Cadence and Intensity in Children and Adolescents (CADENCE-KIDS)

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1) Protocol Title

Cadence and Intensity in Children and Adolescents (CADENCE-KIDS)

2) Objectives*

The primary aim of this exploratory/developmental R21 study (**CADENCE-KIDS**) is to identify and evaluate objectively monitored cadence (steps/min) cut points associated with markers of increasing intensity across age in children and adolescents.

To achieve this aim, we will identify and recruit 10 participants (5 boys, 5 girls) from each age-year between 6- 20 years (a span of 15 age-years for a total of 150 participants) to a lab-based study of cadence. Cadence and oxygen uptake data will be collected during a treadmill assessment of incrementally faster paces and also using portable metabolic testing of common free-living activities, *to test the following hypothesis*:

- *Children's activity intensity (oxygen uptake) will increase in a linear or nonlinear (curvilinear) fashion as cadence increases such that we will be able to develop statistical models for predicting markers (cut points) of intensity from cadence. This will be tested in the lab-based study that will provide objective and directly measured data of both cadence and intensity markers.*

The information derived from this exploratory/developmental study will be used to calibrate children's and adolescent's cadence data. The information will be used to inform a future study of cadence as an indicator of intensity in determining healthful levels of children's and adolescent's free-living physical activity. No similar data exist at this time so the approach described in this application is a critical first step to providing a common and interpretable objectively monitored metric.

3) Background*

The multiple and robust health benefits of a physically active lifestyle extend to children and adolescents. Physical activity guidelines from around the world are typically expressed in terms of frequency, duration, and intensity parameters. There

is growing interest in translating public health physical activity recommendations in terms of the number of steps taken (i.e., steps/day), and this is also true for children and adolescents. Such an output does not reflect intensity, an important constituent of public health guidelines. However, capture and analysis of patterns of minute-by-minute cadence, alone or together with steps/day, represents an overlooked opportunity in terms of both analysis and interpretability. In addition, cadence (steps/min) represents one of the few measures that can be collected and interpreted across different instrumentation without worrying about deriving or otherwise adjusting data.

Cadence is just one of the temporal-spatial parameters of gait. Cadence multiplied by stride length equals speed. Assembled from adult studies of cadence and MET (metabolic equivalent - an indicator of absolute intensity) levels, the correlation between steps/minute and MET level is strong (r=0.93).[1] Cadence is known to be the primary strategy for increasing free-living walking speed in adults[2] and children[3] and although stride lengthening becomes relatively more important in running, cadence still increases with running speed.[4] In both children and adults it can be used to infer intensity of activity. The five studies[5-9] that have directly measured cadence and verified absolutely-defined moderate intensity activity in adults came to similar conclusions: despite inter-individual variation, 100 steps/minute represents a reasonable heuristic value associated with moderate intensity walking. We would expect that the cadence associated with moderate intensity in the growing child would be higher than this, however, there have been no studies at this time that have similarly looked at directly measured cadence and verified absolutely-defined moderate (or any other level) intensity activity in children and adolescents spanning these developmental years.

4) Inclusion and Exclusion Criteria*

Print and email advertisements will be developed to inform potential participants about CADENCE-KIDS, directing them to a web-screener or to call into the Pennington Biomedical Research Center Recruiting Core. The web-screener will be developed with the aid of the Recruiting Core to assess initial eligibility, focusing on the assessment of potential participants' demographic information, health history, and ambulatory ability. Potential participants who are not rejected by the web-screener will be contacted via telephone by a Pennington Biomedical Recruiting Core member as a follow-up and asked to complete a confirmatory telephone-based screening questionnaire. Potential participants may choose to directly contact the Pennington Biomedical Recruiting Core via telephone without completing the web-screener, and these individuals will be administered the same telephone-based screening questionnaire to assess initial eligibility. Interested and eligible participants will then be asked to schedule for an orientation session at the Pennington Biomedical Research Center to learn more about the study. Following the orientation session, those eligible potential participants who remain interested in the study will then be asked to schedule for the single testing session (although we

will accommodate schedules if they wish to spread the testing out over two separate days) required to complete the CADENCE-KIDS study protocol.

See the following table (Table 1) for initial eligibility criteria to be assessed by phone screen.

Table 1. Initial inclusion criteria
• Children and adolescents between the ages of 6 and 20 years of age.

See the following table (Table 2) for exclusion criteria to be assessed by phone screen.

Table 2. Initial exclusion criteria	
Ambulatory ability	• Since the focus herein is on ambulatory activities, participants who use wheelchairs or other impairments that prevent normal ambulation will be excluded. This criteria is similar to that used by NHANES when selecting individuals (6+ years of age) to wear motion sensors.[10]
Other exclusions	• Hospitalization for mental illness within the past 5 years. • Any condition/medication that may affect heart rate response to exercise testing. • Previous history of, or clinical symptoms or signs of, cardiovascular disease, stroke or TIAs (transient ischemic attacks), chest pain, unusual dyspnea during physical activity/exercise, severe ankle edema, or intermittent claudication. • Previous history of musculoskeletal injuries or problems causing severe pain during physical activity or exercise which interferes with daily activities. • Participant has a pacemaker or other implanted medical device (including metal joint replacements). • Participant is pregnant. • Participant is unable to complete all testing (1 or two sessions, as preferred) within a maximal two week period.

