Effect of relative weight group change on NMR spectroscopy derived lipid particle size and concentrations among adolescents

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Abstract

Objective—To examine whether longitudinal changes in relative weight category (as indicated by change in BMI classification group) were associated with changes in nuclear magnetic resonance (NMR) derived lipoprotein particles among US youth.

Study design—Secondary analysis of data from clustered RCT. BMI and fasting blood samples were obtained from 2069 participants at the start of 6th grade and end of 8th grade. BMI was categorized as normal weight, overweight or obese at both time points. Lipoprotein particle profiles were measured using NMR spectroscopy at both time points. Regression models were used to examine changes in relative weight group and change in lipoprotein variables.

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Results—38% of participants changed relative weight category (BMI group) over the 2.5 year study period. Low density lipoprotein cholesterol and non-high density lipoprotein cholesterol decreased almost universally, but more with improved BMI category. There were adverse effects on LDL size and total LDL particles, high density lipoprotein size and cholesterol for participants who remained obese or whose relative weight group worsened. Changes in relative category had no impact on HDL particles.

Conclusion—Improvement in relative weight group from 6th to 8th grade was associated with favorable changes in non-HDL-C, VLDL size, LDL size, HDL size and LDL particles, but had no effect on HDL particles. Findings indicate that an improvement in relative weight group between 6th and 8th grade had an effect on NMR derived particles sizes and concentrations among a large group of adolescents, which overrepresented low-income minorities.

There is substantial evidence that insulin resistance in adults and children (1) is associated with high triglyceride levels and low levels of high density lipoproteins. Recent adult studies using nuclear magnetic resonance (NMR) spectroscopy have suggested that low density lipoprotein particle (LDL-P) concentration and size may have stronger associations with insulin resistance and the metabolic syndrome than traditional lipoprotein lipid measures (2). LDL-P and LDL particle size may provide early markers for cardio-metabolic risk and both incident type 2 diabetes (T2DM) and cardiovascular disease (CVD)(3, 4).

Emerging evidence indicates that NMR lipoprotein profiles are associated with obesity and insulin resistance in children. For example, Magge et al reported there was no difference in levels of low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) comparing obese, children with pre-diabetes with obese but children with normo-glycemia (5). However, participants with pre-diabetes had higher concentrations of small LDL-P and a smaller average LDL particle size. Moreover, a number of studies have shown that obese children have higher levels of small and total LDL-P than non-obese children(6, 7).

In adults, a diet and exercise regime that reduces total and visceral fat and improves insulin sensitivity has been shown to yield favorable changes in NMR-derived lipoprotein particles (8). Longitudinal data have shown that non-obese adults who were overweight in childhood have levels of elevated lipids comparable with individuals who had a healthy weight at both time points (9). Thus, we examined the associations between 2.5-year changes in relative weight category and changes in NMR-derived lipoprotein particles in 2069, 6th graders, 75% of whom were Black or Latino, and 50% of whom were overweight or obese.

METHODS

This report is an analysis of stored blood from the HEALTHY Study, a US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) cluster randomized controlled trial that aimed to reduce the prevalence of risk factors for type 2 diabetes

mellitus among middle school children (6th – 8th grade). The main study design has been detailed elsewhere (10, 11, 12). Briefly, participants were recruited from 42 middle schools across the US. Schools had at least 50% of students eligible for free or reduced-price lunch or belonging to an ethnic minority group and an annual student attrition rate 25%. The intervention included changes to the physical education curriculum school food service, health education, and a school wide social marketing campaign (11, 13–17). The sample for this study is limited to participants who provided parental consent and child assent for ancillary analyses of stored blood, and for whom complete data were available. The study was approved by the Institutional Review Boards at each field center, and written informed parental consent and child assent were obtained.

Height and body mass were measured without shoes using the Prospective Enterprises PE-AIM-101 stadiometer and the SECA Corporation Alpha 882 electronic scale. Body Mass Index (kg/m^2) was calculated and converted to an age- and sex-specific BMI percentile using CDC 2000 criteria (18). Students with BMI 5th percentile and <85th percentile were classified as healthy weight. The healthy weight range was then subdivided into 2 groups: BMI 5th percentile and <50th percentile and BMI 50th percentile and <85th percentile. Youth with BMI 85th percentile but <95th percentile were classified as overweight, those with BMI between 100% and 119% of the >95th percentile classified as obese and those at or above 120% of the 95th percentile classified as severely obese (19) and those with BMI <5th percentile were classified as underweight. Waist circumference was taken using a Gulick tape measure (G-tape) with a tension device on bare skin measured just above the iliac crest.

At baseline (beginning of 6th grade) and follow-up (end of 8th grade) fasting blood samples were collected from all participants. Standard lipid profiles including total cholesterol (TC), TG, and HDL-C were measured by CDC-standardized direct assay at the University of Washington (20). LDL-C was calculated using the Friedewald equation (21). Analyses of glucose were performed using reagent from Roche Diagnostics. Insulin was measured by a two-site immuno-enzymometric assay. Fasting insulin (performed using a Tosoh 1800 auto-analyzer) and glucose (performed on a Roche P module auto-analyzer by the hexokinase method) were used to calculate the homeostatic model assessment of insulin resistance (HOMA-IR) according to the formula: Glucose*Insulin / [μU/L] 22.5 (22).

