The virtual cognitive health (VC Health) study: design, recruitment, and baseline characteristics of a fully remote single-arm clinical trial to prevent or delay cognitive impairment in older adults

Nick Bott¹,², PsyD; Shefali Kumar³, MPH; Caitlyn Krebs², BS; Jordan M Glenn², PhD; Erica N Madero², MPH; Jessie L Juusola³, PhD

¹Department of Medicine, School of Medicine, Stanford University, Stanford, CA, United States
²Neurotrack Technologies, Inc., Redwood City, CA, United States
³Evidation Health, San Mateo, CA, United States
ABSTRACT

Background: A growing body of evidence supports the use of lifestyle interventions for preventing or delaying the onset of Alzheimer’s disease (AD) and other forms of dementia in at-risk individuals. The development of virtually delivered programs would increase the scalability and reach of these interventions, but requires validation to ensure similar efficacy to brick and mortar options.

Objective: The objectives of this study are to examine the impact of a remotely delivered lifestyle intervention on (1) cognitive function, (2) depression and anxiety, and (3) various lifestyle behaviors, including diet, exercise, and sleep. Supplemental analyses will explore participants’ engagement patterns with the program, as well as the relationships between program engagement and outcomes. Here we report the study design and data analysis plan, as well as the baseline participant characteristics of the sample for the virtual cognitive health (VC Health) study.

Methods: Older adults (age 60-75) with subjective memory decline as measured by the Subjective Cognitive Decline (SCD-9) questionnaire, and who reported feeling worried about their memory decline, were eligible to participate in this single-arm pre-post study. All participants enrolled in the year-long virtual intervention, which consists of health coach-guided lifestyle change for improving diet, exercise, sleep, stress, and cognition. All components of this study were conducted virtually, including the collection of data and the administration of the intervention. Participants were assessed at baseline, 12 weeks, 24 weeks, and 52 weeks with online surveys and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test. Intention-to-treat analysis will be conducted on all outcomes.

Results: A total of 85 participants enrolled in the intervention and 82 are included in the study sample (3 participants withdrew). The study cohort is 74% female, 88% Caucasian, 78% overweight or obese, and 67% have at least a college degree. The average baseline RBANS score was 95.9±11.1, which is within age-adjusted norms. The average SCD-9 score was 6.0±2.0, indicating minor subjective cognitive impairment at the beginning of the study. Average baseline Generalized Anxiety Disorder (GAD-7) scores were 6.2±4.5 and Patient Health Questionnaire (PHQ-9) scores were 8.5±4.9, indicating mild levels of anxiety and depression at baseline.

Conclusions: Virtually delivered lifestyle interventions represent a scalable solution for the prevention or delay of AD. The results of this study will provide the first evidence for the efficacy of a fully remote intervention and lay the groundwork for future investigations.

Trial Registration: NCT02969460

Keywords: cognitive impairment; dementia; Alzheimer’s disease; lifestyle intervention; digital health; health coaching
Introduction

Cognitive impairment is a growing public health epidemic worldwide, representing one of the most prevalent chronic medical conditions in older adults\[1\]. In 2010, the direct and indirect costs of care associated with dementia totaled $600 billion globally, amounting to roughly 1% of the world’s gross domestic product\[2\]. The global costs associated with Alzheimer’s disease (AD), the most common form of dementia, are projected to increase ~400% from $186 billion in 2018 to $750 billion in 2050\[1\]. The challenge posed by dementia is amplified by the decades-long failure to develop effective pharmacological agents for the disease. The success rate of AD drugs is only 0.4%, compared to 19% for oncology compounds\[3\], leading some major pharmaceutical companies to abandon research efforts in the face of continued failures. The drugs currently approved for AD only treat the symptoms rather than the underlying causes of the disease, and fail to prevent or delay the progression of neurodegeneration involved in AD and other forms of dementia\[4\].