In addition to the exclusion criteria listed above, those participants between 6-17 years of age whose refuse to provide assent (verbal for 6-8 year-olds, written for 9-17 year-olds), or whose parents/legal guardians refuse to sign an informed consent document will be excluded from the study. Also, those participants (18-20 years of age) who refuse to sign a written informed consent document will be excluded from the study. Consent/assent will be obtained upon each participant's arrival at the Pennington Biomedical Research Center's Outpatient Clinic before participating in any study procedures. To further safeguard participant safety and internal validity

of the study, inclusion and exclusion criteria will be reassessed by Pennington Biomedical Research Center clinic staff following the completion of required assent/consent forms. The inclusion/exclusion form used for this assessment is provided in Appendix A.

5) Study-Wide Number of Subjects

All participants will be recruited to participate and complete all study-related procedures at the Pennington Biomedical Research Center in Baton Rouge, Louisiana. We will identify and recruit 10 participants (5 boys, 5 girls) from each age-year between 6-20 years (a span of 15 age-years) for a total of 150 participants. This is an exploratory/developmental R21 study to collect preliminary data for the purpose of investigating the statistical relationships between objectively monitored cadence (steps/min) and increasing intensity, specifically metabolic equivalents or METS, measured in a laboratory treadmill setting and in free-living among young people ages 6-20 years. Calibration studies have typically been conducted using small select samples.[11] Freedson et al.[12] has recommended that calibration studies in children be conducted with at least 10 participants in each age group (e.g., 8-10, 10-12 years of age, etc.). We exceed this requirement by enlisting 10 participants for each sex-age year, for a total of 150 participants. This strategy will make this the second largest accelerometer calibration study to date among children and adolescents, but the most age-distributed study. Mattocks et al.[13] studied 246 children, but all age 12 years, and Freedson et al.[12] studied children and adolescents 6-18 years of age, but only 80 in total. The estimates of statistical relationships and variability in cadence and intensity markers within sex-age specific cohorts will be used to power a larger study with expanded objectives.

6) Study-Wide Recruitment Methods*

This is not a multi-center trial and all recruitment will be conducted by the Pennington Biomedical Research Center's Recruiting Core, with all testing occurring at the Pennington Biomedical Research Center.

7) Study Timelines*

It will take 1 day (approximately 3 hours) for CADENCE-KIDS participants to complete all the study procedures taking place at Pennington Biomedical Research Center (consent/assent and entire research protocol). However, we will accommodate each participant's preferences should they wish to split the testing over 2 days, as long as both testing days are scheduled within a two-week period.

We anticipate that it will take approximately 18 months to recruit, enroll, and complete all data collections on the 150 participants in CADENCE-KIDS. The estimated date for completing recruitment is December 31, 2014 and for the completion of the CADENCE-KIDS study is June 30, 2015.

8) Study Endpoints

The primary endpoints of interest that we will evaluate are oxygen uptake (METs) and cadence (steps/minute) during treadmill walking and various free-living activities. Oxygen uptake will be measured using a portable metabolic system (COSMED, K4b^2). Cadence will be measured using a variety of step measuring devices (Pedometers, Accelerometer, Multi-Sensor Devices), all of which are non-invasive. We will utilize appropriate statistical modeling techniques (e.g., linear [ordinary linear and polynomial] models, piecewise models, receiver operating characteristic (ROC) curve analysis) to identify cut-points of cadence (steps/minute) corresponding to intensity of activity during treadmill and selected free-living activities.

9) Procedures Involved*

CADENCE-KIDS is an exploratory study (cross-sectional – one assessment period) which will collect treadmill and selected free-living physical activity data performed in the Pennington Biomedical Research Center Exercise Testing Lab using a number of wearable step measuring devices while oxygen uptake is concurrently measured via a portable metabolic system. Results from this study will help to inform future investigations by establishing best methodology practices when collecting and/or analyzing step data from step measuring devices. A brief overview of the procedures to be completed in CADENCE-KIDS is presented in Table 3 (below). Each procedure is presented in more detail following the table.

Table 3. CADENCE-KIDS procedures (approximately 3 hours in total)
• Screening questions (approximately 3-5 minutes)   o Screening questions to determine participant eligibility.
• Height and weight measures data collection (approximately 10 minutes)   o Measures of height, body weight, body fat percentage, and waist circumference.

• Instrument attachment, treadmill walking, free-living activities (approximately 140 minutes)
  o Participants will be fitted with non-invasive devices to measure/monitor physical activity throughout the testing session.
  o Participants will then complete several low intensity free-living activities while their physical activity and oxygen uptake are concurrently assessed. Specifically, participants will rest in a chair, watch a portion of a child-friendly movie while seated in a chair, and color in a coloring book while seated in a chair. Each activity will last for 5 minutes and a 2 minute rest will occur between each activity.
  o Participants will then complete a series of walking bouts on a treadmill while their physical activity and oxygen uptake are concurrently assessed. The walking bouts start at 0.5 miles per hour and end at 5 miles per hour (0.5 miles per hour increments).

Treadmill testing stops when the participant finishes the bout where they naturally select to jog/run, or following the completion of the last bout at 5.0 miles per hour, whichever occurs first. A 2 minute rest will occur between each treadmill bout.

- Participants will then complete three additional free-living activities where physical activity and oxygen uptake continue to be concurrently measured. Specifically, participants will step up and down on an aerobic step at 88 beats per minute, dribble a basketball, and perform jumping jacks at 126 beats per minute (63 jumping jacks per minute). Each activity will last for 5 minutes and a 2 minute rest will occur between each activity.

