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The promotion of physical activity for the prevention of Alzheimer's disease in adults with Down Syndrome: Rationale and design for a 12 Month randomized trial

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ABSTRACT

Nearly all individuals with Down Syndrome (DS) display pathology associated with Alzheimer's disease (AD) beginning as early as age 30. Previous research in typically developed adults suggests that increased moderate-to-vigorous physical activity (MVPA) may improve cognitive function and protect against age-related structural and functional changes in the brain; however, the potential impact of increased MVPA on the development of AD in adults with DS has not been evaluated. Despite the potential positive impact of MVPA on cognition and AD risk, participation in MVPA among young adults with DS is low. The limited research evaluating strategies for increasing MVPA in adults with DS has been unsuccessful in increasing MVPA. Results from our preliminary investigation where we remotely delivered real-time MVPA, led by a trained health educator, to groups of adults with DS in their homes via video conferencing on a tablet computer demonstrated high attendance, increased MVPA during group sessions, and improvements in cognitive function. However, the sustainability, impact on total daily MVPA, optimal session frequency, and potential impacts on cognitive function and brain health of remotely delivered group MVPA sessions in adults with DS are unknown. Therefore, we will conduct a trial in 80 non-demented adults with DS to determine the feasibility and potential efficacy of remotely delivered group MVPA sessions to increase daily MVPA, relative to a usual care control. Secondarily we will assess the impact of MVPA on cardiovascular fitness, quality of life, cognitive function and brain parameters related to AD.
NCT registration: NCT04048759.

1. Introduction

Down syndrome (DS) or trisomy 21 is the most common chromosomal abnormality which has impact both during childhood and later on in adult life leading to an intellectual and development disability (IDD) [1]. The number of people with Down Syndrome (DS) living the US has grown from ~50,000 to ~250,700 over the past 70 yrs [2]. Nearly all individuals with DS display pathology associated with Alzheimer's disease (AD) beginning as early as age 30 [3,4]. Previous research suggests that increased moderate-to-vigorous physical activity (MVPA) may improve cognitive function and may prevent or delay the development of dementia in adults without DS [5–8]; however, the potential impact of increased MVPA on the development of AD in adults with DS has not been evaluated.

Abbreviations: MVPA, moderate to vigorous physical activity; DS, Down Syndrome; AD, Alzheimer's Disease; RL, remote low; RH, remote high; UC, Usual Care.

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Despite the potential positive impact of MVPA on cognition and AD risk, participation in MVPA among young adults with DS is low. Reports suggest that ~9% of adults with IDD, including DS, meet the current 150 min/wk public heath recommendation for MVPA [9,10]. The limited research evaluating intervention strategies for increasing MVPA in adults with DS includes adults with all IDDs and has been unsuccessful in increasing short-term (≤12 wks) or long-term MVPA (18 mo) [11–13].

Adults with DS face numerous barriers to participation in MVPA including lack of appropriate options and educational materials relative to physical activity, lack of self-confidence to exercise with typically developed peers, lack of social support, poor motor skills, and issues relative to financial burden and transportation [14,15]. Our group recently developed and conducted a preliminary investigation of a remote method which delivers real-time MVPA, led by a trained health educator, to groups of adults with DS in their homes, via video conferencing on a tablet computer [16,17]. This approach eliminates the need for transportation, provides social interaction and support from both the health educator and other participants, and requires minimal caregiver/staff involvement. In our preliminary 12-wk. trial, 27 young adults with DS were randomized to 1 or 2, remotely delivered group MVPA sessions/wk. lasting 30 min each. Participants were asked to complete MVPA outside of the group sessions, and to attend weekly 30-min video chat sessions designed to support intervention compliance. All participants completed the 12-wk. intervention. Attendance at group sessions was high and did not differ between groups (1 session/wk. = 90%; 2 sessions/wk. = 89%). As expected, MVPA obtained during group sessions was higher in participants in the 2 session/wk. (57.7 ± 15.3 min/wk) compared with the 1 session/wk. group (26.6 ± 3.0 min/wk). Participants in both groups showed improvements in working memory, attention and reaction time as assessed by the CANTAB® battery for DS.

The results of our pilot were encouraging; however, the sustainability, impact on total daily MVPA, optimal session frequency, and potential impacts on cognitive function of remotely delivered group MVPA sessions in adults with DS is unknown. This led to the development of the current randomized trial in adults with DS designed to determine the feasibility and potential efficacy of remotely delivered group MVPA delivered at two different frequencies to increase daily MVPA, relative to a usual care control.

2. Methods and materials

2.1. Overview of study design (Table 1)

Eighty non-demented adults with DS will be randomized to a 12-mo. trial to compare changes in daily MVPA will assessed by portable accelerometer (ActiGraph wGT3XBT, ArchiMed Co, Lyon, Auvergne-Rhone-Alpes, France). Adults with DS will be randomized (2:2:1) to attend 40 min remotely delivered group MVPA sessions (Zoom™ Video Conferencing Inc., San Jose, CA) at a low frequency (1 session/wk., RL) or high frequency (3 sessions/wk., RH), or a usual care control (UC). All participants will be given an iPad tablet computer (Apple Inc, Cupertino, CA and a step counter (Versa Lite™, Fitbit, San Francisco, CA). Participants in both the RL and RH arms will receive weekly group MVPA sessions, access to resources for increasing MVPA, and twice monthly remotely delivered (FaceTime®) individual support/education sessions. Content for both the RL and RH arms will be identical with the exception of group MVPA session frequency (1 vs. 3/wk.). Participants in the UC arm, access to resources for increasing MVPA, and twice monthly (FaceTime®) individual support/education. The primary aim is to assess daily MVPA (min) in the RL, RH, and UC arms assessed at baseline, 3, 6, 9, and 12 mos, and obtain effect sizes for change in MVPA over 12-mos. All secondary outcomes will be assessed at baseline, 6 and 12 mos. Secondary aims will: 1) Assess the impact of MVPA across the RL, RH, and UC arms on cardiovascular fitness, quality of life, cognitive function and brain parameters related to AD (whole and regional brain volume, functional connectivity, structural connectivity, cerebral blood flow), and 2) determine the feasibility (retention, session attendance, use of recorded sessions (RH/RL only)) and safety of RL, RH, and UC arms. The results of this trial will determine the feasibility and potential effectiveness of the RL, RH, and UC interventions on MVPA, and gather initial estimates of the impact of MVPA on cognition and brain parameters related to AD in adults with DS. This information is required to inform the development of adequately powered, late stage confirmatory trials to evaluate the role of increased MVPA to prevent or delay AD in adults with DS.

2.2. Theoretical model

The proposed intervention is based on Social Cognitive Theory [18]. Specifically, we will employ participant goal setting (weekly MVPA goals), self-monitoring of MVPA (Fitbit), stimulus control (strategies to decrease cues for less desirable, and increase cues for more desirable physical activity behaviors), prompts (iPad calendar reminders), scheduling time for MVPA, environmental cues, modeling (by other participants), positive reinforcement/social support (group session leader, caregiver/study partner, other participants), and other self-regulatory techniques in both intervention arms. Social support [14,15,19], caregiver support [20,21], self-efficacy for exercise [14], and motor fitness [22] have all been associated with higher levels of physical activity in individuals with DS and IDD.

2.3. Participant eligibility

Primary care physician (PCP) clearance will be required for all participants. To enhance generalizability, individuals on medications for common chronic diseases, i.e., depression, blood pressure, lipids, type 2 diabetes, and those with previous congenital heart defects will not be excluded. Inclusion/Exclusion criteria are presented in Table 2.

Recruitment/Randomization. Project staff will contact local community agencies serving adults with DS, case managers, and Community Developmental Disabilities Organizations (CDDOs) by mail/email, provide presentations at CDDO meetings, and text for CDDO newsletters describing the project. Interested parents/guardians, caregivers, or adults with DS will be asked to contact the study coordinator via email, our website, or a dedicated toll-free study phone number that will be included in all recruitment materials. The study coordinator will contact

Table 1
Design overview for the 12-month physical activity intervention in adults with down syndrome.

	Intervention Arms		
	Remote High (RH)	Remote Low (RL)	Usual Care (UC)
MVPA recommendation	150 min/wk.	150 min/wk.	150 min/wk.
Group MVPA sessions	Yes	Yes	No
Delivery format	Zoom™ video conferencing	Zoom™ video conferencing	NA
Frequency	3 d/wk.	1 d/wk.	NA
Intensity	≥3 METS	≥3 METS	NA
Duration	40 min	40 min	NA
Content	Stretch/aerobic activity/RE	Stretch/aerobic activity/RE	NA
Access to PA resources	Yes	Yes	Yes
MVPA Self-monitoring	Fitbit	Fitbit	Fitbit
Education/support/ feedback sessions	Yes	Yes	Yes
Participants	DS adult + Study Partner	DS adult + Study Partner	DS adult + Study Partner
Frequency	2x/mo.	2x/mo.	2x/mo.
Delivery format	FaceTime®	FaceTime®	FaceTime®
Duration	20 min/session	20 min/session	20 min/session

Note: NA = not applicable, RE = resistance exercise.

Table 2
Participant eligibility criteria for a 12-month physical activity intervention in adults with down syndrome.