Conversely, non-pharmacological lifestyle-based interventions are gaining traction as an effective way to prevent or delay disease progression. Epidemiological studies estimate that modifiable risk factors, such as diabetes, hypertension, obesity, smoking, depression, physical inactivity, and low educational attainment account for as many as 30% of dementia cases\[5, 6, 7\]. In the absence of a cure, delay of AD or dementia onset by as little as one year is associated with enormous cost savings, with an estimated potential savings of $219 billion by 2050 in the US alone\[8\]. Additionally, a 5-year postponement could almost halve the projected AD prevalence by 2050\[9, 10, 11\]. Due to the proven ability to decrease some of the modifiable risk factors implicated in AD\[12, 13\], lifestyle-based interventions hold the potential to greatly reduce the burden of dementia as populations continue to age worldwide.

The lifestyle intervention for cognitive decline used in the multidomain Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)\[14\] has been at the forefront of these AD-related behavioral modification efforts and served as the primary inspiration for the program used in this study. The landmark FINGER study is an ongoing randomized controlled trial (RCT) demonstrating the efficacy of a multidomain lifestyle intervention as a preventive measure in older adults at risk for cognitive decline and dementia. The lifestyle intervention primarily focuses on exercise, diet, cognitive training, and management of vascular risk factors. The 2-year results\[15\] clearly showed that 1) individuals can be motivated to make long-term changes in their lifestyle to preserve cognitive function, and 2) a multidomain lifestyle intervention can improve composite cognitive performance at a two year follow-up.

The FINGER study, which used a clinic-based lifestyle intervention, was the first RCT to provide proof of concept that attending to lifestyle and vascular factors can protect against cognitive decline\[15\]. The success of the FINGER study has spawned numerous in-clinic replication studies around the globe, including the Singapore-based SINGER\[16\], China-based MIND-CHINA\[17\], and U.S.-based U.S. POINTER\[18\] studies. However, face-to-face lifestyle
change programs like the ones used in these studies are constrained by geographical and other logistical challenges, therefore warranting the exploration of internet-based programs that are better suited for widespread adoption in a real-world setting. The Maintain Your Brain study is a large-scale clinical trial in Australia aiming to demonstrate the efficacy of a fully digital, multidomain intervention at preventing cognitive decline[19]; however, results will not be available for a number of years. The Virtual Cognitive (VC) Health study described here is the first trial to our knowledge that explores the efficacy of a commercially available virtual lifestyle intervention aimed at preventing or delaying cognitive decline in at-risk older adults.

The primary objective of the VC Health study is to investigate the feasibility and effectiveness of a remotely delivered multidomain intervention for the prevention or delay of cognitive impairment in older adults at increased risk of cognitive decline. Secondary analyses will assess the effectiveness of the program at ameliorating symptoms of depression and anxiety, which are both risk factors for AD[20, 21]. Supplemental analyses will examine patterns of user engagement with the program and changes in various lifestyle behaviors. The year-long intervention consists of 6 months of active multidomain lifestyle change and 6 months of habit reinforcement during the maintenance phase. The main components of the intervention include coach-directed exercise, nutritional guidance, cognitive training, and social engagement. We hypothesize that this digital intervention modeled after the pivotal FINGER study[15] will result in 1) significant improvements in composite cognitive performance and 2) positive changes in depression and anxiety levels. Here we report the study design and analysis plan, as well as baseline characteristics of the study population for the VC Health study.

Methods

Study Design

The VC Health study is a 52 week-long, prospective intent-to-treat, single-arm, pre-post, virtual nationwide clinical trial to evaluate the impact of the VC Health program on cognitive function and mental health in older adults in the United States. While conventional clinical trials rely on in-person interactions for recruitment, screening, enrollment, data collection, and data monitoring, virtual clinical trials are enabled by advances in technology and digital health, allowing for fully remote participation in clinical trials[22]. For the VC Health study, an online study platform (Achievement Studies, Evidation Health Inc.; San Mateo, CA) was used to screen, consent, and enroll participants into the study, as well as to collect and monitor study data and guide participants through the trial. The study was approved by the Solutions Institutional Review Board (Columbia, MD) and is registered with clinicaltrials.gov (NCT02969460). The study protocol was designed and written by the investigators at Evidation Health, with input and review from the VC Health intervention team.
Participant Selection and Recruitment

Study participants were recruited through various digital platforms, including online patient communities, social media, and targeted advertisements across all 50 US states. Potential participants learned about the trial through a web portal explaining the study details. Those who were interested in participating then completed an online screener that assessed eligibility for the study.

