, the prevalence of high LDL cholesterol was 2.5-fold higher in the obese apo E4 group than the nonobese apo E4 group ($P < .001$), and hypertriglyceridemia without high LDL cholesterol was 4.2-fold higher in the obese apo E2 group than the nonobese apo E2 group ($P < .01$).

DISCUSSION

The present longitudinal study shows that the apo E allele-specific differences in the levels of LDL cholesterol and HDL cholesterol are maintained consistently during young adulthood, and this genetic polymorphism modulates the effect of obesity on developing dyslipidemias. These observations are based on a community-based sample whose apo E allele frequencies and lipoprotein levels were representative of the Bogalusa study population.[20,44] Further, the observed longitudinal (intraindividual) differences in the cohort, like intrapair differences in monozygous twin pairs, are useful in elucidating the effect of interaction between the apo E polymorphism and gain in adiposity on lipoprotein changes without the confounding effects of gene-gene interactions, because the gene-gene interactions remain the same within an individual over time.[45]

The apo E allele-specific effect on LDL cholesterol in the study cohort is consistent with the earlier studies showing lower and higher values in e2 and e4 carriers, respectively, than those homozygous for the e3 allele.[15-19,21] The present study, as in some previous studies,[20,22,46,47] also shows higher HDL

Table 3. Levels of Serum Triglycerides at Baseline and Follow-up and Change Over Time in Young Adult Cohort by apo E Phenotype Group

	Mean ± SD, mg/dL		
Triglycerides	E2	E3	E4
Baseline			
Whites	117 ± 61 (60)*	108 ± 63 (343)	100 ± 48 (136)
Blacks	85 ± 43 (32)	91 ± 51 (103)	105 ± 116 (44)
All	106 ± 57 (92)	104 ± 61 (446)	102 ± 75 (200)
Follow-up			
Whites	122 ± 72	128 ± 106	121 ± 81
Blacks	102 ± 46	94 ± 68	90 ± 56
All	115 ± 65	120 ± 100	111 ± 75
Change†			
Whites	1 ± 63	22 ± 84	21 ± 60
Blacks	20 ± 50	4 ± 55	−16 ± 82
All	8 ± 59	17 ± 79	9 ± 70

* Sample size at baseline and follow-up.

† Follow-up value − baseline value.

