

# The design and progress of a multidomain lifestyle intervention to improve brain health in middle-aged persons to reduce later Alzheimer's disease risk: The Gray Matters randomized trial

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## Abstract

**Introduction:** Most Alzheimer's disease (AD) prevention studies focus on older adults or persons with existing cognitive impairment. This study describes the design and progress of a novel pilot intervention, the Gray Matters study.

**Methods:** This proof-of-concept randomized controlled trial tests an evidence-based multidomain lifestyle intervention in 146 persons aged 40 to 64 years, in northern Utah. Data collectors were blinded to participants' randomization to treatment (n = 104) or control (n = 42). Intervention targeted physical activity, food choices, social engagement, cognitive stimulation, sleep quality, and stress management, and uses a custom smartphone application, activity monitor, and educational materials. Secondary outcomes include biomarkers, body mass index, cognitive testing, and psychological surveys.

**Results:** Midway through the study, achievements include a 98.7% retention rate, a 96% rate of compliance with app data entry, and positive trends in behavioral change.

**Discussion:** Participants were empowered, learning that lifestyle might impact AD risk, exhibiting positive behavioral changes thus far.

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## Keywords:

Lifestyle behavioral intervention; Randomized controlled trial; Middle age; Multidomain; Technology

Disappointing results from recent drug trials for Alzheimer's disease (AD) medications, including bapineuzumab [1] and solanezumab [2], have led to the development of preventive interventions that complement the pharmacological

search for a cure. The observation that common genetic variants may account for roughly 30% of variance in risk for AD [3], implies that a substantial portion of risk may be the result of modifiable "environmental factors" [4].

Physical activity has been linked to better cognitive function [5] and lower AD risk [6], potentially via neuroprotection through increased neurogenesis and the enhancement of brain cytoarchitecture [7]. Additionally, healthy diet and good nutrition are linked to lower dementia risk, including dietary patterns rich in fruits, vegetables, whole grains,

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<http://dx.doi.org/10.1016/j.trci.2015.05.001>

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and low fat dairy [8]. Sleep disturbances may influence the development of AD via the modulation of biochemical processes that influence AD neuropathology [9], and greater social engagement has been associated with lower rates of incident dementia [10,11].

Midlife health has implications for later dementia as obesity [12], hypertension [13], and serum cholesterol [14] have been linked to higher dementia risk in late life. Because of the multidimensional risk factors for AD and a strong evidence of a long presymptomatic phase [15], multidomain preventive interventions are critically needed in midlife (and earlier) to maximize the effect on AD risk reduction [16].

Recent multidomain randomized controlled trials (RCTs). Encouraging individuals to change multiple domains of their lifestyle has inherent challenges [17]; however, a variety of intervention modalities may be useful and successful. In a recent study of 80 middle-aged persons, King et al. [18] demonstrated that participants using three different smartphone apps focusing on (1) goal setting/monitoring, (2) social comparisons and supports, or (3) operant conditioning, each showed increases in physical activity levels. Smith-DiJulio and Anderson [19] implemented a multimodal lifestyle cardiovascular risk intervention in 60 middle-aged women in Australia, finding that subjects were generally continuing healthy behaviors in a 5-year follow-up survey. Anstey and colleagues are currently conducting a multidomain health education RCT in Australia among 176 middle-aged persons, including three groups—online only, online and face-to-face, and active control [20]. Similarly, multidomain prevention trials are being conducted among older adults at higher AD risk, emphasizing exercise and nutritional advice [21] in combination with cognitive training [22,23] or medical treatment of risk factors [24].

In summary, a number of RCTs designed to lower AD risk via lifestyle behavioral change have commenced in recent years; however, nearly all these studies focus on *older adults* or on *middle-aged persons at higher risk for AD*. Indeed, none were found that targeted the general population of middle-aged individuals, in the United States or elsewhere, and none have taken a holistic approach to encourage positive lifestyle changes in as many domains as the study reported herein.

Gray Matters is a multidomain pilot RCT designed to promote positive changes in lifestyle (exercise, nutrition, cognitive stimulation, social engagement, stress management, and sleep quality), specifically for the purpose of reducing AD risk in healthy middle-aged adults (ClinicalTrials.gov Identifier: NCT02290912). The study serves as a proof-of-concept design; data from the project informs research and will also inform future interventions. The transtheoretical model of behavior change [25] provides a theoretical foundation for the intervention, guiding the assessment of individuals' motivation and readiness to change, alongside the measurement of behavioral and health outcome change. The goal for each domain is to introduce evidence-based associations explaining AD risk and encourage positive changes. This RCT is

currently underway in Cache County, Utah, and we report here the methods and baseline sample characteristics.