Inclusion	
Residential Status:	Living at home with a parent/guardian or in a supported living environment with a caregiver who agrees to serve as a study partner.
Age:	≥18 years
Diagnosis:	Down Syndrome
Ambulatory:	Must be able to participate in physical activity and walk 10 feet unassisted.
Health status:	Must provide physician clearance to participate.
Communication:	Sufficient functional ability to understand directions, communicate preferences, wants, and needs through spoken language
Internet:	Internet access in the home
Exclusion	
Dementia:	Diagnosis of dementia as determine by the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) [23]
Health concerns:	Serious medical risk, such as cancer, recent cardiac event, i.e., heart attack, stroke, angioplasty, or cannot participate in physical activity.
Pregnancy:	Pregnancy during the previous 6 mos, currently lactating or planned pregnancy in the following 24 mos. Participants who become pregnant will be removed from the study and referred to appropriate agencies for consultation.
Physical Activity Level:	Participation in a regular exercise program, i.e. ≥ 20 min/d ≥ 3 d/wk.

the interested individuals by phone to answer questions and conduct an initial eligibility screen. Home visits will be scheduled with those remaining interested, and potentially eligible, to obtain informed consent (participants or legal guardian) and participant assent (if not their own legal guardian) and determine final eligibility based on the DSQIID scores. Project staff will send a form (fax/email) to the potential participant's PCP which describes the study and requests clearance for participation. Participants found to be ineligible will be provided with written materials describing available resources for increasing physical activity. Cohorts of ~10–20 participants will be recruited, and computer randomized. Participants will be stratified by sex and age (18–30 or >30) and then sequentially randomized by the study statistician with 2:2:1 allocation to the RL, RH, and UC arms. This randomization scheme was selected to include more participants in the group video conferencing arms which, if successful, will be included in a later stage trial examining the effectiveness of increased MVPA using the video conferencing approach on cognitive function and brain health in adults with DS. Intervention assignments will be concealed in envelopes and delivered to the study coordinator.

Caregiver role. Caregivers play a potentially pivotal role for lifestyle change in adults with DS, e.g., assisting with scheduling and participation in appropriate physical activity [24]. Caregivers have been included in successful lifestyle interventions by our group [12,17,25] and others [26–28]. However, the limited data on the impact of caregiver support on MVPA in individuals with DS provide conflicting results [29,30]. No clear guidance on how best to involve caregivers in interventions is available [31]. Adults with IDD, including DS, frequently live with a paid caregiver, and turnover among paid caregivers is high [32]. In our previous 18-mo. weight management trial in adults with IDD (DK38359) ~ 74% of participants had a paid caregiver, and ~39% had 2 or more study-specific caregivers across 18 mos. For this current trial, we will recruit either a parent/guardian or residential support staff to serve as a study partner for each participant. Study partners will be allowed to assist multiple adults, provided all adults are in the same intervention group. Study partners will be asked to attend all individual support/education sessions, and to support, encourage, and assist participants in complying with the study protocol, such as reminding them to attend the group exercise sessions (RL and RH only), individual support session (all groups) providing opportunities for increased MVPA, and assisting with self-monitoring of MVPA.

2.3.1. Intervention components

2.3.1.1. MVPA recommendations. We will target 150 min/wk of MVPA (≥3 METs) for all groups as recommended for all adults by the American College of Sports Medicine [33] and the U.S. Department of Health and Human Services [34]. MVPA recommendations will progress from 60 min/wk (3 d/wk, 20 min/d) to 150 min/wk (5 d/wk, 30 min/d) at the beginning of mo. 4 and remain at 150 min/wk through the end of the study. Accumulated MVPA in bouts ≥10 min will be permitted.

2.3.1.2. MVPA self-monitoring. Participants in all 3 groups will be asked to wear a Fitbit Versa Lite activity tracker on their non-dominant wrist over the duration of the 12-mo. trial. This request may appear onerous; however, wearing the Fitbit is akin to wearing a wristwatch. Real-time data from the Fitbit is automatically transferred, via the web, to cloud storage (Fitabase, Small Steps Labs LLC, San Diego, CA), thus participant burden is minimal. Immediate participant feedback via a graphic display of daily steps, minutes of sedentary time, time spent in light, moderate and vigorous PA will be available on the iPad. This data, accessible to health educators, will be used *only* to provide motivation and feedback during the education/support sessions. Outcome data for MVPA will be assessed by accelerometer as described subsequently. Participants will be reminded to wear and charge the Fitbit during the individual support/education sessions, and will receive automatic reminder messages via the iPad using the iCal app.

2.3.1.3. RL and RH intervention. *Orientation*. Each participant and their study partner will be asked to attend an orientation session (~60 min) conducted at the University of Kansas Medical center and led by their health educator. In addition to describing study requirements and distributing iPads, Fitbits, resistance bands, etc., this meeting is designed to establish rapport between the health educator and participants prior to initiating the group video conference sessions. The health educator will describe and demonstrate the Zoom™ software and the Fitbit and will allow time for practice and questions. Additionally, basic stretching exercises, the use of the resistance bands, and simple dance movements will be demonstrated and practiced.

Group exercise sessions-Delivery. All MVPA sessions will be conducted by a health educator experienced in working with individuals with DS and supervised by the principal investigator. Group sessions will be delivered using an iPad tablet computer provided to all participants. The iPad will be pre-loaded with video-conferencing software (Zoom™) which allows participation by multiple users. Participants will be provided with an iPad/HDMI adaptor, which allows video conference sessions to be displayed on a larger TV screen, if desired. Tutorials describing troubleshooting for common technical problems, e.g., internet connectivity etc., will be loaded on the iPad. Participants with technical issues during the intervention can also contact research staff by phone or email. Access to non-study related materials, e.g., web browsing, app store, etc., will be blocked on all iPads. The iPads for both groups will also be pre-loaded with the Fitbit application.

Group exercise sessions-Schedule. Group exercise sessions will be scheduled between 10 a.m. and 7 p.m., 3 days/wk. for RH and 1 day/wk. for RL. This time window was selected based on the preference of participants in our 12-wk pilot trial in individuals with DS. Prompts reminding participants of upcoming sessions will be sent via the iPad. The same health educator will conduct MVPA sessions for both the RH and RL groups in each cohort to minimize health educator effects.

Group exercise sessions-Content. Each session will include a warm-up (~5 min), moderate-to-vigorous intensity aerobic and resistance exercise (~30 min), and cool-down/stretching (~5 min). Resistance exercise may be especially relevant, as adults with DS have reduced muscle

strength compared with their typically developing peers [35]. The aerobic/resistance exercises, accompanied by music, will include walking/jogging in place, dancing, imitating animal movements, vertical/horizontal jumps, squats, and Thera-Band exercises for major muscle groups. Activities will be modified for participants having difficulty with specific movements. The intensity of the initial sessions, as determined by Fitbit, will be light-to-moderate, with intensity increasing to moderate-to-vigorous at ~6 wks. All participants will be able to see, hear, and speak to each other during the group sessions. During each session, health educators will encourage interactions between participants in support of their peer's efforts to increase MVPA and provide participant feedback relative to their level of weekly MVPA as assessed by the Fitbit. As the intervention progresses, participants will be asked to volunteer to create and lead the group in a brief (3–5 min) exercise bout. Participants will also be encouraged to interact with each other by providing verbal support to each other ("great job", "keep it up"), performing activities such as tossing an imaginary ball to other participants, or challenging other participants to complete a skill such as 10 hops on one leg etc. All group sessions will be video recorded.

Homework assignments. The group exercise sessions have the potential to provide 30 min/wk of MVPA for the RL group and 90 min/wk for the RH group. Thus, MVPA outside these sessions will be required to meet the 150 min weekly recommendations. Health educators in the RH and RL groups will provide weekly challenges in the form of meeting a goal for increased steps, trying a new activity, or creating and performing their own exercise routine etc. Participants will be provided access to video recordings of all group exercise sessions that can be followed on their own to help in meeting weekly MVPA goals across the 12-mo. trial, if desired. Recordings will be sent to Dropbox and will be accessible to participants on the iPad. We will also provide information regarding increasing physical activity, available from the National Center on Health, Physical Activity and Disability (NCHPAD) and the Special Olympic athletes home training guide. Participants will be asked to document MVPA outside group sessions using the Fitbit. Participants will be asked to press a button on the Fitbit at the beginning and end of each group exercise session which will allow us to differentiate MVPA obtained during group sessions from other daily MVPA.

Education/support sessions. Twice monthly 20-min. education/support sessions will be delivered to participants and their study partners remotely on the iPad using FaceTime®. These sessions, led by the health educator, will be designed to educate and support participants with meeting their 150 min/wk. MVPA goal. Each session will include a review of MVPA self-monitoring data, goal setting, strategies to increase and support MVPA, and discussion of a topic relevant to MVPA including: the importance of MVPA for health and function, how to include MVPA in the daily schedule, reducing barriers to MVPA, appropriate types of activity, creating a safe environment for MVPA, alternative activities for inclement weather, importance of hydration, etc. Session outlines and materials will be preloaded on the iPad where they can be accessed by participants at any time.

2.3.1.4. Usual care (UC) intervention. *Orientation*. Participants and their study partner will be asked to attend an orientation session (~60 min) conducted at the University of Kansas Medical center and led by their health educator. Like the RL and RH groups, the orientation will be used to described study requirements and distribute iPads and Fitbits. The health educator will describe and demonstrate the FaceTime® software and the Fitbit and will allow time for practice and questions.