***Assessments*:**

Anthropometric measurements: Using standardized procedures, we are collecting weight, height, sitting height, body fat percentage by bioelectrical impedance analysis (BIA; Tanita scale), BMI (calculated from weight and height), and circumferences (waist) on all participants in CADENCE-KIDS. This portion of the assessment should take approximately 10 minutes to complete.

Standing Height. The participant's height is measured using a stadiometer. The participant is required to remove their shoes and have their heels, buttocks and upper part of the back remain in contact with the stadiometer with their arms hanging naturally at their side. The participant is asked to inhale and hold their breath, while the technician lightly applies traction to the patient's head in order to maintain alignment with the Frankfort Plane. A second technician then lowers the slide until it reaches the vertex of the skull and records the reading from the indicator, rounding to the nearest 0.1 centimeter. This process is repeated, and the average of the two heights is used in analysis (a third measurement is obtained if the first two measurements are greater than 0.5 cm apart).

Sitting Height. The participants sitting height will be measured with a stadiometer. Sitting height will be measured to the nearest 0.1 cm with the participant seated on a table with legs hanging freely and arms resting on the thighs. The back of the knees will be close to but not touching the table. The participant will sit as erect as possible and head will be positioned in the Frankfort Horizontal Plane. This process will be repeated, and the average of the two heights will be used in analysis (a third measurement is obtained if the first two measurements are greater than 0.5 cm apart).

Weight, Body Fat Percentage, and Bioelectrical Impedance Analysis. The participant's weight, body fat percentage, and impedance are measured using the portable Tanita Body Composition Analyzer (SC-240) after outer clothing (e.g., coat, jacket) heavy pocket items and shoes and socks are removed. After the unit has been initialized (flashes "step on"), the participant steps onto the middle of the body composition analyzer, with their bare feet situated such that the heels are

placed on the posterior electrodes and the front part of the feet are in contact with the anterior electrodes. The participant stands on the unit in a stable position without bending their knees. This process is repeated and the average of each of the two weights and body fat percentages is used in analysis (a third measurement is obtained if the first two weights are greater than 0.5 kg apart or if the body fat percentages are greater than 2.0% apart).

Circumferences. Waist circumference is measured with a non-elastic anthropometric tape midway between the lower rib margin and the iliac crest, at the end of gentle expiration. The participant is asked to expose the areas to be measured by pulling undergarments down and to stand in an upright position with their feet together and arms relaxed at their sides. Measures are made at the end of normal expiration with special attention paid to ensure the tape lays perpendicular to the long axis of the body and parallel to the floor. This process is repeated and the average of each of the two circumferences is used in analysis (a third measurement is obtained if the first two measurements are greater than 0.5 cm apart).

Derived Anthropometric Indices. The Body Mass Index (BMI) is determined using the following formula: weight (kg)/height (m^2).

Measures of standing height, sitting height, waist circumference, body weight, body fat percentage, and impedance will all be recorded on an anthropometric data recording form.

Portable metabolic testing during sedentary free-living activites (following anthropometric measurements): Following the recommendations of Freedson et al.[14] and Welk[15] for accelerometer calibration in children, we are including an evaluation of a wide variety of common free-living activities using a portable metabolic unit.

Participants will be required to be fasted (no food) for a period of no less than 4 hours prior to the start of the portable metabolic testing. Specific to our primary aim, we will concurrently detect cadence using multiple step measuring devices (Table 4 – below) compared to a criterion of directly observed and counted steps during each activity. We will also obtain measured gases (steady-state oxygen uptake) using a portable metabolic system (COSMED $K4b^2$; COSMED) so we can compute absolute intensity by MET levels. The $K4b^2$ portable metabolic system consists of a small gas analysis unit (6.7 in x 2.2 in x 3.9 in; 0.75 pounds) and a battery (6.7 in x 1.9 in x 3 in; 0.75 pounds) positioned on the abdomen and mid-back, respectively. The units are connected to each other via a strapped harness system (worn like a back-pack) which holds each unit close to the body. A small face mask is used for gas collection and allows for breath-by-breath gas analysis by the COSMED system. The mask is small and fits over the mouth and nose and is secured to the participant by elastic straps which wrap around the head. The mask does not restrict a participant's vision or line of sight. Participants are able to

breathe normally while wearing the mask. The straps securing the mask to the participant's head are adjustable to accommodate different shapes and sizes of heads.

Table 4. Wearable Step, Heart Rate, and Metabolic Measurement Devices Used in CADENCE-KIDS

Device	Manufacturer	Body location
Digiwalker Pedometer	Yamax	Waist
NL-1000 Pedometer	New Lifestyles	Waist
StepWatch Activity Monitor	Orthocare Innovations	Right ankle
SenseWear Armband	Body Media	Right upper arm
GT3X+ Accelerometer	ActiGraph	Right hip and non-dominant wrist
GENEActiv Accelerometer	Activinsights	Right hip and non-dominant wrist
Actical Accelerometer	Respironics	Left hip
ActivPal Accelerometer	Pal Technologies	Right thigh
Polar Heart Rate Monitor	Polar	Chest strap
COSMED K4b^2 Portable Metabolic System	COSMED	Positioned around abdomen and lower back (worn like a back-pack). Attached face mask collects expired gases for analysis by unit positioned around abdomen and lower back.

