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Rate of Weight Gain and Cardiometabolic Abnormalities in Children and Adolescents

Chadi A. Calarge, M.D. [Associate Professor],

The University of Iowa Carver College of Medicine, Departments of Psychiatry and Pediatrics, 500 Newton Road, Iowa City, IA 52242, Tel: 319-335-8771, Fax: 319-353-3003

Diqiong Xie, Ph.D.,

The University of Iowa College of Public Health, Department of Psychiatry, 500 Newton Road, Iowa City, IA 52242

Jess G. Fiedorowicz, M.D., Ph.D.,

The University of Iowa Carver College of Medicine, Departments of Psychiatry and Internal Medicine, The University of Iowa College of Public Health, Department of Epidemiology, 200 Hawkins Drive, Iowa City, IA 52242

Trudy L. Burns, Ph.D., and

The University of Iowa College of Public Health, Department of Epidemiology, The University of Iowa Carver College of Medicine, Department of Pediatrics, 200 Hawkins Drive, Iowa City, IA 52242

William G. Haynes, M.D.

The University of Iowa Carver College of Medicine, Department of Internal Medicine, 200 Hawkins Drive, Iowa City, IA 52242

Chadi A. Calarge: chadi-calarge@uiowa.edu

Abstract

Objective—To investigate whether the rate of weight gain is associated with cardiometabolic risk, independent of weight measured concurrently.

Study design—Healthy 7–17 year-old risperidone-treated patients (n=105, 88% male) had blood pressure, anthropometry, and laboratory tests performed. Growth history was extracted from medical records. The rate of change in age-sex-adjusted weight and body mass index (BMI) z-score after the initiation of risperidone was individually modeled. Multivariable linear regression analyses explored the association of the rate of weight (BMI) z score change with cardiometabolic outcomes, independent of last measured weight (BMI) z score.

Results—Following a mean of 1.9 years (sd=1.0) of risperidone treatment, the absolute increase in weight and BMI z-scores was 0.61 (sd=0.61) and 0.62 (sd=0.73), respectively. After controlling for the final weight z-score, the rate of change in weight z-score was significantly associated with

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Correspondence to: Chadi A. Calarge, chadi-calarge@uiowa.edu.

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final glucose ($p<0.04$), C-peptide ($p<0.004$), HOMA-IR ($p<0.02$), HDL cholesterol ($p<0.0001$), a metabolic syndrome score ($p<0.005$), adiponectin ($p<0.04$), and hsCRP ($p<0.04$). After controlling for the final BMI z-score, the rate of change in BMI z-score was associated with final HDL cholesterol ($p<0.04$), leptin ($p<0.03$), and adiponectin ($p<0.04$), with a suggestion of an association with final HOMA-IR ($p<0.08$).

Conclusions—The rate of weight gain in risperidone-treated children explains equally or more of the variance in certain cardiometabolic outcomes (e.g., HDL cholesterol: $\Delta R^2=11\%$ vs. $\Delta R^2=8\%$ and hsCRP: $\Delta R^2=9\%$ vs. $\Delta R^2=5\%$) than the weight measured concurrently, and may serve as a treatment target.

Keywords

Antipsychotics; Risperidone; Weight Gain; Cardiometabolic Abnormalities; Children; Adolescents

Obesity has reached an epidemic level with established deleterious health effects [1]. In the general population, most obese individuals gain weight relatively slowly. Thus, studies have focused on the link between absolute body mass index (BMI) and cardiometabolic abnormalities and/or risk for cardiovascular disease. Little attention has been paid to the rate of weight gain, specifically whether the speed at which weight is gained affects cardiovascular risk factors, independent of absolute BMI. One exception is the Minneapolis Children's Blood Pressure Study which found the rate of increase in weight during childhood and adolescence to be associated with higher insulin, lipids, and systolic blood pressure in young adulthood [2]. Importantly, however, the analysis did not adjust for the weight measured in young adulthood.