Lipoprotein particle profiles were measured by NMR spectroscopy with the LipoProfile-3 algorithm at LipoScience, Inc (Raleigh, NC) on frozen EDTA plasma specimens of participants who provided informed consent for ancillary studies. VLDL, LDL and HDL subclasses were quantified from the amplitudes of their spectroscopically-distinct lipid methyl group NMR signals, and weighted-average particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.[21] Diameter range estimates for the subclasses were as follows: large VLDL-P, >60 nm; medium VLDL-P, 35–60 nm; small VLDL-P, 29–35 nm; intermediate-density lipoprotein particles (IDL-P), 23–29 nm; large LDL-P, 20.5–23 nm; small LDL-P, 18 to 20.5 nm and very small LDL-P <20.5 nm); large HDL-P, 9.4–14 nm; medium HDL-P, 8.2 to 9.4 nm; small HDL-P, 7.3–8.2 nm. VLDL-P, LDL-P and HDL-P are the totals of the particle numbers of the respective VLDL, LDL and HDL subclasses. Also

reported is a multivariate lipoprotein insulin resistance score (LP-IR) which is derived by combining the 6 lipoprotein subclass and size measures most strongly associated with insulin resistance (large VLDL-P, small LDL-P, large HDL-P, and VLDL, LDL, and HDL size) (23). LP-IR values range from 0 (most insulin sensitive) to 100 (most insulin resistant). Inter-assay reproducibility (coefficient of variation), determined from 80 replicate analyses of 8 plasma pools over 20 days, was 6% for LP-IR, 8, 3, and 2% for total VLDL-P, LDL-P, and HDL-P; 0.7% for LDL and HDL size; 4% for VLDL size; 7, 13, and 22% for large, medium, and small VLDL-P; 43, 12, and 10% for IDL-P, large, and small LDL-P; and 9, 14, and 6% for large, medium, and small HDL-P, respectively.

Pubertal status was self-reported using the Pubertal Development Scale (24) and converted to pubertal stage groups consistent with the five pubertal stages outlined by Tanner (25). Ethnicity and household education were obtained via parental report and sex was self-reported.

Statistical analyses

We created 7 categories to examine shifts in relative weight categories from grades 6 through 8 (categories with small numbers were collapsed): (1) overweight to obese or severely obese; (2) healthy weight to overweight, obese, or severely obese; (3) stayed obese or severely obese; (4) stayed overweight; (5) stayed healthy weight; (6) overweight to healthy weight; and (7) obese or severely obese to overweight or healthy weight. Categories were collapsed further for modeling because of small cell sizes; specifically the first 2 BMI categories collapsed into a "worsened" category and the last 2 categories into an "improved" category. Finally, underweight students (N=43, 2%) were excluded from modeling as shifting to the healthy weight range was not expected to be associated with increased risk.

Descriptive statistics, including means, standard deviations, and percentages were calculated for all variables. The effect of the intervention upon NMR variables was examined using general linear mixed models which took into account sources of variability within and between schools and controlling for baseline values of the NMR variables. As these analyses indicated no consistent effect of the intervention on NMR variables, we evaluated whether longitudinal shifts in relative weight group differed by sex, race/ethnicity, sixth-grade pubertal stage, and highest household education level by using separate general linear mixed models that adjusted for school intervention status and took into account sources of variability within and between schools and controlled for baseline BMI percentiles. Separate mixed models were also used to analyze associations between shifts in relative weight group and changes in lipoprotein measures. Baseline lipoprotein values of interest, school intervention status, sex, race/ethnicity, sixth-grade pubertal stage and highest household education level were included as covariates. All models tested for shifts in relative weight category as main effects. Covariates were also tested as main effects as well as the interaction between the covariates and BMI category shift when the covariates were significant. There was no pattern of significance with the covariates across all models, but based on the results in previous work, subgroup analysis was performed by sex where the interaction between sex and BMI category shift was statistically significant: small LDL-P, HDL size and LP-IR (10). To evaluate the impact of specific shifts in relative weight

category, we conducted pair-wise comparisons between each of the shift categories. P-values <0.05, with Bonferroni corrected p-values applied to multiple comparisons, were considered significant. SAS 9.2 statistical software (SAS Institute, Cary, NC) was used for analyses.

RESULTS

Participant demographic information is presented for all 2069 participants and by sex in Table I (available at www.jpeds.com). Boys were more likely to be overweight and obese than girls. Demographic information and baseline lipoprotein profiles of the participants included and excluded from the analyses due to incomplete data or being classed as "underweight" are presented in the Figure (available at www.jpeds.com). There was a higher BMI percentile (73.6 vs. 67.6, p = 0.0047) and lower HDL-C (52.5 vs. 55.0 mg/dL, p = 0.0296) in those included, vs. those excluded, from NMR analysis.

Table II presents information regarding changes in relative weight categories during the period from 6th to 8th grade. The majority of children (62%) did not change their BMI category. Consistent with the overall results of the trial (12), more children showed an improvement versus a worsening in their relative weight category (479 vs. 306, p<0.0001).