We will obtain heart rate (chest strap) and self-reported rating of perceived exertion (RPE) so we can track relative intensity levels during all testing. A video camera will be aimed at the participant's feet during each activity to record an objectively observed measure of cadence. In addition, a CADENCE-KIDS staff member will use a tally counter to count the number of steps taken during each activity.

The wearable step measuring devices listed in Table 4 will be attached to participants at the locations listed in the table. Devices attached along the waist and hips (Digiwalker Pedometer, NL-1000 Pedometer, Actical Accelerometer, GENEActiv accelerometer, and GT3X+ Accelerometer) will be fastened to the participant's body using an elastic waist-belt on top of clothing. The GT3X+ accelerometer and the GENEActiv accelerometer will also be attached at the wrist using a watch-like strap. The StepWatch Activity Monitor will be wrapped around the ankle with a Velcro strap. In addition, the SenseWear Armband will be wrapped around the right upper-arm using a Velcro strap. The Polar Heart Rate Monitor will be secured around the chest using a chest strap.

Participants will first perform several sedentary free-living activities while wearing the portable metabolic testing unit: resting in a chair, watching a movie (seated in a chair), and coloring books (seated in a chair). We will measure breath-by-breath

oxygen consumption of each activity in 5 minute bouts using the portable metabolic measuring system described above (COSMED K4b^2). A 5 minute rest period will precede the first activity (sitting in a chair) and a 2 minute rest period will occur between activities. Accumulated step counts from displays on several of the instruments (Digiwalker and NL-1000 pedometers) will be read and recorded during the 2 minute rest periods. Heart rate will be assessed continuously during the protocol. RPE will be queried during the final 15 seconds of each bout. Specifically, participants will be asked to point to the number on the scale representing how hard they believe they are working. Participants between 9-20 years of age will use the standard Borg RPE scale. A separate RPE scale specifically designed for and validated in young children (OMNI scale) will be used with the youngest participants (6-8 years of age).[16] During these activities participants will wear all the step measuring devices identified earlier in Table 4. A video camera will be aimed at the participant's feet during all the free-living activities to record an objectively observed measure of steps taken. This portion of the testing will take approximately 25 minutes.

Portable metabolic testing during treadmill walking (following sedentary free-living activities): Participants will begin the treadmill walking portion of the protocol by sitting on a chair positioned next to the treadmill for at least 2 minutes. The chair will be removed and then participants will be asked to step onto the treadmill and walk for 10 – 5 minute bouts at a 0% grade. The test will increase in 0.5 mph increments from a starting speed of 0.5 mph, with a 2-minute standing rest between bouts. Breath-by-breath oxygen consumption during each 5 minute activity bout will be measured using the portable metabolic measuring system described above (COSMED K4b^2). Heart rate will be assessed continuously during the protocol. RPE will be queried during the last 15 seconds of each bout. Specifically, participants will be asked to point to the number on the scale representing how hard they believe they are working. Participants between 9-20 years of age will use the standard Borg RPE scale. A separate RPE scale specifically designed for and validated in young children (OMNI scale) will be used with the youngest participants (6-8 years of age).[16] Accumulated step counts from displays on several of the instruments (Digiwalker and NL-1000 pedometers) will be read and recorded during each 2-minute standing rest period. The treadmill portion of the protocol will cease following completion of the first bout when the participant naturally selects to run instead of walk, or before this as the participant prefers, reflecting their personal tolerance. Based on pilot testing in young adults, we found that all participants were running by approximately 5 mph, and once running occurred increases in cadence were modest compared to changes in stride length. The anticipated range of speeds to be tested (in both meters/min and miles/hour) are shown in Table 5 (below) and should accommodate the full range of ages to be tested. This portion of testing should take approximately 70 minutes.

Table 5. Treadmill Speeds		
Stage	**Meters/min**	**Miles/hour**
1	14	0.52
2	27	1.00
3	40	1.49
4	54	2.01
5	67	2.49
6	80	2.98
7	94	3.50
8	107	3.98
9	121	4.51
10	134	4.99

Portable metabolic testing of select common free-living activities (following treadmill walking): Participants will perform a number of common free-living activities while wearing the portable metabolic testing unit: step up and down on an aerobic step at 88 beats per minute, dribbling a basketball, and jumping jacks at 126 beats per minute (63 jumping jacks per minute). Participants will be instructed to complete the basketball dribbling at their own self-selected (preferred) level of intensity (effort).

This testing will begin following the treadmill testing protocol (5 minute rest before beginning testing of free-living activities). We will measure breath-by-breath oxygen consumption of each activity in 5 minute bouts using the portable metabolic measuring system described above (COSMED K4b^2). A 2 minute standing rest period will occur between bouts. Accumulated step counts from displays on several of the instruments (Digiwalker and NL-1000 pedometers) will be read and recorded during the 2 minute standing rest periods. Heart rate will be assessed continuously during the protocol. RPE will be queried during the last 15 seconds of each bout. Specifically, participants will be asked to point to the number on the scale representing how hard they believe they are working. Participants between 9-20 years of age will use the standard Borg RPE scale. A separate RPE scale specifically designed for and validated in young children (OMNI scale) will be used with the youngest participants (6-8 years of age).[16] During these activities participants will wear all the step measuring devices identified earlier in Table 4. A video camera will be aimed at the participant's feet during all the free-living activities to record an objectively observed measure of steps taken. This portion of the testing will take approximately 25 minutes.