Additional circumstantial evidence highlighting the potential significance of the rate of weight gain comes from studies implicating rapid postnatal growth in later obesity and cardiometabolic abnormalities [3]. However, whether fetal growth restriction, postnatal "catch-up" growth, or their combination accounts for this association remains unclear [4, 5]. Moreover, these studies have largely sought to link changes in weight between two time points and cardiometabolic outcomes. They have not specifically focused on the rate of weight gain. Furthermore, whether it is the rapid growth itself or genetic/environmental triggers (e.g., a thrifty phenotype) that predispose to cardiometabolic sequelae later in life is also unknown.

"Iatrogenic" weight gain can provide a model to shed light on this issue especially when the increase in weight is potentially rapid and substantial. This is particularly true for atypical antipsychotics [6, 7]. Unlike the case with weight-inducing non-psychiatric medications, antipsychotics are prescribed in conditions not characterized by cardiometabolic abnormalities. Such an approach may identify novel mechanisms linking obesity and cardiovascular disease and also have therapeutic implications.

We used a sample of risperidone-treated children to explore whether the rate of weight gain, after starting the antipsychotic, is associated with later cardiometabolic abnormalities, independent of weight when the cardiometabolic outcomes were assessed (i.e., final weight). We hypothesized that, independent of final weight, children with rapid weight gain will exhibit a more disadvantageous metabolic profile and systemic inflammation compared with those who gain weight slowly.

Methods

The primary aim of the original study was to investigate the long-term safety of risperidone [6]. Briefly, 7 to 17 year-old patients treated with risperidone for at least six months were enrolled. Concurrent treatment, at enrollment, with other psychotropics, but not other antipsychotics, was allowed. Participants with neurological or medical conditions that could confound the metabolic assessments (e.g., hypothyroidism) were excluded as were pregnant females and those receiving hormonal contraception.

This study was approved by the local Institutional Review Board. Written assent was obtained from children 14 years of age and consent was obtained from adolescents and parents. As noted above, eligible participants were already on risperidone at study enrollment. Medical records were examined and all height and weight measurements were extracted. In addition, at enrollment, vital signs and anthropometric measurements were obtained following standard procedures as previously described [6]. To account for children's natural growth, age-sex-specific z-scores for weight and BMI were determined [8]. Measurements made during the research visits were compared with those extracted from the medical records that had been collected during clinical encounters falling within a month of the research visit [mean interval=16 days (SD=9) for height (n=69) and 17 days (SD=9) for weight (n=97)]. The intra-class correlation coefficients for unadjusted height and weight as well as for their age-sex-adjusted z-scores were all above 0.97 (95% confidence interval (CI): 0.93–0.99). Reflecting clinical practice, the dataset contained more than twice as many weight as height, and therefore BMI, measurements.

At study enrollment, pubertal stage was independently noted by a physician and the participants, with parental help when necessary [6]. Interrater agreement between the physician and self-rating was high (weighted kappa = 0.81, 95% CI: 0.74–0.88). In addition, a morning blood sample was obtained, after a 9-hr overnight fast, to measure glucose (Roche Diagnostics, Indianapolis, IN), total insulin (Diagnostic Products, Los Angeles, CA), C-peptide (Millipore, Billerica, MA), total cholesterol, HDL cholesterol (HDL), triglycerides (Roche Diagnostics, Indianapolis, IN), leptin and adiponectin (LINCO Research, Inc., St. Charles, MO), active ghrelin collected in EDTA tubes with aprotinin (LINCO Research, Inc., St. Charles, MO), and high-sensitivity C-reactive protein (hsCRP) (ALPCO Diagnostics, Windham, NH). The last four assays were added at a later point in the study, making them available for a subsample. LDL cholesterol was estimated following Friedewald's equation [9]. Measurements for participants who were either not fasting or whose fasting status was missing (11%) were excluded from the analyses that related to the laboratory measures, except for hsCRP [10].

