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# 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 simulation, 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.



*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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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.psycho.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