

**Healthy Bodies, Healthy Kids: Measurement of Cardiometabolic Risk in
Antipsychotic-Treated Children
NCT01222494**

Study Protocol & Statistical Analytic Plan

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APPENDIX I: Protocol Synopsis

SPECIFIC AIMS

The US prevalence of childhood-onset obesity and type 2 diabetes, both predictors of cardiovascular risk, has increased to epidemic proportions in recent decades.^{1,2} Persons with major mental illnesses in the public sector, including childhood-onset illnesses, lose a mean of 25-30 years of potential life expectancy compared to the general population, primarily due to obesity-related conditions like cardiovascular disease (CVD).^{3,4} Children with mental illness who are treated with antipsychotic medications are at additional risk for obesity and related risk conditions,⁵ increasing observed rates of adverse cardiovascular events.⁶ Early results from the Metabolic Effects of Antipsychotics in Children study (MEAC; PI Newcomer, MH072912) indicate that 12 weeks of initial antipsychotic treatment is associated increases in directly-measured adiposity and insulin resistance,^{7,8} a cardiometabolic profile change predictive of CVD and diabetes risk.

Despite known elevations in obesity-related premature mortality seen with childhood-onset versus adult-onset obesity,⁹ including early development of carotid plaques¹⁰ and fatty liver,¹¹ there remains an under-appreciation of these risks in children, and extremely low screening rates for even basic risk factors in children.^{12,13} Progress has been made in the last 10 years, as a variety of noninvasive techniques have begun to be applied in children. These techniques, including carotid intima media thickness (IMT) measured by ultrasound, body composition measured by dual energy X-ray absorptiometry (DEXA), and hepatic triglyceride content measured using magnetic resonance (MR) imaging-estimated proton density fat fraction (PDFF), allow for the early, noninvasive study of metabolic risk. Unfortunately, none of these promising methods have been applied to the high-risk population of children with psychiatric disorders, and cardiac triglyceride content has not been evaluated in children at all.

This project will utilize sensitive, early biomarkers of disease risk, including whole-body adiposity, hepatic triglyceride content and carotid IMT, directly relevant to diabetes and cardiovascular disease risk, respectively. **The overall aim of this two-study research plan is to characterize risk using these sensitive biomarkers in children with mental health disorders, and evaluate the magnitude of change observed in these biomarkers in children receiving an established weekly behavioral weight-loss (BWL) intervention.** This will be accomplished with a randomized, controlled test of the effects of a 16-week behavioral weight loss intervention on CTGC, PDFF and IMT in overweight/obese antipsychotic (AP)-treated children randomized 2:1 to weekly BWL treatment or monthly diet and exercise education or usual care (UC), versus nonpsychiatric (NP) overweight or obese children undergoing the weekly BWL treatment.

Study Aims for this pilot randomized controlled trial:

Aim 1: To evaluate the main effect of time of 16 weeks of a BWL intervention on DEXA-measured whole body adiposity in overweight/obese antipsychotic (AP)-treated children compared to nonpsychiatric (NP) overweight or obese healthy controls, and in AP-treated youth randomized to monthly Usual Care (UC).

Aim 2: To evaluate the main effect of time of 16 weeks of a BWL intervention on PDFF in overweight/obese AP-treated children compared to NP overweight or obese healthy controls, and in AP-treated youth randomized monthly UC.

Aim 3: To evaluate the main effect of time of 16 weeks of a weekly behavioral weight loss intervention on CIMT in overweight/obese AP-treated children compared to NP overweight or obese healthy controls, and in AP-treated youth randomized monthly UC.

Primary Hypothesis: *Change in DEXA-measured total fat and PDFF/IMT will be more pronounced in the weekly weight loss intervention groups compared to the monthly Usual Care intervention.*

Exploratory Aims:

a) To evaluate the effects of 16 weeks' of weekly versus monthly weight loss intervention on changes in standard cardiometabolic risk factors (e.g., fasting lipids, insulin, glucose, adiponectin, fibrinogen, high sensitivity C-reactive protein and very low density lipoprotein particle size).

b) To evaluate baseline psychiatric symptom severity on treatment adherence and changes in biomarkers during treatment.

PARTICIPANT RECRUITMENT & SELECTION

This project aimed to recruit overweight or obese mentally ill antipsychotic treated (AP) and healthy non-psychiatric (NP) participants. The majority of AP participants in the proposed study will be well-characterized subjects participating in the Metabolic Effects of Antipsychotics Children study (MEAC, PI: Newcomer; MH 072912), the Child and Adolescent Psychiatry Clinic at WUSM, BJC Behavioral Health Clinics, community psychiatrists, and the Volunteer for Health Registry. Healthy control subjects will be recruited from Washington University and Children's Hospital general pediatric clinics, referred from community pediatricians, and from Volunteers for Health. Recruitment included all races and ethnic groups and both genders, with targeted enrollment reflecting the overall gender distribution of males and females for "externalizing" disorders (i.e., 3:1, male: female).¹⁴

