Relationship of Apolipoproteins with Subclinical Cardiovascular Risk in Youth

Madeline A. Czeck, MS[1], Elise F. Northrop, BA[2], Nicholas G. Evanoff, MS[1,3], Donald R. Dengel, PhD[1,3], Kyle D. Rudser, PhD[2,3], Aaron S. Kelly, PhD[3,4], and Justin R. Ryder, PhD[3,4]

Objective To examine the association of apolipoproteins with arterial stiffness and carotid artery structure in children and adolescents.

Study design A total of 338 children and adolescents (178 female) with a mean age 13.0 ± 2.8 years were examined. Apolipoproteins (AI, AII, B_{100}, CII, CIII, and E) were measured via human apolipoprotein magnetic bead panel. Applanation tonometry determined pulse wave velocity and ultrasound imaging measured carotid intima-media thickness. Dual X-ray absorptiometry measured total body fat percent. Linear regression models were adjusted for Tanner stage, sex, and race with further adjustments for body fat percent. Linear regression models also examined the interaction between Tanner stage and apolipoproteins.

Results There was a significant positive association between pulse wave velocity and apolipoproteins: AI (0.015 m/s/10 μg/mL [CI 0.005-0.026], $P = .003$), AII (0.036 m/s/10 μg/mL [0.017-0.056], $P < .001$), B_{100} (0.009 m/s/10 μg/mL [0.002-0.016], $P = .012$), E (0.158 m/s/10 μg/mL [0.080-0.235], $P < .001$), and CIII:CII (0.033/μg/mL [0.014-0.052], $P < .001$). After we added body fat percent to the models, pulse wave velocity (PWV) remained positively associated with greater levels of apolipoproteins: AI, AII, B_{100}, E, and CIII:CII. Both with and without the adjustment for body fat percent, there were no significant associations between any apolipoprotein and carotid intima-media thickness. There were no significant interactions between Tanner stage and apolipoproteins.

Conclusions These findings suggest that greater levels of apolipoprotein AII, E, and CIII:CII are associated with increased arterial stiffness in children and adolescents, both with and without adjusting for percent body fat. These specific apolipoproteins may be useful as biomarkers of cardiovascular risk. *(J Pediatr 2020;227:199-203)*.

The pathophysiology leading to cardiovascular disease begins in childhood and is influenced by changes in cholesterol transport and synthesis.[1-3] Apolipoproteins regulate transportation and clearance of cholesterol. Specifically, apolipoprotein AI is carried on high-density lipoproteins (HDLs) and very low-density lipoproteins (VLDLs). Apolipoprotein AII is carried on HDL, whereas apolipoprotein B_{100} is carried on VLDL, intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs), with the B_{100}:AI reflecting a ratio of potentially atherogenic to non-atherogenic particles. Apolipoproteins CII, CIII, and E are carried on VLDL and HDL, with the CIII:CII representing activation or inhibition of lipoprotein lipase. Therefore, each apolipoprotein has functions that may be atherogenic or protective in nature. The association between apolipoproteins and cardiovascular disease risk factors have been reported in adults.[4-9] Greater levels of apolipoprotein B_{100} and CII and lower levels of apolipoprotein AI and E have been shown to be associated with increased risk of cardiovascular disease (ie, elevated triglycerides, increased risk of myocardial infarction).[10-12] In addition, apolipoprotein B_{100}:AI has been associated with greater carotid intima-media thickness (cIMT).[13,14] Increased cIMT has been shown to be associated with atherosclerotic cardiovascular disease events in adults.[15]

Studies in children have primarily focused on apolipoprotein AI and B_{100} concentrations.[16-18] Lower levels of apolipoprotein AI and greater levels of apolipoprotein B_{100} have been observed in children with obesity compared with their counterparts without obesity, showing an association with adiposity.[17,18] To date, few studies have examined apolipoprotein concentrations in relation to measures of subclinical vascular health in children.[19,20] There was a strong

