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Pre-Diabetic Obese Adolescents have a More Atherogenic Lipoprotein Profile Compared with Normoglycemic Obese Peers

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Abstract

Objective—To compare lipoprotein profiles of pre-diabetic to normoglycemic obese adolescents.

Study design—Cross-sectional study of 95 obese, pubertal adolescents (12–17 years), who underwent oral glucose tolerance test, lipid panel, and lipoprotein subclass particle analysis (NMR spectroscopy). Univariate and linear regression analyses compared pre-diabetic and normoglycemic groups.

Results—22.1% (n=21) of adolescents had pre-diabetes. They were similar to normoglycemic adolescents (n=74) in age, race, BMI, standard lipids, total LDL-P, and total HDL-P. However, pre-diabetics had higher concentrations of small LDL-P (714.0±288.0 vs 537.7±266.5nmol/L, p=0.01) and smaller LDL-P size (20.73±0.41 vs 21.18±0.65nm, p=0.003), than normoglycemic youth. Pre-diabetics had higher small HDL-P (18.5±3.8 vs 16.6±3.9umol/L, p=0.046), lower large HDL-P (4.49±2.0 vs 6.32±2.6umol/L, p=0.004), and smaller HDL-P size (8.73±0.31 vs 9.01±0.39nm, p=0.003). After adjusting for demographics, Tanner stage, and BMI using multiple linear regression, all differences remained significant except for small HDL-P. After additional adjustment for HOMA-IR, only LDL-P size difference remained significant.

Conclusion—Obese pre-diabetic adolescents have a significantly more atherogenic lipoprotein profile compared with obese normoglycemic peers. Pre-diabetic adolescents may benefit from more aggressive interventions to decrease future cardiovascular risk.

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Keywords

impaired fasting glucose; impaired glucose tolerance; type 2 diabetes mellitus; lipoprotein subclass particle analysis; cardiovascular risk; body mass index; pediatrics; lipids; abnormal glucose tolerance

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In adults, diabetes is considered to be a coronary heart disease equivalent (4). Pre-diabetes (impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)) is an intermediate condition, identifying those with elevated blood sugars not yet in the diabetic range, who are at high risk of developing diabetes (5). The relative contributions of insulin secretory defect(s) and insulin resistance in pre-diabetes are controversial (6, 7).

Obesity, insulin resistance, and diabetes are often associated with a lipid pattern consisting of elevated triglycerides, decreased HDL-C, and no change in LDL-C, characteristic of the metabolic syndrome (9). Lipoprotein subclass analysis by NMR spectroscopy can provide important additional information. Insulin resistance is associated with increased concentration of small LDL-P, decreased large LDL-P, decreased LDL-P size, decreased HDL-P size, decreased large HDL-P, and increased large VLDL-P in adults (10), with similar results in children (11). In adult studies, Festa et al (12) demonstrated that nondiabetic adults in the IRAS study who eventually converted to diabetes at follow-up already had a pro-atherogenic pattern of lipoprotein abnormalities at baseline.

The aim of this study was to compare lipids and lipoprotein subclass particles between obese prediabetic and obese normoglycemic pubertal adolescents. We hypothesized that obese, pre-diabetic adolescents would have a significantly more atherogenic lipoprotein profile compared with their obese, normoglycemic peers, independent of BMI.

METHODS

This was an observational, cross-sectional study of normoglycemic and pre-diabetic obese pubertal adolescents. Inclusion criteria were: 1. ages 12–17 yrs, 2. pubertal (Tanner stage >1), and 3. obese (BMI $\geq$ 95%ile for age and sex). Exclusion criteria were the existence of: 1. major chronic illness, 2. pregnancy, 3. genetic syndrome known to affect glucose tolerance, 4. known familial hypercholesterolemia, 5. treatment with medications known to affect insulin sensitivity (metformin, or systemic steroids in the last 1 month) or lipid profiles (statins, high dose vitamin A), 6. previous diagnosis of IGT and/or IFG, 7. diabetes mellitus, and 8. treatment with high doses of inhaled steroids (>1000 mcg/day). Obese adolescents were recruited from four primary care clinics affiliated with The Children's Hospital of Philadelphia (CHOP) serving a largely African American population, from inner-city Philadelphia. The electronic medical record was used to identify potential participants meeting inclusion criteria, and families were then screened over the phone. A small number of participants presenting with obesity were recruited from the CHOP outpatient Endocrinology Clinic as well. Written informed consent and age-appropriate assent were obtained on the day of the study visit from all subjects before participation, and the study was approved by the CHOP Institutional Review Board.