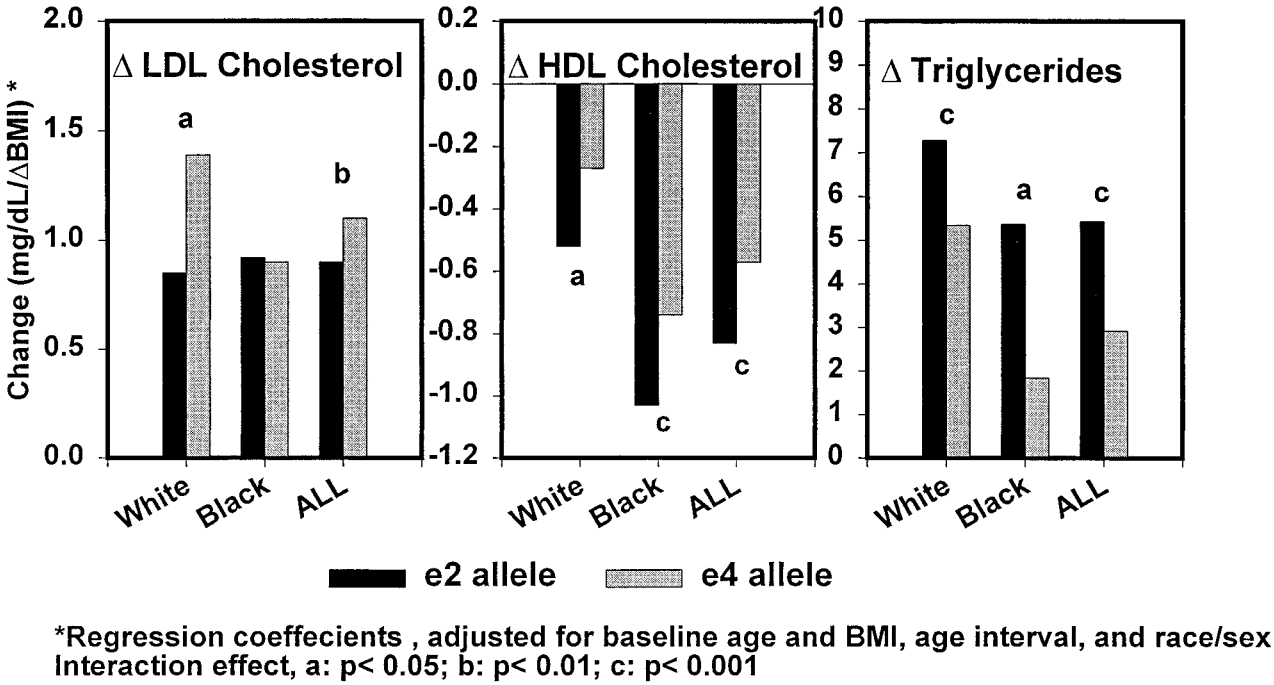

Fig 1. The influence of apo E polymorphism on the association between longitudinal change (Δ) in BMI and concomitant changes in Δ LDL cholesterol, Δ HDL cholesterol, and triglycerides.

cholesterol levels in e2 carriers. With respect to triglyceride levels, a meta-analysis of 45 population samples suggests that both the e2 and e4 alleles may be associated with higher values.[22] However, no such association was found in the present, as well as other previous population-based studies by us and others.[15,16,20,21,23,40] It has been reported that the proportion of variance in triglycerides that was due to apo E genotype was higher in older than in younger age groups,[25] which may, in part, account for the discordant results.

Consistent with earlier findings,[30,40,48] the longitudinal changes in the levels of LDL cholesterol, HDL cholesterol, and triglycerides were not influenced by the apo E polymorphism in the study cohort. However, our results clearly show that the apo E polymorphism alters the longitudinal changes in the levels of

Table 4. Incidence of Dyslipidemias at Follow-up in Young Adult Cohort According to Status of Obesity at Baseline and apo E Phenotype Group

	Incidence (%)			
Dyslipidemia*	E2	E3	E4	*P* for Trend
High LDL cholesterol				
Obese†	0	11	25	.033
Nonobese†	8	12	20	.035
Low HDL cholesterol				
Obese	20	15	32	.301
Nonobese	6	8	12	.210
High triglycerides				
Obese	43	24	22	.390
Nonobese	14	15	9	.309
High triglycerides without high LDL cholesterol				
Obese	43	15	0	.025
Nonobese	5	10	8	.958

* Race- and sex-specific values at follow-up above the 75th percentile (high) or below the 25th percentile (low).

† Obese, BMI > 30 at baseline; nonobese, BMI < 25 at baseline.

Table 5. Prevalence of Dyslipidemias in Persistently Obese Versus Nonobese Young Adult Cohort by apo E Phenotype Group

	Prevalence (%)			
Dyslipidemia*	E2	E3	E4	*P* for Trend
High LDL cholesterol				
Obese†	10	32	57	.007
Nonobese†	3	18	23	.020
Low HDL cholesterol				
Obese	30	42	52	.219
Nonobese	6	14	16	.210
High triglycerides				
Obese	50	43	35	.377
Nonobese	12	12	12	.913
High triglycerides without high LDL cholesterol				
Obese	50	28	9	.010
Nonobese	12	9	6	.270

* Race- and sex-specific values at follow-up above the 75th percentile (high) or below the 25th percentile (low).

† Obese, BMI > 30 at baseline and follow-up; nonobese, BMI < 25 at baseline and follow-up.

lipoproteins accompanied by gain in adiposity, measured as BMI.

