FULL PROTOCOL

THE HEALTH AND AGING BRAIN STUDY (HABS): A PREVENT-AD OPTIONAL PILOT STUDY
"An intergenerational behavioural intervention to enhance physical activity in older adults at risk for Alzheimer's disease"

Principal Investigator: **Maiya R. Geddes, MD, FRCPC**
*Assistant Professor,
Department of Neurology and Neurosurgery, McGill University
*Associate Researcher,
McGill Centre for Research Studies in Aging (MCSA),
The Douglas Mental Health University Institute
CIUSSS de l'Ouest-de-l'île-de-Montréal
*Behavioral Neurologist and Clinician Scientist,
Montreal Neurological Institute-Hospital (The Neuro)
3801 University Street, Montreal, QC H3A 2B4
514-398-8751
maiya.geddes@mcgill.ca

Co-Investigator: **Judes Poirier Ph.D.,** Professor,
Department of Psychiatry, Douglas Hospital, McGill University
Sylvia Villeneuve Ph.D., Assistant Professor,
Department of Psychiatry, Douglas Hospital, McGill University
Arthur F. Kramer Ph.D., Professor,
Center for Cognitive and Brain Health, Northeastern University
Adrián Noriega de la Colina M.D. Ph.D.
Montreal Neurological Institute-Hospital, McGill University
Caitlin Walker, PhD Candidate,
Montreal Neurological Institute-Hospital, McGill University

Collaborators:

Jennifer Tremblay-Mercier M.Sc., Research Coordinator
The Douglas Mental Health University Institute, McGill University
Christine Déry M.Sc., Research Assistant
Montreal Neurological Institute-Hospital, McGill University
Meishan Ai B.Sc., Ph.D. Candidate, Psychology, Department of Health Sciences, Northeastern University
Nagashree Thovinakere B.Sc., graduate student, McGill University
Linda Li, Undergraduate student, McGill University
Sarah Elbaz, Medical Student, Université Laval
Helen Pallett-Wiesel, Graduate student, McGill University
Nicolas Lavoie, Medical student, Université Laval
Garance Barnoin, Undergraduate student, McGill University
Johanie Victoria Piché, Medical student, McGill University
Ying Wen, Medical Student, McGill University
Adelina Dobromir Angheluta, Medical student, McGill University
Ryan Kara, Medical student, McGill University

Source of Support: *PI Startup funding from Brain Canada/Alzheimer Society; National Institutes of Health (NIH) Roybal Award "Under Review"*

Executive Summary

Physical inactivity increases the risk for multiple chronic diseases, early mortality, and accelerated cognitive decline in aging adults. Interventions to enhance physical activity among older adults are needed to improve health outcomes and reduce the burden on healthcare systems. We propose a remotely administered behavioural intervention that uses social motivation manipulation, and self-transcendence messages to effectively enhance physical activity in older adults. This randomized controlled trial consists of daily messaging delivered via smart-phone over 4 weeks in 120 healthy but 'at risk' older adults over the age of 60 years from the PResymptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) cohort. Participants are randomly assigned to one of two groups: an intervention group, who are recruited with a child or grandchild (14 years or older) and receive socially motivating feedback, and an active control group, who are recruited without a family member. The primary outcome is the change in physical activity as measured by accelerometers following the intervention compared to a pre-intervention baseline. Recruitment takes place among current participants of the PREVENT-AD cohort as an optional sub-study. These participants have already undergone MRI and Alzheimer's disease biomarker assessment as part of the PREVENT-AD cohort. During the present sub-study, these participants will be assessed remotely using telephone/videoconference and computerized neuropsychological tests, computerized behavioural measures, and psychosocial surveys at baseline and after the intervention. Assessment of cognition, affect and fitness will serve as secondary outcome measures. Participants in each group will be offered the opportunity to participate in a cross-over second period of the study, to ensure that participants in the active control group have access to a potentially beneficial intervention and to serve as a longer-term follow-up of both groups. This study will assess the effectiveness of a novel behavioural intervention at enhancing physical activity in older adults and examine the neurobehavioural mechanisms underlying any such behavioural change.

1. Introduction

There is overwhelming evidence that increased exercise in older age improves cognitive, affective and physical well-being, and may prevent the progression of age-related illnesses [1]. Already, previous findings from the FINGER study, a large, long-term, randomized controlled trial suggests that multidomain interventions (targeting diet, exercise, cognitive training, vascular risk monitoring) could improve or maintain cognitive functioning in at-risk elderly people from the general population [2]. Nevertheless, despite the overwhelming health benefits of physical activity, many older adults are sedentary [3]. The Public Health Agency of Canada (PHAC) reports that on average adults spent 9.6 hours per day being sedentary [4]. The COVID-19 pandemic made it more difficult for older adults to stay physically active, as they were disproportionately impacted by the severity of the disease [5]. Isolation from other individuals including friends and family members further compounds the challenges to engage in physical activity [6]. Developing and understanding techniques that motivate older adults to engage in physical activity has the potential to impact a spectrum of health-related behaviours and to improve brain health and quality of life [7]. Motivational processes change across the lifespan [8]. Despite a decline in the neurobehavioral influence

of motivation on learning, older adults demonstrate relatively preserved reward sensitivity compared to younger adults [9].

Social rewards may be particularly salient for older adults and offer a promising avenue for physical activity engagement [10]. Social motivation constitutes an evolutionary adaptation encompassing a set of psychological dispositions and biological mechanisms that bias the individual to preferentially orient to the social world, to seek and take pleasure in social interactions, and to work to foster and maintain social bonds [11]. In younger adults, the presence of peers or friends has proven effective in motivating them to stay physically active [12]. In older adults, similar strategies seem to be effective; bringing a friend to group exercises, walking while talking with a friend, walking to a colleague's office rather than emailing, etc. [13]. Thus, there is reason to postulate that interventions that tap into these motivational processes would be effective in reducing time spent sedentary in older adults.

Self-transcendence convenes a change in an individual's mindset to focus on the well-being of others rather than self-interest [14]. Focusing on values and activities that transcend the self can allow people to see that their self-worth is not tied to a specific behaviour in question, and in turn become more receptive to subsequent, otherwise threatening health information. Health message interventions in older adults using self-transcendence priming were associated with increased activity in subregions of the ventromedial prefrontal cortex, implicated in self-related processing and positive valuation, which predicted later decreases in sedentary behaviour [14]. These findings suggest that having a positive self-transcendent mindset can increase behaviour change, in part by increasing neural receptivity to health messaging [14]. Moreover, health messaging is another potential way to bolster physical activity [15]. The framing of health messages matters. Therefore, in this study, we will use a social motivation manipulation combined with self-transcendence messaging to take advantage of both of these techniques to enhance physical activity in vulnerable older adults who have a family history of Alzheimer's disease, and thus, stand to benefit from a lifestyle change.

2. Objectives and Hypothesis

This remotely administered multidisciplinary pilot proposal focuses on examining the efficacy of factors that have shown promise in motivating sedentary older adults to become more physically active as well as to investigate changes in patterns of activation of the neural networks, as indexed by MRI and fMRI, that support these factors and changes in physical activity. Brain imaging data has already been collected as part of the PREVENT-AD longitudinal cohort. We will not acquire any new brain or biomarker data but rather capitalize the dataset on these participants that already exist.

Aim 1: To determine the efficacy of a novel motivational intervention to enhance physical activity in at-risk older adults. In a four-week two-arm randomized controlled trial with cognitively normal older adults at-risk for AD, we hypothesize that social motivation combined with positively-framed health messaging + home-based physical training will increase physical activity compared to positively-framed health messaging + home-based physical training. We will examine the extent to which any differential physical activity engendered in the two groups is maintained at the longer-term crossover baseline period post-intervention or active control. In addition, we will test the extent to which participants

at higher risk of AD differentially benefit from the intervention and changes in physical activity. The primary outcome will be objectively-measured physical activity, secondary outcomes will be cognitive performance and functional brain connectivity, and tertiary outcomes will be fitness, mood and quality of life.

Aim 2. To determine the individual differences in cognitive processes that moderate behavioural change in older adults. We hypothesize that individual differences in cognitive processes moderate behaviour change in older adults. Therefore, we will test the extent to which differences in adaptive decision-making (i.e., reward-effort computations) and dimensional measures of motivational traits (i.e., grit and growth mindset) moderate the effects of the intervention on change in physical activity. We will capture individual differences in motivation to exert effort for rewards using the Effort Expenditure for Rewards Task (EEfRT): This is an established computerized cognitive paradigm that maps onto the reward valuation/effort construct in the Research Domain Criteria (RDoC) framework. This approach will provide a novel, mechanistic understanding of how dimensional constructs of motivation influence adaptive decision-making and behavioural change.

Aim 3: To define brain markers that predict successful real-world behavioural change in aging. We will test the hypothesis that successful behavioural change (i.e., increased physical activity post-intervention versus baseline) is associated with enhanced activation of self-referential (i.e., ventromedial prefrontal cortex) and reward valuation (i.e., ventral striatum, ventral tegmental area) brain networks as indexed by task-based and resting-state fMRI. Acquisition of baseline brain imaging data will allow us to ask whether and what neuromarkers predict successful behavioural change as a function of the intervention.