## 1. Methods

### 1.1. Study design

This pilot study is an RCT; immediately after the pretest data collection (to ensure examiners were blinded), subjects were randomly assigned into treatment or control condition. The treatment group was not given a strictly prescribed regimen and consequently a wide range of engagement levels was anticipated. Hence, two-thirds of the sample was randomized to treatment and one-third to control, using a uniform (0,1) random number generator within SPSS v. 21. The intervention was delivered over a 6-month period (starting April 2014) with posttest data collection planned at 6 months.

### 1.2. Participants

The study used a convenience sampling approach. Recruitment efforts included a marketing flyer distributed through USU listservs, local health fairs, and county health department liaisons. Interested persons completed a prescreening eligibility survey. To achieve 80% statistical power to detect a medium effect size (Cohen's  $d = 0.50$ ) when comparing the difference between two independent means at a 2:1 treatment:control ratio, 96 treatment and 48 control (144 total) participants were needed (G\*Power; <http://www.psych.uni-duesseldorf.de/abteilungen/aap/gpower3/>). The 2:1 ratio was chosen because it maximized the number of individuals receiving treatment, while minimizing cost (budgets were restricted because of the pilot-nature of the study). Additionally, given that the intervention program allowed participants to create their own custom behavior change plan, the 2:1 ratio facilitated the option at study's end to examine change within each behavioral domain among the subsample of participants who indicated that it was their priority to focus change efforts on the given domain. We enrolled the first 146 persons who met eligibility criteria. After randomization, both spouses in 12 married couples were assigned to the same group to avoid the intracouple contamination of intervention content. The final assignments included 104 participants in the treatment group and 42 participants in the control group, resulting in final statistical power of 78%. A flowchart depicting recruitment, enrollment, randomization, and follow-up throughout the study, following the Consolidated Standards of Reporting Trials guidelines, appears in Fig. 1.

Eligibility criteria included the following: (1) age between 40 and 64 years, (2) body mass index no higher than 41, (3) possession of a smartphone or tablet (iOS or Android), (4) fluency in the English language, (5) residence in Cache County, and (6) not having any of the following exclusionary medical conditions: pregnancy, dementia, unmanaged diabetes, or untreated major depression. Note

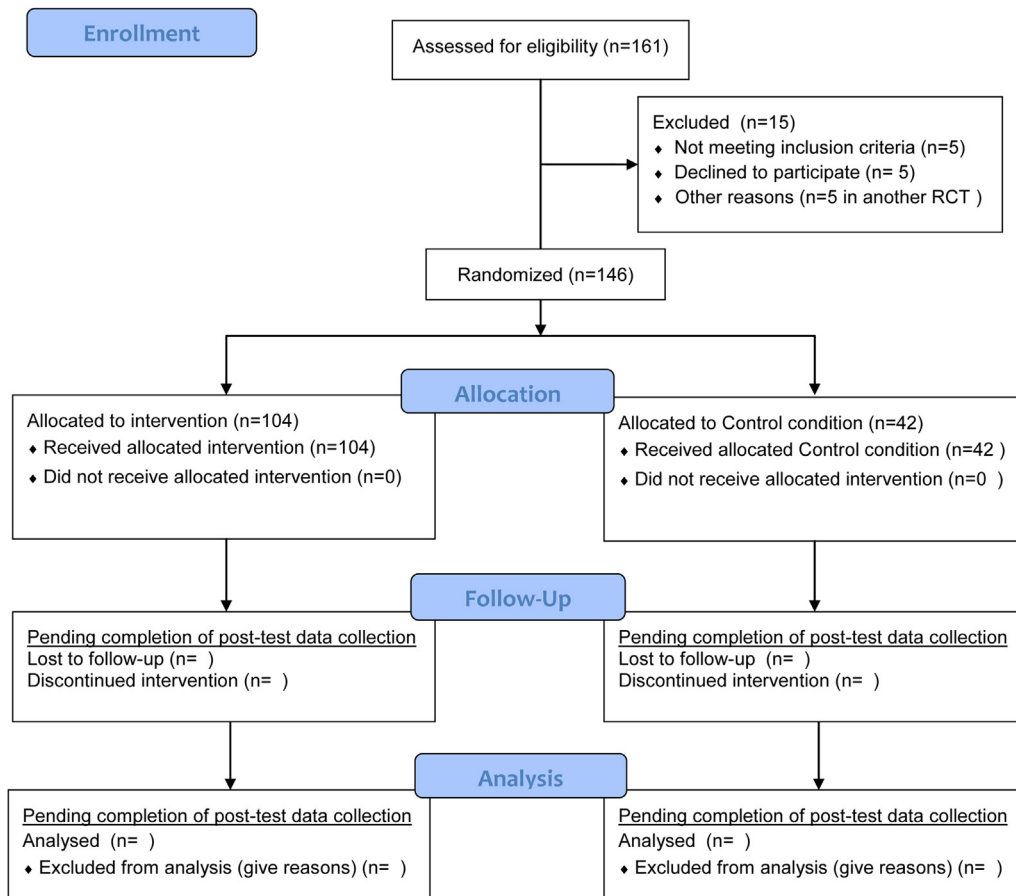


Fig. 1. Flow diagram of participant recruitment, enrollment, randomization, and follow-up in the Gray Matters Alzheimer's Disease Prevention Study.

that although a dementia diagnosis was exclusionary, mild cognitive impairment was not.