Eligible participants were aged 60-75; endorsed subjective cognitive decline with worry as assessed by the validated nine-item Subjective Cognitive Decline (SCD-9) questionnaire and the one-item subjective cognitive decline with worry item, which have been shown to have early predictive value for progression to mild cognitive impairment (MCI) and AD; had reliable access to phone, text, and internet; and were interested in using a coaching program for cognitive health (Table 1). Study candidates were considered ineligible if they had a history of mental illness, substance abuse, learning disability, neurologic conditions, or dementia; had ophthalmologic or visual problems that would interfere with computer use; were already using a cognitive-training coaching program; or were currently pregnant.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Age ≥60 years old but ≤75</td>
<td>● Significant history of mental illness, substance abuse, learning disability, or neurologic conditions</td>
</tr>
<tr>
<td>● Individuals who show signs of subjective cognitive decline (assessed by scoring ≥ 1 on the Subjective Cognitive Decline (SCD-9) Questionnaire and endorsing the Personal Worry Item on the questionnaire)</td>
<td>● History of dementia</td>
</tr>
<tr>
<td>● Have the ability to make and receive phone calls</td>
<td>● Ophthalmologic/visual problems that prevent individual from viewing a computer screen at a normal distance (e.g., legal blindness, detached retinas, occlusive cataracts)</td>
</tr>
<tr>
<td>● Have the ability to send and receive text messages</td>
<td>● Currently participating in a formal cognitive-training coaching program</td>
</tr>
<tr>
<td>● Access to a desktop computer, video-teleconferencing and reliable internet connection</td>
<td>● Currently pregnant</td>
</tr>
<tr>
<td>● Motivated to use a daily coaching program</td>
<td></td>
</tr>
</tbody>
</table>

Enrollment and Study Procedures

Study candidates who met the eligibility criteria and who were interested in participating provided electronic informed consent on the online study platform, and then completed an online...
baseline assessment, which consisted of questions about demographic characteristics, lifestyle and overall health behaviors, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder scale (GAD-7), and self-reported sleep, diet, and activity levels. Next, study candidates were asked to schedule a baseline Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test. The RBANS was virtually administered via video-teleconference by a licensed psychologist (Echelon Group; Woodstock, GA). Once the participant completed the RBANS test, they were asked to complete their first Virtual Cognitive Health coaching session. This session lasted approximately 60 minutes and was conducted over the phone. A study candidate was considered enrolled once they completed their first coaching session.

Once enrolled, participants completed online assessments and RBANS tests at 12 weeks, 24 weeks, and 52 weeks. Since there are four alternate forms of the RBANS test, designed to reduce practice effects during repeated testing over time, participants in this study were given a different form for each of the four testing periods. Participants were able to engage with the VC Health Program throughout the 12-month study period. A total of 85 participants enrolled in the study and 3 participants withdrew, leaving 82 participants in the intent-to-treat (ITT) analysis set.

Virtual Cognitive Health Program

The VC Health Program is comprised of two phases; a 6-month active phase of lifestyle change and a 6-month maintenance phase of habit reinforcement. The individually tailored intervention encourages a healthy diet, physical exercise, cognitive training, and social engagement, all of which are supported by a coach who is reachable via telephone, email, and text messaging. To supplement all coaching interactions, participants were provided with psychoeducational material to help guide and pace individual learning.

Health Coaching

Each participant was assigned a health coach for the duration of the intervention. All coaches were certified as personal trainers through nationally accredited programs, where the basic level of certification requires mastery of exercise physiology safety and nutritional health practices. To further ensure safety, a VC Health Program nurse was available to assist coaches with the more complex behavioral health needs of participants.