Data Analyses

Body fat was estimated using skinfold thickness measurements following Slaughter et al [11], and the homeostasis model assessment insulin resistance index (HOMA-IR) was estimated as: $[\text{insulin } (\mu\text{UI/ml}) \times \text{glucose (mg/dl)}]/405$ [12]. Blood pressure measurements were converted to age-sex-height-adjusted z-scores [13]. The values of HOMA-IR, triglycerides, leptin, active ghrelin, and hsCRP were natural log (log) transformed to normalize their distributions. A metabolic syndrome score was constructed by first regressing waist circumference, mean arterial pressure, the negative of HDL, (log) triglycerides, and (log) HOMA-IR on age, tanner stage, sex, and race/ethnicity [14]. The standardized residuals from each of the five regression models were then summed to generate a metabolic syndrome score. One participant with hsCRP > 5 mg/l, representing acute inflammation [15], and one with a triglyceride concentration of 601 mg/dl were excluded from relevant analyses, although including these two participants did not appreciably alter the results.

We defined the date of initiation of risperidone as “baseline” and the enrollment date as “final” because this was when the cardiometabolic outcomes were measured. We estimated individual regression models of weight (or BMI) z-scores versus time. Because risperidone-induced weight gain plateaus, time was log transformed (This resulted in a better model fit compared with modeling time with a linear and quadratic term). Also, measurements recorded before age 5.5 years were excluded from the BMI analyses to avoid the phase of BMI “rebound” [8]. A standardized slope estimate was calculated by dividing the estimated slope by its standard error. The standardized and un-standardized slope estimates were highly correlated (Spearman $r = 0.79$ for weight slopes and $r = 0.82$ for BMI slopes, $p < 0.0001$). Nonetheless, we decided a priori to use the more conservative standardized slopes in the analyses because they are adjusted for variability in the number of observations (of weight and BMI z-scores: median=34 [interquartile range (IQR)=23] and 15 [IQR=11] observations, respectively) used to estimate the slope for each participant. The standardized slope for weight (or BMI) z-score was subsequently used as the index of rate of change and included as a predictor variable in multivariable linear regression analyses that modeled cardiometabolic outcomes, adjusting for final weight (BMI) z-score, age, and sex. The latter two were not included in models predicting body fat, systolic and diastolic blood pressure z-scores, and the metabolic syndrome score because they were already taken into account in computing these outcomes.

Antipsychotic-induced weight gain equally affects children across development [7]. Nonetheless, in a sensitivity analysis, we repeated the most relevant analyses in children in Tanner stage 1 at enrollment ($n=48$; Table I; available at www.jpeds.com), to exclude the possible confounding effect of the growth spurt and of the concurrent transient insulin-resistant state during puberty [16]. Additionally, we split the overall sample into fasting boys with negative or null rates of change in weight z score and those with positive rates. Then, within three groups of pubertal development (Tanner 1, Tanner 2/3, and Tanner 4/5), we matched boys with positive rates of change with those having non-positive rates on their final weight (or BMI) z-score. We calculated standardized between-group mean differences in the outcomes of interest [17]. Finally, we also substituted the change in weight (BMI) z score for the rate of change in the multivariable regression analyses to explore whether our findings would be better accounted for by the absolute change in weight (BMI) z score during risperidone treatment. All the statistical tests performed were two-tailed, using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC).

Results

Data were available to compute a weight or BMI z-score slope for 105 participants (88% males) (Table I). They had been taking risperidone for a mean of 1.9 years (range: 0.5 – 4.0), primarily to target disruptive behavior (83%). Polypharmacy was prevalent, with psychostimulants (71%), antidepressants (65%), and α_2 -agonists (32%) being most commonly co-prescribed.

Table I includes the means and standards deviations of the clinical and laboratory outcomes of interest. The mean absolute change between baseline and final weight z-score was 0.61 (sd=0.61, range: -1.19 to 1.94). Overall, 7 participants (7%) showed a reduction in their weight z-score, 32 (30%) had no change, and the majority ($n=66$, 63%) had an increase. Similarly, the mean absolute change in BMI z-score was 0.62 (sd=0.73, range: -1.48 to 2.56) with two participants (2%) showing a reduction in their BMI z-score, 50 (50%) having no significant change, and 48 (48%) exhibiting an increase.

