Study Protocol and Statistical Analysis Plan

DATE: October 26, 2021

PROTOCOL TITLE: Mobile health (mHealth) nutrition intervention for children with Autism Spectrum Disorder

Clinical Trial Registration: This study was registered at clinicaltrials.gov as NCT03424811

OBJECTIVES:

Primary Aim: To test, in a 3-month randomized controlled trial, the efficacy of the mHealth intervention on changing consumption of targeted healthy and less healthy foods/beverages in children with ASD who are picky eaters. We hypothesized that, by the end of the intervention, children in the intervention group, but not children in the education group, would show a significant increase (expressed as % change from baseline) in intake of FV and a decrease in calories consumed from salty and sugary snacks and SSB.

Secondary Aim: To perform a comprehensive evaluation of the mHealth intervention by measuring parent and child engagement, motivation, user friendliness, and ease of use.

CHARACTERISTICS OF THE STUDY POPULATION:

1. Target Population and Accrual:

The study aimed to include 46 racially/ethnically diverse boys/girls with ASD, ages 6-10 years, and their parent/legal guardian (referred to 'parent' for ease of use). The age range was chosen to ensure that children have the cognitive skills to interact with the technology. Our multi-pronged recruitment plan utilized the CHOP health system and community-based organizations throughout Philadelphia. The study was open to subjects of all races and ethnicities. Parents must be the children's primary caregiver (i.e., person responsible for grocery shopping/feeding). Children and parents must have access to a smartphone or tablet to be eligible for study participation. For this exploratory trial, we aimed to recruit a well-defined, homogenous group of children to determine the efficacy of this intervention. Only children without significant developmental delay (i.e., IQ ≥80 and comparable verbal ability) were enrolled to increase the likelihood of comprehension and engagement with the technology. Children with a range in weight were included to explore if the intervention is equally effective in normal-weight and overweight/obese children.

This project's primary purpose was to evaluate feasibility, acceptability, and utilization of the mHealth intervention and to obtain preliminary effect size estimates. A power analysis was conducted (PASS software, Version 11, NCSS LLC, Kaysville, UT) for Primary Aim 2 using 3-month changes in intake of targeted healthy foods (FV) as the primary outcome variable. The estimated mean (±SD) for baseline FV intake (2.57 ± 1.20 servings/day) was derived from our pilot study in children with ASD. Based on this estimate, a sample size of 46 children and an attrition rate of 10%, we had 80% power to detect a statistically significant increase in FV intake of 1.1 servings/day (or 43%) in the intervention group relative to the education group at the alpha 0.05 level, based on a two sample t-test. The magnitude of this increase is comparable to that achieved in behavioral interventions in TDC and represents ~one-fifth of the RDA of FV for children of that age.

2. Key Inclusion Criteria:

To be included in the study, children had to:

1) Were age 6 to 10 years;
2) Were fluent in English;
3) Had an ASD diagnosis using the DSM-IV-TR or DSM-5 criteria, confirmed using gold standard diagnostic criteria (e.g., ADOS or ADI-R administration), or expert clinical judgment;
4) Had cognitive skills within low average (or higher) range with IQ measurement of ≥80 and comparable verbal ability;
5) Met the definition of picky eater (i.e., parent endorses at least two out of the three items on the Picky Eating Subscale of the Child Feeding Questionnaire (CFQ), and have pickiness related to the intervention's targeted healthy and less healthy foods;
6) Had access to a mobile device.

These criteria were confirmed by expert review of reports of previous research or community-based diagnostic evaluations.

3. Key Exclusion Criteria:

Children were excluded if they:

1) Had moderate-severe hearing/visual or motor impairment (e.g., non-ambulatory);
2) Were taking antipsychotic medications related to uncontrolled eating;

3) Were on a special diet (e.g., gluten/casein-free diet);
4) Were underweight (i.e., BMI-for-age < 5th percentile).