Study visits took place from October, 2007 through April, 2011 at the Clinical Translational Research Center (CTRC) of CHOP and the Hospital of the University of Pennsylvania. Urine pregnancy tests were performed on menarchal females. Demographic information and medical history were obtained from the guardian and participant. Pediatric endocrinologists used Tanner staging for pubertal assessment, based on breast development in girls and testicular volume in boys. Weight was measured with the subject wearing a light gown

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without shoes by use of a Scaletronix digital scale (Scaletronix, White Plains, NY), calibrated daily. Height was measured using a wall-mounted stadiometer (Holtain Inc., Crymych, UK). BMI was calculated as weight in kilograms divided by height in meter squared, and BMI percentiles were assessed using age- and sex-specific BMI reference data (13). Measurements were repeated three times, and average values were utilized.

Participants were instructed to have 3 days of a high carbohydrate diet prior to the study visit in preparation for a two-hour oral glucose tolerance test (OGTT) during the study visit. After a 12-hour overnight fast, a blood sample was obtained for glucose, insulin, HbA1c, lipid panel, and lipoprotein subclass particle analysis. Subjects were then asked to ingest a glucose solution (1.75 g/kg up to max of 75g) over 2 minutes. Blood was again drawn for glucose and insulin at 120 minutes. Subjects found to have IFG (fasting glucose 100 mg/dL) or IGT (2-hour glucose 140–199 mg/dL) were categorized as pre-diabetic (5). Any subject found to have diabetes (fasting glucose 125 mg/dL and/or 2-hour glucose 200 mg/dL (5)) was excluded from the analysis. Most subjects also had a repeat fasting blood draw the following day. IFG from either day categorized the patient as pre-diabetic. Note that HbA1c was not used to categorize individuals as pre-diabetic, as the addition of this criterion in the American Diabetes Association guidelines occurred after the onset of this study (5). Fasting insulin and glucose from Day 1 were used (unless sample was significantly hemolyzed or otherwise made unreliable, in which case Day 2 levels were used) to calculate Homeostasis Model Assessment – Insulin Resistance Index (HOMA-IR) as follows: [fasting insulin (uIU/mL) x fasting glycemia (mmol/L)]/22.5. Triglycerides, total cholesterol, and HDL-C were assayed on a Hitachi 912 using Roche reagents. LDL-C was calculated using the Freidwald equation (LDL-C = TC − HDL-C − (TG/5)). No subjects had a triglyceride level >4.52 mmol/L (400 mg/dL), which would have made the equation invalid. Insulin was measured by ELISA, using a kit from ALPCO Diagnostics (Salem, NH). Lipoprotein subclass analysis was performed by LipoScience, Inc. (Raleigh, NC), using NMR spectroscopy. For the purposes of this manuscript, lipid cholesterol levels will be designated by "-C" following the lipoprotein, and lipoprotein particle numbers measured by NMR will be designated with "-P" following the lipoprotein.

Statistical analyses

Statistical analyses were performed using SPSS software (SPSS Inc.: SPSS for Windows: Release 16. Chicago, IL: SPSS Inc., 2007.). A p-value of 0.05 was considered statistically significant.

Histograms and Kolgomorov-Smirnov tests were used to examine the distribution of variables. Logarithmic transformations were applied as needed. Lipids and lipoprotein subclass particles were compared between obese normoglycemic subjects versus obese pre-diabetic subjects using two-sample t-tests or Wilcoxon Rank Sum tests depending on normality of distribution.