### 1.3. Intervention program

The intervention provides evidence-based information linking lifestyle behaviors and cognitive decline or risk for AD or other dementia. Six behavioral domains associated with AD risk were targeted: physical activity, healthy food choices, social engagement, cognitive stimulation, stress management and sleep quality. *Activity Monitor*: Each participant received a Nike FuelBand SE activity monitor, tracking steps taken, calories burned and a proprietary metric, "Nike Fuelpoints." The monitors also provided a visible reminder to engage in physical activity daily.

#### 1.3.1. Educational components

After an initial "kickoff event" with a motivational speaker and six informative booths, the intervention included the following elements: A series of 39 "booster events" were delivered over the 6-month intervention period. Booster sessions were designed to emphasize the link between a behavioral domain and AD risk and to give participants experiential opportunities to try example behaviors, the overall behavioral domain being promoted, rather than specific activities. For

example, individual nutrients or food items were not promoted, rather, a healthy overall dietary pattern rich in fruits, vegetables, whole grains, fish and lean meats, akin to the Dietary Approaches to Stop Hypertension diet [26], the Mediterranean diet [27], and the United States Department of Agriculture dietary recommendations [28]. Participants were advised to check with their physicians before substantially increasing their physical activity, and were given Centers for Disease Control and Prevention recommendations of 150 minutes/week of moderate and 75 minutes/week of vigorous physical activity as a general guideline.

#### 1.3.2. Social engagement workbook

A weekly workbook was provided, featuring activities based on empirical findings related to quality social support, perceived support, conflict resolution, and emotional/instrumental support. The workbook was designed to help participants set goals, follow through, and reflect on building or maintaining quality social support and relationships.

#### 1.3.3. Smartphone application

Participants were given an app created for this study and designed to work on Apple iOS and Android OS smartphones and tablets. This technology included three primary functions (Fig. 2). *Information*: Tapping a "daily fact"