4. Subject Recruitment and Screening:

Families were consecutively recruited for participation in the study over the duration of the study. Recruitment of participants was carried out in collaboration with the Children's Hospital of Philadelphia's (CHOP) Center for Autism Research (CAR; https://www.centerforautismresearch.org/). CAR is one of ten *Centers of Emphasis* of the Research Institute at CHOP and houses >75 faculty and staff. The Research Clinic completes an average of 20 diagnostic and phenotypic characterizations per week. Our multi-pronged recruitment plan utilized the following strategies: (a) CAR's research study page of its website (https://www.chop.edu/centers-programs/autism-integrated-care-program/clinical-trials); (b) CAR's online research registry *autism*Match; (c) CAR's completed research; (d) the Autism Treatment Network center; (e) CHOP's Division of Developmental and Behavioral Pediatrics and Department of Child and Adolescent Psychiatry and Behavioral Sciences; (f) the CHOP Recruitment Enhancement Core; and (g) community-based organizations. Parents provided information about their child's age, sex, height, weight, autism diagnosis, medical history, and medication use. Research staff administerd the CFQ Picky Eating subscale and asked parents to verbally consent to a standard HIPAA Release of Medical Information form to have their child's medical information and previous diagnostic evaluations reviewed.

5. Vulnerable Populations:

Children with a diagnosis of ASD between ages 6 and 10 years were enrolled in this study with their parents' consent. All children in the study who are capable of assenting were asked to provide voluntary assent.

STUDY DESIGN:

A 3-month randomized controlled trial tested the efficacy of a mHealth intervention on changing consumption of targeted healthy (FV) and less healthy (SSB/SSS) foods/beverages in children with ASD who are picky eaters. In this exploratory trial, parent-child dyads were randomly assigned to either an mHealth (+ parent training) intervention group or an education group. Parents in the intervention group received the mHealth nutrition intervention plus training in behavior change strategies and an explanation of the dietary targets. Parents in the education group received a handout with general educational information about healthy eating and an explanation of the dietary targets. Parent trainings in both groups were matched for in-person contact time. Families in the education group received access to the mHealth intervention after they completed the study.

At the end of the intervention, parents in the intervention group were asked to complete a semi-structured interview and a brief questionnaire, which asked them to provide feedback on the usefulness and relevance of the mHealth technology, parent and child engagement and motivation, and to evaluate key features of the mHealth intervention such as user friendliness, ease of use, and technical or time barriers. Children in the intervention group were asked to complete a brief questionnaire that assessed level of enjoyment, learning, and understanding of the mHealth technology.

METHODS:

1. Mobile health (mHealth) Intervention: The mHealth intervention incorporated evidence-based core behavior change strategies that have been empirically tested in family-based behavioral modification nutrition and obesity prevention programs with TDC for over three decades. A novel feature of the mHealth intervention was that both the technology-assisted intervention and the dietary goals were tailored to the specific needs of children with ASD.

Core Behavior Change Strategies: The core behavior change strategies that were incorporated in the mHealth intervention included: 1) specifying target behaviors and goal setting, 2) self-monitoring, 3) stimulus control, 4) positive reinforcement, and 5) self-efficacy.

The mHealth intervention included a 'Nutrition Ninja', which represents a graphical illustration in the form of an avatar who models consuming healthy and limiting less healthy target foods. The Nutrition Ninja aimed to affect behavior change via two components of the mHealth intervention: 1) a parent-child interactive feature and 2) an educational nutrition game. In the parent-child interactive feature, the 'Nutrition Ninja' was directed by the parent and, with input from their child, set dietary goals for a specific period of time (e.g., 1 week). The child was reinforced for making healthy food choices while limiting less healthy food choices in their daily lives by earning points towards a prize. The dietary goals included consumption of a pre-determined amount of targeted healthy foods (FV) and limiting intake of targeted less healthy foods (SSB/SSS). Both the child and the parent were able to track the child's

progress via their smartphones/tablets. Parents provided opportunities for children to taste and eat FV by making these foods available in their homes and they limited exposure to SSB/SSS which children needed to refrain from eating. Children were reinforced for consuming the healthy target foods and limiting the less healthy target foods by earning points towards a prize. Families were able to choose their own rewards. In the app, we provided examples of rewards (e.g., movie night, extra TV or computer time, sleepover party with friend, game night).

The educational nutrition game aimed to educate children about healthy and less healthy food choices. The game used a simplified version of the traffic light system to categorize foods and beverages into healthy (green or 'Go') and unhealthy (red or 'Whoa') choices. Children were reinforced for playing the game and for identifying healthy and less healthy food choices by earning points towards a prize. The Nutrition Ninja interacted with the child throughout the game by praising the child for correct answers, correcting incorrect answers, and modeling healthy food choices. Parents selected real-life prizes, awarded points, and determined the allotted timeframe and number of points it took for the child to earn a prize.