The median levels (with inter-quartile ranges) or mean (plus 95% confidence intervals) of each of the variables are presented for all 6th grade, 8th grade variables as well as the difference (8th grade – 6th grade) are shown in Table III. There was a mean increase in insulin levels and HOMA-IR but a mean decrease in the number of LDL particles across all participants.

The medians and inter-quartile ranges and change from 6th to 8th grade for LDL and HDL measures related to change in relative weight category are presented in Table IV, which also includes a summary of evidence documenting significant changes of these variables among participants as a function of shift in relative weight category. The information in the last column therefore indicates the comparisons that showed a significant relationship between weight category change and variable of interest after adjustment for multiple testing.

Although LDL-C fell in all categories, the greatest decline was present in those whose relative weight group improved. It is noteworthy that LDL-C was around 10–15% higher in the participants who stayed obese than the participants who remained in the healthy weight group, and the magnitude of the between group disparity in LDL-P was much higher (around 50%). This difference could be explained by the smaller LDL particle size in the group that remained obese. Total LDL-P increased in the BMI worsened group but decreased in the BMI improved group suggesting a benefit of improving BMI group on CVD risk.

The medians and inter-quartile ranges and change from 6th to 8th grade of HOMA-IR and the lipid and lipoprotein particle measures most strongly associated with insulin resistance are presented in Table V. When the BMI category improved, VLDL size decreased, LDL-size increased and small LDL-P decreased. Conversely, when the BMI category worsened, VLDL size increased and there was a downstream decrease in LDL size and an increase in

small and total LDL-P. The observed changes in HDL particle size paralleled changes in LDL size; there was an increase in large HDL with a decrease in BMI category and a reduction in large HDL when BMI category increased. There was no evidence of pair-wise differences in HDL-P, however. Also noteworthy among these data were the differences in the HOMA-IR and TG/HDLC levels of the group that remained obese when compared with those remaining at a healthy weight. Similar trends were evident for LP-IR (a composite lipoprotein / insulin score), indicating a difference in potential risk of insulin resistance.

The Figure shows the change in the three variables for which there was a sex interaction (small LDL-P, HDL size and LP-IR), and indicates that for small LDL-P the mean adjusted change was greater in boys than girls in all worsening groups with a particularly marked difference among the BMI increased group. There was a comparable pattern for both HDL size and LP-IR indicating that for these three variables increase in BMI group appears to have a more marked effect on boys than girls.

DISCUSSION

The present findings expand the current understanding of obesity-related risk factors in youth, by providing new information about the impact of change in relative weight category on NMR variables. In this study, the overall number of HDL particles (HDL-P) did not appear to be related to change in relative weight category, but change in category was associated with change in HDL particle size. This finding is consistent with several recent studies which have reported that lifestyle interventions have yielded changes in particle subclass distribution but not the number of particles (26, 30). The full functional significance of HDL subspecies is not known, but an abundance of the larger species may reflect improved insulin sensitivity (31). A relatively greater depletion of large HDL subspecies compared with the smaller forms has been observed in patients with metabolic syndrome (32) and type-2 diabetes (33), suggesting that decreased HDL-P may also be a sensitive risk biomarker for these inflammatory conditions (34). Collectively, these findings suggest that HDL-P is difficult to change with drugs or modest lifestyle intervention, but increased particle size may reflect improved cardiometabolic status.

The analyses reported here demonstrate that with a worsening of relative weight group there are increased numbers of small cholesterol-poor LDL subspecies. Small LDL-P are cleared 30–50% less efficiently than larger particles, and therefore linger in the vascular space, raising the total LDL-P concentration. Higher levels of LDL-P increase the susceptibility to vascular wall interactions which can lead to atherogenesis.(39) Meanwhile, more triglyceride-rich HDL are also generated and metabolized to smaller, more rapidly-cleared HDL subspecies.(34) It has been reported that premature coronary endothelial dysfunction and atherosclerosis in a cohort of adults referred for evaluation of chest pain correlate with LDL-P and inversely with HDL-P, independent of traditional cholesterol measures.(40) Collectively, these findings demonstrate that NMR-derived lipoprotein measures are markers of cardiometabolic risk that track with BMI changes in children, with implications for CVD risk reduction.

The present data show changes in NMR lipid measures from 6th to 8th grade were associated with increased cardiovascular risk for subjects who became or remained obese. These longitudinal changes reflected a more atherogenic lipoprotein profile (with increased VLDL size and decreased LDL and HDL size due to a shift toward smaller LDL and HDL particles), with nascent or persistent obesity. In contrast, over the 2.5 year study interval, traditional lipid measures (LDL-C, TG and non-HDL-C) improved overall. These data are consistent with previously described lipid changes associated with puberty. (48) Nonetheless, even with traditional lipid measures, obesity was associated with the attenuation of these improvements. These observations suggest that the assessment of cardiovascular risk using NMR may be less prone to the confounding effects of puberty, and, therefore, more clearly reflective of CVD risk.