The hypotheses that will be investigated in this study are:

(1) Social-Motivation combined with self-transcendence messaging will increase physical activity in older adults, compared to an active control condition.

(2) Enhanced brain network modularity at baseline will predict exercise-related executive function gains.

(3) Individual differences in structural and functional network connectivity at baseline will predict change in physical activity.

To investigate hypotheses 2 and 3, we will be using previously acquired brain imaging data from the PREVENT-AD cohort study. The overarching goals of this work are to identify and understand novel strategies to enhance physical activity in sedentary older adults and to characterize individual brain and neuropsychological differences that predict behavioural change. Our ultimate goal is to develop personalized behavioural interventions in older adults that tailor persuasive health-related messaging based on an individual's neurobehavioral profile.

We believe that our intervention will provide valuable, novel information about the efficacy of promising factors to enhance physical activity, and in turn cognitive and brain health, in

sedentary older adults as well as the functional brain changes and individual differences that support these potential changes in physical activity.

3. Method

3.1 Recruitment

3.1.1 Initial Contact

Older adult participants will be recruited through the PREVENT-AD cohort as an optional sub-study, by reaching out to potentially eligible participants by phone and email. Screening procedures will involve verbally screening potential participants over the phone. A staff member doing the screening will begin with an overview of the HABS project. The screener will then obtain verbal consent (see telephone script). The telephone script will ask questions concerning inclusion and exclusion criteria. The total time to administer all screening questions is approximately 40 minutes. The telephone screen will also assess the level of physical activity via self-reported physical activity. If eligibility is verified, a date and time will be scheduled for a virtual meeting between the participant and a researcher where the formal study consent will be signed. Those individuals that are deemed ineligible from the screening call will have their forms kept in a separate file on REDCap. This information will be used to quantify how many were ineligible from the screening call and the reasons for ineligibility.

The criteria will be assessed by one of the listed study personnel. No special expertise is required to evaluate screening responses. If a participant requires exclusion due to information received during a session, they will be contacted via telephone or email and informed that they have been excluded from further study, nevertheless remaining part of the PREVENT-AD cohort. The reason provided for their exclusion will be brief and will include a statement such as, "Based on the data collected in your last session, we will not require any further testing. As indicated in the beginning, participation depends on several factors and not all participants qualify for the entire study."

3.1.2 Consent Process for Participants

Participants' consent will be obtained remotely before they begin participating in research activities. The consent process will be administered by experimenters (i.e., research personnel described above). Individuals who agree to participate after the phone screen will receive a copy of the consent document in advance by email and will schedule a time to speak with an experimenter via videoconference. They will be asked to read, but not sign, the consent document before the phone call, and the experimenter will coordinate with the participant so they have enough time to read the document before the call. During the call, the experimenter will explain the study and answer any questions the participant has. If the participant wants to take part in the study, they will then sign the consent document electronically in the REDCap platform; this format is secure and easy for participants to use. The informed consent process will be completed while a researcher is videoconferencing with the participant and can answer any questions they may have. Participants will be made aware that their participation is completely voluntary, and they may quit the experiment at any time.

Participants in the intervention arm will be invited to participate in a social motivation manipulation involving a younger study partner. The intervention group will be asked to invite an interested younger child/grandchild 18 years and older but younger than 40 to join them at the time of consent. The social motivation intervention represents the younger generation family member dyad. The study partner will sign as well informed consent during session T0, follow the same timeline as their older relative, receiving feedback on their relative's accelerometer data. Study partners have a streamlined intervention whereby they do not undergo accelerometry testing and only have two videoconferenced sessions and one phone session. Study partners partake in the 4 weeks of daily messages and receive feedback on their relative's performance. The study partner will complete an overlapping, but briefer battery of pre and post compared to their older adult family members. Study partners will not undergo a remote physical assessment evaluation and will not be required to have physical or virtual contact with their older adult family members other than their regular interactions.

3.1.3 Consent process for minors aged 14 up to before 18 years old.

Younger study partners between the ages of 14 and up before their 18th birthday, will be required to provide remote written assent for their participation in the study by using a unique consent form and the remote written consent of their parent or legal guardian. This special group of intrafamilial study partners will be the grandchildren of the main participant younger than 18 years old. Older participants in the intervention group who do not have grandchildren will be assigned an extrafamilial study partner aged 18 years or older. Written assent from the minor participant and the written consent of their parent or legal guardian will be obtained during session T0. Contact will be through the main study participant who will provide the contact details for their younger study partner (grandchild or child). These study partners will follow the same timeline as their older relatives, receiving feedback on their relative's accelerometer data. Study partners have a streamlined intervention whereby they do not undergo accelerometry testing and only have two videoconferenced sessions and one phone session. Study partners partake in the 4 weeks of daily messages and receive feedback on their relative's performance. The study partner will complete an overlapping, but briefer battery of pre and post compared to their older adult family members. Study partners will not undergo a remote physical assessment evaluation and will not be required to have physical or virtual contact with their older adult family members other than their regular interactions.

**The study will recruit up to 120 younger study partners including individuals between 18-40 years old and between 14 and up to 18 years old.

3.2 Eligibility/ Inclusion Criteria

Participants will not be excluded based on sex, race, or ethnicity. If a participant is excluded for any reason, they will be immediately informed that they have not met all criteria and their participation will be discontinued. All interested participants will be selected to participate until the desired number (n = older adults) is reached. We recognize that women in this age group are over-represented relative to men and are also more likely to volunteer for health-related studies. However, we will attempt to have a diverse sample of participants across cultural, gender, language and educational factors in our sample. Participants will be

randomized to one of the two study conditions and be assigned a coded subject number using REDCap after signing the consent form. Study partners will be over the age of 1 year.

- Men and women of all ethnicities/races and socio-economic status, older than 60 years
- Adequate vision to complete the cognitive tasks
- Able to speak, read, and write English or French
- Ambulatory without a significant increase in pain or the assistance of walking devices
- No diagnosis of a neurological disease
- Wants to engage in more physical activity.
- Regular access to a computer with internet or a smartphone
- Having a child, grandchild older or friend aged 14 years or older that is considered 'close'.

3.3 Exclusion Criteria

- Current or previous formal diagnosis of a DSM-V Axis I or II disorder including Major Depression (not including postpartum depression or anxiety)
- History of major psychiatric illness including schizophrenia
- Current treatment for cancer – except non-melanoma skin cancer
- Neurological condition (MS, Parkinson's, Dementia, Stroke) or moderate to severe traumatic brain injury.
- Current alcohol or substance abuse
- Current treatment for congestive heart failure, angina, uncontrolled arrhythmia, DVT or other cardiovascular condition
- Myocardial infarction, coronary artery bypass grafting, angioplasty or other cardiac event in the six months before enrollment.
- Regular use of an assisted walking device or significant increase in pain when walking
- Use of any antipsychotic, anti-depressant, anti-anxiety, and ADD/ADHD medications, other than for sleep.
- Not fluent in English or French
- No regular access to a smartphone or computer with internet
- Involvement in conflicting research studies currently or recently

3.4. Participants ineligible due to physical activity criteria

Participants who do not want to increase their physical activity levels and are thus ineligible for the main study would have the option to join the study for the first 3 sessions up to before the 4-week intervention. This would allow for the acquisition of behavioural measures up to yellow visits in ineligible participants. The objective would be to understand physical activity as it relates to Alzheimer's disease risk and its related motivational factors. This piece of the study would follow the same parameters, cognitive measures, and questionnaires as the one collected for the main study for the first three sessions up to before the intervention window. Compensation would be provided accordingly.

3.5 Study Partner inclusion criteria

- Can be identified as child or grandchild of participant (biological or adopted), 14 years or older.
- Can be a young adult (18 years or older) who is not a relative of the main participant, in case a grandchild or child is not available.
- Stable on psychoactive medications for more than 6 months.

• In contact with the primary participant more than once per 12 months at baseline
• Lives anywhere accessible by mail in Canada if 18 years and older, or anywhere accessible by mail in Quebec if 14 years and older but younger than 18 years.
• Adequate vision to complete the cognitive tasks
• Able to speak, read, and write English or French
• No diagnosis of neurological disease or unstable health condition
• Regular access to a computer with internet or a smartphone

3.6 Study Partner exclusion criteria
• Not in contact with the primary participant more than once per 12 months at baseline

3.7 Extrafamilial study partners

Young adults (aged 18 to 40) will be recruited from the community to participate as extrafamilial study partners. These participants will be paired with an older adult participant who does not have a child or grandchild that can participate but is otherwise eligible. Young adults will be recruited through flyers posted around the McGill University campus as well as an advertisement posted on the Department of Psychology's SONA participant pool. Participants will receive either 2 SONA credits or $40 CAD for their participation. The study timeline for extrafamilial study partners will consist of one additional, remote visit approximately one week after the formal consent form is signed. This visit will consist of a 1 hour Zoom call with the older adult participant, the extrafamilial study partner, and a member of the research team.

The purpose of this visit will be to introduce the older adult to the younger study partner and provide the participants with an opportunity to get to know one another. This conversation will allow the extrafamilial study partner to create the personalized messages ("kudos") for the social messaging application. The younger study partner will be asked to lead the conversation and will be provided with a list of questions that they can ask in order to get to know the older adult. After the conversation, the older adult will be asked to log off the Zoom call and the younger study partner will be asked to provide the 30 personalized messages.