For each bout during the treadmill walking and free-living activities portions of the protocol, beginning time, ending time, hand tallied steps Digiwalker steps, NL-1000 steps, heart rate, and RPE will be recorded on a separate data collection sheet .

Accommodations: We are able to accommodate participants' (and their families') schedules, and minimize participant burden by insuring that: 1) the research laboratory will be open 5 days per week for 9 hours/day; 2) all laboratory-based

measurements will be scheduled for the same day (i.e., requiring only a single visit) unless the families/participants request testing over multiple days (e.g., treadmill testing one day, metabolic testing of common free-living activities on another day). We anticipate, however, that most families/participants will opt for a single day of testing. Participants and/or their parents/legal guardians will be asked to call as far as possible ahead of time to reschedule appointments.

All testing will be overseen by a trained Pennington Biomedical Research Center exercise technician with an MS or PhD in Exercise Science/Physiology or BS in Exercise Science with ACSM certification as Exercise Test Technologist.

The Pennington Biomedical Research Center, including its Exercise Testing Lab (Exercise Testing Core), has well-defined emergency procedures already in place should any adverse events be encountered. The staff have recently practiced and refined this same protocol on 6 different occasions. As previously mentioned, all testing will be conducted in the presence of a trained Pennington Biomedical Research Center exercise technician. In addition, a physician will always be on call within the Pennington Biomedical Research Center. All Pennington Biomedical Research Center exercise technicians which will oversee/administer testing at the Pennington Biomedical Research Center are trained in basic CPR and/or ACLS.

No drugs will be used in this study. Wearable step and metabolic measuring devices (pedometers, accelerometers, and portable metabolic measuring equipment) are all non-invasive.

10) Data Management*

Each participant will be issued an ID number that will be utilized throughout the study. A secure master file linking names, addresses and ID numbers will be maintained in a confidential computer file accessible only to the investigators. Access to data files can be made only with permission of the Principal Investigator. Privacy in the context of this study includes confidentiality of data and personal information. During interviews and measurements, the study staff will ensure full privacy of participants and will ensure that the data are stored in a secured area. All study staff must be HIPAA certified. The Pennington Biomedical Research Center's Biostatistics Core will cooperate with the data manager who will manage the data entry into the clinical database to ensure quality of data.

The Pennington Biomedical Research Center's Data Management Core will have the prime responsibility for database design and implementation, programming, coordination and manual data entry of the study data into the study database.

This is an exploratory/developmental study to collect preliminary data for the purpose of investigating the statistical relationships between objectively monitored cadence (steps/min) and increasing intensity, specifically metabolic equivalents or METS, measured in a laboratory treadmill setting in young people ages 6-20 years.

Calibration studies have typically been conducted using small select samples.[11] Freedson et al. has recommended that calibration studies in children be conducted with at least 10 participants in each age group (e.g., 8-10, 10-12 years of age, etc.). We exceed this requirement by enlisting 10 participants for each sex-age year, for a total of 150 children/adolescents. This strategy will make this the second largest children's accelerometer calibration study to date, but the most age-distributed study; Mattocks et al.[13] studied 246 children, but all age 12 years, and Freedson et al.[14] studied children/adolescents 6-18 years of age, but only 80 in total.

As previously stated, we hypothesize that children's activity intensity (oxygen uptake) will increase in a linear or nonlinear (curvilinear) fashion as cadence increases such that we will be able to develop statistical models for predicting markers (cut points) of intensity from cadence. This hypothesis will be tested in the lab-based study that will provide objective and directly measured data of both cadence and intensity markers. For each treadmill speed, actual METs will be calculated by dividing steady-state oxygen uptake by 3.5 ml/kg/min. Cadence will be determined for the middle 3-minutes of each treadmill speed (discarding the first and last minute). Stride length (meters/step) will then be determined by dividing treadmill speed (meters/min) by steps/min. Sex- and age-specific linear regression models will be used to initially assess the value of cadence as a predictor of metabolic cost in terms of METs across all treadmill speeds after examining data for potential outliers. Mixed effects regression models will then be analyzed to properly account for the variability among repeated assessments at different treadmill speeds on each participant in addition to gender differences and variability across age groups. Previous research in young adults has indicated that the relationship between cadence and METs is curvilinear.[6,17] See Figure 2 in paper by Abel et al.[17] We expect the relationship between cadence and METs in children to follow a similar pattern, suggesting a polynomial model would be appropriate to predict METs from cadence. However, we will still consider linear models (straight-line) and segmented (piecewise) regression models. We will analyze the data in five 3-year categories (6-8, 9-11, 12-14, 15-17, 18-20 years) which will give us 30 participants per category (15 boys and 15 girls) to analyze for this exploratory study, again a sample size larger than recommended by Dr. Patty Freedson (our consultant) in a comprehensive review of these types of calibration studies.[14]

First, we will fit subject specific second order (quadratic) models for each child using the random coefficients option of SAS proc mixed. This provides all (one set for each of 30 children) estimated subject-specific regression coefficients in a single analysis and enables us to test statistical significance of sex*age interactions and main effects among the regression equations as an interim step to gain insights into the necessity of separate modeling versus possibly collapsing the models into parsimonious subsets such as combining boys' and girls' data. Additional variables including anthropometric assessments (i.e., height, weight, sitting height, leg length) will be investigated for their influence when incorporated in the predictive models. Once the predictive relationship has been determined with both cadence and METS measured as continuous variables, the regression models (equations)

will be used to estimate the cadence cut points corresponding to MET categories considered representative of sedentary, light, moderate, and vigorous activity, commonly expressed as 1-1.49, 1.5-2.99 METs, 3-5.99 METs, and vigorous >6 METs, respectively.[18,19] Since moderate intensity might be more correctly considered to be 4 METs in children,[20] we will also solve for this cadence-intensity cut point. Additionally, we will use receiver operating characteristic (ROC) curves to examine optimal cadence cut points (maximum sensitivity and specificity) for the aforementioned sedentary, light, moderate, and vigorous categories.