The major strength of this report is the ethnically diverse sample of US adolescents. It is also important to highlight that the current analyses were conducted on 87.4% of the overall participants with stored blood. Although this is a significant sub-group of the overall sample, the interpretation of our results requires caution, as there were some significant differences between the participants included versus those excluded from our analyses. Moreover, although self-reported physical activity and dietary data were collected from participants, the high levels of missing data on these variables prevented us from controlling for change in these variables.

It is also important to recognize that our period of assessment occurred when participants were progressing through puberty which exerts profound effects on key outcome variables. We employed a self-reported measure of puberty which, although shown to be valid in this group, is less accurate than physical examination; combined with the high levels of missing data at the 8th grade meant that we cannot adjust for change in pubertal status. Although the models were adjusted for self-reported pubertal status it is possible that some residual confounding by pubertal stage might have remained. Finally, it is important to acknowledge that change in BMI category was used in the analyses and not change in absolute BMI. Among participants whose BMI improved, some participants would have improved more than others and this potential difference is not accounted for in the analysis.

Acknowledgments

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Appendix

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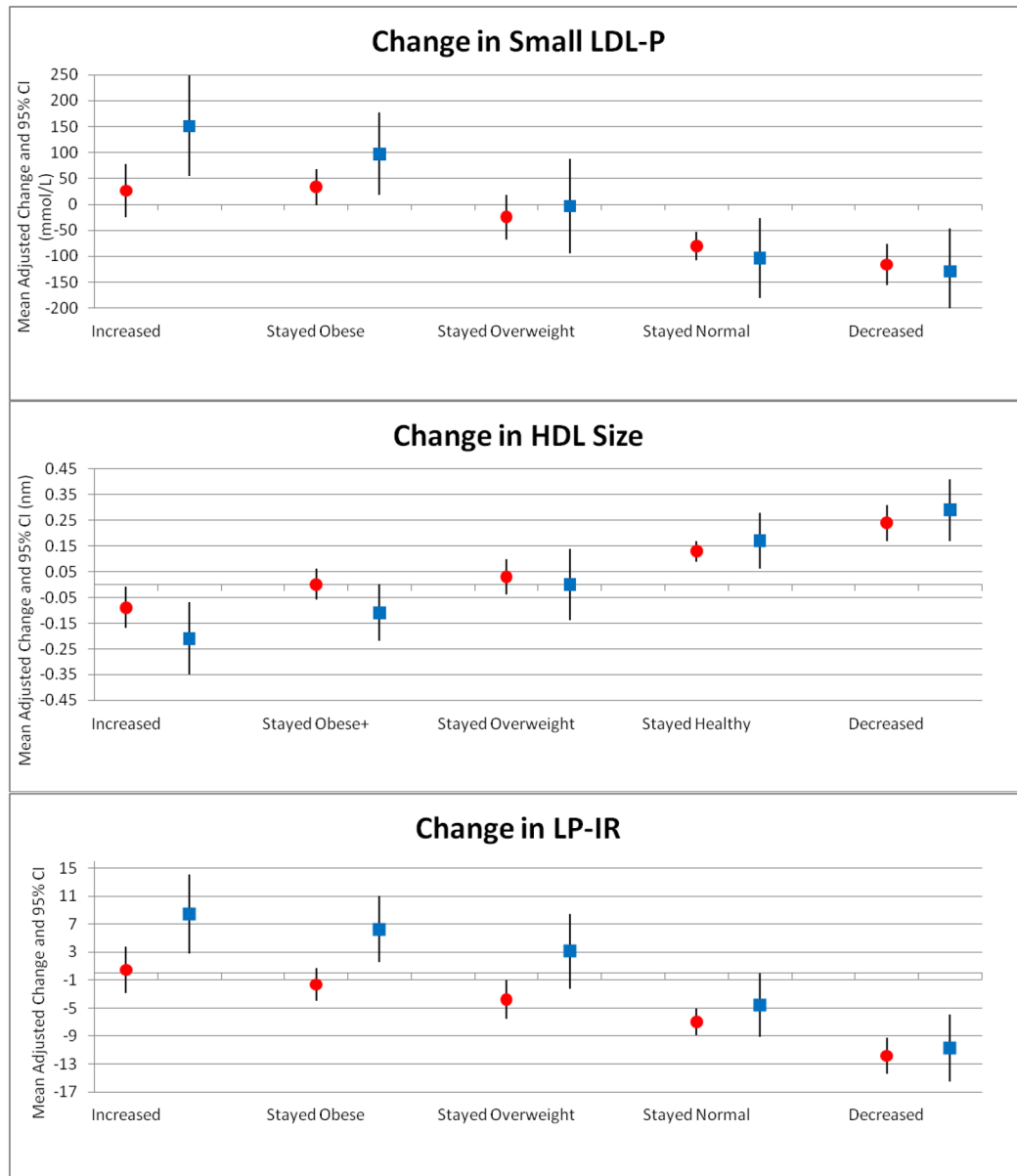
* Girls are denoted by circles in figures and boys by squares.

Figure 1.
Changes (95% CI) in small LDL-P, HDL size, and LP-IR in boys and girls as a function of BMI Category Shifts from 6th Grade to 8th Grade *

* Girls are denoted by circles in figures and boys by squares.