After participants completed baseline testing, they were assigned a coach and completed an initial 1-hour phone call to discuss more detailed information about current exercise and dietary habits. During the first 6 months of the intervention, participants had the option of scheduling weekly phone calls with their coach to discuss questions, difficulties, and/or adjustments to lifestyle behaviors. After the first 6 months, participants were given the option to maintain the weekly cadence of coaching calls or to reduce the cadence to bi-weekly or monthly calls. The option to adjust the call frequency was offered to accommodate the varying levels of self-efficacy that the participants developed throughout the intervention.
All participants received psychoeducation regarding the benefits of physical exercise, such as aerobic and bodyweight training, on cognitive health. As part of the intervention, participants were also provided Fitbit Flex 2 wearable devices (Fitbit; San Francisco, CA) to help track and monitor activity levels. Participants were encouraged to log all exercise data in electronic trackers on the VC Health Program platform. In an effort to prevent overwhelming participants with too much educational content at once, exercise was prioritized for the first month, prior to coaching for diet or cognitive training.

Health coaches assisted participants with creating individually tailored physical activity programs that incorporated aerobic exercise and progressive muscle strength training. Individual aerobic exercise plans prioritized activities preferred by each participant, such as swimming, biking, and walking. The exercise training program represents a modified version of the FINGER study\[15\] physical activity intervention, including bodyweight strength training and aerobic exercise. The bodyweight strength-training program included exercises for all primary muscle groups.

Coaches assessed each participant’s level of fitness at the beginning of the program and used the information to individually tailor exercise recommendations. Based on coach evaluations of self-reported exercise levels at baseline, participants were placed into “low,” “moderate,” and “high” categories. Low exercisers were those who completed aerobic exercise <3 times/week (minimum of 30 min/session) or no body resistance exercise (minimum 30 min). Moderate exercisers were those who completed aerobic exercise 3 times/week (minimum 30 min/session) or body resistance exercise <2 times/week (minimum 30 min/session). High exercisers were those who completed aerobic exercise ≥4 times/week (minimum 45 min/session) and body resistance exercise ≥2 times/week (minimum 45 min/session). Participants were encouraged to set a goal of reaching the next exercise threshold throughout the program or sustaining current levels if they were categorized as “high” at baseline.

All participants received psychoeducation on the benefits of the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet for cognitive health. The MIND diet emphasizes the consumption of foods that have been shown to have positive effects on cognitive health[27]. Combining pieces of the Mediterranean and DASH diets, the MIND diet recommends regular consumption of berries (≥ 5 servings/week), fish (≥ 1 servings/week), nuts (≥ 5 servings/week), beans/legumes (≥ 4 servings/week), poultry (≥ 2 servings/week), green leafy vegetables (≥ 1 servings/day), other vegetables (≥ 1 servings/day), grains (≥ 3 servings/day), and extra virgin olive oil (≥ 3 servings/day)[28]. The MIND diet recommends limited consumption of fried/fast food (≤ 1 servings/week), sweets (≤ 5 servings/week), whole 214fat cheese (≤ 1 servings/week), red meat (≤ 4 servings/week), butter (≤ 1 servings/day), and alcohol (≤ 2 servings/day)[28]. During the initial coaching call, participants were assessed on their current fidelity to the MIND diet and were categorized as either high adherers (meets >7
217MIND recommendations) or low adherers (meets ≤7 of MIND recommendations). Coaches used 218these categories as a baseline for guiding participants through increasing MIND diet adherence 219(Figure 1), helping each subject create an individually tailored diet plan.

220

221Figure 1. Flow for assessing and improving participant dietary habits.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
<th>Week 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Begin administering nutrition assessment at each call</td>
<td>Review participant’s progress on food discussed in previous calls</td>
<td>Discuss recommendations for increasing poultry</td>
<td>Discuss recommendations for decreasing red meat</td>
<td>Discuss recommendations for increasing whole grains and extra virgin olive oil</td>
</tr>
<tr>
<td></td>
<td>Discuss recommendations for increasing berries and fish</td>
<td>Discuss recommendations for increasing nuts and beans/legumes</td>
<td>Discuss recommendations for decreasing whole fat cheese</td>
<td>Discuss recommendations for increasing leafy greens and other vegetables</td>
<td>Discuss recommendations for decreasing butter</td>
</tr>
<tr>
<td></td>
<td>Discuss recommendations for decreasing fast foods and fried foods</td>
<td>Discuss recommendations for decreasing sweets</td>
<td></td>
<td>Discuss recommendations for decreasing alcohol</td>
<td></td>
</tr>
</tbody>
</table>