11) Provisions to Monitor the Data to Ensure the Safety of Subjects

CADENCE-KIDS is a cross-sectional observational study with a minimal level of risk to study participants and does not warrant the establishment of an independent Data and Safety Monitoring Board. This plan describes the safety monitoring procedures for the proposed study, including a description of how often and to whom serious and unexpected adverse events will be reported. The plan will help ensure the safety of all participants. The PI will communicate via electronic submission to the IRB all unanticipated problems as defined by the IRB and all serious adverse events (SAEs) to the program officer within 24 hours. All less serious adverse events will be reported to the program officer within 3 days of occurrence.

The study investigators will monitor conduct of CADENCE-KIDS. Study staff will report adverse events or other problems directly to the PI as they occur. The PI will schedule monthly meetings with study staff to review data on adverse events, and recruitment or adherence to regimen problems. Any significant health problems coming to our attention during the study will be referred to the participant's usual source of medical care, with his/her permission. We will cooperate fully with his/her physician by providing relevant medical records. The following criteria, if detected during any part of the study regimen, will lead to referral to the participant's usual source of medical care:

- *1. Clinical symptoms or signs of CVD to include chest pain suggestive of angina pectoris, unusual dyspnea on exertion, severe ankle edema, symptoms suggestive of transient ischemic attacks or intermittent claudication.*
- *2. Musculoskeletal injuries or problems causing severe pain during exercise or interference with daily activities.*

12) Withdrawal of Subjects*

We anticipate that many of the participants will elect to complete their study procedures in a single visit; therefore reducing the risk and number of dropouts. For those individuals that elect to complete their procedures across multiple days, every possible research based strategy will be utilized to minimize dropouts and maximize the number of participants that complete the trial to insure high internal validity.

This will involve organizing the recruitment, screening, and testing to enhance adherence.

During the course of the study, participants may be withdrawn from the study for the following reasons:

- Unwillingness on behalf of the child or adolescent to participate in the study or cooperate with study staff
- Unwillingness on behalf of the parent/guardian to cooperate with study staff
- Presentation of significant medical symptoms that would warrant termination of study participation to protect the participant's safety
- Termination of the study by the sponsor

Data that has already been collected during the course of study participation from a withdrawn participant will be used, unless a specific request is otherwise received.

13) Risks to Subjects*

The risks for physical, psychological, social, or legal harm to participants and their parents/legal guardians associated with their participation in this study are minimal. The treadmill and free-living activities performed in CADENCE-KIDS are not maximal tests.

There are no known risks associated with the height, weight, and body fat percentage measurements. However, weight and body fat percentage measurements using the bioelectrical impedance analysis scale will not be performed on any participant who is pregnant, or those with medical implants such as a pacemaker or metal joint replacements.

Risks to participating children and adolescents during the treadmill test and free-living activities are rare, but could include:

- Temporary shortness of breath similar to moderate exercise
- Muscle soreness the following day
- Dizziness
- Fainting
- Blood pressure elevation
- Irregular heartbeat or heart attack
- Mild irritation of the skin from the wearable step measuring devices used to measure physical activity
- Mild irritation of the skin around the nose, mouth, and the sides and back of the head from the face mask worn with the K4b^2 portable metabolic system
- Mild irritation of the skin around the shoulders, abdomen, and lower-back from the straps used to secure the K4b^2 portable metabolic system to the body

In addition to the risks listed above, participants may experience a previously unknown risk or side effect.

All testing will be overseen by a trained Pennington Biomedical Research Center exercise technician with an MS or PhD in Exercise Science/Physiology or BS in Exercise Science with ACSM certification as Exercise Test Technologist.

Risks associated with study procedures will be continually assessed and monitored throughout testing by the Pennington Biomedical Research Center exercise technician administering the study protocol. Heart rate telemetry via a chest strap heart rate monitor will be continually captured in real time during all testing. The K4b^2 portable metabolic system wirelessly transmits this data to a laptop which will be running metabolic testing/monitoring software that displays heart rate data (and oxygen consumption data) in real time. Also, the Pennington Biomedical Research Center exercise technician will monitor each participant's heart rate during testing with a watch monitor wirelessly interfaced with the heart rate strap. RPE will also be assessed during the last 15 seconds of each testing bout to gauge each participant's perceived level of effort during testing. Participants will also be verbally asked by the Pennington Biomedical Research Center exercise technician at the mid-point of each 5 minute testing bout and during the rest periods between bouts how they feel and if they wish to continue with testing.