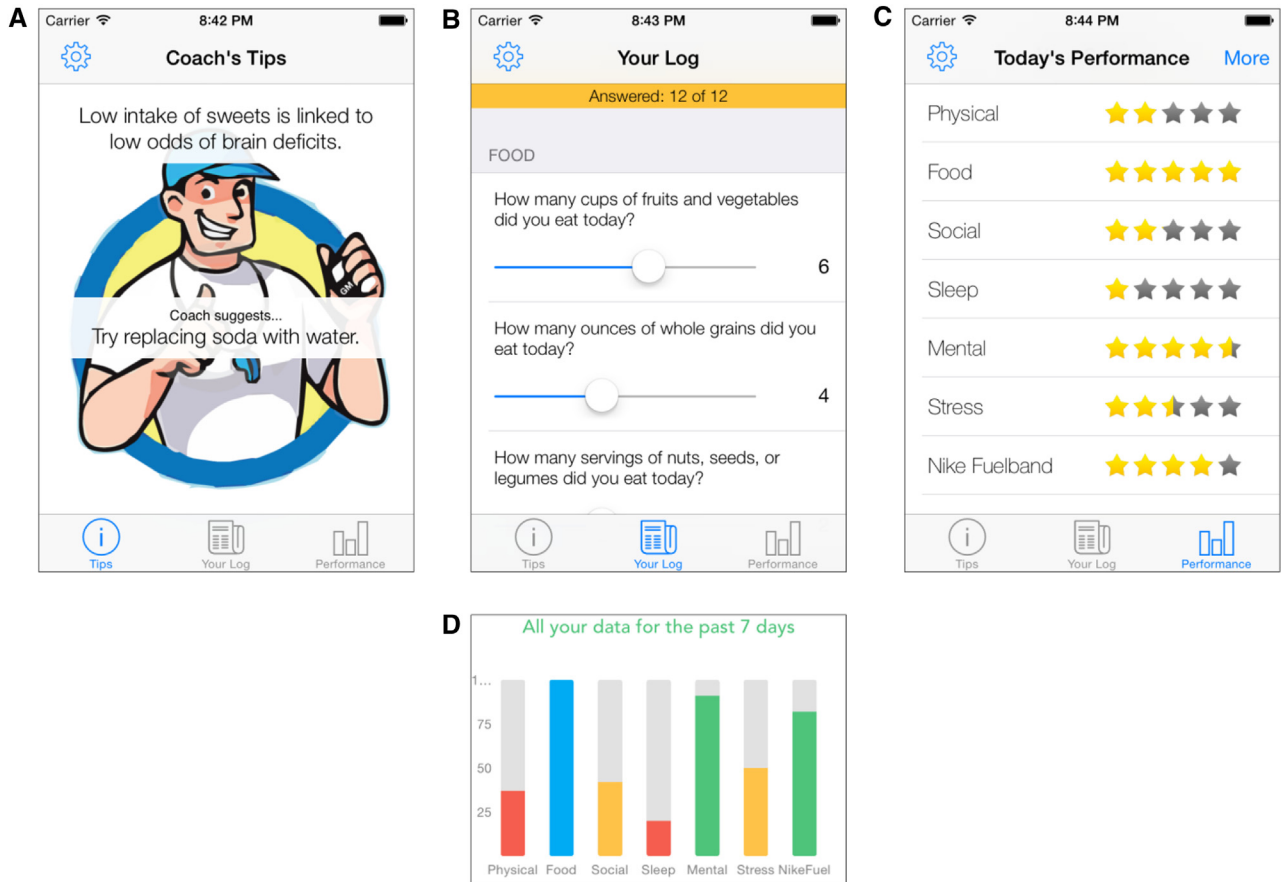


Fig. 2. Key functions of the Gray Matters smartphone app (for smartphone or tablet; iOS or Android). (A) The factoid and suggestion screen (“Tips”). (B) Behavioral data entry screen with 12 questions (“Your Log”). (C) Daily feedback for each domain with star ratings (“Performance”). (D) Weekly summary presented in a bar chart across all domains (“More”).

produced a full reference from the lifestyle/AD literature and concrete suggestions for adoption. (e.g. “Lack of physical activity is a risk factor for AD. Try taking a walk during your lunch break.”) *Accountability*: Subjects were asked daily to respond to a set of 10 behavioral questions, taking 2 minutes/day total to complete. The 10 questions enquired about physical activity level (moderate and vigorous), consumption of fruits/vegetables, whole grains, legumes/nuts, cognitively stimulating activities, novel information processing activities, sleep improvement efforts, social engagement, and stress reduction efforts. Data entry took the form of a user-friendly horizontal “slider.” *Feedback*: The app provided a progress report with two graphical displays (1–5 stars daily and histogram weekly).

#### 1.3.4. Personal coach

A team of 28 student interns volunteered to be “personal coaches” and were trained in motivational interviewing and the transtheoretical model. Coaches provided a weekly email or text message exchange with their “clients” to provide emotional support and encouragement for lifestyle change goals, keeping a log monitored by faculty

researchers, who provided assistance in resolving any questions or issues.

#### 1.3.5. Study website

A website was created and shared with participants, providing intervention content in the six domains. The website provided links to other resources, study technology supports, and an email portal for submitting questions to the research team.

#### 1.4. Procedures

The Institutional Review Board at Utah State University approved this research, and written informed consent was collected from all participants. At each participant’s clinic visit, height, weight, pulse, and blood pressure were measured, and a urine sample and venous blood sample were collected. A clinic nurse (consulting with clinic physician as needed) reviewed the detailed medical history, identified potential exclusionary conditions, and reviewed all current treatment regimens (only two were excluded because of health and safety concerns). Laboratory reports were emailed to each participant. In approximately 10

cases, participants with significant abnormal laboratory results were notified promptly by telephone and were advised to see their primary care provider to discuss further evaluation and treatment, but were allowed to enroll in the study.

Participants completed a 1-hour battery of paper-pencil and computerized cognitive tests at a separate clinic visit, administered by trained psychometrists (extensively trained and field certified by the study neuropsychologist J. Tschanz). Once laboratory work and cognitive testing were completed, participants then completed online surveys. Once pretest data collection was complete and random assignments were made, participants received an email announcing their experimental group assignment. During the course of the 6-month intervention period (April–October, 2014), control subjects received no contact other than data collection whereas treatment subjects received all intervention components as described previously. Treatment subjects were encouraged to make healthy behavioral changes, whereas control subjects were encouraged to “go on about their lives as if they were not in the study” over the intervention period. To better approximate a real-world implementation of this intervention, treatment group participants were not required to follow a strict behavioral regimen over the 6-month intervention period, rather, they were permitted to engage in whichever components of the intervention they desired “cafeteria style.”

Participants from treatment and control groups are slated to complete a posttest data collection protocol October through December 2014, using the same procedures as in the pretest data collection—laboratory work, cognitive testing, and surveys. Control participants were aware via informed consent that the study involved lifestyle behaviors related to risk for AD, but as stated previously, did not have contact with the interventionists over the 6 months of intervention. They are slated to receive the intervention materials immediately on completing the posttest data collection protocol.