Baseline weight and BMI z-scores were inversely related to the magnitude of change in these measures after risperidone was initiated (Pearson's $r = -0.33$, $p < 0.003$ and $r = -0.44$,

$p < 0.0001$, respectively). However, importantly, there was no significant association between baseline weight and BMI z-scores and the rate of change of either weight ($r = -0.06$, $p > 0.5$) or BMI z-score ($r = -0.16$, $p > 0.1$). As expected, the change in weight (BMI) z score was correlated with the rate of change (i.e., slope of weight (BMI) z score) (Spearman's $r = 0.68$ and $r = 0.55$, $p < 0.0001$, respectively).

Table II includes the findings from the multivariable regression analyses exploring these associations. In some instances, the rate of weight gain was more strongly associated with the cardiometabolic outcomes than “final” weight (Figure).

We repeated the significant analyses in prepubertal children. Compared with the overall group, we found, in this subgroup, comparable estimates of regression coefficients for final (log) HOMA-IR, leptin, adiponectin, hsCRP, and, to a lesser extent, for HDL but not for the metabolic syndrome score (data not shown).

Across 23 pairs of boys matched on their final weight z-score, those with positive rates of change had a higher (log) HOMA-IR (Cohen's $d = 0.64$, $p < 0.04$) and metabolic syndrome score (Cohen's $d = 0.53$, $p < 0.09$). However, these differences failed to reach significance across 26 pairs matched on their final BMI z-score (Cohen's $d = 0.44$ and 0.32 , respectively, $p > 0.10$).

When we substituted absolute change in weight (BMI) z score for the rate of change in the multivariable regression analyses, they explained 2% of the variance in HOMA-IR and 0% of the variance in the metabolic syndrome score (all p values > 0.1).

Discussion

This study showed that the rate of weight change during childhood/adolescence is associated with a potentially atherogenic profile, independent of weight itself. Of particular interest is that the rate of change in weight was equally or more predictive of some cardiometabolic outcomes than the concurrently measured weight (or BMI) z-score. These findings did not appear to be influenced by developmental stage.

The association between weight, metabolic syndrome components, and inflammation has been widely replicated in studies involving diverse populations [18]. We have previously shown that risperidone-treated overweight children/adolescents exhibit a number of cardiometabolic abnormalities [6]. However, unlike most forms of idiopathic obesity where weight accrues gradually, the change in weight observed with antipsychotic treatment is often dramatic, with most taking place over the first months of treatment, generally reaching a plateau within the first two years [6, 7, 19]. Remarkably, across a variety of cardiometabolic markers, we here found that the rate of weight (BMI) gain is of clinical significance. Most importantly, the rate appeared to be more predictive of certain outcomes compared with the final weight z-score, obtained when the cardiometabolic variables were measured (Table II and Figure). The findings for the rate of BMI z-score change were comparable, albeit weaker likely due to more imprecision in estimating the trajectory with fewer BMI measurements available per participant.

The mechanism by which rapid weight gain contributes to the emergence of an atherogenic phenotype is not known. We speculate that rapid weight gain overwhelms the capacity of lower-body adipose tissue to store the excess fat, which, as a result, “overflows” into the upper body where it further enlarges abdominal adipocytes, increasing insulin resistance [20–22]. Another potential mechanism includes a larger deposition of adipose tissue in the liver with accelerated weight gain [23].