Wilcoxon, Kruskal-Wallis, ANOVA, t-tests, and correlation coefficients were used to explore the impact of possible confounders (race, sex, age, Tanner stage, BMI, and HOMA-IR) on lipid and lipoprotein subclass particle outcomes. Pearson or Spearman correlation coefficients were used to examine the linear or rank order relationship between age, BMI, and HOMA-IR on the one hand, and the series of lipid and lipoprotein subclass particle levels, on the other hand. Wilcoxon tests or t-tests for independent samples examined differences between the sexes and between the race categories (African American versus all others) on lipid and lipoprotein outcomes, and Kruskal-Wallis tests or ANOVA models examined differences among Tanner stages. Age, BMI, and HOMA-IR were compared between obese normoglycemic subjects versus obese pre-diabetic subjects using two-sample

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t-tests, and the association of group with the categorical covariates (sex, race, and Tanner stage) was examined using Fisher exact tests or chi-square tests.

Hierarchical multiple linear regression models were used to examine the effect of group (obese normoglycemic versus obese pre-diabetic) on lipid and lipoprotein outcomes, while controlling in turn for demographics (age, sex, race [African American versus all others]), Tanner stage (2,3 versus 4 versus 5), BMI (continuous variable), and HOMA-IR (continuous variable). Because there was only one subject who was Tanner 2, Tanner 2 and 3 were combined for regression analysis; therefore, the comparison was Tanner 2 and 3, versus 4, versus 5. In a series of regression models, effect of group was adjusted for demographics, then for demographics and Tanner stage, then for demographics, Tanner, and BMI, and finally for demographics, Tanner stage, BMI, and HOMA-IR. Each lipid and lipoprotein subclass outcome was examined separately. In all models, the grouping variable (obese pre-diabetic versus obese normoglycemic) was entered in the final block, and the unstandardized regression coefficient (*B*) and the change in R^2 were observed.

The primary outcome of interest of the study was LDL-P size. A two group t-test with a 0.05 two-sided significance level has 86% power to detect a difference in means of 0.5 nm, assuming that the common standard deviation is 0.65 (effect size = 0.77), when the sample sizes in the pre-diabetic and normoglycemic groups are 21 and 74, respectively (a total sample size of 95). This difference of 0.5 nm is thought to be clinically relevant as previous studies have shown a similar difference in LDL-P size (0.51 nm) in adults with coronary artery disease compared with those without (14). All additional tests of differences in additional lipid and lipoprotein variables between the pre-diabetic and normoglycemic groups were considered exploratory. With a total of 22 lipid and lipoprotein variables tested between the pre-diabetic and normoglycemic groups (Table I), the Bonferroni correction would imply that only $p < 0.002$ (= 0.05/22) could be considered as statistically significant. In the regression models (Table II), 9 lipid and lipoprotein variables were compared in 4 regression models, and a Bonferroni adjustment would necessitate $p < 0.0014$ (=0.05/(4×9)). These are to be considered as exploratory analyses because we report the raw p-values, unadjusted for multiplicity.

RESULTS

Of approximately 151 obese subjects who were scheduled, 95 completed their study visit. Of the 56 who did not complete the study visit, 2 were ineligible due to pre-pubertal status (assessed during the visit), one was unable to have an IV placed during the visit and did not reschedule, one was ill on the day of the study visit and did not reschedule, and 52 were cancellations/"no-shows" Of 95 obese adolescents enrolled in the study, n=21 or 22.1% were found to have pre-diabetes. Of these, 9 had IFG (42.9%), 2 had both IFG and IGT (9.5%), and 10 (47.6%) had IGT only. Table I shows that the 74 obese normoglycemic and 21 obese pre-diabetic adolescents were similar in age and race distribution. There was a higher proportion of males in the pre-diabetic group compared with the normoglycemic group. Puberty stage was significantly different between the two groups, but by design all participants were pubertal, and the majority of subjects in both groups were Tanner 4 or 5. The pre-diabetic group had significantly higher fasting insulin level and was significantly more insulin resistant by HOMA-IR, compared with the normoglycemic group (Table I).

There were no significant differences between the groups in standard lipids. Although prediabetics had no significant difference in total LDL-P, they had a significantly higher concentration of small LDL-P and a significantly smaller average LDL-P size. In addition, prediabetics had no difference in total HDL-P but had significantly higher concentration of

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small HDL-P, a lower concentration of large HDL-P, and smaller average HDL-P size compared with the obese normoglycemic group.

