Lifestyle Physical Activity and Cognitive Training Interventions: Preventing Memory Loss in Older Women With Cardiovascular Disease

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STATISTICAL DESIGN AND POWER

Power Analysis

***Power Analysis*.** Power was estimated using design effect methods to account for clustering of cases within randomized cohorts. Due to the group meeting component of *Move,* participants will be randomized into groups of 10-11 participants. Assuming 24 cohorts of 10-11 participants each (6 cohorts per cell in the 2x2 factorial design; Figure 3), a 15% attrition rate (a conservative estimate based on our previous results), and a correlation of 0.7 between assessments of memory performance (as measured by neurocognitive tests), we estimate 80% power to detect an interaction effect ($d = 0.30$) for significance ($p < 0.05$) with $N = 254$ participants (216 after accounting for attrition). This is a reasonable minimal effect size for the interaction effect described in Aim 1. Although existing systematic reviews suggest an estimated effect size of $d = 0.50$, we estimate $d = 0.40$ given our previous work as a more conservative estimate for the main effects of the *Move* and *Mind* interventions. Assuming an effect size of $d = 0.40$, our study design has > 90% power. Thus, 254 women with CVD will be recruited (63-64 in each cell).

Data Management

Several electronic resources will be used for data collection and management. Research Electronic Data Capture (REDCap) will be used to manage participant recruitment, scheduling, and tracking. All surveys will be collected via Computer-assisted Personal Interviews in which an interviewer reads the questions and enters the data into REDCap, programmed with variable range checks and skip rules. Fitabase®.com will track data synched from participants' Fitbit devices. Fitabase® is a secure research platform that collects and stores data from devices that connect to the internet. In addition to current data from users, a dashboard will show which devices have been recently synched, as well as individual device battery levels. The BrainHQ program tracks participant level and number of minutes spent in each activity. Data from BrainHQ, Fitabase®, and the accelerometers will be exported (using study ID variables) to SAS for merging and management.

All variables will be checked for errant values. Descriptive statistics will be computed for all items and scale scores. Distributions will be examined for non-normality and outliers. We expect outcome measures to be normally distributed. Data will be examined to determine normality and transformed if necessary. Outcome measures that cannot be transformed to achieve normality will be analyzed by appropriate generalized linear models available in SAS. All statistical tests will use $\alpha = .05$.

Statistical Analyses

Under the direction of Dr. Schoeny, all analyses will use an intent-to-treat approach (i.e., participants analyzed according to their assigned cell; **Figure 3**) independent of their actual dose of each intervention. All analyses will employ multi-level mixed models with repeated observations (baseline, 24, 48, and 72 weeks) nested within participants, and participants nested within cohorts. Three parameters for factorial design will be included in the models: (1) *Move* main effect, (2) *Mind* main effect, and (3) *Move* x *Mind* interaction effect. Time and interactions of time with the factorial design parameters will be included in the models. Potential covariates in the multi-level mixed models are in Table 5. Although many of these covariates may relate to memory level, they are generally less likely to influence change over time. Covariates will be at Level 2 (person level) or Level 1 (assessment level) as appropriate. To minimize the number of covariates in the final models, we will first test each candidate covariate individually in models for each memory outcome change over time (time x covariate interaction). We will retain only significant covariates in the final models.

Time can be handled flexibly with multilevel mixed models, allowing us to model hypothesized patterns of change over time that deviate from linear or quadratic patterns. For example, we expect that *Mind* effects will be greatest from baseline to 24 weeks, followed by a change plateau; thus, a parameterization of time would reflect a relatively large increase from baseline to 24 weeks followed by stabilization after 24 weeks. Adding a term for this discontinuity in memory level (coded 0, 1, 1, 1 for baseline, 24, 48, and 72 weeks, respectively) allows us to test this pattern. In contrast, for the *Move* effects, we expect a more gradual linear change in memory from baseline through 48-72 weeks; therefore, a discontinuity term may not be needed. The general multilevel mixed model for the proposed analyses can be represented by the following equations:

Observation-Level Model

$$Y_{ijk} = \pi_{0jk} + \pi_{1jk}(\text{time}) + \pi_{Pjk}(\text{time-varying covariates}) + \varepsilon_{ijk}$$

Where

Y_{ijk} is the outcome measure at time *i* for person *j* in cluster *k;*

π_{0jk} is the intercept for person *j* in cluster *k;*

π_{1jk} is the level-1 coefficient for the time (change) effect for person *j* in cluster *k;*

π_{Pjk} are the level-1 coefficients for time-varying covariates (as needed) for person *j* in cluster *k; and*
ε_{ijk} is the random error term.