Some have argued that suppression of thermogenesis, specifically in the adipose tissue, and the associated insulin resistance mediate a disproportionate increase in fat mass, compared with lean mass, during postnatal “catch-up” growth or during recovery from starvation and wasting [24]. Importantly, our sample had normal baseline weight/BMI z-scores, at the start of risperidone (Table I). Furthermore, when we restricted the regression analysis predicting (log) HOMA-IR to participants with a baseline weight z-score greater than -1.0 , the rate of change in weight z-score still accounted for nearly half as much of the variance in HOMA-IR (4%, $p < 0.05$) as final weight z-score (9%, $p < 0.004$) (For metabolic syndrome score: 7% ($p < 0.02$) and 26% ($p < 0.0001$), respectively). We also failed to find, in this sample, an association between change in weight z-score between birth and two years of age on the one hand and the rate of weight gain on the other (Calarge et al., submitted). In addition, we found no association between the rate of weight (BMI) z-score change before risperidone was started and the rate of weight gain after it was started (Calarge et al., submitted). Furthermore, although low baseline weight and BMI z-scores were positively associated with the magnitude of weight gain during risperidone treatment, they were not associated with the rate of weight gain. Thus, we conclude that the “suppression of thermogenesis” hypothesis might apply to cases where unfavorable conditions result in weight restriction but does not necessarily explain the development of an atherogenic profile following accelerated weight gain in children of normal baseline weight.

Our study suffers from several limitations. First, although antipsychotic treatment offers a model of rapid and significant weight gain, it is unknown whether our findings would apply to psychotropic-naïve populations. Although psychiatric conditions are less likely to confound the association between the rate of weight gain and cardiometabolic outcomes compared with other medical conditions, including “catch-up” growth, there is some evidence linking psychiatric disorders to excessive weight, cardiometabolic abnormalities, and inflammation [25, 26]. Although medications are extrinsic factors not directly related to the individual’s genetic background, their metabolism, efficacy, and potential to cause weight gain clearly are. This is relevant because the dose of psychotropics might influence the rate of weight gain [27]. Of note, after adjusting for the other covariates, the weighted average daily dose of risperidone was not significantly associated with HOMA-IR or the metabolic syndrome score, minimizing the likelihood of a direct effect of risperidone on insulin resistance. Second, although spanning several years of observation, this study was retrospective. Consequently, patients unresponsive to or intolerant of risperidone would have not been enrolled. However, our specific aim here was not to characterize the trajectory of weight gain or the nature of cardiometabolic abnormalities caused by risperidone. Our design clearly is not optimal for such an investigation. Rather, we took advantage of this convenience sample both because risperidone often causes rapid weight gain [6, 7] and because, compared with other antipsychotics, risperidone-related weight gain is thought to be most susceptible to the influence of patient- and drug-related factors during long-term treatment [28]. Specifically, we anticipated that polypharmacy and changes in the dose of risperidone (whether prescribed or due to partial adherence) over the course of treatment should optimize the ability to test our hypothesis because they will generate variability in the trajectory of weight gain across our participants [27]. A placebo-controlled randomized trial would avoid the shortcomings of an observational study like ours but will likely be difficult to conduct for longer than a few weeks for ethical, budgetary, and practical reasons. In addition, although most antipsychotic-induced weight gain generally occurs within the first months of treatment, such a short period of time may be insufficient to test our specific hypothesis.

Additional study limitations include the fact that, except for those obtained at study enrollment (the “final” measurement), all other anthropometric measurements were extracted from the medical records. However, like others [29], we found these weight and

height measurements to be highly correlated with the corresponding research measurements, obtained within a month. Moreover, because our primary focus was the rate of change in weight (or BMI) z-score during the course of treatment, as opposed to single measurements, it is unlikely that minor deviations would have had major influences. Finally, it is important to replicate our findings in females and individuals from a diverse racial/ethnic background. Moreover, it is necessary to explore whether this finding is more prominent when the weight gain occurs during childhood as opposed to adulthood or in the context of polypharmacy, which was quite prevalent in our participants.

Our findings deserve further investigation because the metabolic syndrome profile tracks from childhood into adulthood and is associated with vascular abnormalities even in childhood [30]. Rapid weight gain might serve as a potential target for interventions to attenuate the long-term cardiovascular sequelae of obesity.

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Figure.