Results of multiple linear regression analyses are shown in Table II, which demonstrates that after controlling for sex, age, race, Tanner stage, both before and after additional adjustment for BMI, the obese pre-diabetic group had significantly higher small LDL-P, lower large HDL-P, smaller LDL-P size and smaller HDL-P size when compared with the obese normoglycemic group. These are all consistent with a more atherogenic profile in the pre-diabetic group. The pre-diabetic group also had a borderline lower HDL-C in the second and third blocks, but this difference did not reach statistical significance. After additionally controlling for HOMA-IR, only smaller LDL-P size remained significantly different between the two groups.

DISCUSSION

The significance of early glucose abnormalities on mortality and CVD risk was examined in an adult, longitudinal, population-based study by Barr et al (15), showing that after adjustment for traditional CVD risk factors, adults with IGT and IFG had a 50% to 60% greater 5-year mortality risk than those with normal glucose tolerance. Furthermore, the risk of CVD mortality was significantly higher in those with IFG, but not IGT, compared with the normal group in that study. Of all of the CVD deaths, 65% occurred in those with known diabetes, newly diagnosed diabetes, IFG or IGT at baseline.

However, because of the lack of endpoints at young ages, it is difficult to fully assess CVD risk in adolescents. Li et al used NHANES 2005–2006 and found the population-based prevalence of pre-diabetes among American adolescents (16) to be 16.1%, with 13.1% having IFG and 3.4% having IGT. Among obese adolescents, the prevalence of pre-diabetes was approximately 30%, including 22.7% with IFG and 9.5% with IGT. Despite large proportions of children with early glucose abnormalities, there is no current consensus as to whether the CVD risk and lipid treatment guidelines for pre-diabetic children should be more similar to normoglycemic children or to diabetics, given the lack of data to inform such decisions.

Our study shows that even with mild glucose abnormalities, pre-diabetic adolescents exhibit a significantly more atherogenic lipoprotein profile than their obese normoglycemic peers, despite the fact that traditional lipids were generally not very different. These findings were independent of demographics, Tanner stage, and BMI. Many of these differences may be accounted for by increased insulin resistance in the pre-diabetic group, given that most differences became nonsignificant after additionally adjusting for HOMA-IR. This is consistent with the findings of Li et al, in which pre-diabetes was highly associated with hyperinsulinemia (16). In that study, a higher prevalence of pre-diabetes was also associated with two or more of four cardiometabolic risk factors. However, as in our study, many of these risk factors were no longer associated with pre-diabetes prevalence after adjustment for hyperinsulinemia. The key role of insulin resistance is also suggested by the findings of Burns et al (11), who divided normal and overweight children into insulin sensitivity quartiles, and found that the most insulin resistant children had higher concentrations of small dense LDL-P, small HDL-P, and large VLDL-P, and had smaller LDL-P and HDL-P sizes. In our study, smaller LDL-P size in pre-diabetics remained significantly different even after additional adjustment for insulin resistance. It is likely that differences in insulin secretion may also be involved, and perhaps factors such as fat distribution or hepatic fat. In a multi-ethnic cohort of obese normoglycemic adolescents, D'Adamo et al found that the relationships between insulin sensitivity and small LDL-P, large HDL-P, and large VLDL-P

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lost significance after adjusting for visceral adiposity or liver fat (17). These additional predictors will need to be the focus of future studies.

The current study has some limitations. Our population of adolescents was largely African American, limiting the generalizability of our results outside of this population. Also, there was a statistically significant difference in Tanner stage between the pre-diabetic and normoglycemic groups (Table I). Insulin resistance during puberty is known to peak during Tanner stage 3 (18). However, statistical adjustment of the analysis for Tanner stage did not change the study findings. In addition, given the relatively small size of our pre-diabetic group, we cannot rule out the possibility of Type II error. It would have been helpful to include adiponectin in the current study. Also, given the discrepancy between the number of participants screened for the study (19), and those who participated, it is possible that selection bias was introduced. However, given that both pre-diabetic and normoglycemic groups were recruited together, and that group assignment was not made until after participation, this is unlikely. Finally, because this is a cross-sectional study, it can only show associations and not causation. Future longitudinal studies will be needed to establish causation.