## 1.5. Measurement

Primary outcome measures were behavior in six targeted domains. Secondary outcome measures included anthropometric measures, blood-based biomarkers, metacognition, motivation, readiness-for-change, sleep quality, social engagement, depression, couple satisfaction (among married persons), and objective cognitive testing.

### 1.5.1. Biomarkers

Body mass index was computed from height and weight. A three-measurement seated resting blood pressure protocol was used. After a 5-minute period, readings 2 and 3 were collected then averaged. Trained phlebotomists drew blood for the following: a complete blood count, comprehensive chemistry and lipid profiles, high sensitivity C-reactive protein (hsCRP), and insulin. A BioPhotonic Scanner<sup>®</sup> which shines a light

emitting diode (LED) at a site on the palm was used to measure the carotenoid level, a clinical marker of phytonutrients from vegetable consumption [29]. ([http://www.nuskin.com/en\\_BN/products/pharmanex/scanner.html](http://www.nuskin.com/en_BN/products/pharmanex/scanner.html)).

### 1.5.2. Cognitive tests

Although we do not hypothesize cognitive performance to change over the short duration of the study in a middle-aged sample, we measured cognition (1-hour battery) at baseline for covariation purposes, and tracked cognitive performance over time to have the ability to demonstrate stability (or to measure unintended positive or negative changes, if they arise). Global cognitive ability was assessed with the Montreal Cognitive Assessment [30], episodic memory was assessed with the Rey Auditory Verbal Learning Test [31], and verbal fluency was assessed with the Controlled Oral Word Association Test [32]. Receptive vocabulary, working memory, processing speed, and executive functioning were assessed using the tests from the National Institutes of Health (NIH) Toolbox: Picture Vocabulary, Flanker Inhibitory Control and Attention Test, List Sorting Working Memory Test, and Oral Symbol Digit Test [33].

### 1.5.3. Surveys

Current depressive symptoms were measured with the 20-item Center for Epidemiologic Studies—Depression scale [34]. Psychological stress was measured with the 10-item Perceived Stress Scale [35]. Sleep quality was measured with the Pittsburgh Sleep Quality Index, consisting of four questions concerning the amount of sleep and 12 questions concerning sleep difficulties and treatments [36]. Metacognitive concern was measured with a set of seven items (each scored from 1 = *much better* to 5 = *much worse*), comparing current memory to how it was 3 years ago, adapted from a questionnaire of functional ability [37], with total score ranging from 7 to 35. The seven items queried remembering: recent events, names/faces of friends/relatives, train of thought, navigation to familiar places, operation of appliances, how to perform household chores/hobbies, and an overall rating. Intrinsic motivation was measured with the Situational Intrinsic Motivational Scale subscale for intrinsic motivation [38]. This scale consists of four items enquiring as to reasons the individual is engaged as a study participant (each scored from 1 = *corresponds not at all* to 7 = *corresponds exactly*), with the total score ranging from 4 to 28. Items included the following: because I think that this activity is interesting, because I think that this activity is pleasant, because this activity is fun, and because I feel good when doing this activity. The Revised University of Rhode Island Change Assessment produced a readiness for change scale [39].

Dietary pattern was measured with the Diet History Questionnaire, a 124-item food frequency questionnaire developed and validated by the National Cancer Institute



[40]. The Dietary Approaches to Stop Hypertension (DASH) diet accordance score was computed by summing across the accordance of six food groups (fruits, vegetables, whole grains, low-fat dairy, nuts/seeds/legumes, red/processed meat) and two nutrients (sodium and added sugar) emphasized in the DASH diet, each with a score of 0 to 10, generating an overall DASH score ranging from 0 to 80.

To measure social engagement, four scales from the NIH Toolbox were used: the Emotional Support Scale (range 8–40), the Friendship Scale (range 8–40), the Loneliness Scale (range 5–25), and the Hostility Scale (range 8–40; National Institutes of Health). Given that stronger marital relationships predict better success at lifestyle change among married persons, we measured couple satisfaction in our married subsample using the 32-item Couple Satisfaction Index [41]. Physical activity level was measured with two questions, enquiring about vigorous and moderate physical activity, in hours per week.

## 2. Results

The Gray Matters sample is almost exclusively middle-income and Caucasian, ranging in age from 40 to 64 years ( $M = 54.6$ ; standard deviation [SD] = 6.9), with two-thirds of the sample female, and 77% college graduates. Participants appear to be somewhat more at-risk than the population generally, with 43.2% having a first-degree relative and 69.2% having a parent, grandparent, aunt, uncle, or sibling with AD or other dementia. Motivational and readiness for change characteristics suggested a highly motivated group of participants, with nearly 40% having served in a dementia care giving role.