Percent of the variation in “final” cardiometabolic outcomes independently accounted for by “final” weight z score and the rate of change in weight z score during risperidone treatment. hsCRP: high-sensitivity C-reactive Protein. MS: Metabolic Syndrome Score.

Table 1

Demographic and Clinical Characteristics of the Participants (n=105)

Characteristic	Mean or N	SD or %
Age, years	11.2	2.7
Tanner Stage: I, II, III, IV, V	48/16/13/21/7	46/15/12/20/7
<i>Anthropometry*</i>		
Baseline Weight z-score (n=80)	0.1	1.1
Final Weight, kg (n=105)	44.8	17.0
Final Weight z-score (n=105)	0.6	1.1
Baseline BMI z-score (n=79)	0.1	1.1
Final BMI, kg/m ² (n=105)	20.0	3.8
Final BMI z-score (n=105)	0.7	1.0
Final Percent Body Fat (n=97)	20.4	8.9
Final Waist Circumference, cm (n=98)	70.2	12.7
<i>Final Blood Pressure (n=105)</i>		
Systolic Blood Pressure, mmHg	107.4	11.5
Systolic Blood Pressure z-score	0.2	1.0
Diastolic Blood Pressure, mmHg	61.7	8.3
Diastolic Blood Pressure z-score	-0.0	0.7
Mean Arterial Pressure, mmHg	77.0	8.4
Pulse Pressure, mmHg	45.7	9.5
Heart Rate, bpm	84.5	14.2
<i>Final Glucose Homeostasis[†]</i>		
Glucose, mg/dl (n=93)	90.0	8.3
Total Insulin, μ UI/ml (n=92)	6.7	4.8
C-Peptide, ng/ml (n=46)	1.7	0.6
HOMA-IR (n=92)	1.5	1.1
<i>Final Lipids[‡] (n=92)</i>		
HDL Cholesterol, mg/dl	57.7	13.9
Total Cholesterol, mg/dl	158.4	24.6
LDL Cholesterol, mg/dl	88.5	21.1
Non-HDL Cholesterol, mg/dl	100.9	25.1
Triglycerides, mg/dl	59.9	35.8
Triglycerides/HDL Cholesterol Ratio	1.2	0.9
<i>Final Metabolic Syndrome Score[‡] (n=92)</i>	-0.0	3.2
<i>Final Regulatory Hormones[‡]</i>		
Leptin, ng/ml (n=92)	5.6	5.2
Adiponectin, μ g/ml (n=46)	15.0	7.0
Active Ghrelin, pg/ml (n=44)	237.0	150.5

Characteristic	Mean or N	SD or %
<i>Final Inflammatory Marker[†]</i>		
High Sensitivity C-reactive Protein, mg/l (N=47)	0.6	1.2

Legend for Table 1:

* The measurements were made at study enrollment except for the baseline weight and BMI ones.

[†] Only fasting samples are included, except for hsCRP. One participant with hsCRP > 5 mg/l and one with a triglyceride concentration of 601 mg/dl were excluded.

[‡] The metabolic syndrome score was generated following Eisenmann.

Table 2

Results for the multivariable regression analyses exploring the association between the slope of change in weight or BMI z-score and cardiometabolic risk factors while controlling for age, sex, and final weight or BMI z-score.