Table 1

Baseline Participant Characteristics (N=2069) and p-values testing for sex differences

	OVERALL	Female (N=1115)	Male (N=954)	
	Mean (SD) or N and %	Mean (SD) or N and %	Mean (SD) or N and %	p-value
Age (years)	11.29 (0.57)	11.24 (0.54)	11.35 (0.60)	<.0001
BMI Percentile	73.65 (27.59)	72.21 (27.42)	75.32 (27.72)	0.0105
BMI Category				0.0005
< 85th Percentile	1018 49.2%	588 52.7%	430 45.1%	
85th – 94th Percentile	402 19.4%	222 19.9%	180 18.9%	
95th Percentile	649 31.4%	305 27.4%	344 36.1%	
Race/Ethnicity				0.0499
Hispanic	1268 61.3%	688 61.7%	580 60.8%	
Black	386 18.7%	218 19.6%	168 17.6%	
White	415 20.1%	209 18.7%	206 21.6%	
Positive Reported 1st Degree Family History of Diabetes	265 12.8%	141 12.6%	124 13.0%	0.8168
Highest Household Education				0.0989
No HS Diploma	556 26.9%	315 28.3%	241 25.3%	
Some college	1100 53.2%	593 53.2%	507 53.1%	
College grad or higher	413 20.0%	207 18.6%	206 21.6%	
Pubertal Status				<.0001
Tanner Stage 1	202 9.8%	59 5.3%	143 15.0%	
Tanner Stage 2	535 25.9%	148 13.3%	387 40.6%	
Tanner Stage 3	849 41.0%	479 43.0%	370 38.8%	
Tanner Stage 4	436 21.1%	384 34.4%	52 5.5%	
Tanner Stage 5	47 2.3%	45 4.0%	2 0.2%	

Table 2

Categories of BMI Percentile (Frequency and Percent) at Baseline (6th Grade) and End of Study (8th Grade)

6th Grade	8th Grade						
	Underweight (N and %)		Healthy (Lower Range) (N and %)		Healthy (Upper Range) (N and %)		
Underweight	13	41.94%	18	58.06%	0	0%	
Healthy (Lower Range)	11	2.73%	266	66.00%	125	31.02%	
Healthy (Upper Range)	1	0.17%	102	17.47%	408	69.86%	
Overweight	0	0%	5	1.24%	150	37.31%	
Obese	0	0%	2	0.39%	23	4.50%	
Severely Obese	0	0%	0	0%	0	0%	
Total	25		393		706		

6th Grade	Overweight (N and %)		Obese (N and %)		Severely Obese (N and %)		Total
Underweight	0	0%	0	0%	0	0%	31
Healthy (Lower Range)	1	0.25%	0	0%	0	0%	403
Healthy (Upper Range)	66	11.30%	7	1.20%	0	0%	584
Overweight	196	48.76%	49	12.19%	2	0.50%	402
Obese	127	29.00%	248	56.62%	38	8.68%	438
Severely Obese	9	4.27%	49	23.22%	153	72.51%	211
Total	399		353		193		2069

Underweight is defined as having BMI < 5th percentile, lower end of healthy range is defined as having BMI between the 5th and 49th percentile, upper end of healthy range is defined as having BMI between the 50th and 84th percentile, overweight is defined as having BMI between the 85th and 94th percentile, obese is defined as having BMI between 100% and 119% of the 95th percentile, severely obese is defined as having BMI at least 120% of the 95th percentile.

Table 3

6th Grade, 8th Grade and Change (8th-6th) in BMI, Waist Circumference, HOMA-IR and NMR Variables with Underweight Dropped

