STATISTICAL ANALYSIS PLAN (SAP)
Efficacy of Movement Breaks in Real-World Settings Trial
Registration: NCT05574426
Version 3: February 26, 2024

BACKGROUND AND AIM:

From November 2022 to December 5, 2023, we completed the randomized clinical trial titled "Efficacy of Movement Breaks in Real-World Settings" at two study sites, McMaster University (Mac) and the University of British Columbia (UBC). The purpose of the study was to determine the efficacy of performing movement breaks as either vigorous-intensity "exercise snacks" (ES) or low-intensity mobility-based control activities (CTL) on indices of cardiometabolic health. All movement breaks involved ≤60-second bouts of activity performed periodically throughout the day. Participants in both groups were given access to a web platform that provided individualized notifications to remind them to complete their ES or CTL bouts at least 3 times per day on at least 3 days per week (i.e., minimum prescription of 9 movement breaks per week). Identical scripted counselling at baseline, week 4, and week 8 assisted with individualization and progression of the two movement break prescriptions. Exercise prescription progression and variety were accomplished by altering the exercises in weeks 1-4 (Phase 1), weeks 5-8 (Phase 2), and weeks 9-12 (Phase 3). The primary outcome measure was change from baseline in cardiorespiratory fitness (CRF; assessed via cycling VO2peak test) following the 12-week exercise intervention. Secondary outcomes included changes in basic anthropometric measures (body mass and waist circumference); fasting plasma insulin, glucose, homeostasis model assessment of insulin resistance (HOMA-IR), and inflammatory cytokines; device-measured and self-reported adherence to movement breaks; and enjoyment and perceived exertion following movement breaks. It was hypothesized that a 12-week technology-enabled real-world ES intervention would improve CRF as compared to CTL in previously inactive adults.

A PRIORI SAMPLE SIZE CONSIDERATIONS

A sample size of 30 participants per group was deemed sufficient to detect a within-between interaction with a medium effect size (Cohen's f=0.25, d=0.50) for the primary outcome (CRF) assuming 90% power with a two-tailed α set at 0.05 (G*Power v3.1). This effect size equates to ~1 metabolic equivalent (MET) increase in CRF (assuming a mean baseline VO2peak of 30-35 mL/kg/min with a SD of 5-7 mL/kg/min[4-9]). The grant was funded by the Canadian Cancer Society Action Grant special call for interventions designed for primary cancer prevention. A 1-MET increase in CRF was deemed clinically relevant for primary cancer prevention based on epidemiological data showing 10-21% decrease in cancer incidence for each 1 MET increase in CRF[1-2]. To preserve power and account for a 20-30% dropout rate, we aimed to recruit 40 participants per group (80 participants total; equal sex distribution). Randomization was stratified based on study site (i.e., Mac or UBC) and participant sex (i.e., male or female). These calculations were documented in the original grant application (Feb 2021), trial protocol (Oct 6, 2022), and SAP (V1 June 2023).

ANALYSIS SET AND STUDY POPULATIONS

The primary outcome of the study will be analyzed according to the intention-to-treat (ITT) principle. The full analysis set of data will be derived from the set of all randomized participants. Participants allocated to a treatment group (i.e., ES or CTL) will be analyzed as members of that group irrespective of their compliance to the planned treatment. Those with both missing baseline and follow-up value will not be included in the analysis, which is unbiased under a plausible missing at random assumption. All outliers that are within the realm of biological plausibility will be included in the analysis and only obvious data errors (e.g., resulting from technical issues) will be excluded. If there are statistical outliers within the realm of biological plausibility (>2.2*IQR), the data will be explored with and without the outliers included for completeness.

ANALYSIS OBJECTIVES, OUTCOMES, AND STATISTICAL METHODS

All data will be collected longitudinally. Statistical analysis will be performed blinded to participant allocation after the last participant has completed the trial. Descriptive statistics will be summarized as mean (SD) for continuous and N (%) for categorical data, 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).

Outcomes

Category	Variable	Timepoints
Anthropomorphic Measures	Weight, Waist circumference, body mass index (BMI)	Baseline, 12 weeks
Blood Pressure	Systolic, Diastolic, Mean Arterial Pressure	Baseline, 12 weeks
Blood Biochemistry	Fasting plasma insulin, fasting plasma glucose, HOMA-IR, fasting plasma cytokines	Baseline, 12 weeks
Complete Blood Count	Total White Blood Cells, Hematocrit, Hemoglobin, Monocytes, Neutrophils	Baseline, 12 weeks
Exercise Behavior (GLTEQ)	Bouts of mild, moderate, and strenuous exercise lasting >15min, weekly leisure-time exercise	Baseline, 12 weeks
Cardiorespiratory Fitness	Cycling? VO2peak, max HR, peak RER, peak power output (W)	Baseline, 12 weeks
Movement Break Adherence (Device-worn)	Device wear time, average minutes per day of total, light, moderate, vigorous, and moderate-vigorous physical activity per day, average minutes of sedentary time per date, sit-to-stand ratio per day	Baseline, week 2 and, week 11
Movement Break Adherence (Self-report)	Weekly surveys assessing number of movement breaks completed	Weekly for 12 weeks
Movement Break Adherence (technology platform)	Number of movement breaks completed within the Seven Movements account	Recorded for each snack
EES	Exercise enjoyment 1 (Not at all) 2 (Very light) 3 (Slightly) 4 (Moderately) 5 (Quite a bit) 6 (Very much) 7 (Extremely)	Following each snack
Borg CR-10 scale	Rating of perceived exertion 0 (Rest) 1 (Very, very easy) 2 (Easy) 3 (Moderate) 4 (Somewhat hard) 5 (Hard) 6 7 (Very hard)	Following each snack

	8 9 10 (Maximal)	

Primary outcome: The prespecified primary outcome for this trial will be a comparison of the change in VO2peak (mL/kg/min) from baseline to 12 weeks between the movement break intervention groups.

The primary data analyses will be intention-to-treat. Data will be analyzed by constrained longitudinal data analysis (cLDA) via a linear mixed model with fixed effects for timepoint (i.e., baseline and week 12), the interaction between timepoint and intervention group (i.e., ES or CTL), and stratified allocation factors (sex, study site) as well as random effects for participants to account for the correlation of repeated measures within participants. The between-group treatment (interaction) effect estimate at 12 weeks with 95% confidence intervals will be reported as the main analyses of interest. 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.

The cLDA approach constrains the baseline means to be equal between the treatment groups, which is a reasonable assumption in the context of a randomized clinical trial. No missing data will be imputed as per contemporary guidelines [3]. Model specification will be assessed visually using normal probability plots and residuals vs. fitted values plots. Models will be run using log-transformed outcome variables when departure from model assumptions is observed.

Secondary outcome measures: To supplement the primary outcome of VO2peak in mL/kg/min we will also analyze peak power output and absolute VO2peak (L/min). Key secondary outcomes will include exercise adherence, enjoyment, and perceived exertion assessed by self-report. Self-reported adherence to the intervention will be determined by user analytics on the Seven Movements platform and using the automated weekly REDCap surveys. We will define high, moderate, or low adherence as completing >67%, 50-66% or <50% of the prescribed intervention (i.e., total # of snacks performed relative to minimum prescription of 9 snacks per week and the number of days when participants completed ≥3 snacks relative to a prescription of 3 days per week). Enjoyment (Exercise Enjoyment Scale) and perceived exertion (Borg CR-10 scale) will be asked following each snack. Adherence, enjoyment, and exertion data will be analyzed using a linear mixed model that will include fixed effects for group (ES vs. CTL), timepoint (week, Phase or session number), their interaction, and stratified allocation factors (site, sex) and random effects for participants. In these analyses, the main effect of group will be most important to identify an overall effect of the intervention on these variables.

Other continuous secondary outcomes assessed at baseline and a follow-up timepoint will be analyzed similarly to the primary outcome using a constrained baseline longitudinal data analysis linear mixed model (with all relevant follow-up timepoints included as a fixed factor of time in the model). Secondary outcomes include:

- Changes in anthropometrics assessed at baseline and 12-weeks.
- Changes in blood markers (fasting plasma glucose, insulin, HOMA-IR, inflammatory cytokines) assessed at baseline and 12 weeks.

- Changes in hematology analysis of complete blood count (total white blood cells, hematocrit, hemoglobin, monocytes, neutrophils) assessed at baseline and 12-weeks.

- Changes in device-worn physical activity and sedentary time assessed at baseline, week 2, and week 11 via device-worn measurement.

- Changes in leisure time physical activity assessed by GLTEQ measured at baseline and 12 weeks.

SENSITIVITY ANALYSIS:

We will perform per-protocol sensitivity analyses on the primary outcome (change in VO2peak at 12 weeks) and secondary outcomes. To be included in these analyses, participants will need to have baseline and week 12 measurements for the outcome of interest and have completed >67% of the prescribed exercise intervention ("high" adherence, equivalent to 6 movement breaks per week, or 72 total exercise snacks)

Within-group changes from baseline for all outcomes will be reported as derived from the model employed for the primary (between-group) analyses outlined above

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EXPLORATORY ANALYSES:

Dose-response analyses exploring whether the number of completed exercise snacks (recorded in the Seven Movements platform and in weekly self-report surveys) and/or differences in RPE (i.e., "intensity") during exercise snacks are associated with changes in key outcomes

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HANDLING OF MISSING DATA AND OTHER DATA CONVENTIONS

No statistical imputations will replace missing data for the outcome measures (data as observed). However, the constrained baseline longitudinal data analysis – in a linear mixed model with restricted maximum likelihood – is a principled approach to addressing missing outcome data, including the baseline value of the continuous outcome measure. The model permits the inclusion of all participants in the analysis with either a baseline or a follow-up value. Thus, missing data will not be imputed for the ITT analyses. If a blood marker value is below the detection limit, we will explore the results following imputation of the value as limit of detection (LOD) divided by the square root of 2 (6).

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