Outcome		Weight Z-score Analysis					BMI Z-score Analysis				
		Age	Sex	Weight	Slope	ΔR ²	Age	Sex	BMI	Slope	ΔR ²
		β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)		β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	
Final Anthropometry											
Percent Fat		--	--	5.45	<i>0.36 ‡</i> (-0.03, 0.75)	0.02	--	--	5.58	0.26	0.01
				(4.25, 6.65)	(-0.12, 0.64)						
Waist circumference		2.92 (2.53, 3.32)	1.22 (-1.88, 4.32)	8.26	0.13 (-0.19, 0.44)	0	3.16 (2.72, 3.59)	1.2 (-2.31, 4.71)	8.1	0.07	0.00
				(7.32, 9.20)	(-0.28, 0.42)						
Final Blood Pressure (BP)											
Systolic BP		--	--	-0.02	0.03 (-0.03, 0.09)	0.01	--	--	0.12	-0.02	0.00
				(-0.21, 0.17)	(-0.08, 0.32)						
Diastolic BP		--	--	-0.01	-0.02 (-0.06, 0.03)	0.01	--	--	0.06	-0.03	0.02
				(-0.14, 0.13)	(-0.08, 0.20)						
Mean Arterial Pressure		0.89 (0.29, 1.49)	2.18 (-2.67, 7.04)	0.95	0.03 (-0.46, 0.52)	0	1.00 (0.38, 1.61)	1.86 (-3.24, 6.95)	1.5	-0.25	0.01
				(-0.57, 2.46)	(-0.11, 3.10)				(-0.75, 0.26)		
Pulse Pressure		1.00 (0.35, 1.66)	-0.17 (-5.48, 5.15)	0.57	<i>0.53 ‡</i> (-0.01, 1.06)	<i>0.03</i>	1.11 (0.44-1.78)	-0.86 (-6.40, 4.68)	1.00	0.19	0.00
				(-1.09, 2.23)	(-0.36, 0.73)						
Heart Rate		-1.36 (-2.40, -0.32)	1.59 (-6.65, 9.82)	0.08	0.67 (-0.15, 1.50)	0.02	-1.66 (-2.70, -0.63)	3.7 (4.67, 12.07)	-0.09	0.64	0.02
				(-2.49, 2.65)	(-2.73, 2.55)				(-0.18, 1.47)		
Final Glucose Homeostasis											
Glucose		0.21 (-0.47, 0.89)	-2.22 (-8.04, 3.60)	-0.43	0.55 (0.03, 1.08)	0.05	0.28 (-0.43, 0.99)	-2.26 (-8.63, 4.10)	-0.12	0.4	0.02
				(2.03, 1.17)	(-0.15, 0.95)						
Total Insulin		0.75 (0.43, 1.08)	0.94 (-1.82, 3.71)	1.5	0.23 (-0.02, 0.49)	0.02	0.83 (0.50, 1.17)	1.93 (-1.10, 4.97)	1.62	0.11	0.01
				(0.73, 2.27)	(0.78, 2.45)				(-0.16, 0.37)		
C-peptide		0.13 (0.08, 0.18)	0.03 (-0.38, 0.45)	0.16	0.05 (0.02, 0.09)	0.09	0.12 (0.07, 0.17)	0.15 (0.27, 0.56)	0.16	0.02	0.01
				(0.04, 0.27)	(0.05, 0.28)				(-0.02, 0.06)		