	6th Grade	8th Grade	Difference (8th-6th)
BMI Percentile	75.06 (73.92, 76.19)	74.45 (73.38, 75.52)	−0.60 (−1.17, −0.04)
Waist Circumference (cm)	76.36 (75.73, 76.99)	81.01 (80.38, 81.64)	4.60 (4.31, 4.89)
Glucose	93.70 (93.42, 93.99)	94.23 (93.86, 94.61)	0.53 (0.16, 0.90)
Insulin	13.62 (13.12, 14.11)	17.45 (16.78, 18.12)	3.83 (3.23, 4.43)
HOMA-IR	3.19 (3.07, 3.31)	4.12 (3.95, 4.28)	0.93 (0.78, 1.08)
Total Cholesterol	155 (139, 174)	146 (130, 164)	−9 (−22, 4)
LDL-C (mg/dL)	86 (71, 101)	78 (65, 93)	−7 (−17, 3)
LDL–P (nmol/L)	682 (516, 894)	636 (495, 832)	−39 (−179, 90)
IDL–P (nmol/L)	113 (72, 164)	88 (55, 126)	−23 (−74, 21)
Large LDL–P (nmol/L)	312 (186, 434)	319 (200, 435)	13 (−106, 133)
Small LDL–P (nmol/L)	189 (27, 495)	147 (27, 438)	−6 (−174, 67)
LDL Particle Size (nm)	21.5 (20.7, 22.2)	21.6 (20.9, 22.2)	0.1 (−0.6, 0.7)
Non-HDL-C (mg/dL)	103 (87, 121)	94 (79, 110)	−8 (−20, 2)
HDL-C (mg/dL)	51 (44, 59)	50 (43, 59)	0 (−6, 5)
HDL–P (umol/L)	33.0 (30.4, 35.8)	31.7 (29.1, 34.2)	−1.5 (−4.1, 1.5)
Large HDL–P (umol/L)	6.0 (3.9, 8.5)	6.2 (4.1, 8.8)	0.2 (−1.1, 1.5)
Medium HDL–P (umol/L)	10.2 (7.6, 13.1)	9.1 (6.6, 11.9)	−1.0 (−3.9, 1.6)
Small HDL–P (umol/L)	16.3 (13.7, 19.1)	15.9 (13.2, 18.5)	−0.6 (−3.2, 1.9)
HDL Particle Size (nm)	9.5 (9.2, 9.9)	9.6 (9.2, 9.9)	0.0 (−0.2, 0.3)
Triglycerides (mg/dL)	78 (56, 108)	72 (53, 99)	−6 (−26, 13)
Triglycerides:HDL-C	1.5 (1.0, 2.3)	1.4 (1.0, 2.1)	−0.1 (−0.6, 0.3)
VLDL-P (umol/L)	38.1 (25.4, 54.9)	34.3 (23.8, 50.8)	−3.0 (−15.3, 9.3)
Large VLDL-P (umol/L)	2.0 (1.2, 4.0)	1.7 (1.1, 2.8)	−0.3 (−1.6, 0.5)
Medium VLDL-P (umol/L)	14.4 (8.1, 24.2)	13.2 (7.2, 22.7)	−1.1 (−8.0, 5.8)
Small VLDL-P (umol/L)	19.3 (12.1, 27.7)	18.0 (12.0, 26.2)	−1.0 (−9.3, 7.2)
VLDL Particle Size (nm)	49.7 (46.7, 53.3)	49.1 (46.3, 52.6)	−0.6 (−4.4, 3.0)
LP-IR	35 (21, 53)	31 (18, 48)	−3 (−14, 7)

HOMA-IR, Total Cholesterol, LDL-C, LDL-P, IDL-P, Large LDL-P, Small LDL-P, LDL Particle Size, HDL-C, HDL-P, Large HDL-P, Medium HDL-P, Small HDL-P, HDL Particle Size, Triglycerides, Triglyceride:HDL-C, VLDL-P, Large VLDL-P, Medium VLDL-P Small VLDL-P, VLDL Particle Size, and LP-IR are presented as medians and (25th percentile, 75th percentile) while BMI percentile, waist circumference, glucose, and insulinare presented as mean and 95% confidence interval.

Table 4

Medians and Inter-quartile Ranges for 6th Grade, 8th Grade, and Change (8th – 6th) in Outcomes with Underweight Dropped for Lipoprotein Measures

	Increased Group (I)[c] (N=125)	Stayed Obese+ (OB) (N=488)	Stayed Overweight (OV) (N=196)	Stayed Healthy (HY) (N=901)	Decreased Group (D)[d] (N=316)	Pairwise Comparisons[a] of Bonferroni Corrected Change[b] in Outcomes
				BMI Movement		
LDL-C (mg/dl)						
6th	88 (74, 104)	91 (76, 107)	87 (71, 102)	82 (68, 95)	88 (73, 105)	
8th	82 (69, 99)	84 (71, 101)	83 (70, 95)	74 (63, 87)	75 (62, 91)	I v HY, I v D, OB v HY, OB v D, OV v D, HY v D
Change	−3 (−14, 8)	−6 (−16, 4)	−5 (−14, 7)	−6 (−16, 2)	−13 (−23, −2)	
NHDL-C (mg/dl)						
6th	102 (87, 124)	115 (98, 132)	105 (87, 124)	95 (82, 111)	107 (91, 125)	
8th	98 (84, 121)	105 (90, 123)	98 (85, 115)	88 (75, 103)	91 (76, 107)	I v HY, I v D, OB v HY, OB v D, OV v D, HY v D
Change	0 (−15, 9)	−9 (−21, 3)	−6 (−16, 5)	−7 (−17, 2)	−18 (−29, −6)	
LDL-P (mmol/L)						
6th	681 (517, 849)	880 (691, 1125)	684 (514, 905)	591 (470, 732)	744 (564, 955)	
8th	747 (583, 979)	839 (637, 1040)	684 (535, 867)	562 (452, 695)	596 (473, 758)	I v OV, I v HY, I v D, OB v HY, OB v D, OV v HY, OV v D, HY v D
Change	70 (−52, 227)	−64 (−221, 93)	0 (−155, 92)	−24 (−139, 90)	−127 (−313, 27)	
LDL Size (nm)						
6th	21.6 (20.8, 22.4)	20.9 (20.2, 21.7)	21.5 (20.6, 22.2)	21.8 (21.1, 22.4)	21.4 (20.5, 22.2)	
8th	21.4 (20.8, 22.1)	21.0 (20.3, 21.9)	21.5 (20.9, 22.2)	21.8 (21.2, 22.4)	21.8 (21.0, 22.3)	I v HY, I v D, OB v OV, OB v HY, OB v D
Change	−0.2 (−0.9, 0.6)	0.1 (−0.5, 0.7)	0.1 (−0.6, 0.7)	0.0 (−0.6, 0.7)	0.2 (−0.3, 0.9)	
HDL-C (mg/dl)						
6th	50 (45, 60)	44 (39, 52)	50 (43, 57)	56 (49, 64)	49 (42, 55)	
8th	47 (42, 55)	43 (37, 50)	49 (42, 56)	55 (47, 63)	52 (45, 59)	I v HY, I v D, OB v HY, OB v D, OV v D, HY v D
Change	−4 (−9, 2)	−1 (−6, 4)	−1 (−6, 7)	−1 (−8, 4)	3 (−2, 9)	
HDL-P (μmol/l)						
6th	32.9 (30.1, 35.2)	33.2 (30.3, 36.3)	32.6 (30.2, 35.2)	33.0 (30.5, 35.8)	33.3 (30.3, 35.8)	
8th	31.8 (29.0, 35.0)	31.7 (28.9, 34.4)	31.9 (28.8, 34.7)	31.7 (29.2, 34.0)	31.8 (29.1, 34.1)	ns
Change	−1.2 (−3.1, 2.1)	−1.6 (−4.3, 1.1)	−1.0 (−3.9, 2.0)	−1.5 (−4.1, 1.2)	−1.4 (−4.1, 1.7)	
HDL Size (nm)						