Another complex issue is that of multiple comparisons. As stated in the Methods, the primary outcome of the study is LDL-P size, which is significantly smaller in the pre-diabetic group. The other comparisons made can only be considered as exploratory, as the raw p-values are reported, unadjusted for multiplicity.

In the future, it will be interesting to investigate differences between those pre-diabetics with IFG and those with IGT, as the two types of pre-diabetic conditions are thought to have different mechanisms (20). With increased obesity and type 2 diabetes prevalence in children, the numbers of pre-diabetics has also increased, and more studies are needed to establish treatment guidelines for these children. The results of this study indicate that pediatric endocrinologists will need to consider whether diabetic treatment cut-offs and guidelines should be applied to adolescents with pre-diabetes as well, and future studies will be needed to determine this.

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Abbreviations

T2DM	type 2 diabetes mellitus
CVD	cardiovascular disease
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
OGTT	oral glucose tolerance test

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CHOP	The Children's Hospital of Philadelphia
CTRC	Clinical Translational Research Center
HOMA-IR	Homeostasis Model Assessment – Insulin Resistance Index

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TABLE 1

Comparison of Obese Prediabetic and Obese Normoglycemic Groups

	Obese Prediabetic N= 21*	Obese Normoglycemic N= 74*	p-value†
Age (years)	14.3 ± 1.4	14.5 ± 1.4	0.61
Sex (% Male)	13 (61.9%)	26 (35.1%)	**0.043**
Race (% African American)	19 (90.5%)	58 (78.4%)	0.34
Tanner Stage (%)			**0.012**
2 or 3	6 (28.6%)	5 (6.8%)	
4	6 (28.6%)	17 (23.0%)	
5	9 (42.9%)	52 (70.3%)	
BMI (kg/m^2)	35.5 ± 6.8	35.0 ± 5.9	0.72
BMI z-score	2.32 ± 0.37	2.26 ± 0.32	0.46
Fasting insulin (uIU/ml)	30.3 ± 15.4	20.8 ± 11.7	**0.015**
Hemoglobin A1C (%)	5.5 ± 0.4	5.3 ± 0.3	0.060
HOMA-IR§	7.26 ± 3.7	4.59 ± 2.7	**0.005**
LDL-C (mmol/L) ‡	2.64 ± 0.80	2.42 ± 0.71	0.23
HDL-C (mmol/L)	0.998 ± 0.20	1.10 ± 0.23	0.060
Triglycerides (mmol/L)	0.97 ± 0.35	0.89 ± 0.39	0.40
Total Cholesterol (mmol/L)	4.08 ± 0.88	3.94 ± 0.77	0.46
Total LDL-P (nmol/L)	1023.9 ± 360.1	902.4 ± 252.4	0.082
Small LDL-P (nmol/L)	714.0 ± 288.0	537.7 ± 266.5	**0.010**
Large LDL-P (nmol/L)	286.8 ± 113.1	349.4 ± 153.9	0.086
Total VLDL-P & Chylomicrons (nmol/L)	47.2 ± 23.6	39.3 ± 21.2	0.15
Small VLDL-P (nmol/L)	29.3 ± 12.4	26.6 ± 13.1	0.40
Medium VLDL-P (nmol/L)	16.5 ± 13.5	12.1 ± 11.9	0.10
Large VLDL-P & Chylomicrons (nmol/L)	1.31 ± 1.6	0.91 ± 1.4	0.060
Total HDL-P (umol/L)	25.8 ± 2.9	25.7 ± 3.2	0.84
Small HDL-P (umol/L)	18.5 ± 3.8	16.6 ± 3.9	**0.046**
Medium HDL-P (umol/L)	3.18 ± 3.4	2.76 ± 2.4	0.52

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	Obese Prediabetic N= 21*	Obese Normoglycemic N= 74*	p-value†
Large HDL-P (umol/L)	4.49 ± 2.0	6.32 ± 2.6	**0.004**
IDL-P (nmol/L)	23.14 ± 25.1	15.22 ± 21.0	0.15
LDL-P size (nm)	20.73 ± 0.41	21.18 ± 0.65	**0.003**
HDL-P size (nm)	8.73 ± 0.31	9.01 ± 0.39	**0.003**
VLDL-P size (nm)	48.22 ± 5.7	47.46 ± 7.3	0.56

*N may vary slightly across variables due to missing values

†Analysis by Fisher exact test for sex and race; analysis by chi-square tests for Tanner stage; analysis for continuous variables by t-test except for large VLDL-P, medium VLDL-P, and IDL-P (used Mann-Whitney test because not normally distributed); analysis by t-test of log-transformed variables for VLDL-P size. Raw p-values reported- unadjusted for multiplicity.