Intervention. The UC intervention will follow the traditional approach to promote increased MVPA in individuals with DS previously used by our group [12,13,25] and others [11,27]. Participants will receive an iPad tablet loaded with information regarding increasing MVPA available from NCHPAD and the Special Olympic athletes home training guide and will also receive resistance bands and a Fitbit for self-monitoring MVPA (described below). Twice monthly 20-min. education/support sessions, identical to the education/support sessions provided in the RL and RH arms, described above, will be delivered to participants and their study partners remotely on the iPad using FaceTime® Session outlines and materials will be preloaded on the iPad where they can be accessed by the participant at any time.

2.4. Health educator training

We currently have 3 health educators with experience in delivering group exercise and individual education and support using video conferencing to groups of adults with DS. If needed, new health educators will be trained by the principal investigator and will shadow an experienced health educator for a minimum of 3 mos prior to delivering the intervention on their own. The principal investigator will conduct weekly meetings with all health educators to discuss issues relative to intervention delivery. Study staff will review recordings from all scheduled group MVPA and individual support sessions. The content delivered will be compared with a checklist of scheduled activities/topics. Feedback will be provided to all health educators; those covering <80% of scheduled activities/topics will receive additional training and will be dismissed if the problem recurs.

2.5. Participant incentives

Reinforcement systems, known as positive behavioral support programs, have been successful in promoting behavioral change in individuals with DS [36]. These strategies provide modest incentives to motivate participants to meet their goals, and were successfully used in our previous trials that included adults with DS [12,13,17]. Participants in all groups who complete self-monitoring of MVPA on 5 of 7 d/wk will receive an electronic star. The allowance iPad app, Rooster Money (Rooster Money LLC, London, England), will be used to distribute stars to participants. Participants will get a notification on their iPad every time they receive a star. Participants will receive $10 each time they obtain 10 stars. Additionally, to compensate for time and travel, participants will receive $150 for completion of each of the 3 outcome assessment laboratory visits (baseline, 6, 12 mos), and $50 for completion of the additional two accelerometer outcome collection periods (3 and 9 mos). As an additional incentive, participants will be allowed to keep the iPad and Fitbit on completion of the trial (12 mos).

2.5.1. Outcome assessments

With the exception of assessment of daily MVPA by accelerometer, all outcomes will be assessed at the University of Kansas Medical Center, in Kansas City, KS. Cognitive function, cardiovascular fitness, and quality of life will be assessed at the Center for Physical Activity and Weight Management and all neuroimaging outcomes will be assessed at Hoglund Biomedical Imaging Center The primary outcome, daily total MVPA will be assessed at baseline, 3, 6, and 12 mos. All secondary and descriptive outcomes (height weight waist circumference) outcomes will be assessed at baseline, 6 and 12 mos.

2.5.1.1. Primary outcome. MVPA will be assessed using an ActiGraph wGT3XBT tri-axial accelerometer. The ActiGraph provides valid and reliable assessments of physical activity in typically developed adults [37–39], and has been widely used to describe physical activity levels in adults with DS [40,41]. Participants will be asked to wear the ActiGraph on a belt over the non-dominant hip at the anterior axillary line during waking hours for 7 consecutive days, with the exception of bathing, swimming, and contact sports. A 7-day monitoring period provides a reliable estimate of MVPA [42,43]. The hip rather than the wrist location will be used due to the lack of comparable data and established protocols for assessment of MVPA using wrist-worn ActiGraphs [44]. Research staff will distribute and demonstrate proper placement of the ActiGraphs at laboratory visits scheduled at baseline 6, and 12 mos.

ActiGraphs will be distributed by mail for the 3, 9 mo assessments. ActiGraphs will be returned by postage paid mail following completion of all assessments. Daily reminders to comply with the ActiGraph protocol will be sent to participants' iPads each morning during the 7-day monitoring period. ActiGraphs will be initialized and downloaded using ActiLife Software version 6.13.3 or higher (ArchiMed Co, Lyon, Auvergne-Rhone-Alpes, France) and set to collect in the raw data mode from all 3 axes at 60 Hz. Accelerometer data will be processed using the protocol for adults used in the 2003–2004 and 2005–2006 cycles of NHANES [45,46]. Data will be aggregated over 60-sec epochs. The following intensity cut-points will be used: sedentary (<1.0 MET; ≤ 100 counts/min), light (1.1–2.99 METs; 101–2019 counts/min.), moderate (3.0–5.99 METs; 2020–5988 counts/min) and vigorous ≥ 6 METs; ≥ 5999 counts/min) [45,46]. Non-wear time will be defined as at least 60 consecutive minutes of zero counts, with allowance for 1–2 min of counts between 0 and 100. Counts ≥20,000/min will be considered spurious [47]. All accelerometer data processing will be completed using custom SAS/R programs developed by our team.

2.5.1.2. Secondary outcomes. *Cognitive Function*. Working memory, processing speed, multitasking, and episodic memory will be assessed using tests selected from the widely used Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, LTD, Cambridge, UK) [48–50]. These standardized tests have been extensively evaluated, provide normative data, and allow for comparisons across trials. CANTAB® tests have acceptable construct [51,52] and concurrent validity [52]. Specifically, we will use the CANTAB® DS Battery which has been used in previous trials in individuals with DS [53,54] including our pilot trial [16]. The tests in this battery, which include measures of multitasking, episodic memory, executive function, working memory, and processing speed, have demonstrated sensitivity to disease-specific cognitive deficits in DS, including those related to hippocampal and frontal lobe dysfunction [55] and are also sensitive to the changes in cognitive function seen in AD [56]. All tests will be administered in a quiet room on an iPad following manufacturer's instructions. Tests will be administered in a random order and scored by a co-investigator who will be blinded to intervention group.

Cardiovascular fitness. Cardiovascular fitness is associated with brain volumes in the medial, temporal, and parietal cortices, suggesting that increasing cardiorespiratory fitness, by increased MVPA, may modify AD-related brain atrophy [7,8]. Cardiovascular fitness will be assessed using a maximal treadmill test, which are commonly used in adults with DS [22,57] using the protocol of Fernhall et al. [58]. The protocol starts with a 2-min warm-up at 0% grade at a comfortable walking speed. After the warm-up, the speed will be adjusted to a individualized brisk walking speed. After 2 min of walking at a brisk speed and 0% grade, the grade will increase every 2 min by 2.5% until a 12.5% grade is reached. From that point, grade will be held constant, whereas speed will be increased by 1.6 or 0.8 km h^{-1} every minute until exhaustion. Heart rate (Polar RS 400) and expired O_2 and CO_2 (ParvoMedics TrueOne 2300 - calibrated prior to each test) will be measured in 20 s intervals. The test will be terminated when participants achieve two or more of the following four criteria of peak effort: 1) volitional exhaustion, 2)VO_2 or HR plateau with an increase in work rate (VO_2 plateau defined as an increase less than 150 mL min^{-1}; HR plateau defined as an increase less than 2 bpm), 3) HR_{peak} within 5 beats of predicted HR_{peak} according to the formulas of Fernhall et al. [58], and 4) an RER ≥1.0. The exercise test will be terminated early if the participants are unable to maintain the treadmill speed or requests that the test be stopped. A cardiologist will be on-site for all treadmill tests per American College of Sports Medicine recommendations for testing individuals with DS [59] and ECG will be monitored continuously.

Quality of Life. Quality of life will be assessed with the Personal Well-Being Index-Intellectual Disability (PWI-ID) [60,61]. This instrument contains 7 items, each corresponding to a quality of life domain: standard of living, health, life achievement, personal relationships, personal safety, community-connectedness, and future security. Cronbach alpha of 0.76, and 1- to 2-wk. test–retest reliability of 0.58 have been reported in adults with IDD [60]. The PWI-ID scale differs from the original Personal Well-Being Index (PWI-A) in that it incorporates a pre-testing protocol to determine whether, and to what level of complexity, respondents are able to use the scale. The ID version also uses more simple and concrete wording. An additional question which asks how happy or sad the respondent is with life as a whole is included. A reduced choice format, illustrated as a series of outline faces, from very sad to happy, is provided to enhance comprehension and substitutes for the Likert scale used in the PWI-A version [61].