BMI Movement

	Increased Group (I) [c] (N=125)	Stayed Obese+ (OB) (N=488)	Stayed Overweight (OV) (N=196)	Stayed Health (HY) (N=901)	Decreased Group (D) [d] (N=316)	Pairwise Comparisons[a] of Bonferroni Corrected Change[b] in Outcomes
6th	9.6 (9.3, 9.9)	9.2 (8.7, 9.5)	9.4 (9.1, 9.7)	9.8 (9.5, 10.0)	9.4 (9.0, 9.7)	I v OV, I v HY, I v D, OB v HY, OB v D, OV v HY, OV v D, HY v D
8th	9.4 (8.9, 9.8)	9.2 (8.7, 9.5)	9.4 (9.2, 9.8)	9.8 (9.5, 10.0)	9.7 (9.3, 9.9)	
Change	−0.2 (−0.5, 0.1)	0.0 (−0.2, 0.3)	0.0 (−0.2, 0.3)	0.0 (−0.2, 0.2)	0.3 (0.0, 0.5)	

NHDL-C=Non-HDL-C,

[a] We conducted 10 pairwise comparisons across BMI categories: 1. Increased v Stayed Obese+ [I v OB]; 2. Increased v Stayed Overweight [I v OV]; 3. Increased v Stayed Healthy [I v HY]; 4. Increased v Decreased [I v D]; 5. Stayed Obese+ v Stayed Overweight [OB v OV]; 6. Stayed obese+ v Stayed Healthy [OB v HY]; 7. Stayed Obese+ v Decreased [OB v D]; 8. Stayed Overweight v Stayed Healthy [OV v HY]; 9. Stayed Overweight v Decreased [OV v D]; and, 10. Stayed Healthy v Decreased [HY v D].

[b] Statistical significance is a Bonferroni corrected p<0.05 in a model that adjusts for the 6th grade value of the cardiometabolic parameter, school intervention status, sex, race/ethnicity, 6th grade pubertal stage, and highest level of household education at baseline.

[c] Increased Group includes those who moved from Overweight to Obese+ and who moved from Health to Overweight/Obese+

[d] Decreased group includes those who moved from Overweight to Healthy weight and who moved from Obese+ to Overweight/Healthy weight

Table 5

Medians and Inter-quartile Ranges for 6th Grade, 8th Grade, and Change (8th – 6th) in Outcomes with Underweight Dropped (N=2028)

