PROJECT TITLE: Efficacy and feasibility movement breaks in real-world settings

CENTRAL KEY QUESTION: Are exercise snacks an effective and feasible solution to combat physical inactivity and low cardiorespiratory fitness in real-life settings?

BACKGROUND INFORMATION

Physical inactivity is an independent risk factor for developing various cancers[1,2]. A pooled analysis of 12 prospective cohort studies involving >1.4M participants reported a >20% risk reduction for seven different cancers and a 10-20% risk reduction for six additional cancers in the most (90th percentile) versus least (10th percentile) physically active individuals after adjusting for traditional risk factors[3]. Improved cardiorespiratory fitness (CRF) is a primary mechanism by which physical activity reduces cancer risk[2]. A strong inverse relationship between CRF and the incidence of cancer independent of traditional risk factors is consistently reported[4–9]. A ~1 metabolic equivalent (MET; 3.5 mL/kg/min) increase in CRF is associated with a 10% and 21% lower incidence of cancer in men[10] and women[11], respectively. Although these findings suggest that high CRF confers protection against cancer risk, >80% of Canadian adults are physically inactive[12]. Relatedly, while participation in traditional exercise interventions involving continuous bouts of activity (e.g., jogging for 30 minutes) can improve CRF, adherence to traditional exercise interventions is notoriously poor. Perceived lack of time and difficulties accessing equipment/facilities are among the most commonly cited barriers for not performing regular exercise[13–19]. Thus, there is a need for novel, feasible and scalable alternatives to traditional exercise that can enhance CRF and help reduce the risk of developing cancer in a practical and time-efficient manner.

Exercise snacks are an accessible and time-efficient strategy involving short (≤1 min) isolated bursts of vigorous exercise performed sporadically during the day. We have recently demonstrated in small lab-based studies that three daily ~20-second bouts of cycling or stair-climbing, performed thrice weekly for 6 weeks, elicit higher CRF in previously inactive adults compared to pre-training[20] and a no-exercise control group[21]. In addition to being time-efficient, exercise snacks alleviate the need for both specialized equipment and dedicated leisure time for structured exercise. Their ability to be incorporated in between activities of daily living (e.g., briskly ascending the stairs at home or work) using readily available aspects of a real-world environment overcomes major barriers that prevent participation in traditional exercise (e.g., lack of time, access to equipment). Exercise snacks appear to be well-tolerated in inactive healthy adults[20–22] and individuals with overweight/obesity[23] further highlighting their potential for widespread application in different populations, including those at risk for developing cancer. Due to the isolated and periodic nature of exercise snacks, an important added benefit of this approach over traditional exercise strategies is their natural ability to interrupt sedentary time – itself an independent risk factor for developing cancer[24–26]. Although our compelling findings suggest that exercise snacks may be a practical and time-efficient approach for improving CRF and contributing to primary cancer prevention, their feasibility and efficacy outside the laboratory has not been determined. As such, the purpose of this study is to test and apply the exercise snacks approach in real-world settings.

PROJECT AIM

To conduct a proof-of-concept randomized trial to determine the feasibility and efficacy of a 12-week technology-enabled exercise snacks intervention for improving CRF in previously inactive adults.

EXPERIMENTAL DESIGN

Rationale

The design of this real-world intervention is a natural extension of our lab-based studies showing improved CRF after exercise snack interventions in previously inactive adults[20,21]. In one of our studies[21], participants completed a supervised 6-week intervention involving either three daily bouts of vigorous stair climbing (~20 seconds each) performed 1-4 h apart thrice weekly (n=12; male/female = 3/9, age = 20±2 yrs) or performed no exercise (n=12; male/female = 2/10, age = 19.3±1.6 yrs). CRF measured using the gold standard peak oxygen uptake (VO_2peak) test was ~5% higher after the exercise snacks intervention compared to the control group (Cohen's d=0.46). The exercise snacks intervention elicited perceived exertion values corresponding to a "hard" effort (~5/10 on the Borg scale) and mean heart rate responses equating ~85% of the age-predicted maximum[21] while being well-tolerated with 100% adherence. In a subsequent lab-based study, inactive adults (n=12, male/female=5/7, age = 22±4 yrs) performed a 6-week cycling-based exercise snacks intervention involving three daily ~20 second bouts of vigorous exercise 1-4 hours apart on three days per week. Similarly to our first study, CRF was ~4% higher after the intervention compared to baseline (Cohen's d=0.57). Although seemingly modest, the ~0.5 MET CRF gain in these studies is impressive for a young healthy population over a relatively short training period. We anticipate that recruiting inactive middle-aged adults (who are typically less fit than their younger counterparts[27]) and increasing