Neuroimaging. Neuroimaging measures will include: brain volume (i.e. structural MRI), functional connectivity (i.e. resting state fMRI (rsfMRI)), structural connectivity (i.e. diffusion tensor imaging (DTI)), and blood flow (i.e. arterial spin labeling (ASL)). We will utilize the scan sequences similar to those implemented by the NIAD and NIH funded Alzheimer's Biomarkers Consortium- Down Syndrome (ABC-DS) and currently used in the IGNITE (Trial [62] examining cognitive changes related to exercise in aging. Scanning will be performed on a 3-T Siemens Skyra scanner (Siemens, Erlangen, Germany) fitted with a 20-channel head coil. Following automated scout image acquisition and shimming procedures to optimize field homogeneity, structural, rsfMRI, DTI, and ASL data will be acquired. Participants will be able terminate the scan at any time during the procedure. Participants who fail to complete the baseline scan, will not be asked to complete subsequent scans at 6 or 12 mos. The structural scan will consist of T1-weighted MRI (3D MPRAGE sequence, TR/TE = 2400/2.31 ms, field of view = 240 × 256 mm^2, 0.8 mm isotropic resolution, 224 slices). Structural MRI imaging has elucidated the specific brain regions impacted by dementia in DS. These grey matter changes are detectable prior to the development of signs of clinical dementia [63,64] and have been impacted by cardiovascular fitness/MVPA(7). Functional and anatomic images obtained in each session will be aligned and normalized to a DS brain template [65]. Volumetric analyses of overall and regional, e.g. hippocampus, brain volumes will be performed using FreeSurfer segmentation using the longitudinal processing stream. Resting state fMRI will be performed using a gradient echo multiband EPI sequence (TR/TE = 1000/40 ms, multiband factor = 8, slice thickness = 2.5 mm, in plane resolution = 2.5 mm, 64 slices, 480 measurements) [66–68]. rsFMRI examines functional connectivity within and between brain networks. Individuals with DS show increased connectivity between networks compared to typically developing adults which has been hypothesized to reflect increased compensatory brain activation [65]. Pre-processing of rsfMRI data will be performed for each participant using Analysis of Functional NeuroImages (AFNI, Medical College of Wisconsin). The rsfMRI images will be realigned to the first slice collected in each scanning session to correct for motion. The images will be spatially smoothed with a 4 mm Full Width Half Maximum (FWHM) Gaussian blur. DTI examines structural connectivity by assessing the integrity of white matter tracks. The DTI scanning parameters include diffusion weighted acquisition in 64 gradient directions (TR/TE = 3050/119.4 ms, multiband factor = 4, slice thickness = 2.5 mm, in plane resolution = 2.5 mm, b-values of 0, 1500, 3000 s/mm^2) [66–68]. DTI analysis will be conducted in AFNI [69] and TORTOISE version 3.2 [70,71]. Processing steps will include eddy current correction modeled with quadratic functions; motion distortion correction; and EPI distortion correction using blip-up/blip-down estimation with DR-BUDDI [72]. Output metrics will include fractional anisotropy (FA), trace maps (TR) and mean diffusivity (MD). A pseudo-continuous ASL sequence [73,74] will be collected to measure changes in blood flow that may be related to increased fitness associated with physical activity. PCASL scanning parameters will include 20 vol of 48 axial slices (TR/TE = 4300/22.42 ms, slice thickness = 2.5 mm, in plane resolution = 3.1 mm, 4 segment readout). ASL analyses will be performed using the USC Laboratory of Functional MRI Technology (LOFT) CBF Preprocess and Quantify packages [75], and the

ASL Data Processing Toolbox (ASLtbx) [76] with Statistical Parametric Mapping version 12 software (SPM12) [77], applying methods that are currently implemented for the Alzheimer's Disease Center registry at KUMC. Processing steps will include motion correction, co-registration to the T1-weighted anatomical image, temporal and spatial filtering, and tissue segmentation of grey matter, white matter, and cerebrospinal fluid compartments for partial volume correction.

2.5.1.3. Descriptive outcomes. Body weight, height and waist circumference will be assessed to characterize the study sample. Weight will be measured in light clothing on a calibrated scale (Model #PS6600, Belfour, Saukville, WI) to the nearest 0.1 kg. Standing height will be measured with a portable stadiometer (Model #IP0955, Invicta Plastics Limited, Leicester, UK). BMI will be calculated as weight (kg)/height (m^2). Waist circumference will be assessed using the procedures described by Lohman et al. [78].

2.6. Feasibility

Retention. Retention will be measured as the percentage of participants who complete the 12-mo. intervention, defined as completing the 12 mo outcome assessments. *Session attendance*. Session attendance for both group MVPA and individual education/support sessions from baseline to 12 mos will be obtained from records maintained by the health educator and expressed as the percent of possible sessions. Attendance at group MVPA sessions will be defined as being logged in to the video conference and remaining on the screen for the entire 40-min session (±5 min). Attendance at individual support/education sessions, for the both exercise and UC conditions, will be defined as answering the FaceTime® all, and being present on screen for the entire session. *Use of recorded exercise sessions (RL and RH only)* will be tracked using Dropbox which provides information on how many times each user watched part of a video. *Safety.* Safety will be measured by number of participants reporting a serious adverse event, i.e., any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or results in persistent or significant disability/incapacity.

2.7. Exit interview

Following completion of the 12-mo. intervention, study staff will conduct structured interviews by phone with a 20% random sample of participants and study partners from each intervention arm to gather information that might be useful for improving the intervention. Topics will include preference for the RH, RL, or UC arms, reasons for missing scheduled sessions, intervention length, difficulties with compliance, suggestions for improvements and overall satisfaction with the intervention, enjoyment of the MVPA and educational sessions, health educators, MVPA recommendations, satisfaction with the MRI scan protocol, and willingness to take part in outcome procedures that could be used in future studies (collection of spinal fluid, PET scan). Qualitative content analysis (Atlas, ti 6.2) will be conducted to search for broad themes across interviews [79].

2.8. Analysis/sample size

2.8.1. Sample Size

We used an expected standard deviation of ~10 min. day^{-1} in MVPA based on data from adults with DS who participated in a recently completed weight management trial (DK83538, PI Donnelly) for our sample size estimates. A proposed sample size 32 participants in both the RH and RL groups will provide a 99% confidence for the estimation of mean total daily MVPA (±5 min) at each timepoint (baseline, 3, 6, 9 and 12 mos) A proposed sample of 16 participants in the UC group will provide 94% confidence for the estimation of total daily MVPA (±5 min) at each time point. Based on our preliminary data, we expect the correlation between baseline MVPA, and MVPA at subsequent timepoints, will be ≥ 0.5. Thus, the standard deviation of change in MVPA will be no greater than the standard deviation of MVPA at a given time point. Therefore, we would have the same ability to assess and detect a between group effect for change in MVPA as we stated for detecting a between group difference in MVPA at given time point, i.e. 10 min/day.

2.8.2. Primary Aim

Our primary aim is to assess total daily MVPA (min.) (exercise sessions + other MVPA) among the RL, RH, and UC arms at baseline, 3, 6, 9, and 12 mos and obtain effect sizes for change in total daily MVPA over 12-mos. We will calculate the mean and standard deviation and 95% confidence intervals of total daily MVPA at each time point for all 3 groups, as well as for the change from baseline to each time point. This descriptive information will be summarized graphically which will aid in determining if, and when group differences in MVPA arise. The corresponding effect sizes at each time point will be calculated as the between group differences in the mean divided by the common standard deviation. We will also estimate the correlation of total daily MVPA over time within individuals. This information will be critical to identifying whether single point in time or longitudinal assessments will be utilized to identify the sample size needed for future large-scale confirmatory trials. A repeated measures ANOVA will be used to compare between group changes in MVPA from baseline to each time point (3, 6, 9, 12 mos) using a linear mixed model approach with an autoregressive correlation structure over time. The model will include main effects of group and time and a group by time interaction which will provide an estimate of the treatment effect when modeling longitudinally. The information on total daily MVPA obtained from this trial will provide solid preliminary data to determine the potential for an intervention effect and inform subsequent trials.

2.8.3. Secondary aim 1

Our first secondary aim will assess the impact of total daily MVPA across the RL, RH, and UC arms on cardiovascular fitness, quality of life, cognitive function, and brain parameters (whole and regional brain volume, functional connectivity, cerebral blood flow) at baseline, 6, and 12 mos. We will estimate the correlation of change in MVPA on changes in cardiovascular fitness, qualify of life, cognitive function, whole and regional brain volume, functional connectivity, structural connectivity, and cerebral blood flow at 6 and 12 mos. This analysis will be completed with the total sample irrespective of study arm (n = 80).

2.8.4. Secondary aim 2

Our second secondary aim will determine the feasibility (retention, session attendance, safety, use of recorded sessions (RH/RL only), and safety) of RL, RH, and UC arms. We will estimate the proportion of participants retained, session attendance, use of recorded sessions and safety, i.e. significant adverse events across the 12 -mo. trial, the proportion that adhere to treatment within each arm.

2.8.5. Missing data

Missing data is anticipated due to either attrition, e.g., participant dropout, or nonresponse, e.g., ActiGraph non-wear or malfunction. Missing data for our primary outcome, total daily MVPA will be imputed, thus we will not over-recruit at baseline to account for participant attrition. Missing observations for total daily MVPA will be handled by Monte Carlo Markov Chain (MCMC) multiple imputation (MI) [80]. A sufficient number of imputed datasets will be created to ensure accurate recovery of missing data and analysis results from each imputed dataset will be combined to make valid statistical inferences. Our imputation process will incorporate a number of auxiliary variables, thereby satisfying the missing at random (MAR) assumption [81]. The state-of-the-science on missing data indicates that FIML and MI are extremely robust and leads to unbiased generalizability [82]. Additionally, our intent-to-treat approach will employ full information

maximum likelihood (FIML) estimation in the modeling, which does not discard participants who dropped out but utilizes all available data from their partial measurements, thereby producing unbiased parameter estimates and smallest possible standard errors.