	Increased Group (I)c (N=125)	Stayed Obese+ (OB) (N=488)	Stayed Overweight (OV) (N=196)	Stayed Healthy (HY) (N=901)	Decreased Group (D)d (N=316)	Pairwise Comparisons[a] of Bonferroni Corrected Change[b] in Outcomes
				BMI Movement		
HOMA-IR						
6th	2.38 (1.68, 3.14)	4.37 (2.92, 6.73)	2.50 (1.86, 3.85)	1.72 (1.18, 2.42)	2.92 (2.18, 4.38)	
8th	3.76 (2.77, 5.25)	5.72 (3.83, 8.19)	3.52 (2.53, 5.05)	2.47 (1.82, 3.48)	2.88 (2.08, 3.96)	I v HY, I v D, OB v OV, OB v HY, OB v D, OV v D
Change	1.47 (0.25, 2.88)	1.20 (−0.87, 3.29)	0.67 (−0.43, 1.75)	0.70 (−0.06, 1.60)	−0.08 (−1.12, 0.93)	
Trig:HDL-C						
6th	1.4 (1.0, 2.1)	2.3 (1.6, 3.5)	1.6 (1.1, 2.3)	1.2 (0.8, 1.6)	1.8 (1.3, 2.7)	
8th	1.7 (1.1, 2.3)	2.2 (1.4, 3.4)	1.7 (1.1, 2.2)	1.2 (0.8, 1.6)	1.3 (0.9, 1.9)	I v OV, I v HY, I v D, OB v OV, OB v HY, OB v D, OV v D, HY v D
Change	0.1 (−0.2, 0.6)	−0.2 (−0.9, 0.5)	−0.1 (−0.6, 0.4)	0.0 (−0.3, 0.3)	−0.5 (−1.1, −0.0)	
LP-IR						
6th	30 (19, 45)	59 (43, 71)	38 (24, 51)	25 (15, 37)	42 (30, 59)	
8th	38 (24, 52)	52 (35, 67)	36 (23, 50)	24 (14, 36)	28 (17, 42)	I v OV, I v HY, I v D, OB v HY, OB v D, OV v HY, OV v D, HY v D
Change	5 (−5, 19)	−6 (−18, 4)	−2 (−13, 9)	0 (−10, 9)	−13 (−25, −1)	
L VLDL-P (nmol/l)						
6th	1.8 (1.2, 2.8)	4.1 (2.3, 7.0)	2.0 (1.3, 3.9)	1.5 (1.0, 2.4)	2.6 (1.5, 4.8)	
8th	1.7 (1.1, 3.0)	2.7 (1.5, 5.4)	1.9 (1.2, 2.8)	1.4 (0.9, 2.1)	1.5 (1.1, 2.4)	I v HY, I v D, OB v OV, OB v HY, OB v D, OV v D, HY v D
Change	0.0 (−0.6, 0.8)	−0.9 (−3.2, 0.4)	−0.3 (−1.6, 0.5)	0.0 (−0.8, 0.6)	−0.8 (−2.6, −0.0)	
VLDL Size (nm)						
6th	48.0 (45.4, 50.5)	53.0 (49.5, 57.9)	49.6 (46.5, 52.9)	48.3 (45.6, 51.0)	49.8 (47.3, 53.5)	
8th	48.9 (46.0, 53.0)	51.3 (47.6, 55.5)	48.8 (46.5, 51.8)	48.6 (45.8, 51.3)	48.4 (46.0, 51.6)	OB v OV, OB v HY, OB v D
Change	1.5 (−2.9, 4.0)	−2.4 (−6.4, 2.0)	−0.5 (−3.7, 2.6)	0.5 (−3.2, 3.6)	−1.6 (−5.4, 2.0)	
S LDL-P (nmol/L)						
6th	58 (23, 442)	503 (249, 745)	239 (33, 521)	39 (21, 267)	301 (36, 541)	
8th	281 (44, 572)	439 (191, 700)	258 (38, 449)	40 (21, 255)	56 (26, 325)	I v OV, I v HY, I v D, OB v OV, OB v HY, OB v D, OV v HY, OV v D
Change	36 (−24, 275)	−39 (−255, 111)	−5 (−180, 121)	0 (−52, 39)	−78 (−334, 12)	
L HDL-P (µmol/l)						

	BMI Movement					
	Increased Group (I)[c] (N=125)	Stayed Obese+ (OB) (N=488)	Stayed Overweight (OV) (N=196)	Stayed Healthy (HY) (N=901)	Decreased Group (D)[d] (N=316)	Pairwise Comparisons[a] of Bonferroni Corrected Change[b] in Outcomes
6th	6.4 (4.6, 8.6)	3.5 (2.2, 5.3)	5.5 (3.8, 7.4)	7.8 (5.9, 9.8)	4.9 (3.4, 6.9)	
8th	4.9 (3.5, 7.2)	3.7 (2.1, 5.7)	5.5 (3.7, 7.7)	7.8 (5.6, 9.9)	6.7 (4.8, 9.2)	I v OV, I v HY, I v D, OB v HY, OB v D, OV v D, HY v D
Change	−1.0 (−2.3, 0.2)	0.1 (−0.9, 1.1)	0.2 (−1.2, 1.7)	−0.1 (−1.4, 1.3)	1.5 (0.3, 3.1)	

S LDL-P=Small LDL-P, L HDL-P=Large HDL-P, Trig:HDL-C=Triglyceride-HDL-C Ratio, L VLDL-P=Large VLDL-P

[a] We conducted 10 pairwise comparisons across BMI categories: 1. Increased v Stayed Obese+ [I v OB]; 2. Increased v Stayed Overweight [I v OV]; 3. Increased v Stayed Healthy [I v HY]; 4. Increased v Decreased [I v D]; 5. Stayed Obese+ v Stayed Overweight [OB v OV];6. Stayed obese+ v Stayed Healthy [OB v HY]; 7. Stayed Obese+ v Decreased [OB v D]; 8. Stayed Overweight v Stayed Healthy [OV v HY]; 9. Stayed Overweight v Decreased [OV v D]; and, 10. Stayed Healthy v Decreased [HY v D].

[b] Statistical significance is a Bonferroni corrected $p<0.05$ in a model that adjusts for the 6th grade value of the cardiometabolic parameter, school intervention status, sex, race/ethnicity, 6th grade pubertal stage, and highest level of household education at baseline.

[c] Increased Group includes those who moved from Overweight to Obese+ and who moved from Health to Overweight/Obese+

[d] Decreased group includes those who moved from Overweight to Healthy weight and who moved from Obese+ to Overweight/Healthy weight