In the study cohort, the gain in adiposity over time raised triglycerides and lowered HDL cholesterol to a larger extent in e2 carriers than e4 carriers, and raised LDL cholesterol in e4 carriers than e2 carriers. In contrast, an earlier longitudinal study, the only study of this nature conducted in a relatively older French cohort, showed a greater increase in both triglycerides and β-lipoprotein levels with weight gain over a 6-year period in e4 carriers than e2 carriers.[30] Earlier cross-sectional studies also gave mixed results, some showing stronger association between adiposity and triglycerides and/or LDL cholesterol in e2 carriers, e4 carriers, or both.[31-35,37]

In the current study, the incidence and prevalence of hypertriglyceridemia without high LDL cholesterol significantly increased in the order apo E2 group > apo E3 group > apo E4 group, with the obese apo E2 group showing significantly higher rates than their nonobese counterparts. In addition, the incidence and prevalence of high LDL cholesterol significantly increased in the order apo E4 group > apo E3 group > apo E2 group in both obese and nonobese groups, thereby maintaining the allele-specific effect, regardless of obesity status. However, the prevalence of high LDL cholesterol was markedly higher in the obese apo E4 group than the nonobese apo E4 group. Taken together, it appears that e2 and e4 carriers with obesity may be relatively more susceptible to have a greater degree of hypertriglyceridemia (without high LDL cholesterol) and high LDL cholesterol, respectively, than their nonobese counterparts in the general population. The reason for the lack of differential effect of apo E polymorphism on HDL cholesterol among those who were already obese (Tables 4 and 5) versus those who gained in adiposity over time (Fig 1) is not clear. It should be noted that unlike intraindividual changes over time, interindividual variance in a population or group reflect both gene-environment and gene-gene interactions, which may in part, account for the observed divergence in results pertaining to HDL cholesterol.

Based on the metabolic consequences of obesity vis-a-vis apo E isoforms on lipoprotein metabolism, certain inferences can be made regarding the mechanisms by which the apo E polymorphism modulates the effect of obesity on lipoproteins. Excess adiposity is associated with overproduction of VLDL and related adverse changes in fasting triglycerides, LDL cholesterol, and HDL cholesterol.[49-51] Although triglyceride levels were not affected by apo E polymorphism in the study cohort as a whole, gain in body fatness over time or condition of obesity was clearly associated with greater increase in triglycerides in e2 carriers than e4 carriers. This suggests that metabolic consequences of apo E isoforms regarding triglycerides may be apparent under conditions of VLDL overproduction. Unlike apo E4, apo E2 binds poorly to high-affinity lipoprotein receptors and their ligands leading to upregulation of LDL receptors[6-8] and is less efficient in converting VLDL to LDL.[11-13] As a consequence, an increased flux of VLDL due to gain in adiposity in e2 carriers may result in greater increase in triglycerides, as well as decrease in HDL cholesterol, a marker for reduced clearance of triglyceride-rich lipoproteins.[52,53] On the other hand, due to high affinity of apo E4 for triglyceride-rich lipoproteins and related enhanced hepatic clearance of remnant particles and downregulation of LDL receptors,[7-10] overproduction of VLDL in e4 carriers may lead to a greater increase in LDL cholesterol.

In the present study, BMI was used as an indicator of adiposity. In younger middle-aged populations in whom weight change primarily reflects change of fat mass, BMI is strongly associated with fat mass.[54] Although BMI does not reflect fat pattern, an earlier study on the interaction effect of apo E polymorphism and body fatness on lipoproteins found similar results using BMI, waist-to-hip ratio, and computed tomography-derived total and intra-abdominal fat.[33] Earlier observations from this population showed a high correlation between the BMI and skinfold thicknesses or the ratio of subscapular to triceps skinfold thickness, measures of fat mass, and fat distribution.[55,56]

In conclusion, the genetic polymorphism of apo E modulates the effect of obesity on dyslipidemias during young adulthood. Although control of obesity is obviously very important, regardless of apo E genotype, the differential effects of apo E alleles on dyslipidemias in obesity may have a bearing on coronary artery disease risk reduction strategies.