3. Discussion

Pathology associated with AD develops in the majority of adults with DS beginning at ~ age 30 [3,4]. The cumulative incidence of dementia in adults with DS is in excess of 90% by age 65 [83], and is one of the main causes of death in individuals with DS [84]. The cause of high rates of AD in adults with DS is unclear. However, it is suspected that the additional copy of the amyloid precursor protein results in over-production of amyloid-beta (Aβ) which accelerates downstream neurodegeneration, plaque deposition, and early development of AD-like pathology in individuals with DS [4,85]. Research suggests that deposition of Aβ occurs decades earlier in adults with DS compared with typically developed adults who generally develop AD symptoms later in life [86,87]. For example, in a study of 29 individuals with DS, ranging in age from 3 to 73 yrs. Aβ deposition was detected as early as age 12 and was present in all subjects age 31 or older [12]. The initial symptoms of AD in adults with DS are deficits in executive function and features of frontotemporal dementia compared with typically developed adults where deficits in the hippocampus (episodic memory) are the earliest signs of AD [12–16]. Thus, strategies for the prevention of AD may differ between typically developed adults and adults with DS(4) thus trial specific to adults with DS are warranted.

Research suggests that increased MVPA may be effective in maintaining components of cognition, including attention, memory, and executive function in typically developed adults with AD [5,7,8,88–90]. In addition to cognitive benefits, research in typically developed adults suggests that increased MVPA may prevent or delay the onset of AD by increasing hippocampal volume, improving cerebral perfusion, facilitating neurogenesis and synaptogenesis, and favorably influencing pathological processes related to AD such as diminishing Aβ accumulation [29,42–45]. In adults with DS, research has demonstrated the potential for acute or short-term (≤12 wks) MVPA to improve cognition. In addition to the potential benefits related to cognition and brain health, increased MVPA in individuals with DS has been associated with decreased body weight [91], improved cardiovascular fitness [92,93], and improved muscular strength and endurance [94,95].

There is virtually no information regarding the effectiveness of intervention strategies designed to increase MVPA in adults with DS. Adults with DS face challenges to engaging in MVPA including not enjoying being active on their own, being self-conscious about participating in physical activity with their typically developing peers, and dependence on caregivers for transportation to a gym or community center to participate in physical activity [14,15]. Our experimental intervention, which includes group MVPA for adults with DS delivered to their home via video conferencing, eliminates these barriers. The group format also allows interaction between participants which has the potential to increase accountability, social support, and rapport in a group with a high potential for social isolation.

Increased MVPA has significant health benefits in adults with DS [11–13,96]. Therefore, we considered it unethical to randomize participants to a non-active control. Our UC arm provides written materials, includes a physical activity tracker for self-monitoring (Fitbit), and provides individual education/support from a trained health educator delivered by video conferencing (FaceTime®). FaceTime® delivery eliminates the travel barrier as most adults with DS are unable to drive. This approach has been well received by participants in our on-going weight management intervention in adults with IDD [97]. We believe using UC instead of a traditional non-active control allows for participants in all intervention arms to have a chance at success and will provide data to which changes in MVPA in the 2 other intervention arms can be compared.

We included low (1 session/wk.) and high frequency (3 sessions/wk.) group MVPA for 3 reasons. *First*, 1 group MVPA session/wk. has the potential to improve total weekly MVPA. Engaging in small amounts of structured exercise, even acute exercise, has been shown to improve quality of life [98,99], cardiovascular fitness [100,101], and exercise self-efficacy [102,103]. Participants in both the RL and RH arms will be asked to complete weekly homework assignments to increase MVPA in addition to that delivered in group sessions. Access to recordings of group sessions delivered to the iPad, weekly education and support, and provision of a Fitbit for self-monitoring will assist participants with completing homework assignments. Therefore, participants in the 1 session/wk. arm have the potential to increase MVPA sufficient to improve meaningful health related outcomes. *Second*, if effective, delivery of 1 session/wk. decreases the burden and cost associated with delivering multiple group MVPA sessions/wk. which may increase the probability that agencies serving adults with DS would implement and sustain the intervention. *Third*, our pilot trial, which included 1 or 2 group MVPA sessions/wk., suggested that 1 group MVPA session/wk. may impact cognitive function, and also suggested a potential dose response on both completion of MVPA outside group sessions, and on changes cognitive function(16). Thus, we included a 3 session/wk. arm to potentially provide a greater separation in MVPA between arms to further examine these dose response associations.

Design and methodologic strengths of this trial include: *1)* Randomized design to groups with concealed allocation of group assignments. *2)* Adequate sample size to address the aims *3)* Strategies to ensure the recruitment of sufficient participants to achieve our desired sample size. *4)* Retention/incentive strategies to reduce loss to follow-up. *5)* The use of a theory-based intervention delivered by trained health educators. *6)* Review of recordings of all scheduled exercise and individual support meetings to ensure intervention fidelity. *7)* Assessments completed by trained staff blind to intervention arm. *8)* Evaluation of staff inter-rater reliability for all assessments (2–3 times/yr.). *9)* Exit interviews with participants and caregivers to obtain information for improving and/or implementing the intervention.

Strategies for promoting healthy brain aging and preventing/delaying AD are needed in adults with DS, a population at high risk of developing AD. The development of effective and sustainable intervention strategies to increase MVPA in adults with DS may improve cognitive function and prevent or delay AD. This trial will determine the feasibility and potential efficacy of remotely delivered group MVPA delivered at two different frequencies to increase daily MVPA, relative to a usual care control. This early stage clinical trial will inform and advance the design of a subsequent late stage clinical trial while providing important data regarding the effect of MVPA on cognition and measures of brain health related to development of AD in adults with DS.

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References

[1] The World Health Organization, Definition: intellectual disability, Retrieved from World Health Organization Regional Office for Europe website, http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/mental-health/news/news/2010/15/childrens-right-to-family-life/definitionintellectual-disability, 2014.

[2] G. De Graaf, F. Buckley, B.G. Skotko, Estimation of the number of people with Down syndrome in the United States, Genet. Med. 19 (4) (2017) 439.

[3] W.B. Zigman, Atypical aging in Down syndrome, Dev. Disabil. Res. Rev. 18 (1) (2013) 51–67.

[4] D. Hartley, T. Blumenthal, M. Carrillo, G. DiPaolo, L. Esralew, K. Gardiner, A.-C. Granholm, K. Iqbal, M. Krams, C. Lemere, Down syndrome and Alzheimer's disease: common pathways, common goals. Alzheimer's & Dementia 11 (6) (2015) 700–709.

[5] K.I. Erickson, A.M. Weinstein, O.L. Lopez, Physical activity, brain plasticity, and Alzheimer's disease, Arch. Med. Res. 43 (8) (2012) 615–621.

[6] N.D. Barnard, A.I. Bush, A. Ceccarelli, J. Cooper, C.A. de Jager, K.I. Erickson, G. Fraser, S. Kesler, S.M. Levin, B. Lucey, Dietary and lifestyle guidelines for the prevention of Alzheimer's disease, Neurobiol. Aging (2014).

[7] J.M. Burns, B.B. Cronk, H.S. Anderson, J.E. Donnelly, G.P. Thomas, A. Harsha, W. M. Brooks, R.H. Swerdlow, Cardiorespiratory fitness and brain atrophy in early Alzheimer disease, Neurology 71 (3) (2008) 210–216.

[8] R. Honea, G.P. Thomas, A. Harsha, H.S. Anderson, J.E. Donnelly, W.M. Brooks, J. M. Burns, Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer's disease, Alzheimer Dis. Assoc. Disord. 23 (3) (2009) 188.

[9] Y.M. Dairo, J. Collett, H. Dawes, G.R. Oskrochi, Physical activity levels in adults with intellectual disabilities: a systematic review, Prevent. Med. Rep. 4 (2016) 209–219.

[10] T. Clarke, T. Norris, J. Schiller, Early release of selected estimates based on data from the 2016 national health interview survey, Nat. Center Health Stat. (2017).

[11] C.A. Melville, F. Mitchell, K. Stalker, L. Matthews, A. McConnachie, H.M. Murray, C. Melling, N. Mutrie, Effectiveness of a walking programme to support adults with intellectual disabilities to increase physical activity: walk well cluster-randomised controlled trial, Int. J. Behav. Nutr. Phys. Activ. 12 (1) (2015) 1.

[12] R.R. Saunders, M.D. Saunders, J.E. Donnelly, B.K. Smith, D.K. Sullivan, B. Guilford, M.F. Rondon, Evaluation of an approach to weight loss in adults with intellectual or developmental disabilities, Am. J. Intellect. Dev. Disabil. 49 (2) (2011) 103–112.

[13] L.T. Ptomey, R.R. Saunders, M. Saunders, R.A. Washburn, M.S. Mayo, D. K. Sullivan, C.A. Gibson, J.R. Goetz, J.J. Honas, E.A. Willis, J.C. Danon, R. Krebill, J.E. Donnelly, Weight management in adults with intellectual and developmental disabilities: a randomized controlled trial of two dietary approaches, Epub 2017/03/24, J. Appl. Res. Intellect. Disabil. : JARID (2017), https://doi.org/10.1111/jar.12348. PubMed PMID: 28332246.

[14] V.A. Temple, Factors associated with high levels of physical activity among adults with intellectual disability, Epub 2008/12/17, Int. J. Rehabil. Res. 32 (1) (2009) 89–92, https://doi.org/10.1097/MRR.0b013e328307f5a0. PubMed PMID: 19077725.