222

223Cognitive Training

224Participants were provided with curriculum on the benefits of cognitive training for 225cognitive health, including a library of curated content on the topic. VC Health Program coaches 226helped participants create an individually tailored cognitive training program. The training 227program was provided by a web-based service (MindAgilis; London, England) and included 228several tasks adapted from protocols previously shown to be effective in shorter-term RCTs, 229focusing on processing speed, executive function, working memory, episodic memory, and 230mental speed[29, 30].

231Social Engagement

232All participants received access to an internal, private social network where they could 233engage in communal support and directed life review. Participants in the study were given the 234opportunity to connect with one another and were also able to invite one family member and one 235friend to join the social network. Participants were asked to respond to a variety of discussion 236prompts, including structured life review questions based on an evidence-based protocol[31, 32], 237and participate in discussions about other study participants’ life review reflections.

238Neurotrack Imprint Eye-Tracking Test

239As part of the intervention, participants were asked to complete the Neurotrack Imprint 240eye-tracking test as an additional measure of cognition[33]. The test consists of a 5-minute visual 241paired-comparison (VPC) task developed by Neurotrack Technologies, Inc. (Redwood City, CA). 242VPC tasks quantify how the test participant splits attention between familiar and novel visual 243stimuli, with a familiarization phase preceding a testing phase. During the familiarization phase,
participants are presented with pairs of identical visual stimuli for a fixed period of time (5 seconds). During the test phase, which follows a delay of either 2 seconds or 2 minutes to assess immediate and delayed recognition memory, participants are presented with additional pairs of visual stimuli, including one from the familiarization phase and one novel stimulus. The ratio of time participants spend gazing at the novel stimulus relative to the total viewing time produces a novelty preference score, with higher scores representing better declarative memory function. Test-retest reliability (r = 0.88–0.92) and inter-rater scoring agreement (κ = 0.81–0.88) for the Imprint test have both been documented as high based on previous literature.

Outcome Measurements

With cognition as the primary focus of this investigation, the RBANS was remotely administered to all participants by qualified clinicians with experience in digital delivery at baseline (week 0), week 12, week 24, and week 52. The RBANS has demonstrated strong efficacy as a dementia assessment tool in community dwelling normal subjects, and can also detect cognitive impairment associated with Alzheimer's disease. The primary outcome in this study was change in RBANS total score from study baseline to week 24 and week 52.

Secondary risk factors for AD (depression and anxiety) were assessed through the nine-item PHQ-9 and seven-item GAD-7 scale at baseline, week 12, week 24, and week 52. These items were chosen because depression and anxiety are predictive of future cognitive decline, with symptoms of both tending to manifest before direct evidence of cognitive decline is present. The PHQ-9 is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 comprises the depression module, which scores each of the nine DSM-IV criteria for depression as "0" (not at all) to "3" (nearly every day) and has been validated for use in primary care. The GAD-7 is a self-report anxiety questionnaire designed to assess anxiety status during the previous two weeks. The items in the questionnaire assess the degree to which an individual has been bothered by nervous, anxious, or on edge feelings; lack of ability to stop or control worrying; worrying too frequently about various things; inability to relax or sit still; ease of becoming annoyed or irritable; and feeling afraid. The secondary outcome of this study was change in PHQ-9 and GAD-7 scores from study baseline to week 24 and week 52.

In addition to depression and anxiety symptoms, participants were asked about their sleep (hours/night) and exercise (days/week) habits during the previous three months. These data were collected at the same time points as the PHQ-9 and GAD-7. At 24 and at 52 weeks, all participants were asked to provide subjective data on their perceived improvements in cognitive ability, physical activity levels, eating habits, sleep patterns, and stress levels. Exploratory analyses will examine changes in self-reported behaviors and how engagement with the VC Health Program is associated with change in RBANS performance.
Sample Size and Statistical Analysis

Given the preliminary nature of this study, the study was not powered to detect any specific difference in RBANS score, and the sample size was determined based on intervention capacity. Ultimately, 85 participants enrolled into the study.