‡To convert from mg/dl of cholesterol to mmol/L of cholesterol, multiply by 0.02586. To convert from mg/dl of triglycerides to mmol/L of triglycerides, multiply by 0.01129.

§Homeostasis Model Assessment – Insulin Resistance Index; HOMA-IR = [fasting insulin (uIU/mL) x fasting glycemia (mmol/L)]/22.5.

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TABLE 2

Comparison of Lipoproteins in Obese Prediabetic and Obese Normoglycemic Groups, after Adjustment for Potential Confounding Variables

Adjustment for →	Demographics*				Demog + Tanner stage†			
Lipids/ Lipoproteins	Coeff	SE	p-56value**	Δ R^2††	Coeff	SE	p-value	ΔR^2
HDL-C	−0.09	0.06	0.13	0.024	−0.11	0.06	0.067	0.034
Total LDL-P	121.14	72.41	0.098	0.030	139.48	75.07	0.067	0.037
Small LDL-P	176.47	69.75	**0.013**	0.065	179.20	72.71	**0.016**	0.063
Large LDL-P	−63.33	35.83	0.081	0.030	−49.62	36.86	0.18	0.017
Large VLDL-P	0.23	0.36	0.54	0.004	0.24	0.38	0.53	0.004
Small HDL-P	1.73	1.00	0.087	0.031	1.58	1.04	0.13	0.025
Large HDL-P	−1.48	0.61	**0.017**	0.054	−1.59	0.63	**0.013**	0.058
LDL-P size	−0.44	0.15	**0.004**	0.078	−0.40	0.16	**0.012**	0.061
HDL-P size	−0.23	0.09	**0.011**	0.059	−0.24	0.09	**0.012**	0.058

Adjustment for →	Demog + Tanner stage + BMI				Demog + Tanner stage + BMI + HOMA-IR			
Lipids/ Lipoproteins	Coeff	SE	p-value	Δ R^2	Coeff	SE	p-value	Δ R^2
HDL-C	−0.10	0.06	0.080	0.029	−0.09	0.06	0.15	0.019
Total LDL-P	129.53	73.44	0.081	0.032	78.72	79.65	0.33	0.010
Small LDL-P	166.86	69.75	**0.019**	0.054	121.19	75.75	0.11	0.024
Large LDL-P	−46.29	36.64	0.21	0.015	−53.26	40.27	0.19	0.017
Large VLDL-P	0.19	0.37	0.61	0.003	−0.26	0.39	0.50	0.004
Small HDL-P	1.55	1.05	0.14	0.023	0.60	1.13	0.60	0.003
Large HDL-P	−1.49	0.61	**0.016**	0.051	−1.19	0.66	0.076	0.027

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Adjustment for →	Demog + Tanner stage + BMI				Demog + Tanner stage + BMI + HOMA-IR			
Lipids/ Lipoproteins	Coeff	SE	p-value	Δ R^2	Coeff	SE	p-value	Δ R^2
LDL-P size	−0.38	0.15	**0.014**	0.054	−0.33	0.17	**0.049**	0.035
HDL-P size	−0.22	0.09	**0.014**	0.049	−0.15	0.10	0.13	0.018

[*] Age, sex, race (African American versus all other racial groups)

[†] comparison of Tanner 2 and 3, versus 4, versus 5

[**] p-value of the coefficient of the Group variable (obese pre-diabetic versus obese normoglycemic); equivalent to the p-value of the significance of the change in the F statistic due to the addition of the Group variable to the pre-existing model; Raw p-values reported- unadjusted for multiplicity.

[††] Δ $\mathbf{R}^2$ is the change in $\mathbf{R}^2$ due to the addition of the Group Variable to the pre-existing model