Supplementary Online Content

Nicol GE, Yingling MD, Flavin KS, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: a randomized clinical trial. *JAMA Psychiatry.* Published online June 13, 2018. doi:10.1001/jamapsychiatry.2018.1088

This supplementary material has been provided by the authors to give readers additional information about their work.

Figure 1. Study Recruitment and Enrollment Timeline

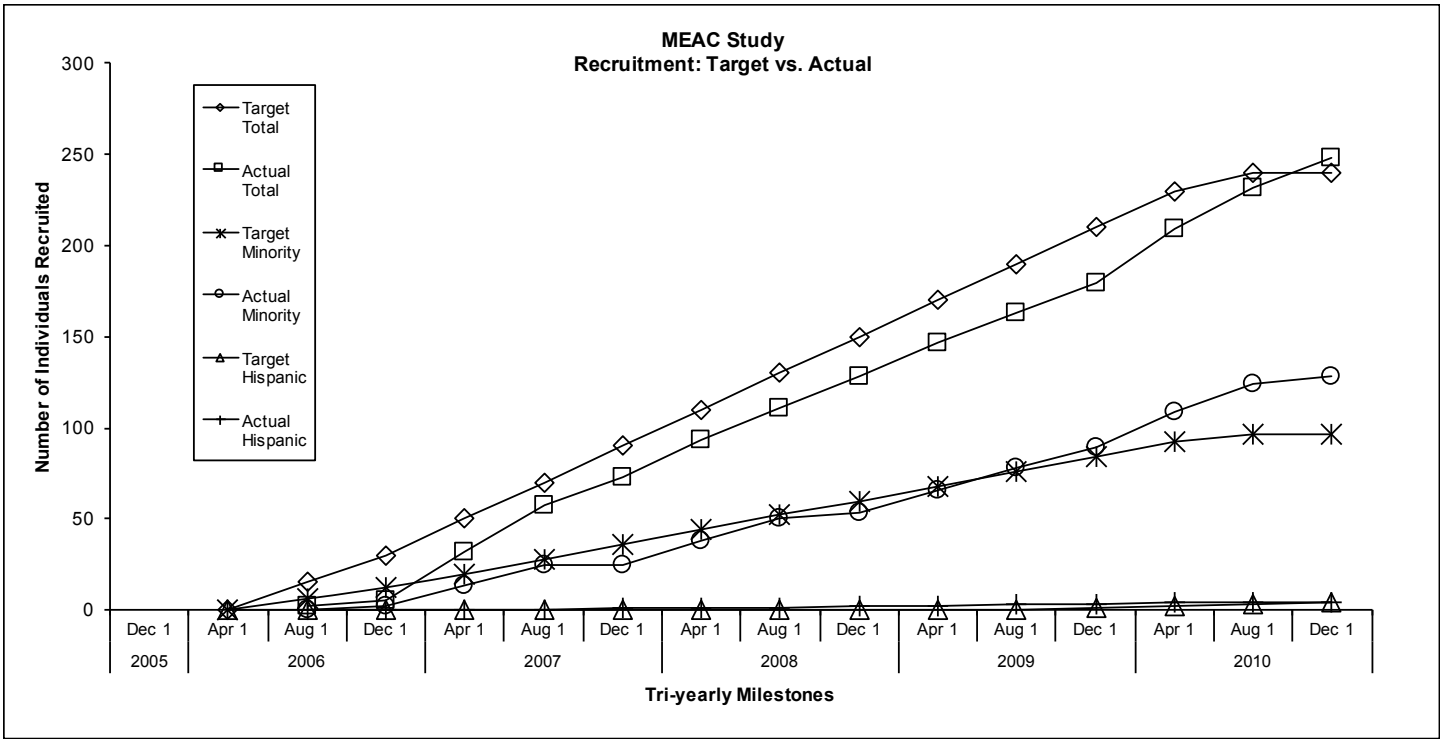


Figure 2. Adverse Events Reporting Scale

MEAC ADVERSE SYMPTOM CHECKLIST

SUBJECT ID:_____ DATE:_____ BASELINE OR 12 WKS (CIRCLE)

During Past Week, Middle of Stage 1 Clamp, Post Clamp

Severity Anchor Points	**RELATION CODE**
0 = Not Present 1 = Minimal (Upper limits of normal) 2 = Mild (Does not hinder the subjects normal functioning, but is an annoyance) 3 = Moderate (Significant impairment of functioning and/or uncomfortable or embarrassing 4 = Severe (Severe impairment of functioning or incapacitation and/or definite threat to well-being	0 = Unlikely 1 = Possible 2 = Probable 3 = Cannot be classified *Dark shaded cells do not need to be completed.*

	During Past Week		Mid Stage 1 (hr 4-5)		End of Clamp After Eating		Comments/ description, action take, etc
Symptom	**Severity**	**Relation**	**Severity**	**Relation**	**Severity**	**Relation**	
Accidental Injury							
Agitation							
Anxiety)							
Confusion							
Constipation							
Depression							
Difficulty Concentrating							
Dizziness (specify when)							
Headache (specify type)							
Drowsiness, Somnolence							
Dry Mouth							
Extra Saliva							
Galactorrhea							
Gynecomastia							
Increased Appetite							
Increased Sweating							
Involuntary Movements							
Headache							
Lightheadedness							
Nausea							
Restlessness							
Runny Nose							
Shakiness							
Sleepiness							
Thirst							
Tingling (hands, feet, lips or tongue)							
Tiredness/Fatigue							
Tremor							
Trouble Sleeping (describe)							
Upset Stomach							
Vomiting							
Weakness							
Weight Gain (cellulite or stretchmarks)							
Other (specify)							

Note: If an adverse symptom is reported later in interview, please code and note here:

Figure 3. Diagnostic Makeup of Intention-to-Treat (ITT) Sample

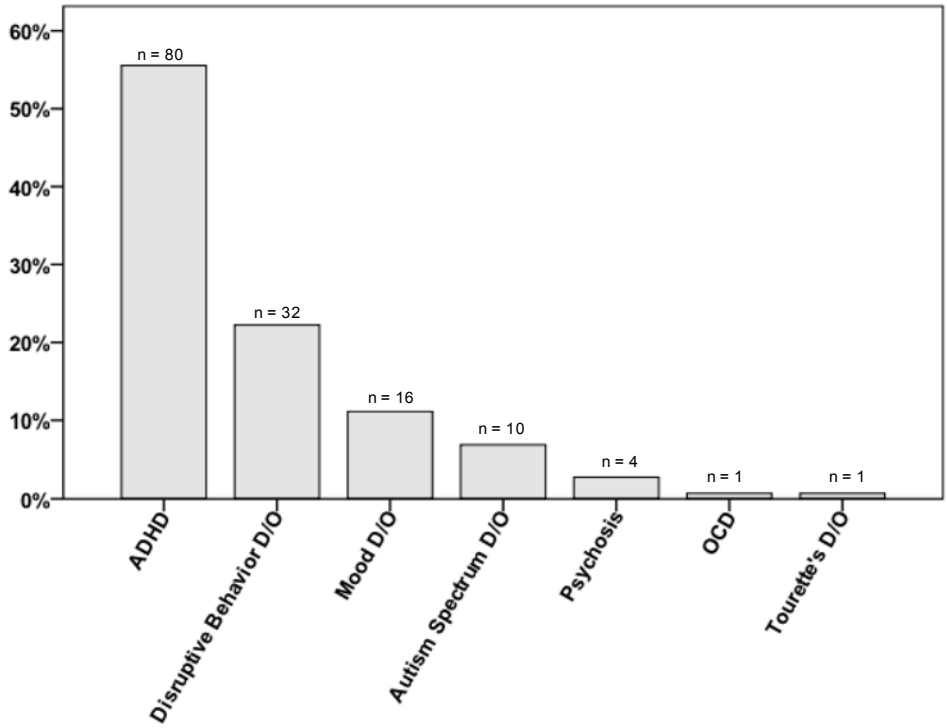
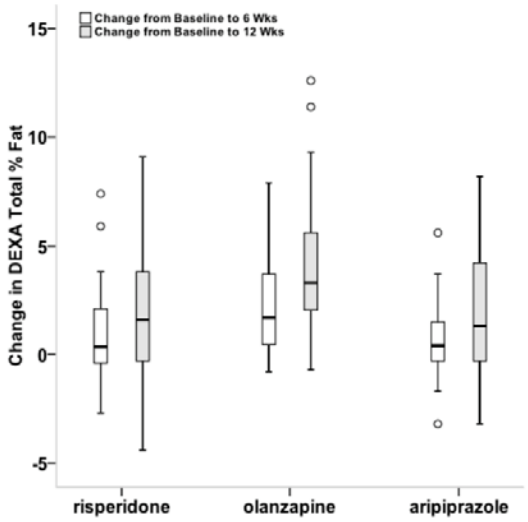
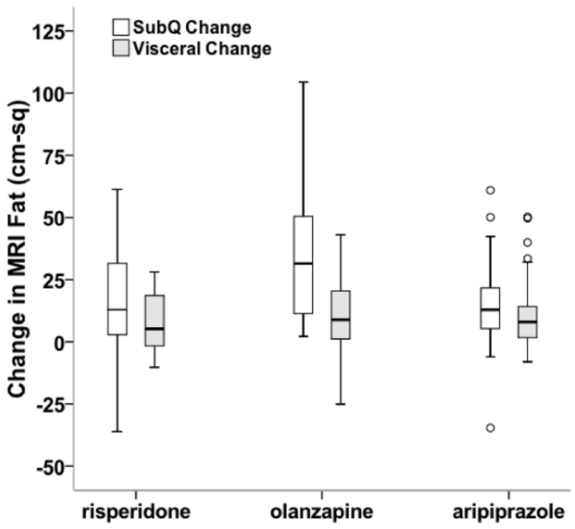


Figure 4. DEXA and MRI Change in Adiposity During Initial Antipsychotic Exposure in Youths

Change in DEXA total percent fat and MRI subcutaneous and visceral fat, respectively, by treatment group. The horizontal lines inside each box indicate the median, the top and bottom of the box indicate the interquartile range, the I bars indicate the 5th and 95th percentiles, and the circles indicate outliers.



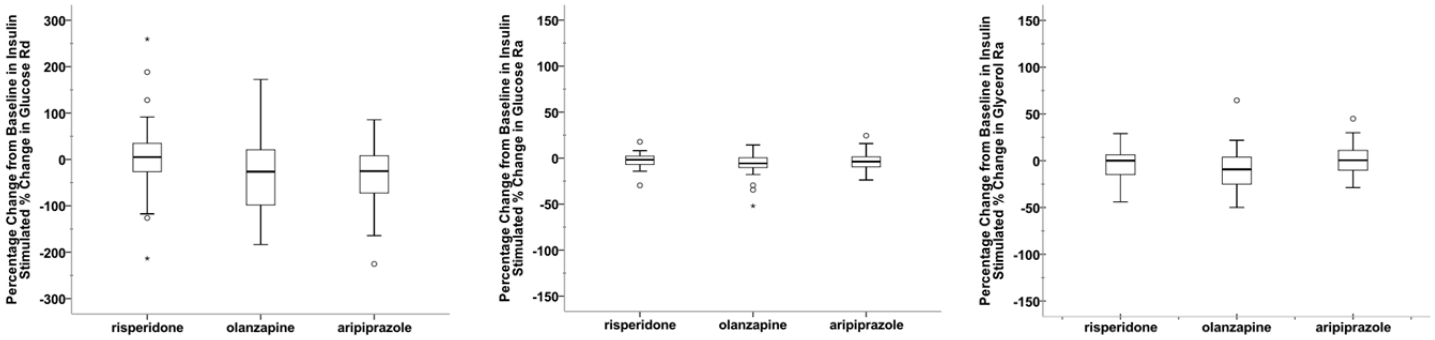
(a)



(b)

Figure 5. Change in Insulin Sensitivity

Changes are represented in muscle (Glucose Rd), hepatic (Glucose Ra) and adipose (Glycerol Ra) tissue during initial antipsychotic exposure. Boxplots depict % change over 12 weeks by treatment group; horizontal lines within boxes indicate the median; top and bottom of the box indicates the interquartile range. I bars indicate 5th and 95th percentiles. Circles indicate outliers, and far outliers are represented by an asterisk.



(b) (a) (c)

eMethods. Protocol Synopsis

This randomized clinical trial aimed to assess the metabolic safety of antipsychotic agents in antipsychotic-naive children with aggression in the setting of various childhood psychiatric disorders during 12 weeks of prospective, randomized treatment with olanzapine, risperidone or aripiprazole.

Primary Aim 1: Evaluate antipsychotic treatment effects on insulin action in skeletal muscle (glucose disposal), liver (glucose production) and adipose tissue (lipolysis). This study hypothesized that treatments causing greater increases in adiposity would be associated with reduced sensitivity to insulin effects on glucose disposal, glucose production, and glycerol/fatty acid release, in comparison to treatments producing less change in adiposity. Hypotheses were evaluated by measuring whole-body glucose and lipid kinetics with the use of stable isotope tracer methodology, using rate of disappearance of glucose (glucose Rd; primary), rate of appearance of glucose (glucose Ra), and rate of appearance of glycerol (glycerol Ra) as endpoints for the assessment of insulin sensitivity.

Primary Aim 2: Evaluate antipsychotic treatment effects on abdominal fat mass and total body fat. This study hypothesized that the selected antipsychotic medications have different magnitudes of adverse effect on direct measures of fat mass. These hypotheses were evaluated by measuring body composition using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI), quantifying percent total body fat (primary) and subcutaneous and visceral abdominal fat as endpoints.