BMI	Body mass index
cIMT	Carotid intima-media thickness
HDL	High-density lipoprotein
IDL	Intermediate-density lipoprotein
LDL	Low-density lipoprotein
PWV	Pulse wave velocity
VLDL	Very low-density lipoprotein

From the [1]School of Kinesiology; [2]Division of Biostatistics; and [3]Center for Pediatric Obesity Medicine, University of Minnesota; and [4]Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN

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positive correlation between flow-mediated dilation and apolipoprotein AI concentration in children of varying body mass index (BMI) values.[19] Therefore, previous studies have explored associations between flow-mediated dilation and apolipoprotein AI and B_{100} concentrations in children and adolescents, but they have not explored the association of pulse wave-velocity (PWV).[19,20] In addition, these studies did not include other potentially important apolipoproteins (ie, AII, CII, CIII, E).

The purpose of this study was to examine the association of a comprehensive panel of apolipoproteins (ie, AI, AII, B_{100}, CII, CIII, E, and the ratio of B_{100}:AI and CIII:CII) with measures of arterial stiffness (ie, PWV), and cIMT among children and adolescents. We hypothesized that apolipoprotein concentrations would be associated with arterial stiffness and cIMT irrespective of degree of body fatness.

Methods

This cross-sectional study included children and adolescents aged 8-17 years recruited between 2011 and 2016 from the Minneapolis and St Paul metropolitan area. Participants were recruited from various pediatric clinics within the community, including the University of Minnesota Masonic Children's Hospital Pediatric Weight Management Clinic (participants with obesity or severe obesity only). Exclusion criteria included untreated obstructive sleep apnea, obesity due to a genetic cause determined by physician diagnosis, previous medical history of weight loss (ie, bariatric) surgery, current use of antihypertensive medications, type 1 and 2 diabetes mellitus, medically documented history of hypercholesterolemia, chronic kidney disease, Kawasaki disease, autoimmune inflammatory diseases, and congenital heart disease. Study approval was given by the University of Minnesota institutional review board. Parents and participants provided informed consent and assent, respectively.

Height was measured using a wall-mounted stadiometer and weight was measured using a calibrated electronic scale. BMI was calculated by using body mass in kilograms divided by height in squared meters. Obesity status was stratified into 4 categories as defined by sex and age specific BMI percentiles: normal weight (≥5th to < 85th BMI percentile), overweight (≥85th to <95th BMI percentile), obesity (≥95th% to <120% of the 95th BMI percentile), and severe obesity (≥120% of the 95th BMI percentile, or absolute BMI >35 kg/m^2). Body fat percent was measured using standard procedures in the total-body supine position using dual X-ray absorptiometry (iDXA; General Electronic Medical Systems, Madison, Wisconsin) and data were analyzed using enCore software (platform version 16.0; General Electric Medical Systems). Age and race were self-reported. Sex and pubertal maturation stage were determined by a trained nurse or physician using classical Tanner staging.[21]

Fasting (>10 hours) blood samples were collected and lipids (total cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were measured using standard methods in the Fairview Diagnostics Laboratories, Fairview-University Medical Center (Minneapolis, Minnesota), a Centers for Disease Control and Prevention–certified laboratory. In addition, apolipoproteins AI, AII, B_{100}, CII, CIII, and E were measured with the MILLIPLEX MAP Human Apolipoprotein Magnetic Bead Panel kit (Millipore, Burlington, Massachusetts) in the University of Minnesota Cytokine Reference Laboratory. Analyte concentrations were obtained using xPONENT software (Luminex Corporation, Austin, Texas). The coefficient of variation for intra-assay and inter-assay was <10% and <20% for each apolipoprotein, respectively.

Pulse waveforms were obtained using an arterial tonometer (SphygmoCor; AtCor Medical, Sydney, Australia) placed over the strongest radial and carotid pulse points relative to the sternal notch to calculate PWV, a measure of arterial stiffness. Participants were connected to a 3-lead electrocardiogram to time the pulse waveforms to ventricular depolarization. Calculations were made via intersecting tangents method within the tonometer device software.