[15] J. Mahy, N. Shields, N.F. Taylor, K.J. Dodd, Identifying facilitators and barriers to physical activity for adults with Down syndrome, Epub 2010/08/18, J. Intellect. Disabil. Res. : JIDR (J. Intellect. Disabil. Res.) 54 (9) (2010) 795–805, https://doi.org/10.1111/j.1365-2788.2010.01308.x. PubMed PMID: 20712696.

[16] L.T. Ptomey, A.N. Szabo, E.A. Willis, A.M. Gorczyca, J.L. Greene, J.C. Danon, J. E. Donnelly, Changes in cognitive function after a 12-week exercise intervention in adults with Down syndrome, Epub 2018/03/05, Disabil. Health J. 11 (3) (2018) 486–490, https://doi.org/10.1016/j.dhjo.2018.02.003. PubMed PMID: 29501470; PMCID: PMC6005720.

[17] L.T. Ptomey, A.N. Szabo, E.A. Willis, J.L. Greene, J.C. Danon, R.A. Washburn, D. E. Forsha, J.E. Donnelly, Remote exercise for adults with down syndrome, Transl. J. Am. Coll. Sports Med. 3 (8) (2018) 60–65. Epub 2018/06/23. PubMed PMID: 29930988; PMCID: PMC6005664.

[18] A. Bandura, Social Foundations of Thought and Action: A Social Cognitive Theory, Prentice-Hall, Englewood Cliffs, New Jersey, 1986.

[19] N. Shields, N.F. Taylor, A student-led progressive resistance training program increases lower limb muscle strength in adolescents with Down syndrome: a randomised controlled trial, J. Physiother. 56 (3) (2010) 187–193. Epub 2010/08/28. PubMed PMID: 20795925.

[20] R. Izquierdo-Gomez, O.L. Veiga, A. Sanz, B. Fernhall, M. Diaz-Cueto, A. Villagra, Correlates of objectively measured physical activity in adolescents with Down syndrome: the UP & DOWN study, Epub 2015/06/05, Nutr. Hosp. 31 (6) (2015) 2606–2617, https://doi.org/10.3305/nh.2015.31.6.8694. PubMed PMID: 26040372.

[21] E.A. Pitchford, E. Siebert, J. Hamm, J. Yun, Parental perceptions of physical activity benefits for youth with developmental disabilities, Epub 2015/12/25, Am. J. Intellect. Dev. Disabil. 121 (1) (2016) 25–32, https://doi.org/10.1352/1944-7558-121.1.25. PubMed PMID: 26701072.

[22] R. Izquierdo-Gomez, D. Martinez-Gomez, B. Fernhall, A. Sanz, O.L. Veiga, The role of fatness on physical fitness in adolescents with and without Down syndrome: the UP&DOWN study, Epub 2015/08/22, Int. J. Obes. (2005) 2015, https://doi.org/10.1038/ijo.2015.164. PubMed PMID: 26293232.

[23] S. Deb, M. Hare, L. Prior, S. Bhaumik, Dementia screening questionnaire for individuals with intellectual disabilities, Epub 2007/05/02, Br. J. Psychiatr. : J. Ment. Sci. 190 (2007) 440–444, https://doi.org/10.1192/bjp.bp.106.024984. PubMed PMID: 17470960.

[24] D. Spanos, C.R. Hankey, S. Boyle, P. Koshy, S. Macmillan, L. Matthews, S. Miller, V. Penpraze, C. Pert, N. Robinson, C.A. Melville, Carers' perspectives of a weight loss intervention for adults with intellectual disabilities and obesity: a qualitative study, Epub 2012/03/01, J. Intellect. Disabil. Res. : JIDR (J. Intellect. Disabil. Res.) 57 (1) (2013) 90–102, https://doi.org/10.1111/j.1365-2788.2011.01530.x. PubMed PMID: 22369631.

[25] L.T. Ptomey, D.K. Sullivan, J. Lee, J.R. Goetz, C. Gibson, J.E. Donnelly, The use of technology for delivering a weight loss program for adolescents with intellectual and developmental disabilities, Epub 2014/12/03, J. Acad. Nutr. Diet. 115 (1) (2015) 112–118, https://doi.org/10.1016/j.jand.2014.08.031. PubMed PMID: 25441960.

[26] C.A. Melville, S. Boyle, S. Miller, S. Macmillan, V. Penpraze, C. Pert, D. Spanos, L. Matthews, N. Robinson, H. Murray, C.R. Hankey, An open study of the effectiveness of a multi-component weight-loss intervention for adults with intellectual disabilities and obesity, Epub 2011/01/25, Br. J. Nutr. 105 (10) (2011) 1553–1562, https://doi.org/10.1017/s0007114510005362. PubMed PMID: 21255473.

[27] D. Spanos, C.R. Hankey, C.A. Melville, The effectiveness of a weight maintenance intervention for adults with intellectual disabilities and obesity: a single stranded study, Epub 2015/04/29, J. Appl. Res. Intellect. Disabil. : JARID (2015), https://doi.org/10.1111/jar.12181. PubMed PMID: 25916495.

[28] F. Martinez-Zaragoza, J.M. Campillo-Martinez, M. Ato-Garcia, Effects on physical health of a multicomponent programme for overweight and obesity for adults with intellectual disabilities, Epub 2015/04/08, J. Appl. Res. Intellect. Disabil. : JARID (2015), https://doi.org/10.1111/jar.12177. PubMed PMID: 25847077.

[29] M. Pett, L. Clark, A. Eldredge, B. Cardell, K. Jordan, C. Chambless, J. Burley, Effecting healthy lifestyle changes in overweight and obese young adults with intellectual disability, Epub 2013/06/06, Am. J. Intellect. Dev. Disabil. 118 (3) (2013) 224–243, https://doi.org/10.1352/1944-7558-118.3.224. PubMed PMID: 23734617.

[30] M.S. McCarran, F. Andrasik, Behavioral weight-loss for multiply-handicapped adults: assessing caretaker involvement and measures of behavior change, Addict. Behav. 15 (1) (1990) 13–20. Epub 1990/01/01. PubMed PMID: 2138405.

[31] R. Hithersay, A. Strydom, G. Moulster, M. Buszewicz, Carer-led health interventions to monitor, promote and improve the health of adults with intellectual disabilities in the community: a systematic review, Epub 2014/02/06, Res. Dev. Disabil. 35 (4) (2014) 887–907, https://doi.org/10.1016/j.ridd.2014.01.010. PubMed PMID: 24495402.

[32] K. Humphries, M.A. Traci, T. Seekins, Food on file: pilot test of an innovative method for recording food intake of adults with intellectual disabilities living in the community, J. Appl. Res. Intellect. Disabil. 21 (2) (2008) 126–173.

[33] W.L. Haskell, I.M. Lee, R.R. Pate, K.E. Powell, S.N. Blair, B.A. Franklin, C. A. Macera, G.W. Heath, P.D. Thompson, A. Bauman, Physical activity and public health: updated recommendation for adults from the American College of sports medicine and the American heart association, Med. Sci. Sports Exerc. 39 (8) (2007) 1423–1434.

[34] Physical Activity Guidelines Adivsory Committee Report, 2008, Department of Health and Human Services, Washington, DC, 2008.

[35] R.V. Croce, K.H. Pitetti, M. Horvat, J. Miller, Peak torque, average power, and hamstrings/quadriceps ratios in nondisabled adults and adults with mental retardation, Arch. Phys. Med. Rehabil. 77 (4) (1996) 369–372. Epub 1996/04/01. PubMed PMID: 8607761.

[36] R.R. Saunders, M.D. Saunders, An analsis of contingency learning in the treatment of aberrant behavior, J. Dev. Phys. Disabil. 7 (54-83) (2000).

[37] N.F. Butte, U. Ekelund, K.R. Westerterp, Assessing physical activity using wearable monitors: measures of physical activity, Epub 2011/12/23, Med. Sci. Sports Exerc. 44 (1 Suppl 1) (2012) S5–S12, https://doi.org/10.1249/MSS.0b013e3182399c0e. PubMed PMID: 22157774.

[38] S.G. Trost, K.L. McIver, R.R. Pate, Conducting accelerometer-based activity assessments in field-based research, Med. Sci. Sports Exerc. 37 (11 Suppl) (2005) S531–S543. Epub 2005/11/19. PubMed PMID: 16294116.

[39] D. Hendelman, K. Miller, C. Baggett, E. Debold, P. Freedson, Validity of accelerometry for the asssesment of moderate intensity physical activity in the field, Med. Sci. Sports Exerc. 32 (2000) S442–S449. Suppl.

[40] M. Nordstrøm, B.H. Hansen, B. Paus, S.O. Kolset, Accelerometer-determined physical activity and walking capacity in persons with Down syndrome, Williams syndrome and Prader–Willi syndrome, Res. Dev. Disabil. 34 (12) (2013) 4395–4403.

[41] R. Izquierdo-Gomez, D. Martínez-Gómez, A. Acha, O.L. Veiga, A. Villagra, M. Diaz-Cueto, UP, group Ds, Objective assessment of sedentary time and physical activity throughout the week in adolescents with Down syndrome. The UP&DOWN study, Res. Dev. Disabil. 35 (2) (2014) 482–489.