Inclusion Criteria: **i)** 6-18 years old (at any point during study participation); **ii)** BMI percentile \geq 85 **iii)** Meet DSM-IV criteria for one or more childhood onset psychiatric disorders including disruptive behavior disorders (attention deficit disorder, conduct disorder, oppositional defiant disorder and disruptive behavior disorder not otherwise specified), affective disorders (bipolar affective disorder, major depressive disorder and mood disorder not otherwise specified), anxiety disorders (generalized anxiety disorder, obsessive compulsive disorder, separation anxiety, social and other specific phobias) as well as other disorders, including autism spectrum disorders (autistic disorder, Asperger's Syndrome and pervasive developmental disorder not otherwise specified), psychotic disorders (schizophreniform disorder, schizophrenia and psychotic disorder not otherwise specified) and movement disorders (tic disorder, Tourette's Syndrome) (*EXCEPT* for the Obese or Overweight Control Group, none of whom can meet criteria for any DSM-IV Axis I psychiatric illness); **iv)** Participants treated with psychotropic medication may not have any medication changes for 1 month prior to study enrollment at the discretion of the PI, and Antipsychotic-Treated Participants must be treated with an antipsychotic \geq approximately 6 months with no antipsychotic medication dose changes for 1 month; **vi)** The Healthy Overweight or Obese Control Group may not be currently taking any prescription medications (multivitamins, over the counter medications, glucocorticoid nasal spray and inhalers are permitted, as well as non-sedating antihistamines such as but not limited to Claritin (loratadine) and Zyrtec (cetirizine)); and **vii)** Participants between 6-17 years old able to give assent and have a parent/guardian that can provide written informed consent, and 18 year-old participants will be able to provide written informed consent.

Exclusion Criteria: **i)** Do not meet DSM-IV criteria for any Axis I psychiatric illness per PI discretion (*EXCEPT* for Overweight or Obese Healthy non-psychiatric participants); **ii)** Any lifetime use of antipsychotics in the non-psychiatric group **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 including antiepileptic medications (lamotrigine is permitted) and Lithium, as these 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, SSRI's and SNRI's are permitted in the Antipsychotic-Treated group in order to maintain the generalizability of the sample); **v)** IQ < 70 (based on school records and/or evaluation by clinician and at the discretion of the PI); **vi)** Current DSM IV diagnosed substance abuse or dependence; **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 in the antipsychotic-treated groups **ix)** Unable to provide assent or informed consent; **x)** active suicidality or a primary diagnosis of depression; and **xi)** unwilling to allow study staff to contact subject's primary care physician to alert to any significant, abnormal clinical findings or test results obtained as part of study participation.

MEDICAL, BEHAVIORAL & DIAGNOSTIC ASSESSMENTS

Diagnostic assessment with both child and caregiver reports was administered with the semi-structured, standardized *MINI Kid*. Behavioral assessments will include *Aberrant Behavior Checklist (ABC)*,^{15,16} and the *Achenbach Child Behavior Checklist/Adult Behavior Checklist (CBCL/ABCL)*. *Medical Records (MR)* and *Medical History Forms* were used to document each participant's personal and family medical history. The *Duke Pubertal Status Questionnaire (PSQ)*¹⁷ was completed by participants at least 10 years old, and by both caregiver and participant when the participant is younger than 10. A *Locator Form*, including extensive contact information of both participant and caregiver that has historically allowed us to achieve a follow-up rate of $\geq 90\%$ in all of our past studies, was completed at baseline to enhance the ability to locate participants throughout the course of the study.

Medication: a medication history will be obtained by self-report clinician interview at baseline and at scheduled study follow-up assessments; medication name, dose and refill history will be verified by contact with prescribing provider and/or pharmacy. Medication may be titrated as necessary for target symptom relief by the patient's treating clinician, but will not be modified through the proposed study or for one month prior to study enrollment.

Locator Form: This form is completed at baseline to enhance the ability to locate participants at the three-month follow-up. This form includes all contact information necessary for locating biological parents, step-parents and parents residing outside of the household as well as spouses, significant others, siblings, grandparents, close friends and neighbors of the participants. In our experience families do not object to supplying this information and understand that it will only be used to locate them without, under any circumstance, revealing why the University is looking for them other than that they are study participants

Medical Records (MR) and Medical History Form: This information is obtained by telephone to acquire mailing or faxing preference and then mailing or faxing consents to the various physicians, other health care providers, and hospitals. Consents accompany mailing materials with prepaid return postage or with instructions for faxing materials back to us. The Medical History Form is administered to the mother about the child.

MINI-Kid:¹⁸ The Mini International Neuropsychiatric Interview (MINI) is a short, structured diagnostic interview developed initially in 1990 by psychiatrists and clinicians in the United States and Europe for DSM-III-R and ICD-10 psychiatric disorders. The interview takes 15 minutes to administer, and is conducted with both parent and child, deferring to parent report when child report is unclear or unreliable.

Aberrant Behavior Checklist (ABC):^{15,16} This instrument is a five-factor scale comprising 58 items under the categories of (I) Irritability, Agitation, Crying; (II) Lethargy, Social Withdrawal; (III) Stereotypic Behavior; (IV) Hyperactivity, Noncompliance; and (V) Inappropriate Speech. The 15-item Irritability subscale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45. It has been estimated that our cut-off of ≥ 18 on this subscale will identify individuals that are 1.3 to 1.5 SD above the mean.