Images of the left carotid artery were obtained via ultrasound (Acuson, Seuoia 512; Siemens Medical Solutions USA, Inc, Mountain View, California) with an 8.0-15.0 MHz linear array probe. Images for determining cIMT, a measure of the thickness of the intima and media layers of the carotid artery, were obtained at end-diastole of the far wall of the common carotid artery. Diastolic and systolic lumen diameters of the imaged common carotid artery were obtained at a fixed point. Images were collected at 20 frames per second for 10 seconds, concurrently with the measurement of peripheral systolic and diastolic blood pressure, to ensure capture of the full arterial diameter change during the cardiac cycle. All artery images were analyzed using an off-line, electronic wall-tracking software program (Vascular Research Tools 5; Medical Imaging Application, LLC, Iowa City, Iowa). The reproducibility for the cIMT measurement in our laboratory has shown a mean difference of 0.02 ± 0.03% for analyses separated by 1 week in healthy young adults.[22]

Descriptive statistics were summarized by mean (SD) or n (%) for continuous and categorical covariates, respectively. All vascular structure measures with a left and right measurement were averaged. Exclusion criteria included 33 participants missing 1 or more apolipoproteins. Linear regression models assessed the association of each apolipoprotein variable with measures of vascular function and structure (ie, PWV and cIMT) after adjusting for Tanner stage (3 categories: 1, 2-4, and 5), sex, and race (3 categories: white, black, and other) (model 1), then additionally adjusted further for body fat percent (model 2). CIs and *P* values were calculated using model-based SEs. Additional linear regression models examined the interaction between Tanner Stage and each apolipoprotein. *P* values for the interaction were calculated using likelihood ratio tests. Multiple comparisons were accounted for within each outcome and model setting using the Holm procedure. Apolipoprotein ratio coefficients were

scaled to 0.1 μg/mL and apolipoprotein coefficients were scaled to 10 μg/mL. All analyses were conducted using R, version 3.5.3.[23]

Results

A total of 338 participants (178 female) were examined in this study (Table I). Participants were aged 13.0 ± 2.77 years old and pubertal maturation spanned from Tanner stage I-V. The cohort was predominantly white (n = 260; 76.9%). There were individuals in all 4 BMI groups: normal weight (n = 132), overweight (n = 24), obesity (n = 69), and severe obesity (n = 113).

Before multiple comparison adjustment, there were statistically significant, positive associations between PWV and apolipoproteins (Table II): AI (0.015 m/s per 10 μg/mL [CI 0.005-0.026], $P = .003$), AII (0.036 m/s per 10 μg/mL [0.017-0.056], $P < .001$), B_{100} (0.009 m/s per 10 μg/mL [0.002-0.016], $P = .012$), E (0.158 m/s per 10 μg/mL [0.08-0.235], $P < .001$), and the CIII:CII (0.033 [0.014-0.052], $P < .001$). After we adjusted for multiple testing, PWV remained statistically significantly associated with AI, AII, B_{100}, E, and the CIII:CII. Before multiple comparisons adjustment, a statistically significant, inverse association between cIMT and apolipoprotein CII (−0.003 mm per 10 μg/mL [–0.005 to 0], $P = .020$) and a positive association between cIMT and the CIII:CII (0.001 [0-0.003], $P = .033$) were observed. However, both associations failed to maintain statistical significance after accounting for multiple testing.