REFERENCES

1. Davignon J, Gregg RE, Sing CF: Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 8:1-21, 1988

2. Uterman G: Apolipoprotein E polymorphism in health and disease. Am Heart J 113:433-440, 1987

3. Wilson PWF, Schaefer EJ, Larson MG, et al: Apolipoprotein E alleles and risk of coronary disease: A meta-analysis. Arterioscler Thromb Vasc Biol 16:1250-1255, 1996

4. Uterman G, Hees M, Steinmetz A: Polymorphism of apolipoprotein E and occurrence of dysbetalipoproteinemia in man. Nature 269: 604-607, 1977

5. Zannis VI, Just PW, Breslow JL: Human isoprotein subclasses are genetically determined. Am J Hum Genet 33:11-34, 1981

6. Weisgraber KH, Innerarity TL, Mahley RW: Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site. J Biol Chem 257:2518-2521, 1982

7. Gregg RE, Brewer HB Jr: The role of apolipoprotein E and lipoprotein receptors in modulating the in vivo metabolism of apolipoprotein B-containing lipoprotein in humans. Clin Chem 34:B28-B32, 1988

8. Havel RJ, Chao Y, Windler EE, et al: Isoprotein specificity in the hepatic uptake of apolipoprotein E and the pathogenesis of dysbetalipoproteinemia. Proc Natl Acad Sci USA 77:4349-4353, 1980

9. Weintraub MS, Eisenberg S, Breslow JL: Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. J Clin Invest 80:1571-1577, 1987

10. Brenninkmeijer BJ, Stuyt PM, Demacker PNM, et al: Catabolism of chylomicron remnants in normolipidemic subjects in relation to the apoprotein E phenotype. J Lipid Res 28:361-370, 1987

11. Stalenhoref AFH, Malloy MJ, Kane JP, et al: Metabolism of apolipoprotein B-48 and B-100 of triglyceride-rich lipoproteins in patients with familial dysbetalipoproteinemia. J Clin Invest 78:722-728, 1986

12. Chung BH, Segrest JP: Resistance of a very–low-density lipoprotein subpopulation from familial dysbetalipoproteinemia to in vitro lipolytic conversion of the low-density lipoprotein fractions. J Lipid Res 24:1148-1159, 1983

13. Ehnholm C, Mahley RW, Chappell DA, et al: Role of apolipoprotein E in the lipolytic conversion of very–low-density lipoproteins to low-density lipoproteins in type III hyperlipoproteinemia. Proc Natl Acad Sci USA 81:5566-5570, 1984

14. Kesaniemi YA, Ehnholm C, Miettinen TA: Intestinal cholesterol absorption efficiency in man is related to apoprotein E phenotype. J Clin Invest 80:578-581, 1987

15. Ehnholm C, Lukka M, Kuusi T, et al: Apolipoprotein E polymorphism in the Finnish population: Gene frequencies and relation to lipoprotein concentrations. J Lipid Res 27:227-235, 1986

16. Boerwinkle E, Visvikis S, Welsh D, et al: The use of measured genotype information in the analysis of quantitative phenotypes in man: II. The role of the apolipoprotein E polymorphism in determining levels, variability and covariability of cholesterol, betalipoprotein and triglycerides in a sample of unrelated individuals. Am J Med Genet 27:567-582, 1987

17. Ordovas JM, Litwack-Klein L, Wilson PWF, et al: Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. J Lipid Res 28:371-380, 1987

18. Hallman DM, Boerwinkle E, Saha W, et al: The apolipoprotein E polymorphism: A comparison of allele frequencies and effects in nine populations. Am J Hum Genet 49:338-349, 1991