Treatment group participants self-prioritized the six behavioral domains, with overall rank order of importance (from top to bottom priority): physical activity, cognitive stimulation, healthy food choices, stress management, sleep quality, and social engagement. A total of 73 (70%) of the 104 treatment group participants have attended at least one “booster event,” with participation ranging from 0 to 10 ( $M = 2.0$ ,  $SD = 2.3$ ) events over the first 3 months of the intervention period. Most of the treatment group participants having had at least two email or text exchanges with their coaches over the initial 3 months of intervention.

Compliance with usage of the smartphone app was high, with the number of app launches averaging approximately 300 launches per week, or about three/week/participant (Fig. 3). Examples of average daily response to behavioral questions on the app, plotted across the first 14 weeks of the study, including within-person regression model statistics, appear in Fig. 4. At study completion, daily behavioral data will be condensed into weekly averages to study behavioral trajectories over the 6-month intervention period for inferential analyses.

Table 1 provides descriptive statistics on a wide range of behavioral, biomarker, and sociodemographic variables,

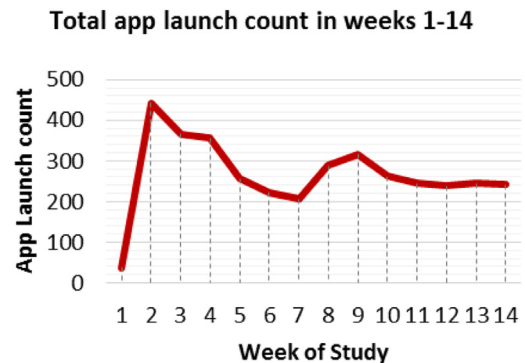


Fig. 3. Average weekly number of app launches over first half of intervention.

with a statistical test comparing treatment and control groups at baseline. Control subjects were somewhat higher in metacognitive concerns and total cholesterol than treatment subjects, but the two groups did not differ on any other measure.

Given the age of participants, clinical evaluations for dementia will not be conducted. It is hypothesized that significantly greater gains in healthy lifestyle behaviors and both subjective and objective outcomes will be observed in the treatment group, compared with control group, over the 6-month intervention period, when these data become available early in 2015. We did not assess side effects related to exercise, such as muscle soreness, however, there were no harms or unintended effects in either group reporting to personal coaches or study coordinators over the duration of the study.

## 3. Discussion

The Gray Matters proof-of-concept study uses a multidomain healthy lifestyle intervention to promote positive behavioral changes that are associated with lower AD risk, with the goal to increase participants' knowledge, intrinsic motivation, and sense of empowerment to make such changes.

The study, although large for a pilot, is revealing the types of experiential activities that are most popular and effective, and the extent to which participants are engaging in meaningful and sustained behavioral change, at least in domains they had initially prioritized. Over the first half of the intervention period, participants exhibited a high adoption rate of the smartphone app, with a promising trend toward increases in the engagement of positive behaviors and reduction in adverse self-reports (e.g. perceived stress) among treatment group participants.

At study conclusion, treatment efficacy will be determined overall and by subgroups defined by baseline behavioral and health characteristics, intrinsic motivation, and engagement with intervention components. Focus groups are planned after the post-test data collection, to gain