the dose (e.g., number, duration and/or intervention length) of exercise snacks will elicit even larger gains in CRF (e.g., ~1 MET) that correspond with a greater estimated reduction (>10%) in cancer risk[10,11].

In the proposed study, participants will perform 3-4 isolated bouts of vigorous exercise per day (on 3-4 days per week) with the exercise stimulus being increased (either via increased exercise duration, complexity, and/or intensity) progressively over the course of the intervention to ensure continuous improvements in health and fitness. To ensure the intervention is individualized to exercise preferences and physical abilities (e.g., fitness, musculoskeletal issues), adaptable to multiple environments (e.g., home, work), and scalable, we will integrate exercise snacks into the well-established, customizable online platform developed by industry partner Seven Movements. The platform provides participants with targeted motivation, support, and feedback to facilitate strong adherence to the intervention. Our approach is backed by evidence supporting the feasibility and efficacy of technology-based applications for improving home-based exercise adherence in adults[28–31]. Co-I Jung is an expert in theory-based exercise adherence trials, including studies of vigorous interval training[32–36] and technology-enabled interventions[37–41].

Study Design

We will conduct a two-centre proof-of-concept parallel arm randomized trial where participants will be randomized (1:1 allocation ratio stratified by sex and centre) into an Exercise Snacks or Placebo Exercise Control group for 12 weeks. Interventions will be delivered at home or work via the functioning Seven Movements platform (www.sevenmovements.com) and individualized via onboarding sessions to develop an action plan for incorporating exercise

snacks or placebo exercise into their daily routines (details below). Efficacy (i.e., the ability to improve CRF) and feasibility (i.e., rates of uptake and adherence) will be measured before and after the intervention with CRF as the pre-defined primary outcome measure. All pre- and post-intervention testing will be performed at UBC Okanagan (Kelowna, BC) or McMaster University (Hamilton, ON); running the trial at two sites will facilitate recruitment, ensuring we can complete the study within the one-year grant timeline. Co-PIs Little (UBCO) and Gibala (McMaster) have an established history of collaboration[20,21,42–44] – including the two exercise snacks studies providing rationale for this project[20,21] and a previous multi-site exercise trial[45].

COVID-19 Safe Research Protocols

This study will follow the Safe Research Protocols in place for research in the Arts and Reichwald Health Sciences Building at UBC Okanagan for all pre- and post-intervention testing. Currently we are using the Safe Work Plan developed and approved for our research by both the Faculty of Health and Social Development and Southern Medical Program for in-person research at these locations. Of course, all research staff and participants will need to follow the latest Public Health Orders. In order to follow these protocols and guidelines (which are ever changing), we will email participants prior to their first visit to remind them of: a) the requirement to wear a mask throughout the visit, and b) reminder to complete a health check on the morning of their visit; and c) ask their vaccination status. Participants must respond to the email indicating that they understand and confirming their completion of the health check and vaccination status.

Participants

80 physically inactive male and female adults will be recruited from Kelowna, BC and Hamilton, ON using online advertisements and emails to local campus community.