Person-Level Model

$\pi_{0jk} = \beta_{00k} + \beta_{01k}(\text{age}) + \beta_{02k}(\text{race}) + \beta_{03k}(\text{education}) + \beta_{04k}(\text{BMI}) + r_{0jk}$
$\pi_{1jk} = \beta_{10k} + \beta_{11k}(\text{age}) + \beta_{12k}(\text{race}) + \beta_{13k}(\text{education}) + \beta_{14k}(\text{BMI}) + r_{1jk}$
$\pi_{Pjk} = \beta_{P0k}$

Where
β_{00k} is the outcome measure for cluster *k;*
β_{01k} through β_{04k} are the coefficients for person-level effects on the intercept;
β_{11k} through β_{14k} are the coefficients for person-level effects on the time slope;
β_{P0k} are the person-level means for the time-varying covariates;
r_{0jk} is the person-level random effect for the intercept; and
r_{1jk} is the person-level random effect for the time slope.

Cluster-Level Model

$\beta_{00k} = \gamma_{000} + \gamma_{001}(\text{Move}) + \gamma_{002}(\text{Mind}) + \gamma_{003}(\text{MindMoves}) + \gamma_{004}(\text{ClinicSite}) + u_{00k}$
$\beta_{01k} = \gamma_{010}$
⋮
$\beta_{04k} = \gamma_{040}$

$\beta_{10k} = \gamma_{100} + \gamma_{101}(\text{Move}) + \gamma_{102}(\text{Mind}) + \gamma_{103}(\text{MindMoves}) + \gamma_{104}(\text{ClinicSite}) + u_{10k}$
$\beta_{11k} = \gamma_{110}$
⋮
$\beta_{14k} = \gamma_{140}$
$\beta_{P0k} = \gamma_{P00}$

Where
γ_{000} is grand mean (intercept) for the outcome measure*;*
γ_{001} through γ_{003} are the intervention main effects and interaction effect on the mean for the outcome measure*;*
γ_{004} is the Clinic Site effect on the mean for the outcome measure*;*
γ_{010} through γ_{040} are the overall effects for the person-level covariates;
γ_{100} is grand mean change over time on the outcome measure*;*
γ_{101} through γ_{103} are the intervention main effects and interaction effect on change over time for the outcome measure*;*
γ_{104} is the Clinic Site effect on change over time for the outcome measure*;*
γ_{110} through γ_{140} are the overall effects for the person-level covariates on change over time of the outcome measure;
u_{0jk} is the cluster-level random effect for the intercept; and
u_{1jk} is the cluster-level random effect for the time slope.

It is expected that the person-level random effects for the intercept (r_{0jk}) and time slope (r_{1jk}) will be significant (i.e., there will be significant between-person variation in level of the outcome and rate of change over time). Although we will include them it the initial models, it is likely that the cluster-level random effects for the intercept (u_{0jk}) and time slope (u_{1jk}) will be non-significant. If non-significant, those random effects will be removed from the models. The time-varying covariates include time of day for the assessment (i.e., for models with BDNF as the dependent variable – see Aim 2 below) and discontinuities (see above).

Aim 1 (primary): **To determine the independent and combined efficacy of *Move* and *Mind* interventions on memory performance among women ≥ 65 years with CVD.** ***Hypotheses: Move and Mind each will improve performance-based memory (main effects). In addition, there will be an interactive effect such that MindMoves will provide greater memory benefit than the sum of the main effects of Move and Mind.***

Aim 1 tests the main effects of the individual interventions (i.e., *Move* and *Mind)* as well as the interaction between the interventions. Outcome measures will be collected at baseline and 24, 48, and 72 weeks post-baseline. Because we hypothesize intervention effects on memory outcomes over time, significant *Move* x Time, *Mind* x Time, and *Move* x *Mind* x Time effects will provide evidence of significant main effects and a

significant interaction effect, respectively (parameters γ_{101}, γ_{101}, and γ_{103} above).

Measures for Aim 1 (see section 4.3):

Primary Measures for Aim 1:
[1] East Boston Memory Test (episodic memory)
[2] Category Fluency (semantic memory)
[3] Digit Span Forwards and Backwards (working memory)

Secondary Measures for Aim 1:
[4] NIH Toolbox® Fluid Cognition Index (episodic memory, working memory, executive function, processing speed)

Aim 2 (secondary): **To determine the independent and combined efficacy of the *Move* and *Mind* interventions on memory-related serum biomarkers (brain-derived neurotrophic factor [BDNF], vascular endothelial growth factor [VEGF], insulin-like growth factor 1 [IGF-1]) among women ≥65 years with CVD.** ***Hypotheses: Move and Mind each will improve serum biomarkers (main effects). In addition, there will be an interactive effect such that MindMoves will show a greater increase in biomarkers than the sum of the main effects of Move and Mind.***

Aim 2 tests the effects of *Move* and *Mind* individually (main effects) and combined (interaction effect) on memory-related serum biomarkers (BDNF, VEGF, IGF-1) at 24, 48, and 72 weeks post-baseline. Analyses will use multi-level mixed models as described in Aim 1. Due to known variation in BDNF levels throughout the day, time of day of assessment will be included as a time-varying covariate for analyses of impact on BDNF.

Some secondary analyses related to Aims 1 and 2 are planned. We will test intervention effects on the target behaviors of physical activity (Actigraph accelerometer, self-report) and cognitive activity (self-report). Although both *Move* and *Mind* have proven efficacy, we will verify their impact on target behaviors. Second, we will explore whether there is evidence that the treatment effects of *Mind* and/or *Move* were attenuated by behavior changes among those who did not receive one or both intervention (e.g., due to increased use/ownership of physical activity monitors and/or computers). For those in the control group, we expect no change in target behaviors (physical activity for *Move*, cognitive activity for *Mind*). From the models in the former secondary analysis described above, we will calculate estimates of the time slope for the appropriate no-treatment groups and confirm that they are not significantly greater than zero. We also will assess change in use/ownership of physical activity monitors and computers.

Measures for Aim 2 (see section 4.3):
[5] BDNF
[6] VEGF-A
[7] IGF-1

Aim 3 (exploratory): **To examine depressive symptoms and genetic factors (*APOE*-ε4 allele, BDNF genotype) as potential moderators of the association between changes in target behaviors (physical activity, cognitive activity) and health outcomes (memory performance, serum biomarkers).**

Aim 3 examines depressive symptoms and genetic factors as potential moderators of intervention efficacy on memory performance and effect on memory-related serum biomarker levels. A continuous measure of baseline depressive symptomatology (CES-D) and dichotomous indicators of *BDNF* genotype and *APOE*-ε4 allele status will be added to the models in Aims 1 and 2. Intervention effect x time x moderator interaction effects will be evaluated for significant moderation of the intervention effects by these three variables. We expect that intervention effects will be attenuated by higher levels of depressive symptoms and by the presence of a $BDNF^{Met}$ genotype or *APOE*-ε4 allele. When significant moderation is found, we will test the extent to which moderation occurs between the intervention and uptake of the target behaviors (e.g., physical activity and cognitive activity) as well as between change in target behaviors and health outcomes (e.g., memory performance and memory-related serum biomarkers). For example, depressive symptoms are hypothesized to reduce the degree to which changes in physical activity and cognitive activity lead to improved memory. In addition, participants with higher levels of depressive symptoms may participate less in the intervention and therefore exhibit fewer changes in target behaviors. Though power is likely to be lower for Aim 3 than for Aims 1 and 2, these analyses will contribute important deductive data for planning future studies.

In terms of the multilevel model presented above, a person-level covariate (β_{15k}) will be added to the time equation (π_{1jk}). A corresponding cluster-level equation for β_{15k} also will be added to the equations. Parameters γ_{151}, γ_{152}, and γ_{153} represent moderation of the *Move* main effect, *Mind* main effect and *MindMoves* interaction effect respectively.

$\pi_{1jk} = \beta_{10k} + \beta_{11k}(\text{age}) + \beta_{12k}(\text{race}) + \beta_{13k}(\text{education}) + \beta_{14k}(\text{BMI}) + \boldsymbol{\beta_{15k}}\textbf{(moderator)} + r_{1jk}$
$\beta_{15k} = \gamma_{150} + \gamma_{151}(\text{Move}) + \gamma_{152}(\text{Mind}) + \gamma_{153}(\text{MindMoves})$

Measures for Aim 3 (see section 4.3):

Dependent Variables
[1] East Boston Memory Test (episodic memory)
[2] Category Fluency (semantic memory)
[3] Digit Span Forwards and Backwards (working memory)
[4] NIH Toolbox® Fluid Cognition
[5] BDNF
[6] VEGF
[7] IGF-1

Moderators
[13] Center for Epidemiologic Studies-Depression Scale
[14] *APOE*- ε4
[15] BDNF gene Val66Met polymorphism