Analyses will be conducted on de-identified aggregate data from the ITT population. The primary analysis will explore mean and median change in RBANS score from study baseline to the 24 week and 52 week primary endpoints. For both the RBANS and online assessments, the 12 week time point was included to allow for an interim non-primary analysis early on in the study. We will also examine the mean and median changes stratified by key participant characteristics, such as gender, age, and education. Secondary analyses will examine the mean and median change in PHQ-9 and GAD-7 scores from study baseline to 24, and 52 weeks. Potential supplemental analyses will examine various measures of user engagement, the relationship between engagement and changes in RBANS scores and secondary outcome measures, and changes in various lifestyle behaviors, such as sleep and exercise habits.

Results

Study recruitment, screening, and enrollment took place between November 2016 and March 2017. A total of 4,255 participants were identified as potentially eligible from recruitment strategies and initiated the screening process. Of these, 2,655 were determined to be ineligible based on factors including but not limited to: baseline cognitive function, history of mental illness, vision issues, and/or current pregnancy. Out of the final 405 individuals deemed eligible, 308 individuals provided informed consent, completed baseline surveys, finished all baseline assessments, were assigned a health coach, and started the VC Health program. Three individuals withdrew from the study due to personal reasons, leaving 82 individuals eligible for data analysis (Figure 2).

Figure 2. Enrollment cascade and study timeline.
Table 3 displays the baseline demographic characteristics of study participants. Overall, the participants were predominantly female (74%) with a mean age of 64 years (range 60-74.9%). Eighty-eight percent of all participants identified as Caucasian, 6% African American, 4% Hispanic, 1% Asian, and 1% Other. Sixty-seven percent of participants (55 out of 82) had a college degree or greater. Average baseline body mass index (BMI) was 30.7 kg/m$^2$ (SD = 7.0), with an average weight of 87.5 kg (SD = 20.8). Enrolled participants represented a geographically diverse population (Figure 2).

At baseline, the average total RBANS score was 95.9 (SD = 11.1), which is within normal age-adjusted ranges. The average SCD-9 score was 6.0±2.0, indicating minor subjective cognitive decline and as previously mentioned, all participants endorsed worry about cognitive decline. The average GAD-7 score was 6.2 (SD = 4.5) and PHQ-9 score was 8.5 (SD = 4.9), respectively indicating mild levels of anxiety and depression at baseline (Table 4).

Table 3 displays the baseline demographic characteristics of study participants. Overall, the participants were predominantly female (74%) with a mean age of 64 years (range 60-74.9%). Eighty-eight percent of all participants identified as Caucasian, 6% African American, 4% Hispanic, 1% Asian, and 1% Other. Sixty-seven percent of participants (55 out of 82) had a college degree or greater. Average baseline body mass index (BMI) was 30.7 kg/m$^2$ (SD = 7.0), with an average weight of 87.5 kg (SD = 20.8). Enrolled participants represented a geographically diverse population (Figure 2).