Tailoring intervention to children with ASD: Children with ASD have specific needs and this mHealth intervention incorporated several features that have been shown in prior treatment studies to help children with ASD meet behavioral goals. One, the use of an animated 'Nutrition Ninja' for guidance (setting dietary goals) and correction (correcting wrong answers during the educational game) not only removed the onus from the parents but it also provided children with behavioral skills training in the virtual space. Two, the dietary goals were very prescriptive (e.g., amount of SSB allowed per week) to provide children with a highly structured and predictable schedule and their progress towards their dietary goals was displayed in a visual graphic. We conducted focus group webinars with parents and caregivers (nurse/teacher) of children with ASD during which they confirmed that these strategies were crucial for successfully engaging children in the intervention and improving their dietary intake.

The intervention was developed using an iterative design process for prototype development, testing and refining. An Advisory Board consisting of autism clinical experts, nutrition/health behavior scientists, a behavior specialist, parents of children with ASD, youth with ASD, and technology developers provided feedback on the functionality and acceptability of the intervention during several sessions which corresponded with major project development phases.

1. Study Instruments:

Assessment of Intake of Target Foods: Targeted healthy foods included FV (fresh, canned, frozen). Parents were instructed to omit energy-dense toppings/sauces on FV. Targeted less healthy foods included 1) SSS (e.g., all types of chips, popcorn, pretzels, party mixes, ice cream, candy, cookies, cakes/pies, sweet rolls, pastries) and 2) SSB (e.g., sugar-sweetened sodas, fruit drinks/punches and fruit juices, sport drinks, and energy drinks). Dietary goals were set by parents and tailored to children's preferences and sensory sensitivities. Children's intake was assessed at baseline and at the end of the intervention using the telephone-based 24-hr dietary recall method; the gold standard for self-reported intake. Each assessment consisted of 3 unannounced recalls (2 weekdays, 1 weekend day), which was conducted by research dietitians from the CHOP Center for Human Phenomic Science. Dietitians were blinded to families' group assignment. During each recall, they asked parents, with help from the children, to describe all foods/beverages consumed by their children during the prior 24 hours and provide detailed information about portion sizes/preparation methods. Data were analyzed for daily FV intake (servings/day; cup equivalents) and calories consumed from SSB/SSS using the University of Minnesota Nutrition Coordinating Center's Food and Nutrient Database. All data were averaged across the 3 days.

Child Height and Weight Measures: At baseline and at the end of the intervention, children had their heights and weights measured. Measurements were taken in triplicate with a portable scale/stadiometer by a trained staff member in children's homes with children wearing light clothing (no shoes). Child age- and sex-specific BMI percentiles and z-scores were calculated using the CDC Growth Charts 2000. Children were classified as normal-weight (BMI-for-age 5–84th percentile), overweight (BMI-for-age 85–94th percentile), or obese (BMI-for-age ≥95th percentile).

Questionnaires: During the telephone screening, parents were asked to complete the Picky Eating subscale of the Child Feeding Questionnaire (CFQ), which consists of the following items: 1) "My child's diet consists of only a few foods"; 2) "My child is unwilling to eat many of these foods that our family eats at mealtimes"; 3) "My child is fussy / picky about what she eats." A child was defined as a picky eater if the parent endorsed at least 2 out of the 3 items. Parents were asked follow-up questions to determine whether a child's pickiness was related to the intervention's targeted healthy and less healthy foods. During the baseline visit, parents completed a Demographic Questionnaire and the 38-item Sensory Profile, 2nd Edition (short form), which assessed children's sensory processing abilities, including oral sensory sensitivity (e.g., sensitivities to food tastes/textures). Children were categorized as having typical or atypical oral sensory sensitivity based on classifications specified by Dunn.

Evaluation of mHealth Intervention: We evaluated the mHealth intervention using the following strategies: 1) Engagement: The mHealth platform kept an automatic log of all user activities, including subjects' log-in frequency, duration of use, features used, goal/progress tracking, number of points and rewards awarded, etc. These log files were automatically generated by the software and enabled us to monitor participants' compliance with the intervention; 2) Semi-structured interviews and brief questionnaires: At the end of the intervention, parents in the intervention group were asked to complete a semi-structured interview and a brief questionnaire, which asked them to provide feedback on the usefulness and relevance of the mHealth technology, parent and child engagement and motivation, and to evaluate key features of the mHealth intervention such as user friendliness, ease of use, and technical or time barriers. Children in the intervention group were asked to complete a brief questionnaire that assessed level of enjoyment, learning, and understanding of the mHealth technology

2. Group Modifications:

Parents in the education group were not asked to participate in the evaluation of the mHealth intervention.