3.8. Financial compensation
Financial compensation will be offered as follows:

3.8.1. Intervention Group

Participant

Remote Meeting	**Pay**
Session 1	$20
Session 2	$20
Session 3	$20
Session 4	$20
Accelerometry Completion	$20
TOTALS	*$100 for all sessions and device returned*

Study partner

REMOTE Session	Pay
TOTALS	$40 for study completion

3.8.2. Control Group

Remote Meeting	Pay
Session 1	$20
Session 2	$20
Session 3	$20
Session 4	$20
Accelerometry Completion	$20
TOTALS	*$100 for all sessions and device returned*

3.8.3 Cross-over segment

3.8.3.a Crossed to Intervention Group

Participant

Remote Meeting	Pay
Session 1	$20
Session 2	$20
Session 3	$20
Session 4	$20
Accelerometry Completion	$20
TOTALS	*$100 for all sessions and device returned*

Study partner

REMOTE Session	Pay
TOTALS	$40 for study completion

3.8.3.b Crossed to Control Group

Remote Meeting	Pay
Session 1	$20
Session 2	$20
Session 3	$20
Session 4	$20
Accelerometry Completion	$20
TOTALS	*$100 for all sessions and device returned*

3.8.3.c Donation to the Alzheimer's Society

Based on the participant's physical activity performance and their pre-set goals (# of steps increase or amount of time increase being active) during the 4-week intervention period, a maximum amount of 3.00$ per week would be saved to be donated to the Alzheimer's society at the end of the intervention (up to 18.00$ for the whole intervention).

Week	**Donation**
Week 1	Up to 3.00$
Week 2	Up to 3.00$
Week 3	Up to 3.00$
Week 4	Up to 3.00$
Total Amount	*Up to 12$*

The 3.00$ will be saved for donation if the participant achieves 100% of their goal on a given week.

3.8.3.d Donation to the Alzheimer's Society of Montréal for the cross-over segment

The donation to the Alzheimer's Society of Montréal will follow the same principle than for the first segment of the study for those participants who cross into the intervention:

Week	**Donation**
Week 1	Up to 3.00$
Week 2	Up to 3.00$
Week 3	Up to 3.00$
Week 4	Up to 3.00$
Total Amount	*Up to 12$*

The 3.00$ will be saved for donation if the participant achieves 100% of their goal in a given week.

4. Methods/Assessments

4.1 Overview

In 120 sedentary and cognitively asymptomatic older adults (60 years and older) we will test whether a behavioural intervention combining social motivation, and self-transcendence messages decreases the amount of time participants are sedentary, as measured by accelerometry. We will use a stratified randomization scheme to ensure that half of the participants in each group will be randomized and stratified by their risk of developing Alzheimer's disease: to the social motivation + self-transcendence messaging (intervention) and the other half will be randomized to a daily activity monitoring group (active control). Participants will not be explicitly told to exercise as part of the study, but during the experiment they will receive messages that encourage walking or decreasing sedentary time. The primary measure of interest is decrease in sedentary behavior. All participants will be recruited from the PREVENT-AD cohort (STOP-AD Centre) at the Douglas Mental Health University Centre. Participants will be screened remotely by researchers affiliated with McGill University under the direction of Dr. Geddes.

4.2. Study design

The HABS study is a remote behavioural intervention that is conducted as a single-blinded randomized controlled trial. Recruited participants will be categorized as either high or low risk for Alzheimer's disease, in accordance with Aim 1 to determine the extent to which the behavioral intervention improves physical activity in at-risk older adults. Participant classification into high and low risk is based on their already known biomarker and cognitive status available from PREVENT-AD using a multimodal risk score. Note, that this does not involve collection of any new data and this data is not shared with participants as per the PREVENT-AD protocol. For participant classification into high risk, an individual's score is taken from a two-tier system of variables. The first tier involves variables where a positive result involves higher risk for Alzheimer's disease: Amyloid Tau Index (ATI) $\leq$1, and p-tau in cerebrospinal fluid, β-Amyloid, and Total tau in PET, or APOE-ε4/ε4 or ε4/ε3status. A single positive value in any of these variables classifies the participant into the higher risk group. The second tier involves variables that independently are not sufficient for higher risk classification but together with a second variable might indicate higher risk: Overall cognitive performance (i.e., Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]), episodic memory (i.e., Rey Auditory Verbal Learning Test [RAVLT]), hippocampal volume on MRI, APOE ε4/ε2 status, Framingham Risk Score, and history of depression or consumption of psychotropic medication. Any combination of two variables from this tier classifies the participant into the higher risk group. Participants that are not classified into the higher risk group either because they had negative results to all risk variables or because they had a positive score to only one risk variable from the second tier, will be randomized into the low-risk group. We expect that approximately 50% of our participants will be in the high-risk group. We are using stratified randomization to ensure that each higher risk participant will be equally distributed across the intervention and control groups. The participants in each risk group are randomized to either a social motivation group (intervention) or control with a ratio of 1:1. The stratified randomization scheme is prepared by the Harvard Catalyst Biostatistical Group using a permuted block method with random blocks [16]. The randomization scheme will be uploaded in the REDCap randomization module. At the end of the first study period, participants will be offered to participate in a follow-up to ascertain maintenance which will consist of a cross-over into the alternative arm to which they initially were randomized. The study consists of two 4-week study periods with at least a 6-week washout period in between. This trial is registered on clinicaltrials.gov with an identifier NCT04315363. This study received ethical approval from Northeastern University Institutional Review Board (IRB).

NOTE ON STUDY DESIGN AND SINGLE-BLINDING: It is important to note that in order maintain the single-blind nature of the study, participants will not be specifically told that the daily messages are the study intervention. Therefore, the consent form will simply mention that some participants may receive motivational messages, but will not elaborate further.

Hence, in terms of the cross-over design, it will be described as a long-term follow up in the ICF in order to maintain the single-blind and not bias the participants. A debriefing session will be held at the end of period 1 to explain to the participants that the motivational messages were the intervention and they will be offered to cross-over into the opposite arm. See section 5.6 for more information regarding the cross-over.

PERSONNEL:

All staff and personnel associated with screening, collecting data, and analyzing data will have been trained and will have undergone all necessary research modules for safety and research ethics. Dr. Geddes will meet with all staff on a regular basis to ensure that they are conducting research protocols appropriately. In addition, all staff who interact with participants are certified in Automatic External Defibrillator (AED) and CardioPulmonary Resuscitation (CPR). All staff who administer remote study sessions will be familiar with an emergency protocol (including calling emergency services) to prepare for the unlikely event that a participant has a medical emergency during a video or phone appointment.

RESEARCH ACTIVITIES:
After obtaining informed consent, participants will complete screening measures for anxiety, depression, and cognitive impairment. If they pass these screenings, they will be randomized into the intervention (social motivation + self-transcendence messaging or control group. After randomization, participants complete a baseline non-exercise cardiorespiratory fitness (CRF) estimation (using heart rate measurement), short virtual physical assessments involving walking and sitting-to-standing, and neuropsychological and behavioural assessment during the 'Consent Session' and at 'Time 1" (Figure 1).

5 Intervention

5.1 *Study timeline*

An illustration of the study timeline can be seen in Figure 1. Informed consent is obtained at the initial video-conferenced meeting. Each participant undergoes a baseline session (T1) one week before the beginning of the intervention. As a baseline, participants wear a wrist-worn accelerometer on their non-dominant hand to assess physical activity (see physical activity monitoring). Physical assessments will be administered at baseline. The accelerometer is worn for a week. The intervention lasts 4 weeks, during which participants receive daily intervention messages via email or phone. Participants are fitted with the accelerometers again for a one-week mid-intervention period. The post-intervention session (T3) is scheduled at the beginning of the last intervention week (week 4), during which participants repeat psychosocial surveys and neuropsychological tests. All sessions are administered remotely through online surveys and computer tasks (please see timeline document).