Table I. Cohort demographics and anthropometric characteristics

Characteristics	Overall	Male	Female
n	338	160	178
Age, y	13.0 (2.77)	13.0 (2.52)	13.0 (2.99)
Weight, kg	68.6 (29.9)	67.6 (32.0)	69.5 (27.9)
Height, cm	157 (14.1)	160 (15.5)	155 (12.4)
BMI, kg/m^2	26.8 (8.92)	25.4 (8.8)	28.0 (8.87)
BMI percentile, %	78.2 (27.8)	74.7 (28.4)	81.4 (27.0)
BMI percent of the 95th percentile, %	105 (30.9)	101 (31.1)	108 (30.5)
Body fat percent, %	36.8 (11.7)	32.5 (12.2)	40.7 (9.72)
Race/ethnicity			
African American or black	34 (10.1%)	14 (8.8%)	20 (11.2%)
White	260 (76.9%)	123 (76.9%)	137 (77.0%)
Other	44 (13.0%)	23 (14.4%)	21 (11.8%)
Latino/Hispanic	38 (11.2%)	20 (12.5%)	18 (10.1%)
Tanner stage			
Stage I	85 (25.1%)	51 (31.9%)	34 (19.1%)
Stage II/III/IV	182 (53.8%)	78 (48.8%)	104 (58.4%)
Stage V	57 (16.9%)	24 (15.0%)	33 (18.5%)
Obesity status			
Normal weight	132 (39.1%)	75 (46.9%)	57 (32.0%)
Overweight	24 (7.1%)	10 (6.2%)	14 (7.9%)
Obesity	69 (20.4%)	32 (20.0%)	37 (20.8%)
Severe obesity	113 (33.4%)	43 (26.9%)	70 (39.3%)

Continuous variables are presented as mean (SD) and categorical variables are presented as n (%).
BMI percent of the 95th percentile (%) is the average BMI percent of the 95th percentile.

We further conducted multiple linear regression analyses to account for any effect of body fat percent on these relationships. Following adjustment for body fat percent, PWV remained significantly, positively associated with greater levels of apolipoproteins: AI (0.016 m/s per 10 μg/mL [0.005-0.026], $P = .004$), AII (0.036 m/s per 10 μg/mL [0.016-0.055], $P < .001$), B_{100} (0.010 m/s per 10 μg/mL [0.003-0.017], $P = .008$), E (0.161 m/s per 10 μg/mL [0.082-0.239], $P < .001$), and the CIII:CII (0.033 [0.014-0.052], $P < .001$) (Table II, model 2).

In addition, we examined the interaction between Tanner stage and each apolipoprotein (Table III; available at www.jpeds.com). There were no significant interactions between Tanner stage and apolipoproteins. Therefore, the effect of apolipoproteins on vascular measures does not significantly differ by Tanner stage.

Discussion

We observed significant associations between apolipoprotein AI, AII, B_{100}, E, and the CIII:CII with PWV after adjusting for degree of body fatness. Despite associations between apolipoproteins and PWV, there were no significant associations with cIMT. Results indicate that apolipoproteins, specifically AI, AII, B_{100}, E, and CIII:CII, may exert their effects on arterial stiffness before observable changes in vascular structure beyond what is observed with excess body fatness. However, this hypothesis will need to be investigated in longitudinal studies with the ability to assess temporal changes over time.

Studies in adults have reported patients with elevated cIMT to have lower mean apolipoprotein AI and greater mean apolipoprotein B_{100} and apolipoprotein B_{100}:AI.[13,14,24] Also, adulthood cIMT is inversely associated with apolipoprotein AI and positively associated with apolipoprotein B_{100} and apolipoprotein B_{100}:AI.[19,25,26] In our study, we observed no associations between cIMT and any of the apolipoprotein variables after P value correction for multiple comparisons and adjustment for demographics. This could be due to the fact that apolipoproteins have a relatively small impact on childhood cIMT and/or that the effects on cIMT begin to surface in adulthood.

Previous studies in children have explored apolipoprotein AI and apolipoprotein B_{100} concentrations across a range of BMI values.[16-18] Specifically, they reported lower levels of apolipoprotein AI and greater levels of apolipoprotein B_{100} in children with obesity compared with their counterparts without obesity.[17,18] Based on these findings, and the fact that our cohort was well represented with participants with a wide range of adiposity, we deemed it necessary to adjust for body fat percent. We observed the significant associations remained with and without the adjustment of body fat percent, indicating that these apolipoproteins may exert their effects on arterial stiffness independent of excess body fatness.