3. Method for Assigning Subjects to Groups:

Statisticians of the Biostatistics Consulting Unit at the Penn School of Nursing carried out the randomization of participants into the intervention and education groups. They used a randomized block design to produce groups that are comparable in weight status.

4. Administration of Surveys and/or Process:

Telephone Screening: The telephone screening involved review of information to determine initial eligibility criteria. In addition, during the screening phone call verbal consent was obtained for completion of the baseline dietary recall interviews with the parent prior to the baseline visit.

Baseline Study Visit: The baseline study visits included the full written consenting/assenting process, measurement of child height and weight, completion of questionnaires, and, for families in the intervention group, orientation to the technology and installation of the software on participants' smartphones. This visit lasted approximately 90 minutes.

3-Month Study Visit: The 3-month study visit (end of intervention) included measurement of child height and weight and, for families in the intervention group, a semi-structured interview and two brief questionnaires to evaluate the mHealth intervention. This visit lasted approximately 60 minutes.

Dietary Recalls: Children's intake was assessed at baseline and at the end of the intervention using the telephone-based 24-hr dietary recall method. Each assessment consisted of 3 unannounced recalls (2 weekdays, 1 weekend day), which were conducted by research dietitians from the CHOP Center for Human Phenomic Science. Each recall lasted approximately 20 minutes.

STUDY PROCEDURES:

Randomized Controlled Trial:

Intervention Group: At baseline, parents in the intervention group received a comprehensive parent training which 1) provided skills training in the five core behavior change strategies and 2) explained the nutritional goals and targeted foods/beverages for the study. The training modules were designed by a behavioral strategist and clinical psychologist, a clinical psychologist, and a nutrition scientist. The modules reviewed examples of the targeted foods/beverages and provided training in how to present feeding opportunities, incorporate healthy target foods in daily family meals and snacks, and substitute the less healthy target foods/beverages for healthier options. The training also addressed how parents can overcome resistance in children trying new foods using differential attention and positive reinforcement techniques. It included instructions on how to use the mHealth technology and showed parents how to set dietary goals, select real-life prizes, award points, and determine the allotted timeframe and number of points it will take for the child to earn a prize. The mHealth intervention was personalized for each child to take into account individual differences in children's food preferences, level of picky eating, sensory sensitivities, etc. Specifically, the mHealth technology enabled parents to tailor the selection of food choices available to the child and customize, with input from the child, food preparation methods (e.g., raw or cooked, seasonings to be added). The training also included a training module for the children to show them how to navigate the technology, orient them to the nutrition intervention, and explained the reward system. Research staff assisted with the software installation on the families' electronic devices and parents were encouraged to use the technology as frequently as possible during meal and snacks times over the course of the 3-month intervention.

Education Group: Parents in the education group were instructed to review a handout, which provided general educational information about healthy eating. It explained the nutritional goals and targeted foods/beverages for the study, but it did not provide parent skills training in the core behavioral strategies. This condition mimiced what families may receive during a routine well-child visit.

Parents in both groups were encouraged to promote children's intake of the healthy target foods and limit their intake of the less healthy target foods/beverages on a daily basis for the next 3 months.

5. Statistical Analysis:

To test Primary Aim 2, a mixed-effects linear model with repeated measures assessed 3-month changes in children's FV (cups/day) and SSB/SSS (calories/day) intake by group. The fixed factor effects in all models were group (incentive, control) and time (baseline, month 3). The group-by-time interaction was tested and removed if not significant. Analysis of covariance assessed if the intervention is equally successful in boys/girls, children of various ages/weights, and children with typical/atypical sensory sensitivity. For Secondary Aim 2, data from log files and questionnaires were analyzed and open-ended responses from the semi-structured interview were coded, compiled into categories, and grouped into themes using a general inductive approach. *P* values were two-sided and $P<0.05$ was considered significant for all tests. First, analyses were conducted with all participants included. Then, a sensitivity analysis were conducted that included only participants who actively participated in the intervention.