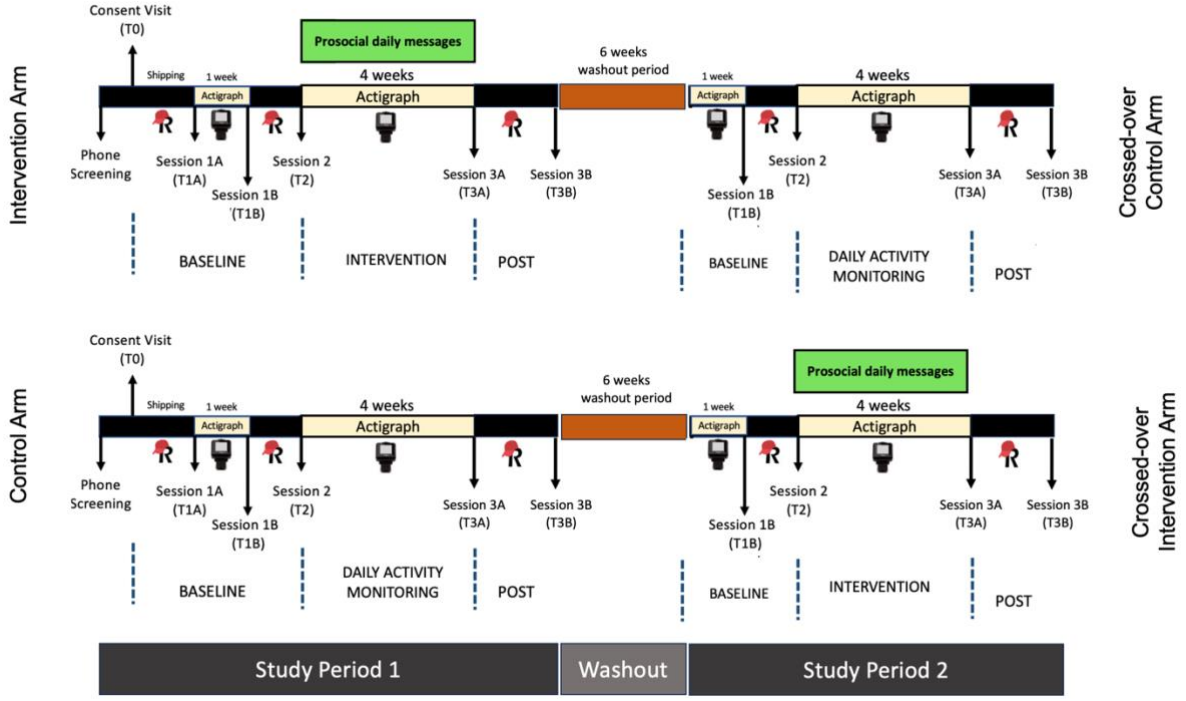

Figure 1. Main participant's timeline (2 arms, Intervention and Control) with Cross-over design.

5.2 *Social Motivation Intervention*

Participants in the intervention arm will be invited to participate in a social motivation manipulation involving a study partner. The same number of study participants will be recruited as the number of older adults in the study given that older adults in the active control group will be offered the opportunity to participate in the intervention after the washout period. The intervention group will be asked to invite an interested younger child/grandchild over the age of 14 years to join them at the time of consent. The social motivation intervention represents the younger generation family member dyad. These individuals will be either a child or a grandchild of the participant in this arm who is older than 14 years old but younger than 40. The study partner will sign as well informed consent, follow the same timeline as their older relative, receiving feedback on their relative's accelerometer data. The younger adult study partner will complete an overlapping, but briefer battery of pre and post assessments compared to their older adult family member. Study partners will not undergo a remote physical assessment evaluation. Minor participants aged 14 years to up before their 18 birthday need to provide written assent by a parent or legal guardian. All study partners will not be required to have physical or virtual contact with their older adult family members other than their regular interactions. Because of the nature of this intervention which involves adolescents, it minimal the risk for minors participating[a,b] and the potential benefits to their well-being of intergenerational social interactions.

[a]National Commission. Report and Recommendations: Research Involving Children. Washington, DC: U.S. Government Printing Office; 1977.
[b]Fernández C; Canadian Paediatric Society (CPS), Bioethics Committee Paediatr Child Health 2008;13(8):707-12
[c]Santini S, Tombolesi V, Baschiera B, Lamura G. Intergenerational Programs Involving Adolescents, Institutionalized Elderly, and Older Volunteers: Results from a Pilot Research-Action in Italy. Biomed Res Int. 2018;2018:4360305. Published 2018 Dec 5.

5.3 *Daily messaging*

The 4-week intervention consists of daily self-transcendence messages via email using the encrypted online software oTree, an open-source platform for implementing messaging surveys, which allows for accessibility via desktop or smartphone [17]. Unique, coded links are assigned to each participant at enrollment. Participants will be requested to: "For the next 30 seconds contemplate the warm feelings you have towards a loved one as vividly as you can. Think about a situation where the following wish comes true for your loved one: May you be well". Examples of daily self-transcendence prompts rotate among:

- May you be well
- May you be happy
- May you be safe
- May you be at ease
- May you be healthy

- May you be peaceful
- May you find wholeness
- May you be joyful

Each day if they reach their physical activity goal, the main participants will receive messages from a pre-set list of messages composed at the consent session by their study partners (see Annex A – time capsule). The participant will then rate their mood and confidence in implementing the health tips, the goal of which is to examine the changing in well-being and self-efficacy of physical activity throughout the intervention. During weeks 2 and 4, they also receive daily reminders to continue wearing their accelerometer. This daily message survey setup is displayed in Figure 2. The researcher's contact information is displayed on each survey page to enhance compliance. Participants' responses are tracked and those that do not complete the survey by a specified time of day are contacted the following day by research assistants to prevent technical failures.

In addition to self-transcendence health messages, participants in the intervention arm will receive feedback about their daily physical activity using the CentrePoint encrypted software package from Actigraph (https://actigraphcorp.com/cdh/). The CentrePoint data hub is a home-based communication gateway that securely transmits data captured by the Actigraph activity monitors to provide near real-time feedback to participants about daily physical activity.

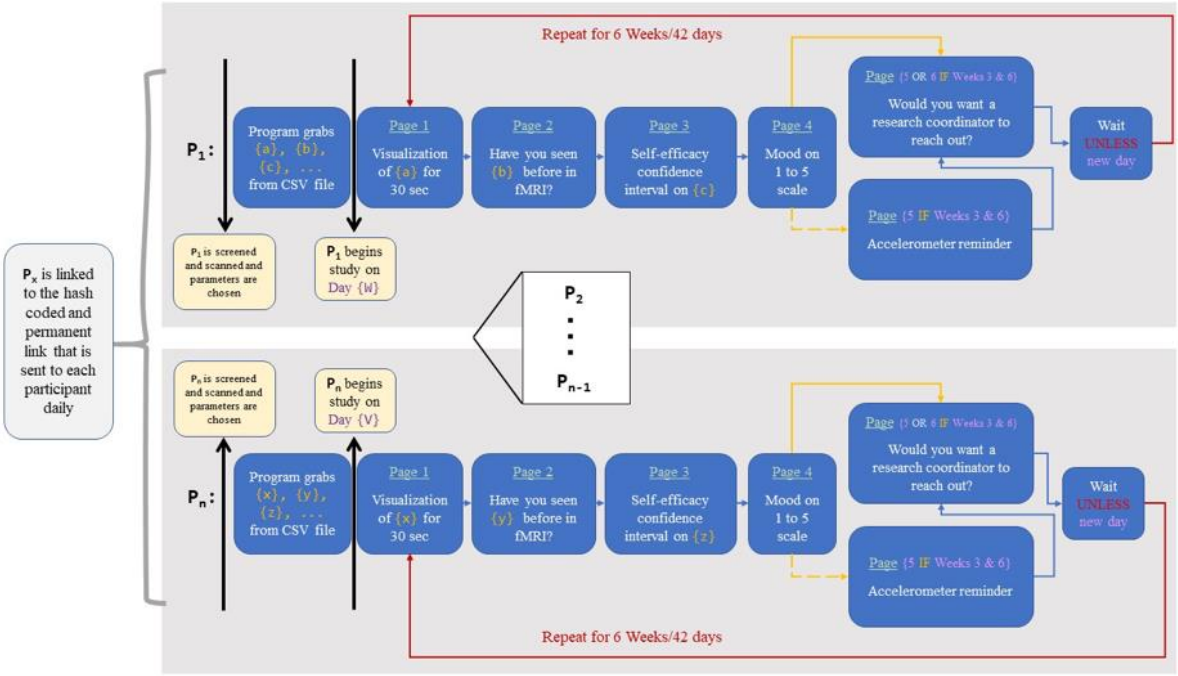

Figure 2. Messaging system setup and logic. Each participant (represented by $\mathbf{P_x}$, where **x** designates the participant number) receives their unique link. In that link, they follow a series of pages each day that contain their unique questions and parameters based on the inputted comma-separated values (CSV) file. The system does not initiate until the participant begins on their first day and then repeats for 28 days (4 weeks) for the duration of the daily messaging intervention. The process occurs synonymously for all other participants. Links that are not activated simply remain idle until a participant is assigned that link

5.4 Non-exercise cardiorespiratory fitness estimate

At baseline, participants will be asked to wear an accelerometer and have their cardiorespiratory fitness (CRF) estimated. The assessment of cardiorespiratory fitness (CRF) is associated with burdens of time, cost, risk and resources. To address this concern, we will take advantage of a non-exercise estimate of CRF. CRF will be estimated by a method developed by Jurca et al. (2005) [18] and validated by Mailey et al. (2010) [26]. The estimation uses a regression equation that includes age, sex, body mass index, resting heart rate, and self-reported physical activity. We will obtain a non-exercise CRF estimation before and four weeks after the intervention. To perform the CRF estimation, we will collect the resting heart rate after participants have rested quietly for ten minutes.