Our results showed a significant positive association of PWV with apolipoprotein AI, AII, B_{100}, E, and the CIII:CII. From a pathophysiologic perspective, this could be due to the interactions of apolipoprotein AI, AII, CII, and CIII

Table II. Associations of APOs with PWV and cIMT

Covariates	Model 1		Model 2	
	Difference per APO unit* (95% CI)	*P* value	Difference per APO unit* (95% CI)	*P* value
Carotid-radial-PWV, m/s				
APO AI	0.015 (0.005-0.026)	.003†	0.016 (0.005-0.026)	.004†
APO AII	0.036 (0.017-0.056)	<.001†	0.036 (0.016-0.055)	<.001†
APO B_{100}	0.009 (0.002-0.016)	.012†	0.01 (0.003-0.017)	.008†
APO CII	0.0 (−0.035, 0.035)	.986	0.001 (−0.034, 0.037)	.943
APO CIII	0.015 (−0.002, 0.032)	.078	0.015 (−0.001, 0.032)	.072
APO E	0.158 (0.080-0.235)	<.001†	0.161 (0.082-0.239)	<.001†
APO B_{100}:AI	−0.009 (−0.018, 0.001)	.067	−0.009 (−0.019, 0.001)	.078
APO CIII:CII	0.033 (0.014-0.052)	<.001†	0.033 (0.014-0.052)	<.001†
cIMT, mm				
APO AI	0.0 (0.0-0.001)	.535	0 (−0.001, 0.001)	.728
APO AII	0.001 (0-0.002)	.172	0.001 (0-0.002)	.194
APO B_{100}	0.0 (−0.001, 0.0)	.454	0 (0-0)	.908
APO CII	−0.003 (−0.005, 0.0)	.020	−0.002 (−0.004, 0)	.059
APO CIII	−0.001 (−0.002, 0.001)	.326	0 (−0.001, 0.001)	.548
APO E	0.001 (−0.004, 0.006)	.663	0.003 (−0.003, 0.008)	.309
APO B_{100}:AI	0.0 (−0.001, 0.001)	.936	0 (0-0.001)	.362
APO CIII:CII	0.001 (0.0-0.003)	.033	0.001 (0-0.003)	.049

APO, apolipoprotein.
Model 1 adjusted for Tanner stage, sex, and race.
Model 2 adjusted for Tanner stage, sex, race, and body fat percent.
*APO variables were scaled to 10 ug/mL and APO ratios were scaled to 0.1 μg/mL.
†Significant *P* values after accounting for multiple comparisons using Holm's method.

with important enzymes (ie, lecithin-cholesterol acyltransferase and lipoprotein lipase) in lipoprotein metabolism.[10,27,28] In addition, each apolipoprotein has a major lipoprotein carrier, and that can determine which apolipoproteins are more atherogenic vs protective. Because apolipoprotein B_{100} is a major protein component of VLDL, IDL, and LDL, with only 1 apolipoprotein B_{100} per lipoprotein particle, it is a marker for the number of atherogenic lipoproteins. Also, apolipoprotein E is a ligand for clearance of lipoproteins containing apolipoprotein B_{100} (ie, IDL and VLDL) except for LDL. The apolipoprotein E gene is polymorphic, with previous research observing that allele type impacts cholesterols levels.[29,30] The ε4 allele has been observed to increase the risk of cardiovascular disease.[29-32] Therefore, presence of the ε4 allele could increase arterial stiffness and favor the development of atherosclerosis.[33-35] Consequently, arterial stiffness may be associated with metabolic activity that promotes decreased HDL and increased LDL levels. These data may indicate these specific apolipoproteins may impact arterial stiffness early in life.