19. Kamboh MI, Aston CE, Ferrell RE, et al: Impact of apolipoprotein E polymorphism in determining interindividual variation in total cholesterol and low-density lipoprotein cholesterol in Hispanics and non-Hispanic whites. Atherosclerosis 98:201-211, 1993

20. Srinivasan SR, Ehnholm C, Wattigney W, et al: Apolipoprotein E polymorphism and its association with serum lipoprotein concentrations in black versus white children: The Bogalusa Heart Study. Metabolism 42:381-386, 1993

21. Fulton JE, Dai S, Grunbaum JA, et al: Apolipoprotein E affects serial changes in total and low-density lipoprotein cholesterol in adolescent girls: Project HeartBeat. Metabolism 48:285-290, 1999

22. Dallongeville J, Lussier-Cacan S, Davignon J: Modulation of plasma triglyceride levels by apoE phenotype: A meta-analysis. J Lipid Res 33:447-454, 1992

23. Schaefer EJ, Lamon-Fava S, Johnson S, et al: Effects of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. Arterioscler Thromb 14:1105-1113, 1994

24. Wilson PWF, Myers RH, Larson MG, et al: Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. JAMA 272:1666-1671, 1994

25. Jarvik GP, Goode EL, Austin MA, et al: Evidence that the apolipoprotein E genotype effects on lipid levels can change with age in males: A longitudinal analysis. Am J Hum Genet 61:171-181, 1997

26. Albrink MJ, Meigs JW, Granoff MA: Weight gain and serum triglycerides in normal men. N Engl J Med 266:484-489, 1962

27. Garrison RJ, Wilson PW, Castelli WP, et al: Obesity and lipoprotein cholesterol in the Framingham Offspring Study. Metabolism 29:1053-1060, 1980

28. Laskarzewski P, Morrison JA, Mellies MJ, et al: Relationships of measurements of body mass to plasma lipoproteins in school children and adults. Am J Epidemiol 111:395-406, 1980

29. Wattigney WA, Harsha DW, Srinivasan SR, et al: Increasing impact of obesity on serum lipids and lipoproteins in young adults: The Bogalusa Heart Study. Arch Intern Med 151:2017-2022, 1991

30. Gueguen R, Visvikis S, Steinmetz J, et al: An analysis of genotype effects and their interactions by using the apolipoprotein E polymorphism and longitudinal data. Am J Hum Genet 45:793-802, 1989

31. Fumeron F, Rigaud D, Bertiere MC, et al: Association of apolipoprotein epsilon 4 allele with hypertriglyceridemia in obesity. Clin Genet 34:258-264, 1988

32. Eto M, Watanabe K, Ishii K: Apolipoprotein E polymorphism and hyperlipoproteinemia in obesity. Int J Obes 13:433-440, 1989

33. Pouliot M-C, Despres J-P, Moorjani S, et al: Apolipoprotein E polymorphism alters the association between body fatness and plasma lipoproteins in women. J Lipid Res 31:1023-1029, 1990

34. Reilly SL, Ferrell RE, Kottke BA, et al: The gender-specific apolipoprotein E genotype influence on the distribution of plasma lipids and apolipoproteins in the population of Rochester, Minnesota. II. Regression relationships with concomitants. Am J Hum Genet 51: 1311-1324, 1992

35. Srinivasan SR, Ehnholm C, Wattigney WA, et al: Relationship between obesity and serum lipoproteins in children with different apolipoprotein E phenotypes: The Bogalusa Heart Study. Metabolism 43:470-475, 1994

36. Uusitupa MIJ, Karhunen L, Rissanen A, et al: Apolipoprotein E phenotype modifies metabolic and hemodynamic abnormalities related to central obesity in women. Am J Clin Nutr 64:131-136, 1996

37. Boer JMA, Ehnholm C, Menzel H-J, et al for the EARS Group: Interaction between lifestyle-related factors and the apoE polymorphism on plasma lipid and apolipoproteins. The EARS Study. Arterioscler Thromb Vasc Biol 17:1675-1681, 1997