5.5 Neuropsychological Assessment

If participants pass this second screening, they will complete neuropsychological and behavioural inventories. We expect testing to take about 3 hours and will administer the assessments with breaks every ~40 minutes to reduce fatigue. They will complete behavioural inventories that capture individual differences in traits potentially predicting responsiveness to the intervention. These measures (listed in the attached spreadsheet) include validated questionnaires to assess factors like motivation for physical activity, self-efficacy for exercise, self-efficacy for walking, barriers to exercise, mood, conscientiousness and grit, growth mindset, loneliness, future time perspective, and purpose in life. Participants' educational attainment and total personal income levels will also be collected to create a measure of socioeconomic status, as described by Hartanto et al. (2019) [19]. These questionnaires will be administered through REDCap, a "secure, HIPAA-compliant, web-based application… housed in a secure local data center, behind the Tufts Medical Center firewall, and all web-based information is encrypted" (tuftsctsi.org/research-services/informatics/redcap-research-electronic-data-capture/).

Participants will also complete a cognitive battery (also listed in the attached spreadsheet) that examines important cognitive constructs that have been associated with changes in physical activity and aging including executive function (i.e., the Brief Test of Adult Cognition by Telephone [BTACT]), working memory (n-back, WAIS-IV Digit Span Forwards and Backwards), sustained attention and motor speed (WAIS-IV Coding test, simple reaction time), verbal fluency (Category and Phonemic Fluency tests), and episodic memory (Hopkins Verbal Learning Test – Revised (HVLT-R). Neuropsychological measures will be administered remotely via telephone encrypted videoconferencing (using HIPAA compliant Zoom software) and secure, coded platforms such as Test My Brain (testmybrain.org). Additional paradigms are described below:

The *Intrinsic Motivation Effort Expenditure for Rewards Task* (EEfRT), captures the construct of Reward Valuation and Effort. This multi-trial computerized task presents participants with a (variable) level of reward and a (variable) amount of work (effort) to win that reward. For each trial, the participant must accept or reject the proposal based on whether they think the reward is worth the effort. If they accept the trial, they have a 1/3 chance of then being asked to perform that work. The "work" is fast key presses on the left and right arrow keys, using the right-hand index and middle fingers. The amount of work is communicated using a vertical rectangle with a horizontal line through it at different heights; the higher the line, the more key presses are required. Participants are given visual feedback during the trial as the line is moved to the bottom and is progressively raised with each button press, with the goal of

raising the line up to its original height for that trial. Rewards come from three domains: monetary rewards (hypothetical money), social rewards (hypothetical time with loved ones), and intrinsic rewards from curiosity (the answers to trivia questions). There are 6 "levels" of reward in each of the three domains, and 5 levels of work.

The *Option Generation Task* [22] measures participants' fluency and ability to generate options for future behaviour. In each trial, the experimenter will present the participant with a hypothetical "open" (e.g., It's a rainy and cold Sunday. What could you do?) or "problem-solving" situations (e.g., You are in a foreign city and you are lost. What could you do?).

The participant will be given 2 minutes to generate options for action. They will be encouraged to describe each option briefly, mainly using keywords.

The *Delay Discounting Task* is a measure of temporal discounting; the tendency for people to prefer smaller, immediate monetary rewards over larger, delayed rewards. Participants will respond to a series of 27 questions that ask them to choose between a smaller, immediate reward (e.g., $25 today) versus a larger, later reward (e.g., $35 in 25 days). The 27 items are divided into three groups according to the size of the larger amount (small, medium, or large). Modeling techniques are used to fit the function that relates time to discounting. The main dependent measure of interest is the steepness of the discounting curve such that a more steeply declining curve represents a tendency to devalue rewards as they become more temporally remote (Science of Behavior Change, Columbia University).

The *Future Time Perspective Task* [24, 25] assesses the length of individuals' views of the future, where more limited views of the future have been linked with pathological impulsive behavior like drug use. Participants will be asked to generate a list of five future life events and respond orally, without a time limit. After the events are generated, the experimenter will ask the participant to estimate how far into the future each event might occur. The two dependent measures for this task are the 'extension', which is the maximum length of time generated by each subject, and the mean future time period for all five items.

In the *simple reaction time task*, the participant will be presented with a blank white screen and asked to press a button as quickly as possible each time a large, black "X" appears. The "X" will always appear in the same spot in the center of the screen. This measures the participant's reaction times.

In summary, in order to understand the variability in participants' responses to persuasive messaging, we will explore a rich dataset of individual differences across behavioural traits and cognitive, structural, and functional brain measures. All brain imaging and biomarkers have been already collected under the auspices of the ongoing PREVENT-AD study, of which the PI, Dr. Geddes, is a formal collaborator. Some of these tests will be administered verbally by adapting in-person, pen and paper versions to phone calls or video conferencing formats. Certain phone-based tasks require researchers to collect audio recordings of participant responses for timing and other scoring purposes. Online replacement tests will be administered using TestMyBrain.org and Pavlovia.org.

TestMyBrain was developed by Dr. Laura Germine and colleagues in 2008 and is updated continuously. TMB provides online alternatives to classic pen-and-paper neuropsychological assessment tools and has normative data from thousands of online test subjects aged 12 to 90. TMB only provides tests that have been validated online and shown to be comparable to hard-copy versions. The TMB Neuropsychology Toolkit follows HIPAA regulations and does not collect personal identifiable data or demographic information. They retain test performance data for quality assurance and temporarily store access information (IP address, access URL, timestamp, and user agent) for 14 days to help prevent or identify security breaches or other fraudulent behaviour.

Pavlovia was created by John Pierce and colleagues at the University of Nottingham and is now run by Open Science Tools LTD. It is fully GDPR, or General Data Protection Regulation, compliant. The GDPR concerns data protection and privacy in the European Union and the European Economic Area. Source: https://pavlovia.org/docs/home/ethics

Participants will be assessed remotely with accelerometers and have their cardiorespiratory status estimated. The estimation uses a regression equation that includes age, sex, body mass index, and resting heart rate. We will obtain a non-exercise CRF estimation before and after the four-week intervention. To perform the CRF estimation, which will be remote, we will ask participants to report their supine resting heart rate after they have rested quietly for ten minutes. Participants will also complete a remote physical assessment focused on their basic walking speed, their ability to transition repeatedly from sitting to standing, and their balance.

Accelerometers, chargers, and related materials will be sent to participants through the mail after the consent meeting and will be returned after the end of the first study period. Accelerometry data will be recorded during wakefulness and sleep, with the exception of bathing or swimming, for the week between T1 and T2 (before the intervention begins; i.e., baseline), for two separate weeks during the 4-week intervention (with additional days during this timeframe for any participant who does not wear the devices consistently during the original period). This will characterize changes in physical activity from baseline and maintenance. It will be assessed using two accelerometers worn simultaneously. The first is a wrist-worn tri-axial accelerometer (ActiGraph GT3X Link, Pensacola, FL). This accelerometry data will be downloaded in 60-second epochs (ActiLife software, ActiGraph, Pensacola, FL) and will be screened for wear time using standard methods [26]. The second device is a tri-axial accelerometer and inclinometer and will be worn on the thigh using an adhesive.

Physical activity will be measured with an ActiGraph accelerometer model GT9X Link (ActiGraph LLC, Pensacola, FL). The ActiGraph GT9X Link is a small (3.5 x 3.5 x 1 cm) and light (14 g) device that measures acceleration in three planes: vertical, anteroposterior and mediolateral. Participants will wear the device on their wrists 24 hours a day to improve compliance. The 24-hour protocol has resulted in greater compliance over waking time wear protocol [27]. Participants will be instructed to take the device off for swimming, showering and bathing. Data from this device will be synced with the CentrePoint app (HIPAA compliant, also through ActiGraph) on the participant's phone or computer. Raw data will be reduced and processed using ActiLife software (http://www.actigraphcorp.com). Participants will fill in sleep and activity logs.

The physical assessment administered at T1, T3, and T4 will involve the 2-minute walking test adapted from the NIH Motor Battery, a 20-second sitting-to-standing test (also used in the CDC's STEADI toolbox), and observations of balance while doing everyday activities like putting on shoes. We will record these physical assessments using Zoom. These are sensitive measures often used with older adults that reflect their fitness, especially their lower-body strength. Choosing these sensitive measures makes it more likely that we will be able to detect fitness changes post-test if the intervention results in the behaviour changes we expect.

5.6. Cross-over design

In order to ensure that participants in the active control group have the opportunity to enroll in the intervention, a cross over period 2 is in place. Enrolled participants who complete the first period of the study will be offered, the possibility to participate in a follow-up assessment to ascertain a maintenance effect. While the primary endpoint is at the completion of period 1 for all participants, an identical schedule of acquisition is implemented for period 2. Both groups are offered the opportunity to crossover into the other arm of the study (intervention to active control; active control to intervention). This follow-up will consist in a cross-over to the opposite study arm to which they were initially randomized. The study will include two periods of 4 weeks separated by a washout period of at least 6 weeks.

5.6. Study partner

The study partner (grandchild, child or friend) of the main participant will undergo a shorter cognitive battery and questionnaires. The timeline for the study partner's participation is provided in Figure 3. Their participation will involve two main sessions T1s (pre) and T2s (post). Each session will take between 1.5-2 hours. During the 4-week intervention, each day if they reach their physical activity goal, the main participants will receive self-transcendence messages from a pre-set list of messages composed at the consent session with the study partner. The study partners will receive feedback on their relative's accelerometer performance.