[42] M. Kang, K. Bjornson, T.V. Barreira, B.G. Ragan, K. Song, The minimum number of days required to establish reliable physical activity estimates in children aged 2-15 years, Epub 2014/10/24, Physiol. Meas. 35 (11) (2014) 2229–2237, https://doi.org/10.1088/0967-3334/35/11/2229. PubMed PMID: 25340374.

[43] K.L. Cain, J.F. Sallis, T.L. Conway, D. Van Dyck, L. Calhoon, Using accelerometers in youth physical activity studies: a review of methods, J. Phys. Activ. Health 10 (3) (2013) 437–450. Epub 2013/04/27. PubMed PMID: 23620392.

[44] M. Hildebrand, V.T. Vanh, B.H. Hansen, U. Ekelund, Age group comparability of raw accelerometer output from wrist- and hip-worn monitors, Epub 2014/06/03, Med. Sci. Sports Exerc. 46 (9) (2014) 1816–1824, https://doi.org/10.1249/mss.0000000000000289. PubMed PMID: 24887173.

[45] R.P. Troiano, D. Berrigan, K.W. Dodd, L.C. Masse, T. Tilert, M. McDowell, Physical activity in the United States measured by accelerometer, Med. Sci. Sports Exerc. 40 (1) (2008) 181–188. Epub 2007/12/20. PubMed PMID: 18091006.

[46] C.E. Matthews, K.Y. Chen, P.S. Freedson, M.S. Buchowski, B.M. Beech, R.R. Pate, R.P. Troiano, Amount of time spent in sedentary behaviors in the United States, 2003-2004, Am. J. Epidemiol. 167 (7) (2008) 875–881.

[47] L.C. Masse, B.F. Fuemmeler, C.B. Anderson, C.E. Matthews, S.G. Trost, D. J. Catellier, M.S. Treuth, Accelerometer data reduction: a comparison of four reduction algorithms on select outcome variables, Med. Sci. Sports Exerc. 37 (11) (2005) S544–S554. Suppl.

[48] D.W. Falconer, J. Cleland, S. Fielding, I.C. Reid, Using the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess the cognitive impact of electroconvulsive therapy on visual and visuospatial memory, Epub 2009/09/25, Psychol. Med. 40 (6) (2010) 1017–1025, https://doi.org/10.1017/s0033291709991243. PubMed PMID: 19775495.

[49] G. Fernie, D.M. Bennett, J. Currie, J.S. Perrin, I.C. Reid, Detecting objective and subjective cognitive effects of electroconvulsive therapy: intensity, duration and test utility in a large clinical sample, Epub 2014/07/30, Psychol. Med. 44 (14) (2014) 2985–2994, https://doi.org/10.1017/s0033291714000658. PubMed PMID: 25065412.

[50] F.C. Soares, T.C. de Oliveira, L.D. de Macedo, A.M. Tomas, D.L. Picanco-Diniz, J. Bento-Torres, N.V. Bento-Torres, C.W. Picanco-Diniz, CANTAB object recognition and language tests to detect aging cognitive decline: an exploratory comparative study, Epub 2015/01/08, Clin. Interv. Aging 10 (2015) 37–48, https://doi.org/10.2147/cia.s68186. PubMed PMID: 25565785; PMCID: Pmc4279672.

[51] T.W. Robbins, M. James, A.M. Owen, B.J. Sahakian, A.D. Lawrence, L. McInnes, P.M. Rabbitt, A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery, J. Int. Neuropsychol. Soc. : JINS. 4 (5) (1998) 474–490. Epub 1998/09/24. PubMed PMID: 9745237.

[52] H.S. Kim, Y.M. An, J.S. Kwon, M.S. Shin, A preliminary validity study of the cambridge neuropsychological test automated battery for the assessment of executive function in schizophrenia and bipolar disorder, Epub 2014/11/15, Psychiatr. Invest. 11 (4) (2014) 394–401, https://doi.org/10.4306/pi.2014.11.4.394. PubMed PMID: 25395970; PMCID: Pmc4225203.

[53] S.-A. Cooper, M. Caslake, J. Evans, A. Hassiotis, A. Jahoda, A. McConnachie, J. Morrison, H. Ring, J. Starr, C. Stiles, Toward onset prevention of cognitive decline in adults with Down syndrome (the TOP-COG study): study protocol for a randomized controlled trial, Trials 15 (1) (2014) 202.

[54] S. Vicari, M. Pontillo, M. Armando, Neurodevelopmental and psychiatric issues in Down's syndrome: assessment and intervention, Psychiatr. Genet. 23 (3) (2013) 95–107.

[55] B.F. Pennington, J. Moon, J. Edgin, J. Stedron, L. Nadel, The neuropsychology of Down syndrome: evidence for hippocampal dysfunction, Child Dev. 74 (1) (2003) 75–93. Epub 2003/03/11. PubMed PMID: 12625437.

[56] A. Égerházi, R. Berecz, E. Bartók, I. Degrell, Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease, Prog. Neuro Psychopharmacol. Biol. Psychiatr. 31 (3) (2007) 746–751.

[57] B. Fernhall, L. Millar, G. Tymeson, L. Burkett, Cardiovascular fitness testing and fitness levels of adolescents and adults with mental retardation including Down syndrome, Educ. Train. Ment. Retard. (1989) 133–138.

[58] B. Fernhall, J.A. McCubbin, K.H. Pitetti, P. Rintala, J.H. Rimmer, A.L. Millar, A. De Silva, Prediction of maximal heart rate in individuals with mental retardation, Med. Sci. Sports Exerc. 33 (10) (2001) 1655–1660. PubMed PMID: 11581548.

[59] ACMS's, Guidelines for Exercise Testing and Prescription, ninth ed., Lippincott, Williams and Wilkens, Baltimore MD, 2014.

[60] J. McGillivray, A.Y. Lau, R. Cummins, G. Davey, The utility of the well-being intellectual disability scale in an Australian sample, J. Appl. Res. Intellect. Disabil. 22 (3) (2009) 276–286.

[61] R. Cummins, A.L. Lau, G. Davey, J. McGillivray, Measuring subjective well-being: the personal well-being Index - intellectual disability, in: R. Kober (Ed.), Enhancing the Quality of Life of People with Disability, Springer, Inc., New York, NY, 2010, pp. 33–46.

[62] K.I. Erickson, G.A. Grove, J.M. Burns, C.H. Hillman, A.F. Kramer, E. McAuley, E. D. Vidoni, J.T. Becker, M.A. Butters, K. Gray, H. Huang, J.M. Jakicic, M. I. Kamboh, C. Kang, W.E. Klunk, P. Lee, A.L. Marsland, J. Mettenburg, R. J. Rogers, C.M. Stillman, B.P. Sutton, A. Szabo-Reed, T.D. Verstynen, J.C. Watt, A. M. Weinstein, M.E. Wollam, Investigating gains in neurocognition in an intervention trial of exercise (IGNITE): protocol, Epub 2019/08/30, Contemp. Clin. Trials 85 (2019) 105832, https://doi.org/10.1016/j.cct.2019.105832. PubMed PMID: 31465859; PMCID: PMC6815730.

[63] D.C. Matthews, A.S. Lukic, R.D. Andrews, B. Marendic, J. Brewer, R.A. Rissman, L. Mosconi, S.C. Strother, M.N. Wernick, W.C. Mobley, Dissociation of Down syndrome and Alzheimer's disease effects with imaging, Alzheimer's Dementia: Transl. Res. Clin. Intervent. 2 (2) (2016) 69–81.

[64] M. Rafii, H. Wishnek, J. Brewer, M. Donohue, S. Ness, W. Mobley, P. Aisen, R. Rissman, The down syndrome biomarker initiative (DSBI) pilot: proof of concept for deep phenotyping of Alzheimer's disease biomarkers in down syndrome, Front. Behav. Neurosci. 9 (2015) 239.

[65] P.J. Lao, B.L. Handen, T.J. Betthauser, K.A. Cody, A.D. Cohen, D.L. Tudorascu, C. K. Stone, J.C. Price, S.C. Johnson, W.E. Klunk, Imaging neurodegeneration in Down syndrome: brain templates for amyloid burden and tissue segmentation, Brain Imag. Behav. (2018) 1–9.

[66] S. Moeller, E. Yacoub, C.A. Olman, E. Auerbach, J. Strupp, N. Harel, K. Ugurbil, Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI, Epub 2010/05/01, Magn. Reson. Med. 63 (5) (2010) 1144–1153, https://doi.org/10.1002/mrm.22361. PubMed PMID: 20432285; PMCID: PMC2906244.

[67] D.A. Feinberg, S. Moeller, S.M. Smith, E. Auerbach, S. Ramanna, M. Gunther, M. F. Glasser, K.L. Miller, K. Ugurbil, E. Yacoub, Multiplexed echo planar imaging for sub-second whole brain FMRI and fast diffusion imaging, Epub 2010/12/29, PloS One 5 (12) (2010), e15710, https://doi.org/10.1371/journal.pone.0015710. PubMed PMID: 21187930; PMCID: PMC3004955.

[68] J. Xu, S. Moeller, E.J. Auerbach, J. Strupp, S.M. Smith, D.A. Feinberg, E. Yacoub, K. Ugurbil, Evaluation of slice accelerations using multiband echo planar imaging at 3 T, Epub 2013/08/01, Neuroimage 83 (2013) 991–1001, https://doi.org/10.1016/j.neuroimage.2013.07.055. PubMed PMID: 23899722; PMCID: PMC3815955.