Eligibility criteria are as follows: 1) aged 40-64 years; 2) physically inactive (performing <150 minutes of moderate-to-vigorous intensity aerobic exercise per week, assessed by pre-screening Get Active Questionnaire); 3) body mass index: 18.5-30.0 kg/m^2; 4) not currently diagnosed with or being treated for cardiometabolic disease (e.g., coronary artery disease, diabetes); 5) not a current smoker; 6) cleared to engage in physical activity using the Get Active Questionnaire and, if applicable, consultation with a CSEP CEP Qualified Exercise Professional; 7) access to a computer, tablet or smartphone for intervention delivery and tracking. Given our targeted age-group, it would be impractical to recruit drug-naïve individuals only; we will therefore include participants taking ≤2 commonly prescribed medications for the prevention of cardiometabolic disease (e.g., statins, antihypertensives) but will ask participants to maintain doses throughout the trial.

Exclusion criteria include: 1) chronic health condition preventing participation in exercise; 2) current or previous diagnosis of cancer; 3) lack of access to internet connection.

Protocol

Once deemed eligible for participation based on the above-mentioned criteria, they will be randomized (1:1 allocation ratio stratified by sex and centre) into an Exercise Snacks or Placebo Exercise Control group for 12 weeks. Following baseline testing (Visit 1 details below), individualized interventions will be delivered at home or work via the functioning Seven Movements platform (www.sevenmovements.com) where participants will be instructed to

perform 3-4 isolated bouts of vigorous exercise per day (on 3-4 days per week) with the exercise stimulus being increased (either via increased exercise duration, complexity, and/or intensity) progressively over the course of the intervention to ensure continuous improvements in health and fitness. To ensure the intervention is individualized to exercise preferences and physical abilities (e.g., fitness, musculoskeletal issues), adaptable to multiple environments (e.g., home, work) participants will have a virtual or phone pre-intervention meeting (Step 3) wherein any physical limitations will be documented and a research assistant will discuss the exercise snacks (or placebo stretching) concept with participants in order to determine when and where the participants will plan to perform their exercises. This information will be used to create an individualized exercise prescription for each participant detailing exercise options and suggested time of day to perform them. This prescription will be inputted and integrated into the well-established, customizable online and app-based platform developed by industry partner Seven Movements. Subsequently, participants will start the intervention with a virtual onboarding visit (Step 4) wherein a research assistant will introduce the Seven Movements platform, provide their login information, discuss their individualized prescription, and guide the participant through their first exercise snack. The same approach and individualized exercise prescription and platform structure will be used for both groups, with the only difference being the exercise snacks group will be prescribed movements that increase heart rate with the intention of improving fitness whereas the placebo stretching group will be provided with static stretching and low-intensity mobility exercises (e.g., ankle flexion/extension, neck mobility) that are designed to not raise heart rate. After 12 weeks, participants will be asked to return to the lab for follow-up testing (Step 6 details below).

While participants cannot be blinded in exercise interventions, specific study hypotheses (e.g., exercise snacks improving CRF) will not be disclosed to participants as the study will be pitched as testing low versus high-intensity "movement breaks". Given the known detrimental impact of prolonged uninterrupted sedentary behavior on various mental and physical health outcomes, we anticipate that participants in both groups will achieve some benefit from breaking up their sedentary time. Outcome assessors will be blinded to the participants' group allocation. Researchers administering VO_2peak tests assessing the primary outcome (CRF) and interviews for feasibility outcomes will not be involved in trial administration or interact with participants during the intervention. Biological samples used for the assessment of cardiometabolic health markers will be coded so researchers remain blinded until completion of all analyses.

STEP 1: Online Assessment of Eligibility (30 minutes)

Participants will be asked to log-in to the REDCap platform - a secure virtual application for research data collection instruments - and complete the following questionnaires online:

a) Provide informed consent;

b) CSEP Get Active Questionnaire;

c) International Physical Activity Questionnaire (IPAQ)

STEP 2: In-Person Visit 1 – Baseline Testing Day (80 minutes)

This visit will be scheduled in advance, and participants will be asked to come into the laboratory in room 115 of the Arts building (ART) at UBC Okanagan. Participants will be asked to report to the lab in a fasted state (no food or drink except for water for ≥8 hours) for this visit.