Outcome	Weight Z-score Analysis					BMI Z-score Analysis				
	Age	Sex	Weight	Slope	ΔR^2	Age	Sex	BMI	Slope	ΔR^2
	β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)		β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	β Estimate (95% CI)	
HOMA-IR (log)	0.11 (0.07, 0.16)	0.23 (-0.14, 0.61)	0.17 (0.07, 0.28)	0.04 (0.01, 0.08)	0.04	0.12 (0.08, 0.17)	0.44 (0.03, 0.85)	0.18 (0.07, 0.30)	0.03 [‡] (-0.00, 0.07)	0.03
Final Lipids										
HDL Cholesterol	-0.92 (-1.90, 0.07)	1.45 (-6.85, 9.75)	-3.73 (-6.01, -1.44)	-1.43 (-2.18, -0.68)	0.11	-1.36 (-2.43, -0.29)	-1.63 (-11.16, 7.91)	-4.14 (-6.74, -1.53)	-0.86 (-1.69, -0.04)	0.04
Total Cholesterol	0.6 (-1.43, 2.62)	13.31 (-4.08, 30.70)	-0.26 (-5.10, 4.58)	-1.25 (-2.83, 0.33)	0.03	0.36 (-1.67, 2.39)	11.45 (-6.83, 29.73)	1.96 (-3.07, 6.99)	-0.94 (-2.52, 0.64)	0.02
LDL Cholesterol	-0.21 (-2.01, 1.59)	7.74 (-7.48, 22.96)	1.11 (-3.08, 5.31)	-0.01 (-1.39, 1.37)	0.00	-0.05 (-1.91, 1.80)	8.38 (-8.15, 24.91)	2.59 (-1.93, 7.11)	-0.06 (-1.49, 1.36)	0.00
Non-HDL Cholesterol	1.41 (-0.69, 3.51)	11.59 (-6.13, 29.32)	3.44 (-1.48, 8.37)	0.21 (-1.40, 1.82)	0.00	1.58 (-0.52, 3.68)	12.75 (-5.95, 31.45)	6.17 (1.04, 11.31)	-0.06 (-1.68, 1.55)	0.00
Triglycerides (log)	0.08 (0.04, 0.12)	0.12 (-0.25, 0.49)	0.13 (0.03, 0.24)	0.01 (-0.02, 0.04)	0.00	0.08 (0.04, 0.13)	0.25 (-0.14, 0.64)	0.15 (0.04, 0.26)	0.01 (-0.03, 0.04)	0.00
Triglycerides/HDL Cholesterol Ratio	0.12 (0.05, 0.19)	0.36 (-0.22, 0.95)	0.24 (0.08, 0.41)	0.06 (0.01, 0.12)	0.05	0.13 (0.06, 0.20)	0.57 (-0.06, 1.19)	0.31 (0.14, 0.48)	0.01 (-0.04, 0.07)	0.00
Final Metabolic Syndrome Score	--	--	1.46 (0.95, 1.97)	0.23 (0.07, 0.39)	0.06	--	--	1.52 (0.99, 2.06)	0.1 (-0.07, 0.26)	0.01
Final Regulatory Hormones										
Leptin (log)	0.03 (-0.03, 0.09)	0.55 (0.06, 1.04)	0.41 (0.27, 0.54)	0.04 [‡] (-0.01, 0.09)	0.02	0.05 (-0.01, 0.10)	0.84 (0.35, 1.33)	0.45 (0.31, 0.58)	0.05 (0.01, 0.09)	0.04
Adiponectin	-1.07 (-1.75, -0.39)	-2.54 (-8.38, 3.30)	-0.56 (-2.17, 1.04)	-0.54 (-1.04, -0.04)	0.08	-1.14 (-1.86, -0.42)	-4.96 (-11.04, 1.12)	-0.99 (-2.66, 0.69)	-0.62 (-1.21, -0.03)	0.08
Active Ghrelin (log)	-0.10 (-0.17, -0.03)	-0.25 (-0.83, 0.33)	0.00 (-0.16, 0.16)	0.00 (-0.05, 0.05)	0.00	-0.10 (-0.17, -0.02)	-0.24 (-0.84, 0.37)	-0.04 (-0.21, 0.13)	-0.01 (-0.07, 0.05)	0.00
Final Inflammatory Marker										
High Sensitivity C- reactive Protein (log)	0.03	-0.33	0.23	0.10	0.09	0.05	-0.08	0.28	0.05	0.02

Outcome	Weight Z-score Analysis						BMI Z-score Analysis					
	Age	Sex	Weight	Slope		ΔR^2	Age	Sex	BMI	Slope		ΔR^2
				β Estimate	β Estimate					β Estimate	β Estimate	
	(-0.10, 0.15)	(-1.42, 0.77)	(-0.07, 0.53)	(0.01, 0.20)		(-0.09, 0.19)	(-1.32, 1.15)	(-0.05, 0.61)	(-0.06, 0.17)			

Legend for Table 2:

*The measurements were all made at study enrollment except for the baseline weight and BMI ones.

† Only fasting samples are included, except for hsCRP. One participant with hsCRP > 5 mg/l and one with a triglyceride concentration of 601 mg/dl were excluded.

‡ The metabolic syndrome score was generated following Eisenman.