The secondary aims of this study were to evaluate the effects of selected antipsychotic treatments on 1) fasting plasma lipids and waist circumference, which are indirect or surrogate measures for insulin sensitivity and adiposity, in order to assess the extent to which changes in the primary endpoints, measured directly with gold-standard tools, are also detectable using measures commonly available to clinicians, and 2) effectiveness for treatment of symptoms of aggression and irritability, using the Clinical Global Impressions Scale (CGI) as the primary endpoint.

Exploratory aims included the assessment of metabolic effects of antipsychotic treatment in children with and without concomitant stimulant therapy. Age-related differences in vulnerability to treatment-induced adverse metabolic changes were also explored.

Recruitment Procedures

We screened 390 potentially eligible participants and enrolled 248 youth ages 6-18 with clinically significant symptoms of aggression and irritability, defined by a score of ≥18 on the Irritability subscale of the Aberrant Behavior Checklist[1,2] in the context of one or more Axis I DSM IV-TR[3] childhood psychiatric disorders, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism spectrum disorders, attention deficit-hyperactivity disorder, bipolar affective disorder and schizophrenia, who assented to participate and whose guardian(s) gave informed consent for participation in the study. Individuals with clinically significant suicidal ideation, who were not clinically stable, or whose primary psychiatric disorders had not been adequately treated with first-line medications or behavioral treatments were referred back to their providers for appropriate treatment and stabilization before being considered for study participation. All participants were 6-18 years of age and the study population included all races and ethnic groups and both genders (supplemental Figure 1, Appendix II), with targeted enrollment reflecting the overall gender distribution of males and females for so-called "externalizing" disorders (i.e., 2.5:1, male:female).[4] Recruitment involved targeted community outreach to child psychiatrists, pediatricians, schools and family support groups, as well as screening potential participants from the Washington University Child and Adolescent Psychiatry Clinic and the BJC Behavioral Health System. Clinical Research Coordinators performed a telephone screen (See Screening Instrument in Appendix III) to identify children who were unlikely to meet inclusion criteria or who met exclusion criteria. Those families not excluded by telephone screen were given appointments for a clinical assessment with a study physician, and for baseline assessments. Once participants were enrolled, research staff maintained at least weekly contact with participants and relevant family members to enhance retention. See Figure 1 in Appendix II for timeline of recruitment and enrollment milestones. Each family received reminder phone calls in the days and weeks prior to the follow-up visit from the research study staff.

Participant Characteristics

The mean number of concurrent psychotropic medications was 0.90 (SD = 0.91) per participant; 58 participants were on study medication only during study participation; 50 participants were taking one additional psychotropic medication; 29 participants were taking 2 additional psychotropic medications; 6 participants were taking 3 concurrent psychotropic medications, and one subject was taking 4 concurrent psychotropic medications. The most common type of concurrent medication was a stimulant (n=77) (manuscript Table 1), followed by SSRI (n=16) (manuscript Table 1). Additional psychotropic medications included trazodone (n=6), atomoxetine (n=5), lamotrigine (n=5), extended-release valproate (n=1), oxcarbazepine (n=1), clonazepam (n=1) and extended-release venlafaxine (n=1). The diagnostic makeup of the sample is presented in the manuscript, Table 1 and in Figure 2, Appendix II.

Inclusion & Exclusion Criteria

Inclusion Criteria: i) age 6-18 years ii) generally healthy and a score of ≥18 on the Aberrant Behavior Checklist for irritability in the context of one or more Axis I DSM IV childhood psychiatric disorder, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder, autism, pervasive developmental disorder, attention deficit disorder, bipolar affective disorder and schizophrenia; iii) Children's Global Assessment Scale (CGAS) Score ≤ 60; iv) not previously treated with an antipsychotic; individual participants with a remote (i.e., > 1 year), brief (i.e., < 1 week) prior antipsychotic exposure were considered for enrollment by the PI on a case by case basis; v) patient assent and informed consent obtained from the parent or guardian; vi) no clinically significant (based on PI determination) changes in permitted medications (e.g., stimulants, SSRI's) for approximately 1 month prior to Baseline Evaluations.

Exclusion Criteria: i) active suicidality or a primary diagnosis of major depressive disorder; ii) any lifetime use of antipsychotics; individual participants with a remote, brief prior antipsychotic exposure were considered for enrollment as above; iii) the presence of any serious medical disorder that may confound the assessment of relevant biologic measures or diagnoses, including: significant organ system dysfunction; endocrine disease, including type 1 or type 2 diabetes mellitus; coagulopathy; anemia; or acute infection; all based on PI discretion; iv) participants regularly taking within the last 3 months any glucose lowering agent, lipid lowering agent, exogenous testosterone, recombinant human growth hormone, or any other endocrine agent that might

confound substrate metabolism, oral glucocorticoids (glucocorticoid nasal spray and inhalers are permitted), sedating antihistamines (non-sedating antihistamines such as but not limited to Claritin (loratadine) and Zyrtec (cetirizine) are permitted), and certain mood stabilizing agents, as some medications may themselves worsen or otherwise alter weight gain, glucose and lipid regulation or otherwise make it difficult to assess the effects of the antipsychotic alone; (note that exposure to many psychotropic agents including stimulants and SSRI's is permitted in order to maintain the generalizability of the sample); v) IQ < 70 (based on school records and/or evaluation by clinician); vi) current substance abuse; vii) past history of, or current dyskinesia; viii) stimulant dosage significantly higher (per PI judgment) than the equivalent of approximately 2 mg/kg/day methylphenidate equivalent dose.

Study Assessments

1. Specific screening tests and procedures:

Medical examination and history: All subjects were screened with a detailed history and physical examination performed by a study physician, routine blood tests including a glycated hemoglobin (A1C) level, and resting 12-lead electrocardiogram. Family history of diabetes mellitus, obesity and body mass index of subjects' parents were also collected.

Fasting labs and anthropomorphic measures: In addition to the exploratory aim of assessing non-metabolic adverse events, a secondary aim of the study is to assess the extent to which changes in the primary endpoints, measured directly with gold-standard tools, are also detectable using surrogate or derivative measures that are commonly available to clinicians. Routine blood tests were performed including A1C, complete blood count with differential, comprehensive metabolic panel, and a fasting lipid panel. Blood pressure and a measure of waist circumference were obtained.