The Pennington Biomedical Research Center, including its Exercise Testing Lab (Exercise Testing Core), has well-defined emergency procedures already in place should any adverse events be encountered. The staff have recently practiced and refined this same protocol on 6 different occasions. As previously mentioned, all testing will be conducted in the presence of a trained Pennington Biomedical Research Center exercise technician. In addition, a physician will always be on call within the Pennington Biomedical Research Center. All Pennington Biomedical Research Center exercise technicians which will oversee/administer testing at the Pennington Biomedical Research Center are trained in basic CPR and/or ACLS.

14) Potential Benefits to Subjects*

Participants will receive up to $50 in financial compensation for completing the CADENCE-KIDS protocol.

No other benefits for participating in CADENCE-KIDS can be promised. However, participants may benefit from having their medical and health history reviewed as part of the study.

15) Vulnerable Populations*

The CADENCE-KIDS study will involve children as participants (6-17 years of age). As such, their parents and/or legal guardians will have to provide written informed consent allowing their child to participate in the study. In addition, participating children (6-17 years of age) will provide assent as well (verbal assent for children 6-8 years of age, written assent for children 9-17 years of age).

All participants will be explicitly told that their participation is voluntary and that they may end (stop) their participation in CADENCE-KIDS at any time. If a participant indicates that they wish to stop participating, all study procedures they are undertaking at that time will stopped to protect their rights and welfare.

16) Multi-Site Research*

N/A

17) Sharing of Results with Subjects*

Individual participant results will not be provided; however, results from the study will be submitted for manuscripts in scholarly journals and presentations. All study reports will present only aggregated data to minimize the risks that a participant can be identified from their participation in the study. A detailed publication plan will be developed as the study progresses.

18) Setting

Potential participants will be recruited utilizing the recruiting services (Recruitment Core) of the Pennington Biomedical Research Center. All research procedures will be performed at the Pennington Biomedical Research Center, namely, at the Outpatient Clinic and the Exercise Testing Lab (Exercise Testing Core).

19) Resources Available

The Pennington Biomedical Research Center is a model for clinical and translational research, since it houses basic, clinical and population research programs in one facility. The Pennington Biomedical Research Center is well-equipped to administer and support the CADENCE-KIDS research project. All study-related procedures will be completed in Pennington Biomedical Research Center's Outpatient Clinic Building (including the Exercise Testing Lab) which has all the necessary equipment and research staff needed to perform the testing described herein.

The study personnel and staff working on this study are highly qualified with extensive research backgrounds and experience conducting trials involving human participants, both here at the Pennington Biomedical Research Center, and at previous institutions. Dr. Catrine Tudor-Locke (Co-Investigator) is a walking behavior researcher who is a recognized world leader in objective physical activity assessment and promotion, specifically focused on pedometer or accelerometer-determined ambulatory activity captures as steps/day. Dr. Tudor-Locke will oversee all aspects of the CADENCE-KIDS research project. Dr. Hsia will oversee clinical aspects of screening and testing. In addition, Dr. Hsia will be engaged in day-to-day scientific decisions and problem solving. Dr. William Johnson is the Director of the Pennington Biomedical Research Center's Biostatistics and Data Management

Core. He supervises a staff that includes PhD and master's level biostatisticians and skilled programmers, and data entry personnel. Dr. Johnson will be responsible for statistical analyses relevant to this funding.

The greater Baton Rouge area has a considerable population (802,484 individuals) which serves as a more than adequate base to recruit the 150 required participants (6 to 20 years-old) for CADENCE-KIDS.

Dr. Tudor-Locke will work closely with the investigators and staff to ensure that the study is executed with the utmost scientific integrity. Dr. Tudor-Locke will also provide oversight of the protocol to ensure adherence.

20) Prior Approvals

N/A

21) Recruitment Methods

We will use a variety of recruitment strategies including newspaper advertising and stories, television news stories, mass mailings, health fairs, and other strategies (including school-based recruitment efforts). Participants will be recruited from the greater Baton Rouge area in Louisiana. Recruitment will begin in fall 2013 and is expected to end in winter 2014/2015. These strategies have been successful in our previous studies. We will develop recruitment materials and submit them to the IRB for expedited review as they are developed. Materials will be used to inform prospective participants about the overall nature of the study, the basic eligibility criteria, the measurement protocols and timeframes, and the time commitment of the study. Following an initial recruitment web-screen (followed by a telephone screen) or telephone screen, potential participants will attend an orientation session at the Pennington Biomedical Research Center to learn more about the study. Following the orientation session, those eligible potential participants who remain interested in the study will be scheduled for their testing session at the Pennington Biomedical Research Center with their parent/guardian (if between 6-17 years of age) where clinic staff will obtain signed informed consent (and child assent if between 6-17 years of age), before participants take part in any of the study related procedures.

22) Local Number of Subjects

We will recruit and enroll 150 participants from the greater Baton Rouge area in Louisiana.

23) Confidentiality

All data collected in this project will be subject to the same confidentiality requirements that are in place for our other studies at the Pennington Biomedical Research Center. Study files will be kept in locked cabinets and access restricted to study staff. All Pennington Biomedical Research Center staff sign a confidentiality

statement. Personal identifiers are not included in computer files. No individual's data will be released without their specific written consent.

24) Provisions to Protect the Privacy Interests of Subjects

Privacy in the context of this study includes confidentiality of data and personal information. During interviews and measurements, the study staff will ensure full privacy of participants and will ensure that the data are stored in a secured area.

25) Compensation for Research-Related Injury

No form of compensation for medical treatment or for other damages (i.e., lost wages, time lost from work, etc.) will be available for this research study. In the event of injury or medical illness resulting from the research procedures, participants will be referred to a treatment facility.

26) Economic Burden to Subjects

Participants will be required to bear the cost of any transportation to and from the Pennington Biomedical Research Center to complete the testing required in this study. In recognition of this and each participants time commitment to the study (approximately 3 hours), participants will receive $50 in compensation for participating in CADENCE-KIDS.

27) Consent Process

Informed consent (and assent when appropriate) will be obtained by Pennington Biomedical Research Center clinic staff prior to conducting any testing procedures. The study procedures will be explained to parent(s) and participants (6-17 years of age) or to participants only (those 18-20 years of age). Parents/legal guardians and participants will be asked if they have any questions about the study. The informed consent process will then proceed as follows for the three age categories (18-20 years of age, 9-17 years of age, and 6-8 years of age) represented in CADENCE-KIDS.

For participants between 18-20 years of age:

- Participants will be given an informed consent form to read and sign before participating in any study procedures.

For participants between 9-17 years of age:

- Parents/legal guardians will be given an informed consent form to read and sign indicating their permission to allow their child to participate in the study.

- Following the obtainment of written parental consent, participants 9-17 years of age will be given a written assent form to read and sign before participating in any study procedures.

For participants between 6-8 years of age:

- Parents/legal guardians will be given an informed consent form to read and sign indicating their permission to allow their child to participate in the study.

- Following the obtainment of written parental consent, participants 6-8 years of age will be orally read an assent script by a Pennington Biomedical Research Center clinic staff member. The last sentence in the oral script will ask the participant if they wish to participate in the study, inquiring for a "yes" or "no" response. The Pennington Biomedical Research Center clinic staff member will then mark the appropriate box on the assent script indicating the participant's voluntary response ("yes" or "no").

All participants and parents/legal guardians (if participant is between 6-17 years of age) will be verbally informed during the consent/assent process that their consent or assent can be withdrawn at any time for any reason and that they can stop participating at any time. In an effort to continually reassess assent or consent, participants will be asked if they wish to continue with the testing procedures at the mid-point of each 5 minute testing bout and during the scheduled rest periods between testing bouts.

Cognitively Impaired Adults

- N/A

Adults Unable to Consent

- N/A

28) Drugs or Devices

Table 6 (below) lists the different devices which will be used in the CADENCE-KIDS study. The StepWatch, SenseWear Armband, GT3X+ Accelerometer, GENEActiv accelerometer, Actical Accelerometer, ActivPal Accelerometer, and K4b^2 Portable Metabolic System all require initialization prior to being used. These devices will be initialized to collect data each scheduled day of testing (prior to testing). Data from each instrument will be downloaded onto a secure laptop (only accessible to study personnel) following the completion of all testing procedures (same day). Data from the Digiwalker and NL-1000 Pedometers will be recorded on a hard-copy data collection sheet and entered into an electronic database after the completion of all testing procedures (same day).

Table 6. Devices Used in CADENCE-KIDS		
Device	**Manufacturer**	**Body location**
Digiwalker Pedometer	Yamax	Waist
NL-1000 Pedometer	New Lifestyles	Waist
StepWatch Activity Monitor	Orthocare Innovations	Right ankle
SenseWear Armband	Body Media	Right upper arm
GT3X+ Accelerometer	ActiGraph	Right hip and non-dominant wrist
GENEActiv Accelerometer	Activinsights	Right hip and non-dominant wrist
Actical Accelerometer	Respironics	Right hip
ActivPal Accelerometer	Pal Technologies	Right thigh
Polar Heart Rate Monitor	Polar	Chest strap
COSMED $K4b^2$ Portable Metabolic System	COSMED	Positioned around abdomen and lower back (worn like a back-pack). Attached face mask collects expired gases for analysis by unit positioned around abdomen and lower back.

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APPENDIX A
CADENCE-KIDS
Pennington Biomedical Research Center
Inclusion / Exclusion

Inclusion Criteria
A* NO *answer disqualifies a potential participant from entry into the study

Yes ***No***
___ ___ Participant is at least 6 years-old but no older than 20 years-old on day of signing informed consent/assent

Exclusion Criteria
A* YES *answer to any of the Exclusion Criteria disqualifies a potential participant from entry into the study

Yes ***No***
___ ___ Participant uses a wheelchair or has another impairment that prevents normal daily physical activities such as walking

___ ___ Participant has been hospitalized for a mental illness within the past 5 years

___ ___ Participant has a known medical condition/medication that may affect heart rate during physical activity or exercise

___ ___ Participant has a previous history, or clinical symptoms or signs of, cardiovascular disease, stroke or TIAs (transient ischemic attacks), chest pain, unusual shortness of breath during physical activity or exercise, severe ankle edema, or intermittent claudication (pain caused by lack of blood flow during exercise)

___ ___ Participant has previous history of muscle and/or bone injuries or problems causing severe pain during physical activity or exercise that interferes with daily activities

___ ___ Participant has a pacemaker or other implanted medical device including metal joint replacements

___ ___ Participant would be unable to complete all testing (1 or two session, as preferred) within a period of less than 2 weeks. For reference, the entire testing protocol takes approximately 3 hours

___ ___ (For females only) - Participant is pregnant

_____ _____
Signature of person completing form Date Completed