38. The Bogalusa Heart Study: 20th Anniversary Symposium. Am J Med Sci 310:S1-S138, 1995 (suppl 1)

39. Srinivasan SR, Berenson GS: Serum lipoproteins in children and methods for study, in Lewis LA (ed): Handbook of Electrophoresis. Boca Raton, FL, CRC, 1983, pp 185-204

40. Lehtimäki T, Moilanen T, Viikari J, et al: Apolipoprotein E phenotypes in Finnish youths: A cross-sectional and 6-year follow-up study. J Lipid Res 31:487-495, 1990

41. Havekes L, de Knijff P, Beisiegel U, et al: A rapid micromethod for apolipoprotein E phenotyping directly in serum. J Lipid Res 28: 455-463, 1987

42. Lahoz C, Osgood D, Wilson PWF, et al: Frequency of phenotype-genotype discrepancies at the apolipoprotein E locus in a large population study. Clin Chem 42:1817-1823, 1996

43. Templeton AR: The general relationship between average effect and average excess. Genet Res 49:69-70, 1987

44. Srinivasan SR, Ehnholm C, Elkasabany A, et al: Influence of apolipoprotein E polymorphism on serum lipids and lipoprotein changes from childhood to adulthood. The Bogalusa Heart Study. Atherosclerosis 143:435-443, 1999

45. De Knijff P, Boomsma DI, de Wit E, et al: The effect of the apolipoprotein E phenotype on plasma lipids is not influenced by environmental variability: Result of a Dutch twin study. Hum Genet 91:268-272, 1993

46. Lapinleimu H, Viikari J, Niinikoski H, et al: Impact of gender, apolipoprotein E phenotypes, and diet on serum lipids and lipoproteins in infancy. J Pediatr 131:825-832, 1997

47. Tiret L, de Knijff P, Menzel H-J, et al for the EARS Group: ApoE polymorphism and predisposition to coronary heart disease in youths of different European populations. The EARS Study. Arterioscler Thromb 14:1617-1624, 1994

48. Srinivasan SR, Ehnholm C, Wattigney WA, et al: Influence of apolipoprotein E polymorphism on the tracking of childhood levels of serum lipids and apolipoproteins over a 6-year period. The Bogalusa Heart Study. Atherosclerosis 127:73-79, 1996

49. Grundy SM, Mok HY, Zech L, et al: Transport of very–low-density lipoprotein triglycerides in varying degrees of obesity and hypertriglyceridemia. J Clin Invest 63:1274-1283, 1979

50. Kesaniemi YA, Grundy SM: Increased low-density lipoprotein production associated with obesity. Arteriosclerosis 3:170-177, 1983

51. Despres JP: Obesity and lipid metabolism: Relevance of body fat distribution. Curr Opin Lipidol 2:5-15, 1991

52. Nikkilä EA, Taskinen MR, Sane T: Plasma high-density lipoprotein concentration and subfraction distribution in relation to triglyceride metabolism. Am Heart J 113:543-548, 1987

53. Tall AR: Plasma high density lipoproteins: Metabolism and relationship to atherogenesis. J Clin Invest 86:379-384, 1990

54. Spiegelman D, Israel RC, Bouchard C, et al: Absolute fat mass, percent body fat, and body-fat distribution: Which is the real determinant of blood pressure and serum glucose? Am J Clin Nutr 55:1033-1044, 1992

55. Srinivasan SR, Bao W, Wattigney WA, et al: Adolescent overweight is associated with adult overweight and related multiple cardiovascular risk factors: The Bogalusa Heart Study. Metabolism 45:235-240, 1996

56. Freedman DS, Srinivasan SR, Valdez RA, et al: Secular increases in relative weight and adiposity among children over two decades: The Bogalusa Heart Study. Pediatrics 99:420-426, 1997