Limitations of this study include the cross-sectional design of the study; therefore, causality and temporal relationship between apolipoprotein concentrations and PWV or cIMT cannot be determined. Also, neither categories nor percentiles exist for apolipoprotein concentrations, limiting the ability to interpret the findings from a clinical perspective. This study is also limited in the interpretation on the effect of apolipoprotein B on CVD risk, because the present study explored the effect of apolipoprotein B_{100} and did not have data on apolipoprotein B_{48}.

The results from this study indicate that greater levels of specific apolipoproteins are associated with greater levels of arterial stiffness in children and adolescents. These observations held with and without adjustment for body fat percent. Apolipoproteins (specifically AII, B_{100}, E, and CIII:CII) may be useful biomarkers of cardiovascular risk in children and adolescents, but further investigation of their utility is warranted. ■

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Reprint requests: Madeline A. Czeck, MS, University of Minnesota, Room 100 Cooke Hall, 1900 University Ave SE, Minneapolis, MN 55455. E-mail: czeck010@umn.edu

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Table III. Associations of APOs with PWV and cIMT

		Model 1			Model 2		
Covariates	Subgroup	Difference (95% CI)	Unadjusted *P* value	Adjusted *P* value for interaction*	Difference (95% CI)	Unadjusted *P* value	Adjusted *P* value for interaction*
Carotid-radial-PWV, m/s							
APO AI	Tanner 1	0.013 (−0.008, 0.034)	.220	>.999	0.013 (−0.008, 0.034)	.218	>.999
	Tanner 2-4	0.017 (0.004-0.03)	.011		0.017 (0.004-0.031)	.012	
	Tanner 5	0.013 (−0.012, 0.038)	.308		0.013 (−0.012, 0.038)	.307	
APO AII	Tanner 1	0.042 (0.004-0.08)	.031	>.999	0.041 (0.004-0.079)	.032	>.999
	Tanner 2-4	0.038 (0.011-0.065)	.006		0.037 (0.01-0.064)	.008	
	Tanner 5	0.026 (−0.015, 0.068)	.208		0.027 (−0.014, 0.068)	.200	
APO B_{100}	Tanner 1	0.006 (−0.009, 0.021)	.459	>.999	0.006 (−0.009, 0.021)	.416	>.999
	Tanner 2-4	0.013 (0.004, 0.022)	.006		0.013 (0.004, 0.022)	.004	
	Tanner 5	0.002 (−0.013, 0.017)	.800		0.003 (−0.013, 0.018)	.722	
APO CII	Tanner 1	−0.091 (−0.171, −0.011)	.025	.298	−0.091 (−0.171, −0.011)	.026	.283
	Tanner 2-4	0.022 (−0.021, 0.065)	.314		0.023 (−0.02, 0.066)	.297	
	Tanner 5	0.022 (−0.065, 0.11)	.618		0.024 (−0.064, 0.111)	.595	
APO CIII	Tanner 1	0.003 (−0.031, 0.038)	.845	>.999	0.004 (−0.031, 0.04)	.808	>.999
	Tanner 2-4	0.016 (−0.005, 0.038)	.140		0.016 (−0.005, 0.037)	.143	
	Tanner 5	0.025 (−0.013, 0.063)	.201		0.026 (−0.012, 0.065)	.179	