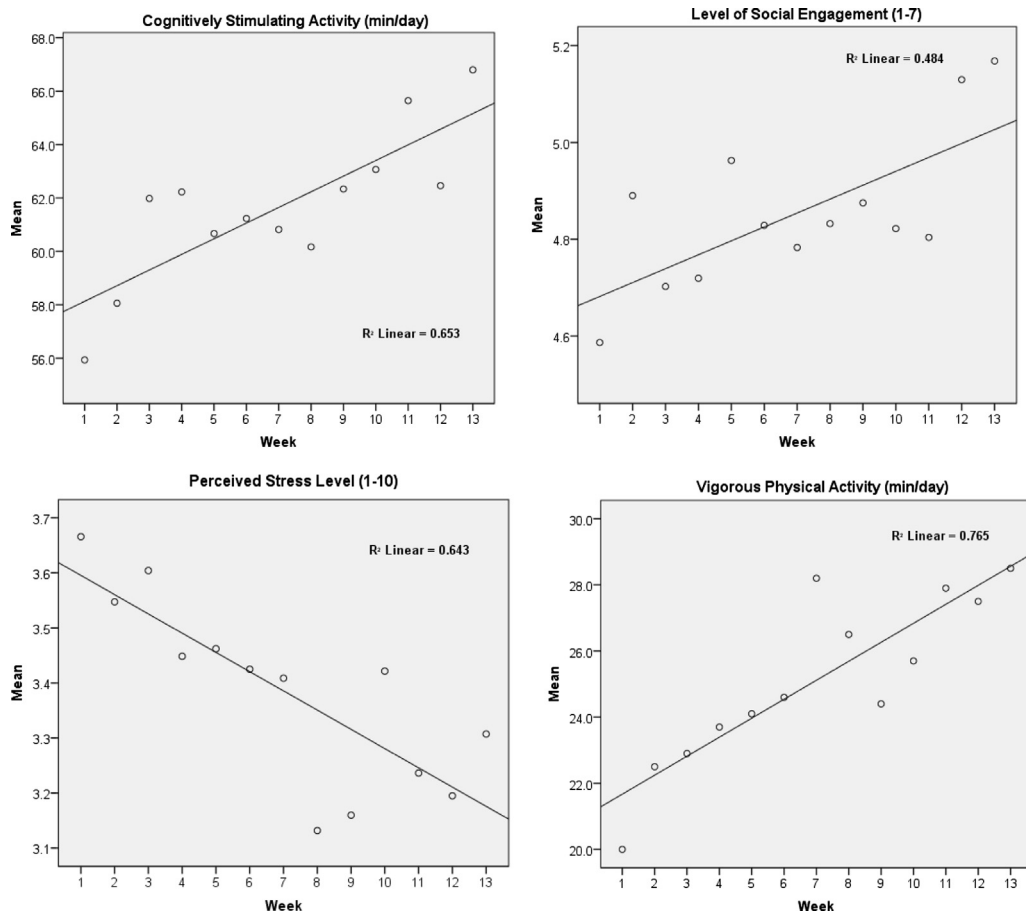


Fig. 4. Weekly averages of four daily behavioral levels (per smartphone application, averaging daily values within each week) for cognitively stimulating activities ( $\beta = 0.81$ ,  $P = .001$ ), social engagement ( $\beta = 0.70$ ,  $P = .008$ ), perceived stress ( $\beta = -0.81$ ,  $P = .001$ ), and physical activity ( $\beta = 0.88$ ,  $P < .001$ ; all coefficients are standardized).

qualitative inferences. App data will be examined to determine if engagement and behavioral change varied across the course of the intervention. This pilot study has already proven to be extremely informative in helping the research team to fine-tune the intervention and plan additional investigations. Future studies will test for the efficacy of specific intervention components. Although a maintenance phase was originally planned, because of shortage of funding, this is being removed from the study protocol. Future expansion of the app will personalize various functions to incorporate each participant's personal history, recent behavioral gains/losses, health status, and predisposition to engage. This stratified medicine approach may be the most powerful to maximize the likelihood of success with individuals across a wide range of readiness for change.

The racially and culturally homogeneous current sample may limit the generalizability of study findings to other groups. Nevertheless, contextual variables which might otherwise confound results are generally absent and thus, internal validity is increased. Future studies are planned to test the efficacy of this intervention in a more ethnically and socioeconomically diverse sample, mindful of the need

for cultural sensitivity. A question to be more fully addressed at this study's conclusion is whether we can profile and then target those participants who will engage, sustain, and benefit from the intervention. We note that 43.2% of the sample had a first degree relative with AD or other dementia. Such individuals may be more highly motivated for lifestyle changes because of perceived genetic risk for AD, which may impact the generalizability of this pilot to a nationally representative sample. Future research will examine whether family history of AD predicts increased behavioral change.

A cure for AD may still be years or even decades away, and even when discovered may have contraindications for universal application. Although genetics are largely non-modifiable, interventions that assist individuals with making and sustaining lifestyle behavioral changes that lower AD risk are urgently needed as a complement to pharmacologic therapies. Extensive research supports associations between poorer lifestyle behaviors and cardiovascular risk, and interventions to improve lifestyle behaviors have shown promise. To date, research has established associations between poorer lifestyle behaviors and reduced

Table 1

Comparison of 104 treatment and 42 control group participants at pretest (t-test for independent groups with continuous variables, and chi-square test for independence with categorical variables)