Body composition analyses: Body composition was evaluated at baseline, 6 weeks, and 3 months. Percent total body fat and percent total fat-free mass was determined by DXA (Hologic QDR 1000/w, Waltham, MA).[5] The error of regional fat free mass determination by this technique, as compared with computerized tomography, is less than 5%.[5, 6] Magnetic resonance images of the abdomen were obtained at baseline and 3 months to directly quantify abdominal (subcutaneous and intra-abdominal) adipose tissue mass.[7] Images were acquired on a 1.5-T superconducting magnet (Siemens, Iselin, NJ) using a T_1-weighted pulse sequence with a TR of 500 msec and TE of 12 msec. The imaging matrix was 256x256, and section thickness was 8 mm with a 2mm intersection gap. Consistent slice localization was accomplished by using a rigid landmark (i.e., the iliac crest) to position the subject in the machine and by using coronal scouting images to identify the site for image acquisition (i.e., the L_3-L_4 interspace). Three cross-sectional images at the level of the umbilicus, one above, and one below the umbilicus section, were obtained. Twenty-three slices were analyzed by selecting the first 8 sequential slices beginning at the inferior pole of the most superior kidney and continuing inferiorly. Visceral (VAT) and subcutaneous (SAT) adipose tissue surface area (cm^2) were calculated for each slice and reported as a mean value over the 8 slices. Image analysis was performed using software developed at the Malinkrodt Institute of Radiology by Kyongtae T. Bae, MD. Images were assessed using the semiautomated image

segmentation software in the Analyze software system (v 5.0, Mayo Clinic Foundation, Biomedical Imaging Resource, Rochester, MN). This method has been utilized to quantify adipose tissue in children and adolescents.[8]

Hyperinsulinemic-euglycemic clamp study: Participants were instructed to begin fasting, except for water, at 2000 the night before the study assessment, following a standard meal provided by their parent or caregiver. The following morning at approximately 0600, participants were admitted to the Pediatric Clinical Research Unit for the clamp procedure. At approximately 0700, a catheter was inserted into an antecubital vein of one arm to infuse stable isotopically labeled glucose, dextrose and insulin. Another catheter was inserted into a contralateral hand or forearm vein heated to 55 °C using a thermostatically controlled hand-warming box to obtain arterialized blood samples. [9] At approximately 0800, prior to beginning the tracer infusion, blood samples were taken to obtain baseline measurements of glucose and glycerol enrichments. Then, a 3-h primed-constant infusion of [6,6-$^2H_2$]glucose in 0.9% NaCl solution (22 μmol/kg prime and 0.25 μmol·kg^{-1}·min^{-1} infusion rate) was used to determine basal glucose kinetics. After 120 min of tracer glucose infusion, a 1-h primed-constant infusion of [1,1,2,3,3-$^2H_5$]glycerol (1.2 μmol/kg prime and 0.08 μmol·kg^{-1}·min^{-1} infusion rate) was used to determine basal glycerol kinetics. After the 180 minute basal tracer infusion period, a euglycemic, hyperinsulinemic clamp was initiated and continued for 180 minutes.[10] During the clamp, insulin was infused at a rate of 40 mU·m^{-2}·min^{-1} for 180 minutes (initiated with a two-step priming dose of 160 mU·m^{-2}·min^{-1} for 5 min followed by 80 mU·m^{-2}·min^{-1} for 5 min), to achieve plasma insulin concentrations of approximately 90 μU/ml. This plasma insulin concentration provides an optimal level for evaluating insulin's effect on glucose production and lipolysis.[11] Euglycemia was achieved by infusing a variable rate of 20% dextrose enriched to ~2.5% with [6,6-$^2H_2$]glucose to minimize changes in plasma glucose tracer to tracee ratio.[12] The infusion of [6,6-$^2H_2$]glucose was decreased by 50% of basal from 180-360 minutes to account for the expected decline in hepatic glucose production.[13, 14] The infusion of [1,1,2,3,3-$^2H_5$]glycerol was also decreased by 50% of the basal rate during the clamp because of the expected decline in whole-body lipolytic rate.[15] Blood glucose was measured every 5-10 minutes during the clamp procedure to adjust dextrose infusion rate, with either a glucose oxidase method using a glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio 45387

USA) or a validated portable blood glucometer when necessary to decrease the total amount of blood drawn in smaller individuals. Blood samples were also collected every 10 min during the last 30 min of both the basal and insulin clamp periods to determine glucose and glycerol isotopic enrichments and the determination of glucose and glycerol kinetics, [13] [14] [15] and plasma hormone (insulin, C-peptide, glucagon, growth hormone, epinephrine, norepinephrine, free fatty acide and leptin) concentrations. For children < 77 lbs, collection of plasma catecholamines, growth hormone, free fatty acid and leptin samples were restricted to limit total blood draws to no greater than 3 ml/kg body weight. [16]

2. Psychiatric/Medical Diagnostic Assessment Methods:

Missouri Assessment of Genetics Interview for Children (***MAGIC):*** The MAGIC interview is a revised version of the Diagnostic Interview for Children with six versions: Child, Adolescent, Young Adult and Adult are self-report versions, and the Parent and Parent of Young Adult are parent reports on siblings.[17] The MAGIC uses criteria of the DSM-III-R, DSM-IV and ICD-10 to diagnose child, adolescent, young adult, and adult psychiatric disorders. The DSM-IV diagnoses include domain impairment and duration requirements. The specific sections included in the MAGIC interviews are: Demographics, Attention Deficit/Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, Alcohol Abuse, Tobacco and Glue-Sniffing Abuse, Marijuana and Street Drug Abuse, Gambling, Depression, Mania, Dysthymia, Separation Anxiety, Panic Disorder, Phobias, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Posttraumatic Stress Disorder, Eating Disorders, Premenstrual Dysphoric Disorder, Somatization, Psychosis and Schizophrenia, Psychosocial History, Home Environment, Peer and Sibling Relationships, Perinatal History, and Health Services Usage. Reliability and prospective stability studies have been completed on the MAGIC; in particular, for diagnosis of ADHD, inter-rater reliability for the Child, Adolescent, and Parent versions was excellent, (kappa >.9 for DSM-IV ADHD subtype diagnoses as well as for the endorsement of the 18 individual DSM-IV Criterion A ADHD symptoms). The 18-month prospective stability (done with raters blind to the initial diagnosis) for a diagnosis of ADHD was also good (kappa =.78); kappas for population-defined ADHD subtypes including inattentive and combined subtypes were .76 and .67, respectively.[18]

Wechsler Intelligence Scale for Children, Version 4 (WISC-IV): To confirm the exclusion of intellectual disability that would impair ability to assent to study procedures, and to give a general estimate of intellectual ability, all participants were be administered the Vocabulary subtest of either the WISC-IV (children/adolescents) or Wechsler Adult Intelligence Scale (WAIS-III).[19] Normal scoring protocols were used to create a standardized score. This assessment was performed by a trained study clinician prior to baseline assessments.

Pubertal Status Questionnaire (PSQ):[20] This instrument was completed by parents or adult caregivers as well as by subjects at least 10 years of age. The PSQ has demonstrated high reliability with physical examination. Rather than a physical exam, the PSQ relies on participant self-report of Tanner Stage by endorsement of the appropriate cartoon representation of the respondent's pubertal status. The PSQ has been accepted by the Washington University IRB for the evaluation of pubertal status.

Establishing DSM-IV Diagnoses: All research materials (assessment instruments, school reports, agency records, pediatrician/medical charts) were reviewed in consensus conferences including all non-blinded study raters and clinicians to establish a final consensus diagnoses.

Blinding, Training and Maintaining Interrater Reliability of Research Clinicians: Raters were blind to treatment group assignment. Families were instructed not to reveal treatment group assignment. Research staff were trained to interrater reliability and recalibrated annually. All raters had virtual 100% agreement on diagnostic categories and symptom severity ratings five times in a row as both interviewer and observer.

Antipsychotic Treatment Protocol

Quality of Care: During the randomized treatment phase of the study, subjects continued to receive care from their primary care physician and outpatient behavioral health provider, with weekly telephone contact from study staff and monthly follow up visits for medication titration with a study physician so that all subjects were monitored at a level that exceeds the standard of care. Frequent communication with outpatient providers was maintained by study staff with permission from parents or legal guardians to inform them of treatment progress and any test results. Providers were encouraged to maintain stable doses of allowed concurrent psychotropic medications when possible. If doses were changed, data was flagged. In cases where initiation of a new psychotropic medication was being considered by an outpatient provider to address symptoms of aggression or irritability, study clinicians would coordinate with that provider to make sure the assigned study medication was titrated appropriately to address symptoms. In cases where participants were psychiatrically hospitalized during study participation, this was reported as an adverse event. In cases where the hospitalization was study treatment related, participants were excluded from further study participation and the study clinician and staff facilitated coordination of ongoing outpatient psychiatric and medical care.

Choice of Specific Treatment and Experimental Conditions: The antipsychotic medications selected for this project were chosen in order to compare specific newer antipsychotic medications needed to address the study questions, where the use in child populations is either well supported by current literature and/or the drug is used extensively in aggression based on national and state prescribing patterns or showing rapid growth for this indication. At the time of funding, olanzapine and risperidone were the most frequently prescribed antipsychotic medications for aggression associated with psychiatric illness, with aripiprazole use increasing. Olanzapine is associated with the greatest amount of weight gain and metabolic effects in reports to date, making it an ideal positive control in this study. Risperidone is widely used in this population, and is the best supported by published literature, with intermediate weight gain and metabolic effects among the newer medications. Aripiprazole, recently approved by the FDA at the time of study initiation, appeared to have a favorable side effect profile in children, especially with respect to weight gain and metabolic effects in adults.

Medication Dosing: All study medications were initiated at the lowest available clinical dose, and titrated to effectiveness at the study clinician discretion by week 2 of study participation. In some cases, as noted above, medication doses were titrated at monthly study follow up visits in order to optimize treatment response.

Safety Precautions and Adverse Events Reporting

Study-related adverse events associated with treatment (Figure 1), and reported by 5% or more of participants at baseline or endpoint, are presented in supplemental Table 1, Appendix II. Adverse events occurring during the hyperinsulinemic-euglycemic glucose clamp procedure, and reported by 5% or more of participants at baseline or endpoint, are presented in supplemental Table 2, Appendix II. Additional safety monitoring was proposed for any subject with a greater than 10% increase in weight from baseline, fasting glucose >100 mg/dL or fasting triglycerides >250 mg/dL; this included additional study visits at three week intervals for follow-up weight and/or fasting metabolic parameters. Home urine ketone and glucose testing strips were provided with instructions to test once weekly and report results to a study coordinator during weekly contact. The development of frank diabetes or hyperlipidemia during study participation was considered grounds for study discontinuation, with subsequent referral to the appropriate medical specialist for further medical testing and follow up. No participants met criteria for additional safety monitoring during study participation.

Table 1. Adverse Events Associated With Study Medication

Adverse Events Reported by 5% or more of participants at Baseline or Endpoint*

AE's Reported (During Past Week)	% Reporting at Baseline				% Reporting at Endpoint			
	Pooled	Risperidone	Olanzapine	Aripiprazole	Pooled	Risperidone	Olanzapine	Aripiprazole
Accidental Injury	9.86	8.33	8.70	12.50	8.59	11.11	7.50	6.98
Agitation	82.39	83.33	80.43	83.33	40.63	35.56	52.50	34.88
Anxiety	38.46	34.69	34.78	45.83	24.81	28.26	25.00	20.93
Confusion	5.59	8.16	2.17	6.25	0.78	2.17	0.00	0.00
Constipation	9.86	10.42	10.87	8.33	7.87	15.56	5.00	2.38
Depression	26.06	35.42	17.39	25.00	7.87	8.89	12.50	2.38
Difficulty Concentrating	65.73	63.27	54.35	79.17	29.69	34.78	30.00	23.81
Dizziness	5.59	12.24	0.00	4.17	3.13	4.35	0.00	4.76
Drowsiness/Somnolence	14.69	14.29	10.87	18.75	22.66	17.39	25.00	26.19
Headache	19.58	26.53	13.04	18.75	10.16	10.87	10.00	9.52
Increased Appetite	15.49	18.75	15.22	12.50	50.00	33.33	77.50	41.86
Involuntary Movements	9.15	10.42	13.04	4.17	3.91	8.89	2.50	0.00
Restlessness	49.65	44.90	41.30	62.50	29.46	30.43	30.00	27.91
Runny Nose	14.79	20.83	13.04	10.42	6.30	2.22	2.50	14.29
Sleepiness	11.97	12.50	6.52	16.67	14.17	8.89	22.50	11.90
Thirst	5.63	2.08	2.17	12.50	3.94	2.22	7.50	2.38
Tiredness/Fatigue	12.59	8.16	10.87	18.75	10.94	4.35	15.00	14.29
Trouble Sleeping	45.77	54.17	47.83	35.42	11.81	17.78	7.50	9.52
Weight Gain	3.52	6.25	2.17	2.08	42.19	44.44	57.50	25.58

Table 2. Adverse Events Associated With Clamp Procedure

Adverse Events (AEs) Reported by 5% or more of participants during Hyperinsulinemic-Euglycemic Glucose Clamp at Baseline or Endpoint (presented as %)

AE's Reported (Mid-Stage of Clamp)	% Reporting at Baseline				% Reporting at Endpoint				Average			
	Pooled	Risperidone	Olanzapine	Aripiprazole	Pooled	Risperidone	Olanzapine	Aripiprazole	Pooled	Risperidone	Olanzapine	Aripiprazole
Agitation	7.10	9.38	9.09	2.94	8.10	8.57	13.79	2.86	7.60	8.97	11.44	2.90
Anxiety	10.10	6.25	9.09	14.71	10.00	5.71	10.34	13.89	10.05	5.98	9.72	14.30
Difficulty Concentrating	11.10	6.25	12.12	14.71	12.20	2.86	21.43	14.29	11.65	4.55	16.77	14.50
Drowsiness/Somnolence	15.20	21.88	18.18	5.88	21.40	14.29	17.86	31.43	18.30	18.08	18.02	18.66
Headache	3.00	3.13	3.03	2.94	7.00	11.43	6.90	2.78	5.00	7.28	4.96	2.86
Restlessness	36.40	28.13	39.39	41.18	27.30	20.00	37.93	25.71	31.85	24.06	38.66	33.45
Runny Nose	8.10	6.25	15.15	2.94	3.00	2.86	3.45	2.86	5.55	4.55	9.30	2.90
Tiredness/Fatigue	22.20	28.13	27.27	11.76	23.50	14.29	32.14	25.71	22.85	21.21	29.71	18.74
Upset Stomach	5.10	0.00	12.12	2.94	5.10	2.86	14.29	0.00	5.10	1.43	13.20	1.47

Table 3. Change in All Primary, Secondary, and Clinical Outcome Variables Over Time

Variable	Risperidone				Olanzapine				Aripiprazole				Time x Treatment F- and P-Values
	Week 0	Week 12	Δ	F- and P-Values	Week 0	Week 12	Δ	F- and P-Values	Week 0	Week 12	Δ	F- and P-Values	
Adiposity													
DXA Total % Fat[a]	26.43 (10.82)	28.24 (10.92)	1.81 (3.11)	F[1,45] = 15.63, p < 0.0001	24.45 (10.52)	28.57 (10.82)	4.12 (3.10)	F[1,39] = 70.73, p < 0.0001	27.13 (11.14)	28.79 (11.27)	1.66 (2.65)	F[1,41] = 16.54, p < 0.0001	F[4,196.22] = 6.17, p < 0.0001
DXA Total Fat (kg)[a]	12.50 (9.81)	14.21 (9.85)	1.71 (1.89)	F[1,45] = 37.70, p < 0.0001	10.70 (6.97)	14.36 (8.28)	3.66 (2.30)	F[1,39] = 101.28, p < 0.0001	13.46 (9.74)	15.22 (10.11)	1.76 (1.95)	F[1,41] = 34.15, p < 0.0001	F[2,124] = 12.93, p < 0.0001
DXA Total % Lean[a,b]	70.12 (10.52)	68.47 (10.57)	-1.65 (3.01)	F[1,45] = 13.83, p = 0.001	72.03 (10.30)	68.19 (10.50)	-3.84 (2.99)	F[1,39] = 65.65, p < 0.0001	69.48 (10.88)	67.98 (10.98)	-1.50 (2.55)	F[1,41] = 14.51, p < 0.0001	F[2,124] = 8.07, p = 0.001
DXA Total Lean (kg)[a,b]	29.76 (11.00)	31.71 (11.60)	1.95 (1.58)	F[1,45] = 69.38, p < 0.0001	30.05 (10.30)	32.87 (11.02)	2.82 (1.74)	F[1,39] = 105.54, p < 0.0001	31.67 (13.36)	33.50 (13.81)	1.83 (1.26)	F[1,41] = 87.93, p < 0.0001	F[2,124] = 6.10, p = 0.003
MRI Subcutaneous Fat (cm^2)[c]	127.87 (129.29)	146.08 (132.81)	18.21 (22.27)	F[1,29] = 20.06, p < 0.0001	85.97 (67.98)	120.23 (86.91)	34.27 (27.22)	F[1,25] = 41.21, p < 0.0001	107.78 (89.11)	123.63 (95.44)	15.84 (19.02)	F[1,29] = 20.82, p < 0.0001	F[2,82] = 6.44, p = 0.003
MRI Visceral Fat (cm^2)[c]	26.20 (19.56)	33.06 (24.87)	6.85 (10.99)	F[1,29] = 11.66, p = 0.002	20.39 (20.87)	31.11 (20.02)	10.73 (14.50)	F[1,25] = 14.23, p = 0.001	26.83 (24.40)	38.87 (34.95)	12.04 (15.11)	F[1,29] = 19.05, p < 0.0001	F[2,82] = 1.27, p = 0.29
MRI Total Fat (cm^2)[c,d]	154.08 (144.57)	179.14 (150.37)	25.07 (30.94)	F[1,29] = 19.69, p < 0.0001	106.35 (86.15)	151.35 (101.55)	44.99 (35.87)	F[1,25] = 40.91, p < 0.0001	134.61 (111.64)	162.49 (128.07)	27.88 (31.18)	F[1,29] = 23.99, p < 0.0001	F[2,82] = 3.94, p = 0.02
Weight (kg)	44.86 (19.52)	48.61 (19.79)	3.75 (2.69)	F[1,45] = 89.51, p < 0.0001	43.35 (14.27)	49.83 (15.95)	6.48 (3.41)	F[1,39] = 144.10, p < 0.0001	49.81 (24.31)	53.44 (24.92)	3.63 (2.71)	F[1,42] = 76.82, p < 0.0001	F[2,125] = 13.67, p < 0.0001
BMI Percentile[e]	61.65 (30.59)	72.05 (25.86)	10.40 (14.32)	F[1,45] = 24.24, p < 0.0001	56.57 (31.90)	74.38 (25.13)	17.81 (14.88)	F[1,39] = 57.35, p < 0.0001	65.00 (30.41)	73.29 (27.43)	8.28 (12.62)	F[1,42] = 18.52, p < 0.0001	F[2,125] = 4.67, p = 0.01

BMI Z-Score[e]	0.48 (1.16)	0.85 (1.00)	0.37 (0.43)	F[1,45] = 34.46, p < 0.0001	0.25 (1.15)	0.91 (0.95)	0.66 (0.47)	F[1,39] = 79.49, p < 0.0001	0.58 (1.18)	0.89 (1.08)	0.31 (0.37)	F[1,42] = 30.01, p < 0.0001	F[2,125] = 7.44, p = 0.001
Waist Circumference (cm^2)	68.50 (13.88)	71.69 (13.87)	3.19 (3.37)	F[1,45] = 41.13, p < 0.0001	66.49 (11.46)	73.57 (12.83)	7.08 (4.41)	F[1,39] = 103.16, p < 0.0001	70.86 (15.79)	74.19 (16.67)	3.33 (3.59)	F[1,42] = 37.06, p < 0.0001	F[2,125] = 14.09, p < 0.0001
Insulin Sensitivity (mean, SD)													
Insulin-Stimulated % Change in Glucose Rd[f]	165.28 (77.35)	167.58 (98.28)	2.30 (83.91)	F[1,38] = 0.03, p = 0.87	169.84 (83.11)	140.50 (93.07)	-29.34 (85.56)	F[1,32] = 3.88, p = 0.06	156.48 (82.18)	126.22 (73.48)	-30.26 (65.46)	F[1,39] = 8.55, p = 0.006	F[2,108] = 2.70, p = 0.07
Clamp Insulin Concentration	40.68 (7.95)	41.99 (10.55)	1.30 (10.27)	F[1,38] = 0.63, p = 0.43	39.64 (8.80)	41.14 (13.97)	1.50 (9.35)	F[1,32] = 0.85, p = 0.36	41.87 (13.65)	43.91 (15.17)	2.04 (10.04)	F[1,39] = 1.65, p = 0.21	F[2,108] = 0.10, p = 0.90
% Change in Glucose Rd Corrected for Insulin[f]	426.83 (228.50)	421.20 (261.77)	-5.63 (244.26)	F[1,38] = 0.02, p = 0.89	460.04 (274.09)	390.07 (317.13)	-69.98 (261.75)	F[1,32] = 2.36, p = 0.13	416.01 (246.46)	331.00 (229.86)	-85.01 (163.21)	F[1,39] = 10.85, p = 0.002	F[2,108] = 1.57, p = 0.21
Insulin-Stimulated % Change in Glucose Ra[g]	83.23 (11.27)	80.72 (8.91)	-2.50 (7.61)	F[1,38] = 4.23, p = 0.05	82.42 (10.04)	75.85 (19.19)	-6.57 (13.16)	F[1,32] = 8.22, p = 0.007	82.57 (12.28)	79.30 (10.47)	-3.27 (9.27)	F[1,39] = 4.99, p = 0.03	F[2,108] = 1.80, p = 0.17
Clamp Insulin Concentration	40.68 (7.95)	41.99 (10.55)	1.30 (10.27)	F[1,38] = 0.63, p = 0.43	39.64 (8.80)	41.14 (13.97)	1.50 (9.35)	F[1,32] = 0.85, p = 0.36	41.87 (13.65)	43.91 (15.17)	2.04 (10.04)	F[1,39] = 1.65, p = 0.21	F[2,108] = 0.10, p = 0.90
% Change in Glucose Ra Corrected for Insulin[g]	212.55 (50.76)	203.60 (56.58)	-8.94 (42.53)	F[1,38] = 1.72, p = 0.20	219.17 (61.30)	201.66 (79.59)	-17.51 (47.11)	F[1,32] = 4.56, p = 0.04	216.74 (76.18)	206.24 (93.51)	-10.50 (75.04)	F[1,39] = 0.78, p = 0.38	F[2,108] = 0.18, p = 0.83
Insulin-Stimulated % Change in Glycerol Ra[g]	56.23 (13.76)	52.58 (15.58)	-3.65 (17.23)	F[1,37] = 1.71, p = 0.20	56.21 (15.49)	47.92 (18.08)	-8.29 (22.39)	F[1,30] = 4.25, p = 0.05	50.45 (15.43)	52.16 (13.37)	1.70 (16.79)	F[1,38] = 0.40, p = 0.53	F[2,104] = 1.33, p = 0.27
Clamp Insulin Concentration	40.84 (8.00)	42.01 (10.69)	1.18 (10.37)	F[1,37] = 0.49, p = 0.49	39.94 (8.98)	41.32 (14.41)	1.38 (9.60)	F[1,30] = 0.64, p = 0.43	41.17 (13.07)	42.87 (13.85)	1.71 (9.94)	F[1,38] = 1.15, p = 0.29	F[2,104] = 0.04, p = 0.96

% Change in Glycerol Ra Corrected for Insulin[g]	144.63 (49.49)	133.19 (50.84)	-11.44 (48.60)	F[1,37] = 2.10, p = 0.16	149.20 (57.07)	124.69 (54.57)	-24.51 (66.83)	F[1,30] = 4.17, p = 0.05	133.90 (57.68)	136.79 (61.04)	2.90 (47.63)	F[1,38] = 0.14, p = 0.71	F[2,104] = 1.52, p = 0.22
Whole Body Sensitivity[h]	12.52 (5.03)	11.85 (4.66)	-0.66 (3.14)	F[1,39] = 1.79, p = 0.19	12.16 (4.29)	10.88 (4.96)	-1.28 (3.89)	F[1,33] = 3.66, p = 0.06	12.29 (5.93)	10.37 (4.85)	-1.92 (3.09)	F[1,39] = 15.52, p < 0.0001	F[2,110] = 1.87, p = 0.16
Clamp Insulin Concentration	40.52 (7.92)	41.61 (10.69)	1.08 (10.23)	F[1,39] = 0.45, p = 0.51	39.52 (8.69)	40.95 (13.80)	1.43 (9.21)	F[1,33] = 0.82, p = 0.37	41.43 (13.44)	43.58 (15.07)	2.15 (10.02)	F[1,39] = 1.84, p = 0.18	F[2,110] = 0.16, p = 0.85
Whole Body Sensitivity Corrected for Insulin[h]	32.71 (16.12)	30.69 (15.00)	-2.02 (9.87)	F[1,39] = 1.68, p = 0.20	32.80 (14.90)	29.97 (17.76)	-2.84 (11.70)	F[1,33] = 2.00, p = 0.17	34.25 (22.90)	28.16 (18.25)	-6.08 (10.62)	F[1,39] = 13.14, p = 0.001	F[2,110] = 1.57, p = 0.21
Clinical Variables													
CGI-Severity of Illness[i]	4.61 (0.49)	3.43 (0.65)	-1.17 (0.68)	F[1,45] = 138.42, p < 0.0001	4.55 (0.50)	3.63 (0.54)	-0.93 (0.62)	F[1,39] = 90.34, p < 0.0001	4.49 (0.51)	3.44 (0.67)	-1.05 (0.69)	F[1,42] = 99.36, p < 0.0001	F[2,125] = 1.47, p = 0.24
ABC-Irritability/Agression[j]	28.24 (5.59)	11.40 (8.40)	-16.84 (7.65)	F[1,45] = 222.99, p < 0.0001	27.70 (5.90)	11.98 (8.05)	-15.73 (7.97)	F[1,39] = 155.70, p < 0.0001	27.50 (6.15)	10.32 (8.83)	-17.18 (8.79)	F[1,41] = 160.51, p < 0.0001	F[2,124] = 0.40, p = 0.67
CGAS[k]	52.13 (4.15)	65.20 (6.53)	13.07 (6.65)	F[1,45] = 177.67, p < 0.0001	51.75 (4.90)	63.20 (4.95)	11.45 (4.84)	F[1,39] = 224.28, p < 0.0001	52.09 (4.25)	65.05 (4.83)	12.95 (4.87)	F[1,42] = 303.67, p < 0.0001	F[2,125] = 1.62, p = 0.20
Number of School Suspensions	2.66 (4.32)	0.29 (0.65)	-2.37 (4.08)	F[1,37] = 12.83, p = 0.001	2.00 (2.86)	0.29 (0.62)	-1.71 (2.51)	F[1,23] = 11.11, p = 0.003	2.36 (4.30)	0.48 (0.96)	-1.88 (4.30)	F[1,24] = 4.79, p = 0.04	F[2,83] = 0.68, p = 0.51
Fasting Glucose (mg/dL)	89.43 (8.32)	91.85 (6.82)	2.41 (6.95)	F[1,45] = 5.55, p = 0.02	87.90 (6.56)	89.90 (7.44)	2.00 (7.39)	F[1,39] = 2.93, p = 0.10	88.79 (6.42)	89.86 (7.13)	1.07 (6.74)	F[1,42] = 1.08, p = 0.30	F[2,125] = 0.86, p = 0.43
Fasting Insulin (uU/mL)	7.87 (5.88)	10.45 (7.12)	2.58 (5.25)	F[1,42] = 10.38, p = 0.002	6.44 (3.79)	10.62 (12.98)	4.18 (11.12)	F[1,38] = 5.50, p = 0.02	9.12 (8.83)	12.10 (10.07)	2.98 (7.24)	F[1,42] = 7.28, p = 0.01	F[2,121] = 0.37, p = 0.69
HS-CRP (mg/L)[l]	1.35 (2.11)	1.24 (2.03)	-0.12 (2.16)	F[1,42] = 0.12, p = 0.73	1.30 (3.11)	1.38 (2.13)	0.09 (3.60)	F[1,36] = 0.02, p = 0.88	1.24 (1.64)	1.30 (1.94)	0.07 (1.56)	F[1,39] = 0.07, p = 0.79	F[2,116] = 0.07, p = 0.93

HgA1c (%)[m]	5.47 (0.26)	5.50 (0.31)	0.03 (0.27)	F[1,45] = 0.69, p = 0.41	5.55 (0.35)	5.57 (0.33)	0.03 (0.26)	F[1,39] = 0.37, p = 0.55	5.53 (0.28)	5.55 (0.30)	0.02 (0.21)	F[1,42] = 0.33, p = 0.57	F[2,125] = 0.05, p = 0.95
Total Cholesterol (mg/dL)	144.45 (29.60)	141.54 (25.13)	-2.90 (18.87)	F[1,45] = 1.09, p = 0.30	139.13 (25.18)	142.90 (23.53)	3.78 (19.56)	F[1,39] = 1.49, p = 0.23	135.00 (29.45)	138.26 (28.84)	3.26 (14.58)	F[1,42] = 2.14, p = 0.15	F[2,125] = 1.19, p = 0.31
HDL Cholesterol (mg/dL)[n]	52.55 (12.61)	50.24 (11.52)	-2.32 (6.17)	F[1,45] = 6.48, p = 0.01	52.88 (12.24)	50.99 (14.61)	-1.89 (7.73)	F[1,39] = 2.39, p = 0.13	50.37 (9.88)	49.49 (11.21)	-0.88 (7.26)	F[1,42] = 0.64, p = 0.43	F[2,125] = 0.33, p = 0.72
Triglycerides (mg/dL)	61.86 (33.47)	72.72 (45.23)	10.86 (35.82)	F[1,45] = 4.23, p = 0.05	62.73 (33.32)	76.89 (51.21)	14.16 (49.14)	F[1,39] = 3.32, p = 0.08	53.67 (24.15)	62.05 (24.85)	8.37 (21.91)	F[1,42] = 6.28, p = 0.02	F[2,125] = 0.57, p = 0.57
LDL Cholesterol (mg/dL)[o]	79.63 (26.16)	77.00 (21.59)	-2.63 (15.53)	F[1,45] = 1.32, p = 0.26	73.73 (24.95)	76.48 (19.29)	2.75 (18.49)	F[1,39] = 0.89, p = 0.35	73.93 (27.08)	76.37 (25.63)	2.44 (11.27)	F[1,42] = 2.02, p = 0.16	F[2,125] = 1.02, p = 0.37
ALT (IU/L)[p]	18.11 (7.82)	17.96 (7.11)	-0.15 (8.28)	F[1,45] = 0.02, p = 0.90	13.58 (4.37)	21.46 (11.11)	7.89 (9.01)	F[1,39] = 30.68, p < 0.0001	15.79 (4.58)	20.72 (9.03)	4.93 (8.31)	F[1,42] = 15.16, p < 0.0001	F[2,125] = 6.24, p = 0.003
ALP (IU/L)[q]	214.59 (87.68)	229.93 (95.70)	15.35 (36.87)	F[1,45] = 7.97, p = 0.007	219.45 (78.23)	250.03 (79.59)	30.58 (39.72)	F[1,39] = 23.70, p < 0.0001	204.56 (86.21)	221.86 (96.60)	17.30 (26.79)	F[1,42] = 17.94, p < 0.0001	F[2,125] = 2.33, p = 0.10
AST (IU/L)[r]	25.78 (7.28)	24.46 (7.33)	-1.33 (4.94)	F[1,45] = 3.32, p = 0.08	22.80 (6.32)	27.66 (8.92)	4.86 (6.10)	F[1,39] = 25.38, p < 0.0001	23.93 (7.03)	26.91 (8.27)	2.98 (6.35)	F[1,42] = 9.46, p = 0.004	F[2,125] = 11.15, p < 0.0001
Total Bilirubin (mg/dL)	0.37 (0.25)	0.31 (0.17)	-0.05 (0.19)	F[1,45] = 3.62, p = 0.06	0.42 (0.18)	0.36 (0.17)	-0.06 (0.18)	F[1,39] = 4.24, p = 0.05	0.34 (0.18)	0.31 (0.14)	-0.03 (0.13)	F[1,42] = 2.98, p = 0.09	F[2,125] = 0.33, p = 0.72
Albumin (g/dL)	4.02 (0.26)	3.94 (0.28)	-0.07 (0.30)	F[1,45] = 2.82, p = 0.10	4.04 (0.27)	3.99 (0.22)	-0.05 (0.30)	F[1,39] = 1.13, p = 0.29	4.05 (0.26)	4.04 (0.30)	-0.01 (0.19)	F[1,42] = 0.17, p = 0.69	F[2,125] = 1.21, p = 0.30
Total Protein (g/dL)	6.93 (0.45)	6.81 (0.45)	-0.12 (0.44)	F[1,45] = 3.32, p = 0.08	6.85 (0.38)	6.89 (0.45)	0.04 (0.48)	F[1,39] = 0.28, p = 0.60	6.95 (0.35)	6.90 (0.33)	-0.05 (0.28)	F[1,42] = 1.47, p = 0.23	F[2,125] = 1.18, p = 0.31

a Dual-Energy X-Ray Absorptiometry
b Not including bone mineral content

c Magnetic Resonance Imaging
d Subcutaneous+Visceral
e Body Mass Index
f Rate of Disappearance
g Rate of Appearance
h mg/kg of fat-mass/min
i Clinical Global Impression Scale
j Aberrant Behavior Checklist
k Clinical Global Assessment Scale
l High-Sensitivity C-reactive Protein
m Hemoglobin A1c
n High-Density Lipoprotein
o Low-Density Lipoprotein
p Alanine Aminotransferase
q Alkaline Phosphatase
r Aspartate Aminotransferase

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