APO E	Tanner 1	0.205 (0.04-0.371)	.015	>.999	0.21 (0.044-0.376)	.013	>.999
	Tanner 2-4	0.139 (0.027-0.252)	.015		0.138 (0.025-0.251)	.016	
	Tanner 5	0.154 (0.021-0.288)	.023		0.161 (0.027-0.295)	.018	
APO B_{100}:AI	Tanner 1	−0.001 (−0.041, 0.039)	.945	>.999	−0.002 (−0.043, 0.039)	.941	>.999
	Tanner 2-4	−0.008 (−0.018, 0.002)	.098		−0.008 (−0.019, 0.002)	.107	
	Tanner 5	−0.028 (−0.072, 0.016)	.218		−0.028 (−0.072, 0.017)	.221	
APO CIII:CII	Tanner 1	0.089 (0.048-0.13)	<.001	.078	0.09 (0.049-0.131)	0.001	.062
	Tanner 2-4	0.017 (−0.008, 0.042)	.192		0.015 (−0.01, 0.04)	.242	
	Tanner 5	0.025 (−0.011, 0.061)	.173		0.026 (−0.01, 0.062)	.155	
cIMT, mm							
APO AI	Tanner 1	0 (−0.001, 0.001)	.922	>.999	−0.001 (−0.002, 0.001)	.439	>.999
	Tanner 2-4	0 (−0.001, 0.001)	.984		0 (−0.001, 0.001)	.476	
	Tanner 5	0.001 (0-0.003)	.082		0.001 (0-0.003)	.148	
APO AII	Tanner 1	0 (−0.002, 0.003)	.840	>.999	0 (−0.002, 0.002)	.971	>.999
	Tanner 2-4	0.001 (−0.001, 0.003)	.374		0.001 (−0.001, 0.003)	.396	
	Tanner 5	0.002 (−0.001, 0.005)	.150		0.002 (−0.001, 0.005)	.119	
APO B_{100}	Tanner 1	0 (−0.001, 0.001)	.557	>.999	0 (−0.001, 0.001)	.809	>.999
	Tanner 2-4	0 (−0.001, 0)	.205		0 (−0.001, 0)	.536	
	Tanner 5	0.001 (0-0.002)	.243		0.001 (0-0.002)	.091	
APO CII	Tanner 1	−0.001 (−0.006, 0.004)	.639	>.999	−0.001 (−0.005, 0.004)	.825	>.999
	Tanner 2-4	−0.004 (−0.006, −0.001)	.006		−0.003 (−0.006, −0.001)	.013	
	Tanner 5	0.001 (−0.005, 0.007)	.722		0.002 (−0.004, 0.008)	.500	
APO CIII	Tanner 1	−0.001 (−0.003, 0.001)	.357	>.999	0 (−0.003, 0.002)	.674	>.999
	Tanner 2-4	−0.001 (−0.002, 0.001)	.292		−0.001 (−0.002, 0.001)	.285	
	Tanner 5	0.001 (−0.002, 0.004)	.470		0.002 (−0.001, 0.004)	.236	
APO E	Tanner 1	−0.007 (−0.017, 0.004)	.228	>.999	−0.005 (−0.016, 0.005)	.345	>.999
	Tanner 2-4	0.005 (−0.003, 0.012)	.213		0.006 (−0.001, 0.013)	.114	
	Tanner 5	0.001 (−0.009, 0.011)	.817		0.003 (−0.006, 0.013)	.488	
APO B_{100}:AI	Tanner 1	−0.001 (−0.004, 0.001)	.287	>.999	0 (−0.003, 0.002)	.942	>.999
	Tanner 2-4	0 (−0.001, 0.001)	.772		0 (0-0.001)	.370	
	Tanner 5	0 (−0.003, 0.002)	.777		0.001 (−0.002, 0.003)	.663	
APO CIII:CII	Tanner 1	−0.001 (−0.004, 0.002)	.486	.513	−0.001 (−0.003, 0.002)	.704	>.999
	Tanner 2-4	0.003 (0.001, 0.004)	.002		0.002 (0-0.004)	.011	
	Tanner 5	0 (−0.003, 0.004)	.892		0.001 (−0.003, 0.004)	.703	

Model 1 adjusted for Tanner stage, sex, and race.
Model 2 adjusted for Tanner stage, sex, race, and body fat percent.
APO variables were scaled to 10 μg/mL and APO ratios were scaled to 0.1 μg/mL.
APO, apolipoprotein.
**P* value for likelihood ratio test for the interaction between Tanner stage and APO adjusted by Holm's method.