Continuous variables	Treatment group; mean (SD)	Control group; mean (SD)	t-test (P-value)
Intrinsic motivation subscale of SIMS measure (range: 4–28)	16.6 (5.2)	15.0 (4.6)	–1.596 (.11)
Metacognitive concerns (range: 7–35)	22.1 (2.7)	23.5 (2.1)	2.751 (.01)
Dietary approaches to stop Hypertension diet score (range: 0–80)	47.5 (7.0)	46.8 (7.3)	–0.499 (.62)
Moderate intensity physical activity (minutes/week)	223.0 (222.8)	174.4 (148.6)	–1.183 (.24)
Vigorous intensity physical activity (minutes/week)	103.5 (190.5)	94.4 (132.2)	–0.259 (.80)
Body mass index	27.6 (5.2)	28.4 (5.1)	0.835 (.41)
Systolic blood pressure (mmHg)	115.9 (14.3)	116.4 (11.5)	0.210 (.83)
Diastolic blood pressure (mmHg)	74.4 (9.8)	74.8 (8.4)	0.207 (.84)
Pulse (beats/minute)	65.8 (9.3)	63.0 (9.8)	–1.659 (.10)
Carotenoid palm scan (Raman counts)	34159 (11914)	35281 (13693)	0.493 (.62)
Age (yrs)	54.6 (6.7)	52.9 (7.3)	–1.286 (.20)
Number of relatives with dementia	1.1 (1.0)	1.1 (1.0)	–0.162 (.87)
Total cholesterol (mg/dL)	192.9 (32.9)	206.6 (36.2)	2.204 (.03)
C-reactive protein (mg/L)	2.4 (4.3)	3.1 (3.8)	0.888 (.38)
Triglycerides (mg/dL)	104.7 (54.3)	111.5 (49.2)	0.701 (.49)
Insulin ( $\mu$ IU/mL)	10.0 (9.3)	9.3 (6.5)	–0.488 (.63)
Serum glucose (mg/dL)	92.5 (9.8)	95.5 (16.8)	1.358 (.18)
Categorical variables	Treatment group, N (%)	Control group, N (%)	Chi-square (P-value)
Gender			
Male	36 (35.0%)	11 (31.4%)	0.144 (.70)
Female	67 (65.0%)	24 (68.8%)	
Education			
HS/GED	1 (1.0%)	1 (2.9%)	1.564 (.67)
College/trade	19 (18.6%)	4 (11.4%)	
School/associate's college			
Graduate/bachelor's	42 (41.2%)	16 (45.7%)	
Graduate/professional degree	40 (39.2%)	14 (40.0%)	
Overall health			
Fair	8 (7.8%)	5 (14.3%)	1.397 (.50)
Good	60 (58.8%)	18 (51.4%)	
Excellent	34 (33.3%)	12 (34.3%)	

Abbreviations: SD, standard deviation; SIMS, Situational Intrinsic Motivational Scale; HS, high school; GED, general education development.

cognitive performance in late life and/or AD risk. Before we can determine whether lifestyle interventions such as Gray Matters actually reduce AD risk, we need to understand whether individuals will modify lifestyle behaviors when presented with knowledge and resources concerning the associations between these behaviors and AD risk. Such is the purpose of the Gray Matters pilot intervention, and preliminary data are promising. The delivery of these interventions to middle-aged persons, decades before likely disease onset, may alter cognitive health trajectories. Building infrastructures for international collaborations, as is occurring in Europe [42] will be necessary for addressing the projected AD incidence at a global level.

## Acknowledgments

This research was supported by the Office of the Vice President for Research and Graduate Studies, Utah State University, the Emma Eccles Jones College of Education

and Human Services, Utah State University, Nike Corporation, the Intermountain Logan Regional Hospital Foundation, the Department of Education and Learning Northern Ireland, and the Computer Science Research Institute at the University of Ulster. The authors want to express appreciation and extend thanks to the following individuals and organizations in the Cache County, Utah area who assisted with the development and delivery of intervention components: Rich Gordon, Roxane Pfister, Martha Cannon, Craig Jessop, J.R. Dennison, Lester Pappa, Stephanie Behrens, Elizabeth Nix, Dave Wallace, the Sports Academy and Racquet Club, Cache Valley Strength & Conditioning, Kubex Fitness, the City of Logan Aquatic Center, the Whittier Community Center, and Natural Philosophy Yoga Studio. Finally, the authors are grateful to have had the enthusiastic involvement and hard work of the team of 51 student research interns and the support and participation of the 146 community residents who were subjects in this pilot study.



## RESEARCH IN CONTEXT

1. Systematic review: Published studies of randomized controlled trials (RCT) of lifestyle interventions targeting cognitive health were reviewed, along with observational and RCT studies within specific behavioral domains, to ascertain strength of association with lowered Alzheimer's disease (AD) risk.
2. Interpretation: This manuscript alerts the AD clinical and research communities that this novel approach to AD prevention, in the form of a lifestyle behavioral intervention with custom smartphone application, among middle-aged persons, is underway. To date, preliminary behavioral change trajectories show promising results.
3. Future directions: Six months hence, the results from the treatment versus control group comparisons examining change over the 6-month intervention will become available. These results will clarify the extent to which the intervention affects change in biomarkers, body mass index, cognitive status, and other outcomes. Additional RCT studies are planned in more ethnically diverse samples, and to evaluate whether positive effects are sustained over a subsequent 2-year maintenance phase.

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