[69] R.W. Cox, AFNI: software for analysis and visualization of functional magnetic resonance neuroimages, Comput. Biomed. Res. 29 (3) (1996) 162–173. Epub 1996/06/01. PubMed PMID: 8812068.

[70] C. Pierpaoli, L. Walker, M.O. Irfanoglu, A. Barnett, P. Basser, L.-C. Chang, C. Koav, S. Pajevic, G. Rohde, J. Sarlls, M. Wu, TORTOISE: an integrated software package for processing of diffusion MRI data, in: ISMRM 18th Annual Meeting; Stockholm, Sweden, 2010.

[71] M.O. Irfanoglu, A. Nayak, J. Jenkins, C. Pierpaoli, TORTOISEv3: improvements and new features of the NIH diffusion MRI processing pipeline, in: ISMRM 25th Annual Meeting; Honolulu, HI, 2017.

[72] M.O. Irfanoglu, P. Modi, A. Nayak, E.B. Hutchinson, J. Sarlls, C. Pierpaoli, DR-BUDDI (Diffeomorphic Registration for Blip-Up blip-Down Diffusion Imaging) method for correcting echo planar imaging distortions, Epub 2014/11/30, Neuroimage 106 (2015) 284–299, https://doi.org/10.1016/j.neuroimage.2014.11.042. PubMed PMID: 25433212; PMCID: PMC4286283.

[73] Y. Wang, S. Moeller, X. Li, A.T. Vu, K. Krasileva, K. Ugurbil, E. Yacoub, D.J. Wang, Simultaneous multi-slice Turbo-FLASH imaging with CAIPIRINHA for whole brain distortion-free pseudo-continuous arterial spin labeling at 3 and 7 T, Neuroimage 113 (2015) 279–288.

[74] E. Kilroy, L. Apostolova, C. Liu, L. Yan, J. Ringman, D.J. Wang, Reliability of 2D and 3D pseudo-continuous arterial spin labeling perfusion MRI in elderly populations–comparison with 15O-water PET, J. Magn. Reson. Imag.: JMRI 39 (4) (2014) 931.

[75] K. Jann, R. Smith, E.R. Piedra, X. Xiao, D.J. Wang, LOFT_CBFquantify.m. 3.0 Ed, 2017.

[76] Z. Wang, G.K. Aguirre, H. Rao, J. Wang, M.A. Fernández-Seara, A.R. Childress, J. A. Detre, Empirical optimization of ASL data analysis using an ASL data processing toolbox: ASLtbx, Magn. Reson. Imag. 26 (2) (2008) 261–269.

[77] K.J. Friston, J. Ashburner, C.D. Frith, J.B. Poline, J.D. Heather, R.S. Frackowiak, Spatial registration and normalization of images, Hum. Brain Mapp. 3 (3) (1995) 165–189.

[78] T.G. Lohman, A.F. Roche, R. Martorell, Anthropometric Standardization Reference Manual, Human Kinetics Books, Champaign,Ill, 1988, 1988.

[79] V. Braun, V. Clarke, Using thematic analysis in psychology, Qual. Res. Psychol. 3 (2) (2006) 77–101.

[80] C.K. Enders, Applied Missing Data Analysis, Guilford Press, New York, NY, 2010.

[81] J.L. Schafer, J.W. Graham, Missing data: our view of the state-of-the-art, Psychol. Methods 7 (2002) 147–177.

[82] J.W. Graham, P.E. Cumsille, E. Elk-Fisk, Research Methods in Psychology, John Wiley & Sons, New York, NY, 2003 pp.87–114.

[83] M. McCarron, P. McCallion, E. Reilly, N. Mulryan, A prospective 14-year longitudinal follow-up of dementia in persons with D own syndrome, J. Intellect. Disabil. Res. 58 (1) (2014) 61–70.

[84] A. Englund, B. Jonsson, C.S. Zander, J. Gustafsson, G. Annerén, Changes in mortality and causes of death in the Swedish Down syndrome population, Am. J. Med. Genet. 161 (4) (2013) 642–649.

[85] F.K. Wiseman, T. Al-Janabi, J. Hardy, A. Karmiloff-Smith, D. Nizetic, V. L. Tybulewicz, E.M. Fisher, A. Strydom, A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome, Nat. Rev. Neurosci. 16 (9) (2015) 564.

[86] D.M. Mann, The pathological association between Down syndrome and Alzheimer disease, Mechan. Age. Dev. 43 (2) (1988) 99–136. Epub 1988/05/01. PubMed PMID: 2969441.

[87] B. Rumble, R. Retallack, C. Hilbich, G. Simms, G. Multhaup, R. Martins, A. Hockey, P. Montgomery, K. Beyreuther, C.L. Masters, Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease, Epub 1989/06/01, N. Engl. J. Med. 320 (22) (1989) 1446–1452, https://doi.org/10.1056/nejm198906013202203. PubMed PMID: 2566117.

[88] D.E. Barnes, K. Yaffe, The projected effect of risk factor reduction on Alzheimer's disease prevalence, Lancet Neurol. 10 (9) (2011) 819–828.

[89] R. Andel, M. Crowe, N.L. Pedersen, L. Fratiglioni, B. Johansson, M. Gatz, Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 63 (1) (2008) 62–66.

[90] L.F. DeFina, B.L. Willis, N.B. Radford, A. Gao, D. Leonard, W.L. Haskell, M. F. Weiner, J.D. Berry, The association between midlife cardiorespiratory fitness levels and later-life DementiaA cohort study, Ann. Intern. Med. 158 (3) (2013) 162–168.

[91] J.H. Rimmer, T. Heller, E. Wang, I. Valerio, Improvements in physical fitness in adults with Down syndrome, Am. J. Ment. Retard. 109 (2) (2004) 165–174.

[92] G.V. Mendonca, F.D. Pereira, B. Fernhall, Effects of combined aerobic and resistance exercise training in adults with and without Down syndrome, Arch. Phys. Med. Rehabil. 92 (1) (2011) 37–45.

[93] P.H. Boer, S.J. Moss, Effect of continuous aerobic vs. interval training on selected anthropometrical, physiological and functional parameters of adults with Down syndrome, Epub 2016/01/26, J. Intellect. Disabil. Res. : JIDR (J. Intellect. Disabil. Res.) (2016), https://doi.org/10.1111/jir.12251. PubMed PMID: 26805768.

[94] N. Shields, N.F. Taylor, E. Wee, D. Wollersheim, S.D. O'Shea, B. Fernhall, A community-based strength training programme increases muscle strength and physical activity in young people with Down syndrome: a randomised controlled trial, Res. Dev. Disabil. 34 (12) (2013) 4385–4394.

[95] P. Bartlo, P.J. Klein, Physical activity benefits and needs in adults with intellectual disabilities: systematic review of the literature, Am. J. Intellect. Dev. Disabil. 116 (3) (2011) 220–232.

[96] A.E. Bodde, D.-C. Seo, G.C. Frey, D.K. Lohrmann, M. Van Puymbroeck, Developing a physical activity education curriculum for adults with intellectual disabilities, Health Promot. Pract. 13 (1) (2012) 116–123.

[97] L.T. Ptomey, R.A. Washburn, M.S. Mayo, J.L. Greene, R.H. Lee, A.N. Szabo-Reed, J.J. Honas, J.R. Sherman, J.E. Donnelly, Remote delivery of weight management for adults with intellectual and developmental disabilities: rationale and design for a 24 month randomized trial, Contemp. Clin. Trials 73 (2018) 16–26.

[98] F.J. Penedo, J.R. Dahn, Exercise and well-being: a review of mental and physical health benefits associated with physical activity, Curr. Opin. Psychiatr. 18 (2) (2005) 189–193.

[99] C.K. Martin, T.S. Church, A.M. Thompson, C.P. Earnest, S.N. Blair, Exercise dose and quality of life: a randomized controlled trial, Arch. Intern. Med. 169 (3) (2009) 269–278.

[100] C.J. Lavie, R. Arena, D.L. Swift, N.M. Johannsen, X. Sui, D-c Lee, C.P. Earnest, T. S. Church, J.H. O'keefe, R.V. Milani, Exercise and the cardiovascular system: clinical science and cardiovascular outcomes, Circ. Res. 117 (2) (2015) 207–219.

[101] E.S. dos Santos, R.Y. Asano, G. Irênio Filho, N.L. Lopes, P. Panelli, DdC. Nascimento, S.R. Collier, J. Prestes, Acute and chronic cardiovascular response to 16 weeks of combined eccentric or traditional resistance and aerobic training in elderly hypertensive women: a randomized controlled trial, J. Strength Condit Res. 28 (11) (2014) 3073–3084.

[102] E.A. Olson, E. McAuley, Impact of a brief intervention on self-regulation, self-efficacy and physical activity in older adults with type 2 diabetes, J. Behav. Med. 38 (6) (2015) 886–898.

[103] E. McAuley, B. Blissmer, J. Katula, T.E. Duncan, S.L. Mihalko, Physical activity, self-esteem, and self-efficacy relationships in older adults: a randomized controlled trial, Ann. Behav. Med. 22 (2) (2000) 131.