Study partner's participation is limited to the study period where the main participant is taking part in the intervention arm. This means the study partner will only be involved in one of the study periods. If the main participant starts with the intervention arm, the study partner will only be part of study period 1 (Figure 1), and end its participation before the washout period. If the main participant starts in the control arm, the study partner's role will start after the washout period, i.e. during study period 2, when the main participant crosses over to the intervention arm.

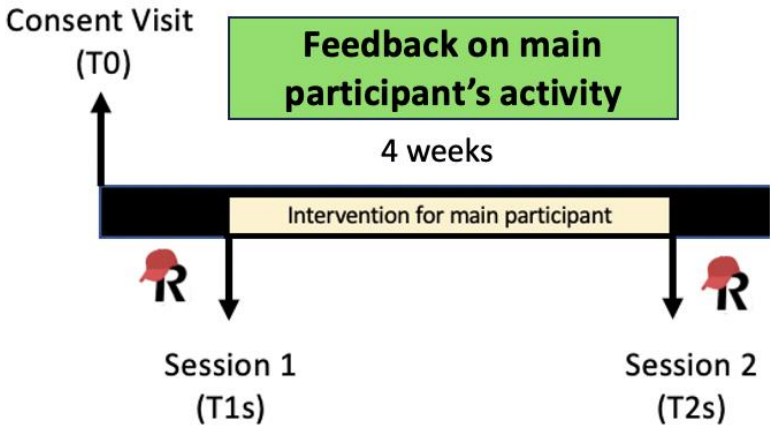

Figure 3. Timeline study participants (Intervention Arm in Periods 1 and 2).

6a. Data management

All research data are coded and only the research coordinator has access to identifiable information stored in a secure location. Data are stored electronically on password-protected servers behind university-protected firewalls. Data collected are stored in one of three ways; (1) MRI data (including tasks) and physical activity monitoring data are extracted from their respective software packages and uploaded directly to a secure data storage environment at a high-performance computing facility. (2) All pen-and-paper psychosocial and neuropsychological assessments are scored and uploaded to REDCap [28]. Computerized psychosocial assessments are collected directly in REDCap and computerized neuropsychological assessments are uploaded to REDCap [29]. The oTree library is used to distribute the daily intervention messages and collect survey data. This system runs on a Heroku server, a cloud-based system that sends and receives hash-encrypted links. Collected anonymized data are stored on the messaging site behind an administrative login on the Heroku server.

6b Data analysis

Outcome measures outside of the neuropsychological assessment battery are as follows:

Outcome measure	Type	Timeframe	Brief description
Total step count (average steps/day)	**Primary**	Week 0 (baseline); Week 2; Week 4.	This metric quantifies the change in the average number of steps taken each day, from the baseline, Week 2, and Week 4. It is a marker of change in habitual ambulatory activity.
Sedentary behavior (average min/day)	**Primary**	Week 0 (baseline); Week 2; Week 4.	This metric quantifies the change in the average amount of time spent sedentary each day, from the baseline, Week

			2, and Week 4. It is a marker of time spent inactive.
Moderate-vigorous activity (average min/day)	Secondary	Week 0 (baseline); Week 2; Week 4.	This metric quantifies the change in the average amount of time spent engaged in moderate-to-vigorous physical activity each day, from the baseline, Week 2, and Week 4. It is a marker of physical activity.
Walking Cadence	Secondary	Week 0 (baseline); Week 2; Week 4	This metric reflects the participant's average steps per minute. We will examine change from baseline over the course of the intervention.
Walking Bouts	Secondary	Week 0 (baseline); Week 2; Week 4	This measures the number of 'bouts' of physical activity (in our case, steps). We will have two counts: the number of 5+ minute bouts and the number of 10+ minute bouts of walking. We will examine changes from baseline over the course of the intervention.

A spreadsheet holding the list of neuropsychological assessments to be used, with brief descriptions, is attached. They will be administered at T1 (Week 0), T2 (Week 1), and T3 (Week 4).

To test our main hypothesis that social motivation + self-transcendence messaging + home-based physical training will produce the largest increase in physical activity over the course of the 4-week intervention compared to the active control, we will perform repeated measures ANCOVAs (with group as a between-subject factor and pre-post session as a within-subject factor). This hypothesis will be examined by analyzing total number of steps and percent time sedentary. We will analyze structural/functional MRI connectivity to test the hypothesis that increased physical activity following the intervention is associated with enhanced brain connectivity between brain regions in reward valuation (i.e., ventral tegmental area and ventral striatum) and social processing (vmPFC). We will conduct seed-based functional connectivity analyses using methods as in our prior research [9, 29-31]. To mitigate the influence of motion, we will identify and address artifactual motion outliers in data modeling, and employ quality assurance software to mitigate head motion artifacts and physiological aliasing (https://www.nitrc.org/projects/artifact_detect). We will control for the effects of demographic variables (e.g., age, sex, education, diet, mood, socioeconomic status, alcohol, vascular risk factors and sleep). We apply a whole-brain height threshold of $p < 0.001$ (T = 3.24) and false discovery rate cluster threshold of $p < 0.05$. We will examine brain modularity, which indexes the segregation between networks, and has previously been shown to predict cognitive gains after a physical exercise intervention [20]. In addition to these hypothesis-driven analyses, we will perform an agnostic, data driven multi-voxel pattern analysis of resting-state data using an approach published by our collaborator [21].

After compiling all data across the 3 different data servers, data will be checked for completeness and correctness using frequency distributions (for missing data and out-of-range A B values). Group differences at baseline are examined for variables including demographic factors (i.e., age, sex, educational level, socioeconomic status, culture), baseline sedentary time, self-report sitting time, and estimated fitness, in order to detect potential confounding factors. For the primary hypothesis that social motivation + self-transcendence messages decrease sedentary time more than an active control, all outcome measures about sedentary behaviour are first quantified using available software. Changes in sedentary behaviour (% daily sitting and lying time, minutes/per day in physical activity, count of steps) over time (3-time points) are analyzed using linear mixed effect models to account for the correlated data and likely heterogeneous variability.

Non-linear changes across 3-time points are also examined by including quadratic effects. These models will include a random intercept and slope to account for subject-specific changes as well as a group (2) x time (3) interaction fixed effect. This allows for modelling of the effect of our intervention as a function of both groups and time as well as accounting for potentially confounding covariates. All model assumptions will be tested both visually and formally and associations between covariates will be assessed to protect against multicollinearity.

Analyses on the resting state and task-based fMRI analyses are considered secondary. Briefly they will be modeled using the general linear model approach. First-level analyses will include all necessary nuisance regressors to minimize motion artifacts influence, spatial smoothing kernel and high pass filtering, as well as physiological aliasing for the low-frequency fluctuations in resting state data. To answer questions about the intervention effect and prediction of behavioural change, both a priori ROI seed-based analyses of functional connectivity are performed as well as data-driven whole-brain multi-voxel pattern analysis, modularity analyses and graph theory per several previous publications using data-driven approaches to predict clinical outcomes. Besides the primary outcomes, adherence and drop-outs are also included in the prediction model as outcome variables, to examine what individual characteristics affect participation in the current intervention. Robust-prediction models of MRI data and psychosocial measures will be generated using cross-validation methods to improve the generalization of the results.

Selection bias will also be considered in our study by comparing characteristics between the source population (i.e., PREVENT-AD participants) and the study sample. For eligible participants invited to participate in the study, we will document the proportion of those who decline and agree to participate. We will compare demographic information (age, sex, education, ethnicity, socioeconomic status, smoking status, and self-reported physical activity) between those who agree and those who refuse to participate using t-tests and chi-square tests of independence. Multivariate logistic regression models will be used to determine whether these characteristics are associated with acceptance relative to refusal to participate in the study.

7. Data confidentiality and protection

To reduce the risk of breach of confidentiality we will separate all information obtained during the screening period from identifying documents. All research data will be anonymized. These documents will be stored in a separate location from the data and the screening information on REDCap, in a project file to which only lab personnel have access. Data that is saved electronically (computer system) is protected by the REDCap firewalls. During data collection from participants, staff will converse with participants and have knowledge of names, but will be encouraged to maintain a first-name basis whenever possible. All data will be blinded and only used in aggregate to understand physical activity effects on the brain and cognition.

We will ensure participant confidentiality by using PREVENT-AD's coding for all participants' data according to their numbering system and separating it from the informed consent. All informed consent documents and data files pertaining to subject data information will be kept in encrypted, password-protected files on an encrypted, password-protected flash drive that only researchers involved in the project will have access to. Multiple levels of password protection (e.g., record, file, directory, server, and computer levels) are employed to ensure data security. All personnel involved in the study will be approved through the IRB and agree to protect the security and confidentiality of identifiable information. All data pertaining to the individual will be stripped of all identifying information. Paper copies of data will be destroyed 7 years from the date of study completion. Trial results will be uploaded to *Clinicaltrials.gov* in compliance with the NIH standards of reporting.

8. Incidental findings

If any study results are revealing a direct implication of the health and safety of the participant (i.e. requiring immediate medical intervention or in the near future), the incidental findings will be transmitted to the physician of the participant indicated on the informed consent form. In cases where the physician is not reachable or not indicated on the informed consent form, the clinical staff of the Douglas Hospital will inform the participant as soon as possible. This procedure will be followed for all participants whether or not they wish to be contacted for less serious incidental findings.