During this visit we will measure body composition (height and body mass), a fasting blood sample will be obtained from a vein in the arm (approximately ~2.5 tablespoon, 24-30 millilitres) and collected into 4-5 separate blood tubes, and a peak oxygen uptake (VO2peak) test will be performed using a maximal-graded cycling test. In addition, all Personnel will follow Health and Safety recommendations, a maximum of two people will be allowed in the laboratory using the personal protective equipment necessary and, as always, all tool/materials, surfaces and materials will be decontaminated with 70% ethanol before and after each visit.

STEP 3: Virtual/Phone Interview for Intervention Planning (30 minutes)

Following pre-intervention testing, a virtual or phone interview will be scheduled at the participant's convenience to discuss participants' daily schedules, physical limitations (e.g., injuries) and/or exercise preferences. This discussion will be used to explain the concept and determine the mode, time of day, and location that is best for participants to complete the exercise snacks for their individual lifestyles. This information will be used to create an individualized exercise prescription for each participant detailing exercise options and suggested time of day to perform them. This prescription will be inputted and integrated into the well-established, customizable online platform developed by industry partner Seven Movements.

STEP 4: Virtual Onboarding (30 minutes)

To introduce the Seven Movements platform and to further individualize the intervention and to promote adherence, an onboarding session will be conducted. During this session, we will provide participants with detailed instructions on how to use the Seven Movements platform using their computer, smartphone, or tablet, allowing them to access instructional videos

detailing their customized movement breaks and to complete post-activity assessment for recording their effort and enjoyment after each movement break.

STEP 5: Intervention Period (12 weeks)

Exercise Snacks Group (referred to as "high-intensity movement breaks" in the consent form) – Participants will be prescribed 3-4 exercise snacks performed periodically throughout the day (at the participants discretion to fit their daily schedules based on the onboarding session) on 3-4 days per week. Our lab-based studies used 3 snacks per day for 3 days per week[20,21] but we have included flexibility in prescription for real-world application. Snack duration, complexity and/or intensity will be increased over the course of the intervention to facilitate progression and accommodate increases in fitness. These adjustments have been designed by the research team in consultation with the Seven Movements team who have a track record of designing "activity breaks" for previously inactive adults in real-world settings. Exercises will be tailored to participant preferences, physical abilities, and environments and include body-weight exercises (e.g., marching in place, step ups, jumping jacks, air squats, lunges), stair-climbing and other aerobically conditioning activities designed to increase heart rate. Instructional videos developed by Seven Movements will be provided for each exercise ensuring participants are comfortable performing the movements safely and effectively.

Placebo Exercise Control (referred to as "low-intensity movement breaks" in the consent form) – An identical intervention delivery approach including the same technology and pre-trial virtual planning/onboarding sessions will be implemented for the placebo group with the exercise snacks being replaced with mobility/stretching based-exercises designed not to stimulate

increases in heart rate and CRF. We selected this as the most appropriate control group in attempts to balance randomization expectations, retention, and ethical considerations compared to a true "hands off" or "no exercise" control.

Technology – Participants will be able to log the timing, duration, and number of exercise snacks completed daily as well as the perceived effort (Borg CR-10 scale [47]) and enjoyment (Exercise Enjoyment Scale[48]) of each snack into the platform. Participants will also be sent weekly self-report adherence surveys via email RedCap link wherein adherence will be assessed by asking participants the total number of snacks completed each week. If participants miss the weekly adherence self-assessment, we will follow-up with an email reminder and (if necessary) a follow-up telephone call to help address any concerns/issues that may have prevented them from completing the weekly assessment. To characterize exercise adherence and track changes in daily physical activity, sedentary time, and sleep patterns, we will provide participants with validated[49,50] thigh-worn triaxial accelerometers (activPAL4) in line with our previous work[51,52]. Accelerometer data will be obtained during two, separate 7-day periods (intervention weeks 2 and 11) and extrapolated to the rest of the intervention. As exercise adherence generally diminishes over an intervention[53], obtaining this data during both early and late stages of the intervention will provide valuable information relating to changes in adherence over the intervention.

Virtual check-ins: To help participants complete their customized movement break plan and to address any potential barriers/challenges that you may encounter of the course of the intervention, we will conduct virtual (phone or zoom) sessions at the 4 and 8 week point of the

intervention. During these sessions, we can also discuss the possibility of adjusting their plan based on your experience performing the activities during the preceding 4-week period (e.g., they initially thought they would prefer performing the activities at work but change their mind and decide they would like to do them at home for the remainder of the intervention).

STEP 6: In-Person Visit 2 – Post-Intervention Testing Day (90 minutes)

Twelve weeks later, participants will be asked to return to the laboratory to complete follow-up testing and self-reported physical activity using the IPAQ. The testing order and procedures will be completed exactly as they will be at Visit 1. Following testing, semi-structured interviews will be conducted with a subset of 10-12 participants to explore barriers and facilitators of the intervention and identify its most effective/ineffective aspects.

OUTCOME MEASUREMENTS & METHODS

Cardiorespiratory Fitness

Participants will perform an incremental maximal oxygen uptake (VO_2peak) test on a cycle ergometer (Load Excalibur Sport) as we perform routinely in our studies[21-23]. The test will start at 30 W and increase at a rate of 15 W / min until volitional exhaustion. A metabolic cart with an online gas collection system (Parvo Medics, TrueOne 2400) will be used to collect expired gas samples continuously. VO_2peak will be calculated using the mean of the highest average oxygen consumption over a 30-s period.

Exercise adherence

Self-reported adherence to the prescribed intervention will be determined using the automated weekly REDCap surveys. 9 exercise snacks or placebo exercises per week (equivalent to performing at least 3 per day on at least 3 days of the week) will be considered the minimum prescription. Participants completing 6 or more, 1-5, or 0 exercises will be classified as adherent, partially adherent, or non-adherent, respectively.

Anthropometric Measurements

Waist circumference (cm), height (cm) and weight (kg), and blood pressure (average of lowest 2 of 3 measurements) will be measured using the standard procedures. Body mass index (BMI) will be calculated as kg/m^2.

Questionnaires

a. Medical screening questionnaire by CSEP Get Active Questionnaire (CSEP GAQ);
b. Pre- and post-intervention International Physical Activity Questionnaire (IPAQ) used to evaluate self-reported physical activity;
c. Rating of perceived exertion (Borg CR-10 scale[47]), and exercise enjoyment (Exercise Enjoyment Scale[48]) after each snack;
d. Customized Weekly Questionnaire that will be used to assess adherence and uptake of the intervention,

Blood Collection

Following an overnight fast (after ≥ 8 hours of the last meal), a single blood sample will be obtained by venipuncture of an antecubital vein and collected into sodium heparin, ethylene-

diaminetetraacetic acid (EDTA - BD Vacutainer), and sodium citrate tubes for subsequent analyses. A total of 4-5 tubes (~4-6 mL each) will be collected. In addition, all Personnel will follow Health and Safety recommendations, a maximum of two people will be allowed in the laboratory using the personal protective equipment necessary and, as always, all surfaces and materials will be decontaminated with 70% ethanol before and after each visit.

Plasma Analyses

Plasma will be prepared by centrifugation for 15 minutes at 1200Xg and frozen for analyses of standard metabolic markers (e.g., blood glucose, insulin, triglycerides) and inflammatory cytokines (IL-6, IL-10 and TNF-α) by MSD multiplex technology, enzyme-linked immunosorbant assays (ELISA), or biochemical assay according to manufacturer's instructions. To explore additional mediators of altered inflammation and immune function, we will also measure IL-10 function (details below) and profile extracellular vesicles (small membrane bound vesicles containing cellular DNA/RNA and proteins) using standard techniques in our lab. EVs will be quantified and characterized using resistive pulse sensing, flow cytometry and cargo profiling. Samples will be stored for 5 years after publication before destroying (additional markers in the stored samples may be measured during this time).

Human whole blood culture

For whole blood stimulation, we will use our published protocol for IL-10 function experiments[74]. Briefly, whole blood will be diluted in a serum-free RPMI media (Sigma) containing 5mM glucose, 50 U/ml penicillin and 50µl/ml streptomycin. Diluted 540µl whole blood will be seeded in 24-well plate (Costar) and stimulated using lipopolysaccharide (LPS, Escherichia coli 055:B5; L6529, Sigma) at 1 or 10 ng/ml with or without recombinant human IL-10. The cultures will be incubated at 37°C in 5% CO_2 and supernatants will be collected at six

hours for analyses of secreted TNF-α on duplicate samples by enzyme-linked immunosorbent assay - ELISA (Human TNF-α DuoSet, R&D System) according to the manufacturer's instructions. The % maximal stimulation is taken as an index of how well the anti-inflammatory cytokine function to inhibit inflammation. A reduction in the ability of IL-10 to inhibit TNF-α production will be an indicative of "resistance" to their anti-inflammatory action.

Flow cytometry

To examine potential changes in anti-inflammatory signalling pathways in circulating immune cells, the proportion of phosphorylated STAT3 (pSTAT3) positive cells will be measured by flow cytometric analysis. Briefly, whole blood samples and isolated monocytes will be stimulated within exogenous IL-10 for 15 minutes at 37°C in a dose-depended manner (0, 1, 10, 50, 100, 1000 ng/ml), 1ml of Lyse/Fix Buffer (BD Phosflow) will be added for erythrocyte lysis and fixation of the phosphorylated status of intracellular proteins. Next, cells will be permeabilized with 1ml of Perm Buffer (BD Phosflow), washed and stained for 60 minutes at room temperature in the dark with the following fluorophore-labelled monoclonal antibodies: anti-CD4-phycoerythrin (PE)-Cy7 (BD Pharmingen, Franklin Lakes, NJ, USA), anti-STAT3 (py705)-AF488 (BD Phosflow), anti-pAMPK (ab23875, Abcam) anti-CD14 (130-094-364, Miltenyi Biotech) and anti-CD210 (BD Biosciences). Stained cells will be analysed by flow cytometry (Cytoflex S, Beckman Coulter).

PBMC isolation

PBMCs will be isolated by gradient density centrifugation to determine changes in immune cell gene expression in response to the intervention. Briefly, whole blood will be diluted

1:1 with warm PBS and layered onto 3 mL of Histopaque-1077 (10771, Sigma) in a sterile 12 mL LeucoSep tube (Greiner Bio-One, Austria) and centrifuged at 800 *g* for 20 min at room temperature. The enriched PBMC layer will be recovered and washed twice with warm PBS with an additional centrifugation step (300 *g* for 10 min) after each wash. Isolated PBMCs will be stimulated with IL-10 and/or liposaccharide for ~1 hour and stored at -80°C until transcriptomics analysis.

Haematology Analysis of Blood

Whole blood specimens will be analysed for complete blood count (e.g., total white blood cells, haematocrit, haemoglobin, monocytes, neutrophils) using a haematology analyser (DxH 520, Beckman Coulter) to determine changes in clinically relevant health markers before and after the intervention.

Semi-Structured Interviews

Semi-structured interviews will be conducted in a subset of 10-12 participants to explore barriers and facilitators of the intervention and identify its most effective/ineffective aspects; this will help refine the approach and future intervention delivery.

Statistical Analysis

Descriptive statistics will be calculated and data will be assessed for skewness and normality using Q-Q plots and Shapiro-Wilk tests (non-normal distributions will be log transformed as needed). The primary data analyses will be intention-to-treat. We will define feasibility of the exercise snacks intervention as >70% of participants completing at least 67%

(i.e., 6 exercise snacks per week) on at least 9 out of 12 weeks. All quantitative dependent variables will be analyzed using linear mixed-effects models with group and time as fixed effects, participant and study site as random effects, and age and baseline fitness as covariates. The between group treatment effect at 12 weeks with 95% confidence intervals will be the main analyses of interest. Although the study is not powered for detecting sex differences, sex will be included in the model to explore its interaction with the treatment effect. Significance will be set at $p<0.05$ and Cohen's d effect sizes will be calculated to estimate the magnitude of between-group differences in pre-post change scores. For qualitative outcomes, an inductive thematic analysis will be conducted on interview transcripts by Co-I Jung to ascertain main barriers and facilitators to acceptability[66,67].

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