At baseline, the average total RBANS score was 95.9 (SD = 11.1), which is within normal age-adjusted ranges. The average SCD-9 score was 6.0±2.0, indicating minor subjective cognitive decline and as previously mentioned, all participants endorsed worry about cognitive decline. The average GAD-7 score was 6.2 (SD = 4.5) and PHQ-9 score was 8.5 (SD = 4.9), respectively indicating mild levels of anxiety and depression at baseline (Table 4).
<table>
<thead>
<tr>
<th>Education Level</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school graduate or GED</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Trade/technical/vocational training</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Some college, no degree</td>
<td>22 (27%)</td>
</tr>
<tr>
<td>College graduate, associate’s or bachelor’s</td>
<td>29 (35%)</td>
</tr>
<tr>
<td>Graduate degree</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>Doctorate degree</td>
<td>7 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race/Ethnicity, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>72 (88%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight, &lt; 18.5 kg/m²</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Healthy weight, 18.5 - 24.9 kg/m²</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Overweight, 25.0 - 29.9 kg/m²</td>
<td>24 (29%)</td>
</tr>
<tr>
<td>Obese, 30 - 34.9 kg/m²</td>
<td>25 (30%)</td>
</tr>
<tr>
<td>Very obese, ≥ 35 kg/m²</td>
<td>15 (18%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average Nightly Sleep Duration, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 hours</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>4 - 5 hours</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>5 - 6 hours</td>
<td>18 (22%)</td>
</tr>
<tr>
<td>6 - 7 hours</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>7 - 8 hours</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>8 - 9 hours</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>9 - 10 hours</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&gt;10 hours</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

*Two participants were excluded due to BMI >60 kg/m²; BMI = body mass index*
Figure 4. Geographic distribution of study participants.

Each dot on the map corresponds to a study participant’s zip code. Larger dots represent multiple individuals from that zip code.

Table 4. Baseline assessment scores of enrolled participants.

<table>
<thead>
<tr>
<th>Characteristics at Baseline</th>
<th>Total (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBANS</strong></td>
<td></td>
</tr>
<tr>
<td>Immediate Memory</td>
<td>99.4 (12.5)</td>
</tr>
<tr>
<td>Delayed Memory</td>
<td>96.6 (12.5)</td>
</tr>
<tr>
<td>Visuospatial / Constructional</td>
<td>90.4 (14.3)</td>
</tr>
<tr>
<td>Language</td>
<td>97.2 (10.2)</td>
</tr>
<tr>
<td>Attention / Processing Speed</td>
<td>102.8 (14.8)</td>
</tr>
<tr>
<td>Total</td>
<td>95.9 (11.1)</td>
</tr>
<tr>
<td><strong>SCD-9</strong></td>
<td>6.0 (2.0)</td>
</tr>
<tr>
<td><strong>PHQ-9</strong></td>
<td>8.5 (4.9)</td>
</tr>
<tr>
<td><strong>GAD-7</strong></td>
<td>6.2 (4.5)</td>
</tr>
</tbody>
</table>

*aRBANS: Repeatable Battery for the Assessment of Neuropsychological Status  
*bSCD-9: Subjective Cognitive Decline Questionnaire  
*cPHQ-9: Patient Health Questionnaire  
*dGAD-7: Generalized Anxiety Disorder scale
Discussion

The VC Health study will investigate the feasibility and efficacy of a remotely delivered multidomain lifestyle intervention for the prevention or delay of cognitive impairment in older adults with subjective cognitive decline. As the virtual delivery of these interventions is a new area of study, validation of this format is needed to ensure similar efficacy to in-person options. The results of this pilot study will provide preliminary insights into the translation of a traditionally in-person multidomain lifestyle intervention to a fully digital format and will help shape future program iterations. While face-to-face interventions like the one used in the FINGER study have shown promise for decreasing risk of cognitive decline, participation in these types of programs is constrained by geographical and logistical complications, such as scheduling conflicts and access to transportation. The successful translation and adoption of digitally delivered lifestyle interventions has the potential to reduce the incidence of AD and medical spending on the disease as the search for effective pharmaceutical agents continues.

Virtual lifestyle interventions have been developed for a variety of health-related conditions. These multipronged interventions have shown efficacy for diabetes prevention, diabetes management, cardiovascular risk reduction, pain management, and smoking cessation. Many of the core components of lifestyle interventions are similar, independent of the health condition they address. These components generally include psychoeducational material, social support from a peer group, access to a health coach, and tracking tools to facilitate the adoption of new health behaviors. The VC Health program contains all of these features, with adjustments tailored to individuals at risk for cognitive decline. Some of the unique aspects of the VC Health Program include the addition of cognitive training exercises, specific dietary recommendations for following the MIND diet, and validated physical activity recommendations specific for enhancing cognitive function. Based on the successful translation of other lifestyle programs into a virtual format, the VC Health intervention should lend itself well to online delivery.