Achenbach Child Behavior Checklist/Adult Behavior Checklist (CBCL/ABCL):¹⁹ The CBCL/ABCL serves as a general screening measure of behavior problems, competencies, and school functioning, and has well-established norms. It obtains reports from parents, other close relatives, and/or guardians regarding children's competencies and behavioral/emotional problems. A shorter version of the CBCL/ABCL, not including the 20 competence items covering the child's activities, social relations, and school performance, was created for the large Missouri sibship study, which does. These shortened versions will be used for the proposed Studies. The revised CBCL/ABCL has 113/126 items that describe specific behavioral and emotional problems, plus one open-ended item for reporting additional problems.

Child Acceptance and Mindfulness Measure (CAMM):²⁰ The CAMM is a 25-item measure of mindfulness and assesses the degree to which children and adolescents observe internal experiences, act with awareness, and accept internal experiences without judging them.

Columbia Suicide Severity Rating Scale (CSSRS):²¹ The rater/clinician-administered versions of the Columbia-Suicide Severity Rating Scale (C-SSRS) for research assess severity and intensity of suicidal ideation, types of suicidal behaviors, and lethality of suicide attempts at time points and over time periods that are typical for randomized control trials. The scale has been validated in children and adolescents, and includes 6 yes or no questions regarding suicidal thoughts, intent and behavior.

The International Physical Activity Questionnaires (IPAQ):²² Comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Pediatric Quality of Life Scale-both child and parent proxy report versions (PedsQL).²³ ages 8-12 (Pediatric Quality of Life Inventory, Version 4) Lists 23 items of potential problems a child might have faced over the past month. Requests a 5-point scale answer for each question from 0 (Never a problem) to 4 (almost always a problem). Questions revolve around possible problems with Physical, Emotional, Social, and School functioning.

Duke Pubertal Status Questionnaire (PSQ): This instrument¹⁷ is completed by participants at least 10 years old. 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 WU HRPO for the evaluation of pubertal status.

Hepatic ¹H Magnetic Resonance Spectroscopy (MRS)-estimated proton density fat fraction (PDFF): 1.5T Siemens Magnetom Vision scanner (Siemens, Erlanger, Germany) were conducted to quantify hepatic triglyceride content.²⁴ Participants were placed in a supine position the scanner using standard array coils. Hepatic triglyceride content was determined within a voxel size of 15 × 15 × 20 mm³ by using a point resolved spectroscopy (PRESS) single-voxel technique. Data were averaged from 20 scans and obtained with a repetition time of 2 seconds. Spectra were acquired at echo times of 24, 30, 35, 40, 50 ms at upper left lobe and mid to lower lobe voxels and at an echo time of 24 ms at the mid-lobe voxel to estimate and correct for the T2 decay of the signals. Images were corrected for relaxation and analyzed using jMRUI, a Java-based graphical user interface quantification package that allows time-domain analysis of *in vivo* MR data.²⁵ All frequencies, i.e., chemical shifts, were measured relative to the principal water ¹H resonance, which is referenced as zero Hz.

Dual Energy X-ray Absorptiometry (DEXA): to assess Percent total body fat and percent total fat-free mass (Hologic QDR 1000/w, Waltham, MA).²⁶ Appendicular skeletal muscle mass will be estimated from these data as described and validated by Heymsfield et al.²⁷ In addition, changes in bone mineral density (BMD) will be calculated for the exploratory aim. The error of regional fat free mass determination by this technique, as compared with computerized tomography, is less than 5%.^{26,27}

9-13-MHZ B-mode Carotid Ultrasound: (Vivid E9, GE Medical Systems using automatic edge detection software) for the measurement of carotid intima media thickness (IMT) in the longitudinal and cross-sectional axes. IMT was expressed as the average minimum, mean and maximum thickness measured over a 1 cm region of the bilateral posterior common carotid walls approximately 1-2 cm proximal to the carotid bulb. Studies will be reviewed and analyzed by two independent readers, who will be blinded to subject data. The intra- and inter-observer intraclass correlation coefficients for IMT measurements at our laboratory are 0.91 and 0.88, respectively.²⁸

Plasma Analyses: including traditional measures of cardiometabolic risk such as fasting lipids, glucose insulin and free fatty acids, high sensitivity C-reactive protein (hsCRP), adiponectin, fibrinogen, very low density lipoprotein (VLDL) particle size, and safety labs, including renal and hepatic function tests, blood electrolytes, a complete blood count and thyroid stimulating hormone (TSH), will be obtained.

Electrocardiography (ECG): will be performed to screen for any cardiac function abnormalities. Medical assessments will be performed by Pediatric Clinical Research Unit (PCRU), Clinical Research Unit (CRU), Clinical Trials Unit (CTU) or Center for Clinical Imaging Research (CCIR) staff under PI Supervision.

BEHAVIORAL TREATMENT DESCRIPTION & FIDELITY MONITORING

Intensive Behavioral Weight Loss: The Family Based Social Facilitation Behavioral Weight Loss Treatment (FBSFT)²⁹ program is a family-based, behavioral weight loss program that is based on the Traffic Light Program and has been employed in studies with overweight and obese children, as well as with children who have diabetes.³⁰ FBSFT was modified to fit the needs of disruptive and behaviorally disturbed youth and their families. It is known that families of children with disruptive behavioral disorders commonly have high dropout rates in therapy studies.³¹ Reasons for high attrition rates are multiple and include difficulty with transportation, as well as school and work absenteeism associated with the frequent visits, especially for low-income families. The modified program includes 16 weeks of weekly sessions with the participating youth and their adult legal guardian and caregiver. Phone contacts will only replace in-person visits if absolutely necessary to achieve the visit. Subjects will be provided transportation to and from visits as needed.

Diet and Exercise Education: The Centers for Disease Control (CDC), American Diabetes Association (ADA), American Heart Association (AHA) and American Academy of Pediatrics (AAP) have all recommended that physicians and families monitor for overweight and obesity, and have issued general guidelines about how to limit caloric intake and promote physical activity. The Society for Adolescent Medicine

recommends that primary care providers counsel youth at regular visits using a program called Project EAT, which combines clinician-provided education regarding physical exercise and healthy diet choices, focusing on positive body image and encouraging family involvement (<http://www.epi.umn.edu/research/EAT>).³² All participants who are not randomized to the behavioral weight loss intervention arm of the proposed study will participate in a therapeutic dietary education-only intervention consisting of the initial recommendations regarding healthy diet and activity levels of a research clinician (Care as Usual). Follow up education will be conducted at monthly intervals concurrent with visits for regularly scheduled study visits.

Treatment Fidelity Monitoring: Behavioral intervention treatment fidelity is determined by structured, direct observation of individuals carrying out the behavioral intervention, evaluating for evidence of 1) adherence to the treatment protocol and 2) competence in the treatment delivery. The demonstration of treatment fidelity is critical to the development of a valid behavioral intervention, such that the intervention cannot be tested for efficacy in a randomized clinical trial, nor can said intervention be considered evidence-based until this critical step is accomplished.^{33,34} Therefore, a primary goal of the proposed project is to demonstrate treatment fidelity of the TLP modified for use in mentally ill children. This will be accomplished by video-taping all sessions, which will be reviewed by the PI for treatment fidelity using an established treatment fidelity and competence rating scale for an evidence-based pediatric behavioral weight loss intervention (personal communication, Denise Wilfley, PhD, 6/2011).

Credibility and Expectations Scale: Patient expectations during psychotherapy are often regarded as a variable that could affect the course of treatment. Both the child and parent prior to initiation of the intervention will complete the Credibility and Expectations for Improvement scale. This information will allow the therapist to fully address the child/parents' expectations during therapy and further educate as needed.

Understanding of Materials Scale: In order to determine the understanding of the scales and program presented, the therapist/research staff will complete an Understanding of Materials Scale after each session with both parent and child participants. This will allow the therapist and PI to periodically evaluate the general level of understanding and determine if changes to the protocol are needed.

Homework Quality Scale: Completion of homework assignments is a major component in the psychotherapy throughout this program, with the ability to impact the successful outcome of the treatment. The Homework Quality Scale will be completed by the therapist/PI after each session and will be used to assess the quality of homework in relation to the outcome of the therapy at the end of the study.

Working Alliance Inventory: The Working Alliance inventory measures the quality of the therapeutic relationship between the therapist and the patient (or youth and parent in this case). For the present study, both parent and child will be asked to anonymously fill out the "Client" version of the inventory and mail back in a self-addressed, stamped envelope provided to them at the 8 and 16 week sessions. The therapist will also fill out the Therapist version of the WAI at the same time points.

Modified TLP Therapist Fidelity Rating Checklist: This checklist includes items to assess therapist fidelity to the manualized therapy, and also includes therapist competency measures. This checklist has been used to monitor therapy fidelity in federally funded studies of both TLP and FBT behavioral weight loss programming.

DATA MANAGEMENT, SAFETY & ADVERSE EVENT REPORTING

Power: Our interest in conducting this study was to evaluate feasibility of delivering the weight loss intervention in antipsychotic (AP) treated versus nonpsychiatric (NP) overweight or obese youth, and to assess the effect of weight loss on metabolic measures of interest – CIMT/DEXA/PDDF in the AP-treated and NP active intervention groups as well as in a usual care (UC) reference group of obese youths. Comparisons of interest were between each of the two active treatment groups and UC, as well as between the two active intervention groups themselves (AP-treated vs. NP). Limited prior research in this area complicated power calculations for this pilot study.

Previously published carotid IMT numbers indicating significant differences between obese children with and without metabolic syndrome criteria provide a crude proxy for the difference between an active intervention group and UC, suggesting that we should be able to detect a difference of 1.27 +/- 0.005 in intima media stiffness (units are logarithmically transformed and are therefore unitless).¹⁰ Power to detect differences in CIMT between the 3 treatment groups using a sample size of 20 per group, an alpha of 0.05, and an effect size of 0.16 was calculated to be 0.17.

Previous reports of hepatic triglyceride content in the general population indicate that 33.6% of the population meet criteria for hepatic steatosis (> 95th percentile of hepatic triglyceride content of 5.56%, corresponding to 55.6 mg/g) based on weight criteria, with obese patients being more likely to meet criteria for steatosis than healthy controls.³⁵ Power to detect differences in Hepatic Triglyceride Content between the 3 treatment groups using a sample size of 20 per group, an alpha of 0.05, and an effect size of 0.49 was calculated to be 0.92.

DEXA power calculations were based on previously noted weight loss of up to 8-10% in other studies of behavioral weight loss interventions between 2 and 5 months in length with known SDs on the observed mean change.^{36,37} Based on our previous experience with antipsychotic treated and untreated children, we anticipated that the baseline DEXA % fat would be 14-15 kg of body fat, or roughly 30-40% body fat. Anticipating up to a 5% loss from baseline fat measured by DEXA, less than the 8-10% observed in other studies, due to potential effects of the ongoing mental health condition and the antipsychotic treatment in this sample, we estimated a difference between active treatment groups (AP-treated vs. NP) of 2 +/-3 kg loss from a baseline of 15 kg total fat. Power to detect differences in DEXA Total Fat between the 3 treatment groups using a sample size of 20 per group, an alpha of 0.05, and an effect size of 0.53 was calculated to be 0.96.

Analytic approach: the primary goal was to compare changes over time in the three risk factors (CIMT/DEXA/PDDF) among three groups: obese AP-treated children randomized to the weekly intervention, obese NP children also receiving weekly behavioral weight loss treatment, and an obese usual care (UC) reference group. Comparisons of interest were between each of the two active treatment groups and UC, as well as between the two active intervention groups themselves (AP-treated vs. NP). Because this is a pre-post design with data collected only at baseline and at 16 weeks, our analytic strategy used an analysis of covariance (ANCOVA), in which the 16-week value of the risk factor is the dependent variable and the predictors are the baseline value of the risk factor and the study group (three level factor), with contrasts of interest listed above. Other analyses performed adjusted for covariates such gender and age to determine whether baseline-adjusted between group differences at 16 weeks can be explained by such covariates. Because of the relatively small sample size in this study, we performed separate analyses of covariance that include precisely one additional covariate, in addition to the baseline value of the risk factor of interest in each analysis.

Recruitment and Informed Consent: All key personnel involved in the design and conduct of the research involving human participants received the required education on the protection of human research participants prior to funding of this project. Procedures to recruit participants for the protocol and obtain their informed consent were conducted and supervised by the P.I. Targeted educational and recruitment in-services were conducted at all appropriate facilities in order to make providers and administrators aware of this project and to assist in identifying eligible participants. Clinicians and administrators at these sites were informed about the purpose, procedures, risks, and benefits of the protocol, as well as the inclusion and exclusion criteria, so that they could best discuss the research project with individual patients/guardians that might be eligible and interested, making referrals as appropriate for study screening. The P.I. or Collaborators discussed the study, including the risks and benefits of participation, with potential participants, their parents/guardians, and relevant family members to obtain informed consent/assent from interested individuals. Written informed consent was obtained from the participant (age 18), or from the guardian with written assent from the participant (ages 6-17). Guardians were included in all informed consent processes. The consent form, which incorporates HIPAA authorization, contained a description of the purpose and procedures, risks and their

minimization, and possible benefits. Participants and their guardians were assured that they are free to withdraw consent/assent at any time and discontinue participation without prejudice to their current or future medical care. The objectives of the project, all of the requirements for participation, and any possible discomforts and risks were clearly explained to the participants orally and in writing in lay terms which they were able to comprehend. Participants and their parents/guardians had at least 24 hours to consider their involvement in the study. The subject/guardian signed an informed consent form, approved by the Washington University School of Medicine Institutional Review Board, before participation in the study. Once written informed consent/assent was provided to the participant and his/her guardian, study staff continued to review what to expect in the next study visit during each phone and face-to-face contact and prior to all procedures. If at any time a subject declined to participate and withdrew consent/assent, they were withdrawn immediately from the study at their request.

Protection Against Risk: The risks of breaching confidentiality were strictly limited by the use of locked and restricted access to data as well as numbers rather than names in the database that were created for this project. No identifiers were included in any computer files or reports generated by this study. All key personnel involved in the design or conduct of research involving the human participants received the required education on the protection of human research participants prior to funding of this project. The discomfort associated with blood drawing or catheter placement is usually mild and brief and if it persisted, participation was discontinued. All blood was drawn on the clinical research units (CRU, PCRU and CTU), well-staffed medical inpatient and outpatient facilities within the Washington University Medical Center. The risk of adverse events during the blood drawing and IV access procedures was monitored by the nurse, who was in attendance at all times; treatment was facilitated by the extensive medical resources available on the clinical research units. The risks of blood drawing and catheter insertion were minimized by use of sterile technique and the exclusion of participants with coagulopathy. If the need for medical attention arises, all the resources of a large teaching hospital were available for subject evaluation and treatment. The clinical research units are equipped with a defibrillator and all appropriate emergency medications. Any physical or emotional discomfort with any procedures was handled by allowing patients to stop and rest, or ultimately to discontinue the procedure whenever they desire.

Only highly trained research staff or physicians were utilized to collect data and these individuals were experts in confidential and professional interaction with study participants. Participants were informed in the informed consent document that any suicidal or homicidal information obtained from a child/adolescent was shared with parent(s) to protect the life of the child/adolescent. If a child/adolescent was found to be suicidal or homicidal during any evaluation, the individual performing the evaluation provided the family with immediate knowledge of suicide and homicide precautions. The research staff member provided the family with appropriate mental health care referrals, if the family did not already have a mental health caretaker. If the suicidal or homicidal participants were 18 years old, precautions and referrals were given directly to the participant and to the participants' adult household members. If the participant was the sole adult household member and suicide/homicide is not deemed to be imminent, precautions and referrals, including emergency room contacts, were provided. If any participant would have been deemed to be imminently suicidal and/or homicidal, 911 was contacted as soon as possible. Participants were also informed in the informed consent document that the research staff member would provide a request for a referral for professional care if clinically warranted. To protect against any misuse of knowledge about study participation, participants were educated in the informed consent document that employers or insurers could act negatively if they learned of the study participation. Furthermore, participants were informed that they may choose not to tell their insurers about their study participation. Participants were also told that the study will be covered by a federal Certificate of Confidentiality, which protects against subpoenas of the research materials.

While the proposed study assumed responsibility for the minimal risks developing during the course of the behavioral weight loss treatment, participation also offered a unique opportunity to decrease these risks through the high-quality care described in the protocol, allowing for early intervention and prevention of cardiometabolic risk potentially associated with childhood obesity. All participants were monitored at a level that exceeds the current standard of care.

The PI reviewed the results of all study-related tests and procedures, including the interpretation of fasting and safety labs, DEXA, CIMT and MRI scans, and ECGs. In the event of an abnormal lab result, the PI notified the participant, guardian and other relevant treating clinicians (e.g. psychiatrist, primary care provider or pediatrician), and formal safety testing and/or stopping rules as noted in section 5 were applied, as defined by existing public health guidelines for diabetes and cholesterol screening in youth. For incidental abnormal DEXA, MRI or ECG findings, an official confirmation by staff radiologist or cardiologist (for DEXA and MRI, or

for ECG, respectively) was obtained. In the event of a confirmation of an abnormal finding with relevant clinical correlation determined by the PI, a clinical consultation would have been obtained and appropriate further medical workup and/or treatment initiated as necessary.

Some patients may not have an adequate psychiatric response to an initial antipsychotic trial. These subjects may be treatment resistant, or have severe symptoms that could benefit from alternative therapies that are not included in the current study. Inclusion criteria included a history of defined adequate response to antipsychotic medication and psychiatric symptom stability in order to ensure that children enrolled in the study are appropriately and optimally treated. In order to maintain clinical equipoise in the proposed study, ongoing evaluation of the need for and safety of antipsychotic treatment is necessary. Clinical evaluation of each subject occurred during study visits, in addition to ongoing clinical care provided by the treating psychiatrist. Study staff maintained weekly phone contact with the family of each participant, and provided additional 24-hour availability for any research-related issues as needed. The development any psychiatric symptom exacerbation, or other adverse events related to psychiatric symptoms was assessed by the PI on an individual basis, and continued participation in the study was determined on an individual basis in consultation with the participant's treating psychiatrist. Any medication changes resulting from psychiatric symptom exacerbation were determined by the participant's treating physician, and the participant's data was flagged as such. Medication changes during the course of the study associated with acute symptom exacerbation did not result in disqualification.

Finally, because the study population for the proposed study consisted solely of children, ongoing assessment for other safety issues related to child abuse and neglect were necessary. The written Informed Consent document contained language notifying participants and their parents/guardians that the study staff will notify the appropriate authorities if child abuse or neglect is suspected. If study staff suspected that a child was being abused/neglected, staff were to immediately notify the PI and the issue would have been discussed with the research and treatment teams. If appropriate, reports would have been made to Division of Child and Family Services child abuse hotline within 24 hours, and the child's family notified of the report.

Data & Safety Monitoring: This study did carry significant risk and was not a Phase III clinical intervention study requiring a Data and Safety Monitoring Committee (DMC). Thus, safety monitoring was conducted as follows. There were no adverse events reported during the study period.

Adverse events (AEs) definition: AEs are defined conventionally as any untoward medical occurrence in a research participant that develops during the planned observation period in the study. The AE and study participation do not have to be causally related.

Serious adverse events (SAEs) definition: SAEs are also defined conventionally, as any medical occurrence that results in death, is life threatening, requires inpatient hospitalization, results in persistent or significant disability, is a congenital anomaly or birth defect, or is an event requiring medical intervention to prevent any of these examples of an SAE. SAEs may be mild (transient, easily tolerated by the participant), moderate (causes discomfort or interrupts the study or the participant's usual activities), or severe (causes considerable interference with usual activities) in severity.

Causality of adverse events: The causality of each AE in terms of relationship to administration of treatment or study-related tests was assessed as definite (reasonable temporal relationship, with or without supporting laboratory data), probable (reasonable temporal relationship and other possible causes can be reasonably excluded), possible (reasonable temporal relationship and other possible causes are at least as or more likely), and unrelated (temporal relationship is not reasonable or other causes are reasonably more likely).

Collecting/reporting of adverse events: In the study, all adverse experiences, whether expected or unexpected, were reported to the DSMC. Any adverse experience occurring to a greater severity than expected was reported to the Washington University Human Research Protection Office (HRPO) and the Pediatric Clinical Research Unit (PCRUC)/Clinical Research Unit (CRUC)/Clinical Trials Unit (CTUC), and to the National Institutes of Health (NIH). The HRPO, PCRUC/CRUC/CTUC, the PCRUC Research Participant Advocate (RPA) and NIH will be notified of any serious unexpected adverse experience within seven working days of occurrence. If the event is fatal, the HRPO, PCRUC/CRUC/CTUC, RPA and NIH will be notified within 24 hours of occurrence. The HRPO, PCRUC/CRUC/CTUC, and NIH received annual reports regarding all adverse experiences.

Data and Safety Monitoring Plan: The Data and Safety Monitoring Plan (DSMP) for this protocol will include adverse event and other reporting by the P.I. to IRB and oversight and monitoring by the P.I. as well as the CRUC/PCRUC Research Participant Advocate (RPA). Summary reports to the IRB will be provided annually. Serious adverse events will be reported to the IRB, to the CRUC/PCRUC Advisory Committee via the RPA, and to the Sponsor: (a) death – immediately; (b) life-threatening—within 7 calendar days; and (c) all other SAEs within 7 calendar days using the Electronic SAE System.

The stopping criteria and guidelines included the following: 1) if, based on a totality of evidence likely to influence clinical practice, there was clear evidence of harm or harmful side effects of the procedures used in this protocol then the protocol would be suspended at least until acceptable modifications have been made; 2) in the event that a SAE occurred that was judged to increase risk to all participants, the study would be stopped and an investigation would be conducted and a findings report generated and provided to the Sponsor, IRB and the CRU/PCRU Advisory Committee via the CRU/PCRU RPA before the study were to be resumed; 3) were there SAEs or AEs that occurred at a frequency greater than 5%, they were added to the consent document if not already addressed, and enrollment would be halted while a determination was made regarding the potential risks to participants. All reports sent to IRB were reported to the Sponsor (NIH), per HRPO guidelines. Thus, the DSMP for this protocol was in full compliance with the Washington University PRU/CPCRU/CTU DSMP.

APPENDIX II: Supplementary Tables and Figures

Table 1: Additional Baseline Clinical Characteristics by Treatment Group. Values presented as mean (SD).

	Combined (N=47)	AP-Treated² (Weekly) (n=19)	AP-Treated² (Monthly) (n=17)	NP¹(Weekly) (n=21)
Study Population Demographics				
Height (m), mean (SD)	1.60 (0.14)	1.58 (0.15)	1.58 (0.17)	1.63 (0.11)
Weight (kg), mean (SD)	80.26 (26.62)	77.08 (32.60)	72.37 (16.11)	85.76 (23.07)
Waist Circumference (cm), mean (SD)	100.83 (16.58)	99.45 (19.35)	99.86 (10.35)	102.40 (16.07)
BMI (kg/m²), mean (SD)	30.52 (5.69)	29.70 (6.83)	28.72 (2.09)	31.86 (5.25)
BMI Percentile, mean (SD)	97.24 (2.60)	96.55 (3.30)	97.77 (1.03)	97.69 (2.16)
BMI Z-Score, mean (SD)	2.06 (0.40)	1.99 (0.47)	2.05 (0.23)	2.13 (0.38)
Percent Overweight, mean (SD)	62.36 (26.50)	57.33 (27.11)	56.91 (14.07)	68.73 (28.60)
Fasting Glucose (mg/dL), mean (SD)	90.02 (7.13)	91.32 (7.42)	93.71 (10.01)	87.62 (4.99)
Fasting Lipids (mg/dL), mean (SD)				
Triglycerides	104.30 (57.35)	106.26 (59.11)	114.43 (44.49)	99.14 (61.30)
Total Cholesterol	164.36 (31.10)	169.47 (37.55)	170.14 (9.67)	157.81 (29.09)
HDL Cholesterol	48.34 (10.04)	46.95 (10.20)	45.00 (6.16)	50.71 (10.74)
LDL Cholesterol	95.32 (24.49)	101.68 (27.32)	102.29 (10.95)	87.24 (23.40)
DEXA Percent Fat, mean (SD)	42.51 (6.97)	41.76 (8.53)	45.40 (6.76)	42.24 (5.38)
DEXA Percent Lean, mean (SD)	54.77 (6.73)	55.48 (8.23)	52.12 (6.81)	55.01 (5.15)
PDDF (%), mean (SD)	6.58 (8.54)	6.52 (8.21)	12.01 (7.82)	4.72 (8.61)
CIMT (cm), mean (SD)	0.0484 (0.0070)	0.0451 (0.0074)	0.0494 (0.0058)	0.0504 (0.0065)
Aberrant Behavior Checklist, mean (SD)				
Total	25.17 (26.11)	35.61 (24.29)	53.43 (20.14)	6.81 (13.39)
Irritability	8.15 (9.13)	11.06 (8.30)	18.57 (8.75)	2.19 (4.81)

Table 2: Change in Additional Metabolic and Behavioral Measures by Treatment Group

Variable (units)	AP-BWI				AP-UC				NP-BWI				Time x Treatment
	Week 0	Week 16	Change	η^2 *	Week 0	Week 16	Change	η^2 *	Week 0	Week 16	Change	η^2 *	
Clinical Outcome Variables													
Height (m)	1.59 (0.15)	1.60 (0.14)	0.02 (0.02)	0.62	1.54 (0.14)	1.56 (0.15)	0.02 (0.02)	0.71	1.65 (0.11)	1.66 (0.11)	0.01 (0.01)	0.40	F[2,34]=1.16, η^2 =0.33
Weight (kg)	78.04 (33.32)	77.93 (32.99)	-0.12 (3.04)	0.00	68.56 (13.77)	70.98 (12.09)	2.42 (2.36)	0.56	88.49 (23.73)	86.19 (24.19)	-2.30 (4.29)	0.23	F[2,34]=3.37, η^2 =0.05
BMI Z-Score	2.01 (0.52)	1.88 (0.63)	-0.13 (0.17)	0.40	2.08 (0.23)	2.05 (0.31)	-0.03 (0.13)	0.05	2.14 (0.40)	1.99 (0.49)	-0.16 (0.17)	0.49	F[2,34]=2.07, η^2 =0.14
Percent Overweight	59.11 (28.96)	54.01 (30.88)	-5.10 (5.52)	0.48	59.42 (13.58)	59.47 (19.07)	0.04 (10.13)	0.00	69.92 (31.02)	61.43 (32.54)	-8.48 (7.83)	0.56	F[2,34]=3.29, η^2 =0.05
Waist Circumference (cm)	100.75 (18.73)	100.57 (21.44)	-0.18 (5.73)	0.00	100.60 (8.19)	99.04 (6.43)	-1.56 (5.30)	0.10	108.62 (14.16)	105.88 (13.71)	-2.75 (6.14)	0.18	F[2,31]=0.69, η^2 =0.51
DEXA % Fat	42.33 (7.78)	40.91 (9.74)	-1.42 (2.63)	0.24	45.77 (7.33)	45.48 (8.12)	-0.29 (1.89)	0.03	43.21 (5.07)	40.73 (5.09)	-2.47 (2.63)	0.48	F[2,34]=1.63, η^2 =0.21
DEXA Total Lean	41.41 (14.95)	42.19 (14.58)	0.78 (1.69)	0.19	35.71 (11.32)	37.27 (11.33)	1.56 (1.00)	0.74	47.33 (14.00)	47.93 (13.51)	0.59 (1.66)	0.12	F[2,34]=0.34, η^2 =0.71
Fasting Glucose (mg/dL)	90.87 (7.09)	89.80 (6.45)	-1.07 (6.86)	0.03	95.00 (10.32)	94.17 (4.83)	-0.83 (8.89)	0.01	87.41 (4.47)	87.76 (6.07)	0.35 (5.51)	0.00	F[2,34]=0.68, η^2 =0.51
Fasting Lipids (mg/dL)													
Triglycerides	105.60 (64.92)	120.80 (79.07)	15.20 (67.91)	0.05	99.17 (20.46)	132.17 (38.41)	33.00 (30.11)	0.59	108.53 (64.23)	105.06 (74.21)	-3.47 (50.76)	0.01	F[2,34]=0.98, η^2 =0.39
Total Cholesterol	160.27 (30.93)	158.33 (31.14)	-1.93 (22.01)	0.01	168.67 (9.69)	150.83 (20.63)	-17.83 (18.15)	0.54	160.53 (31.14)	155.06 (27.40)	-5.47 (20.12)	0.07	F[2,34]=1.05, η^2 =0.36
HDL Cholesterol	45.73 (7.60)	46.20 (10.52)	0.47 (6.48)	0.01	45.00 (6.75)	39.50 (4.42)	-5.50 (5.68)	0.53	49.41 (9.90)	49.65 (11.02)	0.24 (5.17)	0.00	F[2,34]=2.56, η^2 =0.09
LDL Cholesterol	93.93 (23.30)	87.93 (28.78)	-6.00 (19.16)	0.10	103.83 (11.13)	84.83 (17.70)	-19.00 (14.11)	0.69	89.41 (24.63)	85.06 (21.08)	-4.35 (13.26)	0.10	F[2,34]=1.34, η^2 =0.28
Secondary Behavioral Measures													
Aberrant Behavior Checklist													
Total Score	33.40 (24.60)	33.73 (28.84)	0.33 (15.65)	0.00	49.00 (17.94)	52.83 (22.50)	3.83 (12.16)	0.11	7.63 (15.12)	4.75 (6.55)	-2.88 (10.70)	0.07	F[2,33]=1.70, η^2 =0.20
Irritability Subscale Score	11.33 (9.04)	10.07 (8.55)	-1.27 (5.82)	0.05	15.83 (5.38)	18.83 (6.97)	3.00 (4.65)	0.33	2.31 (5.15)	0.94 (1.39)	-1.38 (4.32)	0.10	F[2,33]=6.89, η^2 =0.003
Child Behavior Checklist, Total Score	56.27 (28.91)	51.33 (29.06)	-4.93 (17.86)	0.08	70.50 (28.84)	68.83 (30.08)	-1.67 (22.16)	0.01	17.76 (15.66)	13.06 (10.04)	-4.71 (11.70)	0.15	F[2,34]=2.02, η^2 =0.15

*Main Effect of Time

APPENDIX III: References

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