9. Risks

The procedures, techniques, equipment, and measures to be used in the proposed study are commonly used in educational and research settings involving human subjects, and are not new, untested, or of questionable safety. Experimenters are aware of the potential for serious adverse events to occur with any type of moderate-intensity exercise, but such risks are considered minimal in this population. In addition, the primary focus of this study is the decrease in sedentary behavior and an increase in walking rather than moderate to vigorous exercise. There is a risk of physical injury during exercise, particularly if participants have little to no previous experience. Fatigue and muscle soreness may also occur in participants who do not normally engage in physical activity. Exercise is associated with a very small risk of serious medical complications including heart attack and sudden death, although this risk is particularly small in healthy older adults. Lastly, protocols currently exist to respond to any adverse events by contacting emergency response personnel and facilitating their arrival to the correct rooms (if the event occurs at the Center).

Participants will have contact information for study personnel should they have an unexpected adverse effect or question. The daily health messages contain information on how to contact study personnel if needed. Participants also receive a recruitment packet detailing contact information for study personnel to avoid technical failure (e.g., with accelerometers). We will send biannual safety reports to an independent safety officer, Dr. Etienne de Villers-Sidani, a neurologist and neuropsychologist who is not involved in the study. If an unexpected adverse event arises, the study team will alert the PI, Dr. Geddes and Dr. Geddes will inform Dr. Etienne de Villers-Sidani. The PI will be made aware of any adverse outcomes. All research personnel will be trained in good clinical practice ethics modules.

Access to private health information

There is a potential risk of breach of confidentiality that is inherent in all research protocols. There is a possibility that if research data were to become generally known, this knowledge could potentially impact a subject's future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or in paternity suits or stigmatization.

Exercise

There are several common risks associated with exercise participation including injury to muscles or joints, especially when initiating an exercise program after a period of being sedentary. Further, there is a minor risk of dehydration or heat exhaustion. More commonly, there is a risk of falling. Based on our considerable experience in walking and balance-based research assessments and interventions in adults, many of whom are much older than the cohort anticipated for enrollment into this study, we are confident that this risk is rare, meaning that it will occur in less than .001% (less than 1 out of 100000) of people in the otherwise healthy adults targeted for this study. This risk will be minimized as we are focusing on walking and reductions in sedentary behaviour rather than exercise training. Adverse or unstable cardiovascular or pulmonary response to exercise, including disorders of heart rhythm, heart attack, stroke, or sudden death will be minimized, because assessment of vital signs and history of heart disease are included in our screening procedures, and only those adults with satisfactory results as detailed in our eligibility criteria will be allowed to participate in experimental procedures for this study. As such, we anticipate that this risk is rare. According to American College of Sports Medicine (ACSM), guidelines published in 2000, the risk of myocardial infarction (MI) in symptomatic (categorized with males and females having ventricular arrhythmias) and asymptomatic (without any signs or symptoms indicative of ischemic heart disease) individuals during exercise is less than 0.04%. The risk of death in the same population is less than or equal to 0.01%, and the risk of needing hospitalization (including acute heart attack and/or serious arrhythmia) is less than or equal to 0.2%. The risk of cardiovascular complications occurring during exercise is rare (occurs in less than 1% of people). A retrospective survey by the YMCA revealed 1 death and 1 cardiac arrest per 2,897,057 and 2,253,267 person-hours. To minimize the risk, we are using a *non-exercise estimation of cardiorespiratory fitness* that requires BMI and heart rate measurement only.

Cognitive assessment and questionnaires

Some inconvenience and/or anxiety may occur due to time required to complete formal rating scales and questionnaires. The cognitive assessments impose some risk of emotional discomfort. Fatigue is associated with performing the cognitive tasks. The Geriatric

Depression Scale and the Geriatric Anxiety Inventory may warrant a follow-up if the subject receives a clinically significant score on any of these items (e.g., >5 on the GDS). These items will be scored immediately after completion by the subject.

ActiGraph physical activity monitor

Participants may experience red skin or discomfort from wearing the device around the waist wrist too tightly or for an extended period of time.

PERSONNEL:

All staff and personnel associated with screening, collecting data, and analyzing data will have been trained in their laboratory and will have undergone all necessary research modules for safety and research ethics. Dr. Geddes will meet with all staff on a regular basis to ensure that they are conducting research protocols appropriately.

Regarding use of the physical activity monitoring devices, participants will be guided through the use of the devices at T1 and will be reminded repeatedly throughout the study. We will help participants through the fitting process of the device and alert them to the sound the device will make when it is properly adjusted and ready to collect data. We will ensure that participants understand how the device works and how to correctly wear it to avoid any discomfort or incorrect usage. We will also instruct participants to notify us if any discomfort occurs. If any discomfort does arise as a result of wearing either of the physical activity monitoring devices, we will instruct participants to discontinue the use of the device.

Cognitive assessments: To alleviate any fatigue that may occur, participants are offered breaks during testing periods. They will also be provided with a referral for psychiatric consultation upon request or if their scores on the GDS and GAI are clinically significant, according to each evaluation's scoring guide. Any person scoring highly on the depression, anxiety, or cognitive impairment items will be referred back to their PCP for consultation.

10. End of Study

There is the potential for direct benefit to participants randomized to the social motivation + self-transcendence health messaging arm of the study. Participants may experience direct benefits from participation such as improved cognition, mood, quality of life, physical fitness or decreased sedentary behaviour as a result of participating in the behavioural intervention over 3 months. There may be a reduction in central adiposity and cardiovascular benefits. In addition, we are hoping that participants will maintain reductions in sedentary behaviour beyond the completion of the study. The findings of this study provide information regarding the effect of simple and cost-effective behavioural intervention in reducing sedentary behaviour and improving brain health in a population at risk for cognitive decay. As such, the dissemination of this information stands to improve public health.

11. Transfer of Knowledge

As part of the goals of this study, we intend to publish the results of these trials through scientific articles engaging in open science platforms, as well as through scientific conferences both locally and internationally. We believe that this intervention could be the first step

towards behavioural counselling with a precision medicine goal. This could potentially be a feasible way how to positively influence people's behaviour, especially patients at risk. Furthermore, positive results could potentially be translated into providing the active control group of this trial with the actual intervention. Moreover, if demonstrated that the intervention is successful in fulfilling its goals, we intend to offer it to a wider group of older adults, as we consider it a cheap, scalable, and effective way of motivating physical activity in sedentary older adults.

12. References:

[1] J.A. Harvey, S.F.M. Chastin, D.A. Skelton, Prevalence of Sedentary Behavior in Older Adults: A Systematic Review, International Journal of Environmental Research and Public Health. 10 (2013) 6645–6661. https://doi.org/10.3390/ijerph10126645.

[2] T. Ngandu, J. Lehtisalo, A. Solomon, E. Levälahti, S. Ahtiluoto, R. Antikainen, L. Bäckman, T. Hänninen, A. Jula, T. Laatikainen, J. Lindström, F. Mangialasche, T. Paajanen, S. Pajala, M. Peltonen, R. Rauramaa, A. Stigsdotter-Neely, T. Strandberg, J. Tuomilehto, H. Soininen, M. Kivipelto, A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. (2015). DOI: 10.1016/S0140-6736(15)60461-5.

[3] M.S. Tremblay, S. Aubert, J.D. Barnes, T.J. Saunders, V. Carson, A.E. Latimer-Cheung, S.F.M. Chastin, T.M. Altenburg, M.J.M. Chinapaw, T.M. Altenburg, S. Aminian, L. Arundell, A.J. Atkin, S. Aubert, J. Barnes, B. Barone Gibbs, R. Bassett-Gunter, K. Belanger, S. Biddle, A. Biswas, V. Carson, J.-P. Chaput, S. Chastin, J. Chau, M. ChinAPaw, R. Colley, T. Coppinger, C. Craven, C. Cristi-Montero, D. de Assis Teles Santos, B. del Pozo Cruz, J. del Pozo-Cruz, P. Dempsey, R.F. do Carmo Santos Gonçalves, U. Ekelund, L. Ellingson, V. Ezeugwu, C. Fitzsimons, A. Florez-Pregonero, C.P. Friel, A. Fröberg, L. Giangregorio, L. Godin, K. Gunnell, S. Halloway, T. Hinkley, J. Hnatiuk, P. Husu, M. Kadir, L.G. Karagounis, A. Koster, J. Lakerveld, M. Lamb, R. Larouche, A. Latimer-Cheung, A.G. LeBlanc, E.-Y. Lee, P. Lee, L. Lopes, T. Manns, T. Manyanga, K. Martin Ginis, J. McVeigh, J. Meneguci, C. Moreira, E. Murtagh, F. Patterson, D. Rodrigues Pereira da Silva, A.J. Pesola, N. Peterson, C. Pettitt, L. Pilutti, S. Pinto Pereira, V. Poitras, S. Prince, A. Rathod, F. Rivière, S. Rosenkranz, F. Routhier, R. Santos, T. Saunders, B. Smith, O. Theou, J. Tomasone, M. Tremblay, P. Tucker, R. Umstattd Meyer, H. van der Ploeg, T. Villalobos, T. Viren, B. Wallmann-Sperlich, K. Wijndaele, R. Wondergem, on behalf of SBRN Terminology Consensus Project Participants, Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project process and outcome, Int J Behav Nutr Phys Act. 14 (2017) 75. https://doi.org/10.1186/s12966-017-0525-8.