While the adoption of virtual lifestyle change programs has increased over the years, one of the main barriers to the widespread adoption of remote cognitive tests is the concern about data integrity. The remote delivery of cognitive tests makes it difficult to accurately monitor patients for effort, focus, and test understanding, which is normally completed by an in-person test administrator. However, previous literature has demonstrated the efficacy and effectiveness of remote RBANS delivery via videoconference, supporting its use in the current investigation. The Imprint test, which is embedded in the VC Health program, uses webcam-based eye tracking data, with recorded video from the test providing analysts with “eyes on the patient.” This allows the analysts to assess various elements of data quality and fidelity to test-taking procedures. Remote administration of the RBANS and Imprint tests allows for the feasible and scalable collection of data at multiple time points and for the longitudinal monitoring of cognitive health. The current investigation is the first of its kind in the cognitive...
health space, and is structured to demonstrate that a digital intervention can be delivered from baseline to completion while measuring primary, secondary, and exploratory outcomes with entirely remote mechanisms.

The design of the VC Health study has both strengths and limitations. One strength is the digital administration of the intervention and collection of data in a real-world setting, which provides more ecologically valid results when compared to studies completed in traditional research settings[22]. This is important, as it enhances the generalizability of the results and provides more powerful estimates of how the intervention is likely to perform in broader populations and settings. Another strength is the 52-week study duration, as this allows the results to reflect the long-term impact of the intervention. Examining the long-term outcomes of lifestyle change programs is essential in order to demonstrate the true impact of participation after the program tapers off or ends. Limitations of this study include the small sample size and lack of a control group, which were both a result of the pilot nature of this investigation. However, it should be noted that intervention studies evaluating digital lifestyle programs commonly employ single-arm designs and this design is well accepted in the field for early studies[47, 48, 52, 66, 67]. Lastly, the study sample was primarily Caucasian and well-educated, so the results may not be generalizable to other populations. Future studies require the exploration of similar interventions in more a more diverse group of individuals.

In conclusion, this single-arm pre-post pilot study will provide initial evidence of the feasibility and efficacy of a remotely delivered multidomain intervention to prevent or delay cognitive decline in older adults at risk for dementia. Qualitative information on specific intervention components will be collected and used to inform the ongoing design iterations of the virtual intervention, as well as the design of larger studies investigating the effect of the intervention. The 24- and 52-week longitudinal follow-up periods used in this fully virtual study will be the first to evaluate the efficacy of a virtual intervention to prevent or delay cognitive decline in older adults. In addition to composite cognitive performance, assessment of symptoms of anxiety and depression will allow us to explore the effects of the intervention on other aspects of mental health. The results of this trial are expected to provide crucial insights into the promise of remotely delivered cognitive health interventions, which could have a substantial impact on dementia incidence over the coming decades.

References


47928. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND Diet  
480 Associated with Reduced Incidence of Alzheimer’s Disease. Alzheimers Dement J  
481 Alzheimers Assoc. 2015;11(9):1007-1014. doi:10.1016/j.jalz.2014.11.009

48229. Shah TM, Weinborn M, Verdile G, Sohrabi HR, Martins RN. Enhancing Cognitive  
483 Functioning in Healthy Older Adults: a Systematic Review of the Clinical Significance of  
484 Commercially Available Computerized Cognitive Training in Preventing Cognitive Decline.  

487 on Cognition and Everyday Functioning in Older Adults. J Am Geriatr Soc. 2014;62(1):16-  

491 doi:10.1002/14651858.CD001120.pub2

493 Alzheimer’s disease: a computerized cognitive training combined with reminiscence therapy.  

49533. Bott NT, Lange A, Rentz D, Buffalo E, Clopton P, Zola S. Web Camera Based Eye Tracking  

49834. Crutcher MD, Calhoun-Haney R, Manzanares CM, Lah JJ, Levey AI, Zola SM. Eye  
499 Tracking During a Visual Paired Comparison Task as a Predictor of Early Dementia. Am J  

50135. Galusha-Glasscock JM, Horton DK, