Sedentary Behavior Interrupted: A Randomized Trial of 3-Month Effects on Biomarkers of Healthy Aging and Physical Functioning in the Real World (P2)

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Statistical Plan

Baseline characteristics were compared across the 3 treatment arms using ANOVA for continuous variables and χ^2 or Fisher exact tests for categorical variables. Study-related adverse events were tabulated by group using a standard medical dictionary for regulatory activities body system categories.

The primary analysis comparing the sit less and sit-to-stand interventions with the healthy living controls used the intent-to-treat principle. Linear mixed models (LMMs) were applied, allowing for the inclusion of partially complete records, thereby reducing complete case analysis biases. The model included baseline and 3-month outcomes as dependent variable; time (baseline, 3-month), group (active, control), and the group*time interaction were fixed-effect independent (categorical) variables. A subject-specific (random) intercept was included to model individual heterogeneity in outcomes. A significant group*time interaction indicated that outcome changes differed between that intervention and the control arm; this difference of outcome changes between intervention and control arms represents the intervention effect.

To reduce the chance of false positives, we first fit the aforementioned LMMs for 2 primary composite outcomes: (1) glucoregulatory outcomes defined as the average of 4 *Z* scores of insulin, glucose, HbA1c, and HOMA2-IR; and (2) blood pressure composite defined as the average of 2 *Z* scores of systolic and diastolic blood pressure. The *Z* score for each participant for a specific marker and time point was derived by subtracting the sample baseline mean from the participant's marker value at that time point and dividing this difference by the sample baseline SD. This composite score analysis represents an omnibus test of intervention efficacy across multiple (correlated) outcomes: rejection of the null hypothesis would suggest that the intervention (compared with controls) effected changes across components of the composite score. After this composite score analysis, we compared group differences for each of the outcomes; we present intervention results for the individual markers.

Several secondary analyses were conducted. First, we evaluated intervention effects adjusted for baseline stratification variables (obesity status, employment status). Second, we evaluated group differences in outcomes between the 2 intervention arms. Third, we evaluated changes in physical activity (standing, stepping, light physical activity, and MVPA) by intervention arm. Fourth, we included an indicator variable for COVID-19 (yes or no) and evaluated 3-way COVID-19*group*time interaction (by likelihood ratio tests) to test whether changes in outcomes differed between participants with delayed 3-month assessment because of COVID-19 and those who received the original protocol. Fifth, we explored whether baseline hypertension status was an effect modifier for blood pressure and whether baseline glycemic status (HbA1c < or ≥5.7%) was an effect modifier for glucoregulatory outcomes. We also excluded participants who self-reported having type 2 diabetes at baseline and repeated the LMM analysis. Last, we examined whether changes in MVPA altered the intervention effect estimates by including MVPA at baseline and 3 months as a time-varying covariate, and the MVPA*group interaction in the LMMs.

Gaussian link functions were used in the mixed models, and diagnostic plots were generated to evaluate model assumptions. Insulin, glucose, and HOMA2-IR were log-transformed to better approximate Gaussian distributions, and results were presented as geometric means with 95% CIs derived from model estimates (β coefficients) at baseline and at 3 months, along with mean (95% CI) within group changes. For the other outcomes, sedentary behavior measures, and blood pressure, mean (95% CI) at baseline and 3 months, as well as mean (95% CI) within-group change derived from model parameters (β coefficients), are presented. Treatment effects were calculated as the mean (95% CI) of the difference (compared with the control group) in absolute changes (for all outcomes) and percent changes (for log-transformed outcomes) from baseline to 3 months.

Analyses were implemented in the R statistical programming language, and LMMs were executed by R package nlme. All hypothesis tests were 2-sided. We used significance level $\alpha=0.025$ for the primary analyses to adjust for multiple comparisons (2 intervention groups versus control). No multiple comparison adjustment was made for secondary analyses.