[4] A. Biswas, P.I. Oh, G.E. Faulkner, R.R. Bajaj, M.A. Silver, M.S. Mitchell, D.A. Alter, Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis, Ann Intern Med. 162 (2015) 123. https://doi.org/10.7326/M14-1651.

[5] U. Ekelund, J. Steene-Johannessen, W.J. Brown, M.W. Fagerland, N. Owen, K.E. Powell, A. Bauman, I.-M. Lee, Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women, The Lancet. 388 (2016) 1302–1310. https://doi.org/10.1016/S0140-6736(16)30370-1.

[6] R.S. Falck, J.C. Davis, T. Liu-Ambrose, What is the association between sedentary behaviour and cognitive function? A systematic review, Br J Sports Med. 51 (2017) 800–811. https://doi.org/10.1136/bjsports-2015-095551.

[7] D.E. Rosenberg, J. Bellettiere, P.A. Gardiner, V.N. Villarreal, K. Crist, J. Kerr, Independent Associations Between Sedentary Behaviors and Mental, Cognitive, Physical, and Functional Health Among Older Adults in Retirement Communities, J Gerontol A Biol Sci Med Sci. 71 (2016) 78–83. https://doi.org/10.1093/gerona/glv103.

[8] D. Ding, K.D. Lawson, T.L. Kolbe-Alexander, E.A. Finkelstein, P.T. Katzmarzyk, W. van Mechelen, M.

Pratt, The economic burden of physical inactivity: a global analysis of major non-communicable diseases, The Lancet. 388 (2016) 1311–1324. https://doi.org/10.1016/S0140-6736(16)30383-X.

[9] M.R. Geddes, A.T. Mattfeld, C. de Los Angeles, A. Keshavan, J.D.E. Gabrieli, Human aging reduces the neurobehavioral influence of motivation on episodic memory. (2018) May 1;171:296-310. doi: 10.1016/j.neuroimage.2017.12.053.

[10] E.B. Falk, M.B. O'Donnell, C.N. Cascio, F. Tinney, Y. Kang, M.D. Lieberman, S.E. Taylor, L. An, K. Resnicow, V.J. Strecher, Self-affirmation alters the brain's response to health messages and subsequent behavior change, PNAS. 112 (2015) 1977–1982. https://doi.org/10.1073/pnas.1500247112.

[11] C. Chevallier, G. Kohls, V. Troiani, E.S. Brodkin, R.T. Schultz, The Social Motivation Theory of Autism. 2012 Mar 17. doi: 10.1016/j.tics.2012.02.007.

[12] S.J. Salvy, J.N. Roemmich, J.C. Bowker, N.D. Romero, P.J. Stadler, L.H. Epstein, Effect of peers and friends on youth physical activity and motivation to be physically active. (2009) Mar;34(2):217-25. doi: 10.1093/jpepsy/jsn071.

[13] M.E. Lachman, L. Lipsitz, J. Lubben, C. Castaneda-Sceppa, A.M. Jette, When Adults Don't Exercise: Behavioral Strategies to Increase Physical Activity in Sedentary Middle-Aged and Older Adults. (2018) Jan; 2(1)igy007. doi: 10.1093/geroni/igy007

[14] Kang Y, Cooper N, Pandey P, Scholz C, O'Donnell MB, Lieberman MD, Taylor SE, Strecher VJ, Dal Cin S, Konrath S, Polk TA, Resnicow K, An L, Falk EB. Effects of self-transcendence on neural responses to persuasive messages and health behavior change. Proc Natl Acad Sci U S A. 2018 Oct 2;115(40):9974-9979. doi: 10.1073/pnas.1805573115. Epub 2018 Sep 17. PMID: 30224461; PMCID: PMC6176572.

[15] Falk EB, O'Donnell MB, Cascio CN, Tinney F, Kang Y, Lieberman MD, Taylor SE, An L, Resnicow K, Strecher VJ. Self-affirmation alters the brain's response to health messages and subsequent behavior change. Proc Natl Acad Sci U S A. 2015 Feb 17;112(7):1977-82. doi: 10.1073/pnas.1500247112. Epub 2015 Feb 2. PMID: 25646442; PMCID: PMC4343089.

[16] A.H. Gutchess, E.A. Kensinger, D.L. Schacter, Aging, self-referencing, and medial prefrontal cortex, Social Neuroscience. 2 (2007) 117–133. https://doi.org/10.1080/17470910701399029.

[17] Pocock S. Clinical Trials: A Practical Approach. New York: John Wiley; 1984

[18] P.M. Grant, C.G. Ryan, W.W. Tigbe, M.H. Granat, The validation of a novel activity monitor in the measurement of posture and motion during everyday activities, Br J Sports Med. 40 (2006) 992–997. https://doi.org/10.1136/bjsm.2006.030262.

[19] R. Jurca, A.S. Jackson, M.J. LaMonte, J.R. Morrow, S.N. Blair, N.J. Wareham, W.L. Haskell, W. van Mechelen, T.S. Church, J.M. Jakicic, R. Laukkanen, Assessing Cardiorespiratory Fitness Without Performing Exercise Testing, American Journal of Preventive Medicine. 29 (2005) 185–193. https://doi.org/10.1016/j.amepre.2005.06.004.

[20] E.L. Mailey, S.M. White, T.R. Wójcicki, A.N. Szabo, A.F. Kramer, E. McAuley, Construct validation of a non-exercise measure of cardiorespiratory fitness in older adults, BMC Public Health. 10 (2010) 59. https://doi.org/10.1186/1471-2458-10-59.

[21 A. Hartanto, S.T.H. Lee, J.C. Young, Dispositional Gratitude Moderates the Association between Socioeconomic Status and Interleukin-6. 802 (2019).

[22] T. Sharot, The optimism bias. (2011). https://doi.org/10.1016/j.cub.2011.10.030

[23] T. Sharot, M. Guitart-Masip, C.W. Korn, R. Chowdhury, R.J. Dolan, How Dopamine Enhances an

Optimism Bias in Humans. (2012) doi: 10.1016/j.cub.2012.05.053

[24] M.N. Hartmann, A. Kluge, A. Kalis, A. Mojzisch, P.N. Tobler, S. Kaiser, Apathy in schizophrenia as a deficit in the generation of options for action. (2015) May;124(2):309-18. doi: 10.1037/abn0000048.

[25] D.H. Wolf, T.D. Satterthwaite, J.J. Kantrowitz, N. Katchmar, L. Vandekar, M.A. Elliott, K. Rupare, A motivation in Schizophrenia: Integrated Assessment With Behavioral, Clinical, and Imaging Measures. (2014) Nov; 40(6): 1328–1337. doi: 10.1093/schbul/sbu026

[26] M. Wallace, Future time perspective in schizophrenia. (1956); Mar;52(2):240-5. doi: 10.1037/h0039899.

[27] L.K. Fellows, M.J. Farah, Dissociable elements of human foresight: a role for the ventromedial frontal lobes in framing the future, but not in discounting future rewards. (2005);43(8):1214-21. doi: 10.1016/j.neuropsychologia.2004.07.018.

[28] L. Choi, Z. Liu, C.E. Matthews, M.S. Buchowski, Validation of accelerometer wear and nonwear time classification algorithm. (2011) Feb;43(2):357-64. doi: 10.1249/MSS.0b013e3181ed61a3.

[29] C. Tudor-Locke, T.V. Barreira, J.M. Schuna Jr, E.F. Mire, J.P. Chaput, M. Fogelholm, G. Hu, R. Kuriyan, A. Kurpad, E.V. Lambert, C. Maher, J. Maia, V. Matsudo, T. Olds, V. Onywera, O.L. Sarmiento, M. Standage, M.S. Tremblay, P. Zhao, T.S. Church, P.T. Katzmarzyk, for the ISCOLE Research Group, Improving wear time compliance with a 24-hour waist-worn accelerometer protocol in the International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE). Int J Behav Nutr Phys Act 12, 11 (2015). https://doi.org/10.1186/s12966-015-0172-x

[30] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. González, J.G. Conde, Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support, Journal of Biomedical Informatics. 42 (2009) 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.

[31] Geddes MR, Tie Y, Gabrieli JDE, McGinnis SM, Golby A, Whitfield-Gabrieli S (2016). Altered functional connectivity in lesional peduncular hallucinosis with REM sleep behavior
disorder. Cortex 74, 96 – 106.

[32] Arnold Anteraper, S., Guell, X.*, Whitfield-Gabrieli, S., Triantafyllou, C., Mattfeld, A., Gabrieli, J., Geddes, M.R. (2018). Resting state functional connectivity of the subthalamic nucleus to limbic, associative and motor networks. Brain Connectivity 8(1), 22-32.

[33] Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect, 2(3), 125-141.

List of Annexes:

Annex A. Time Capsule.

Annex B. Study Partner cognitive battery and list of questionnaires.

Annex D. The Benefits of Physical Activity for Older Adults (informational material).

Annex F. Extrafamilial Study Partner Recruitment File.

Annex H. Extrafamilial study partner – script for partnering.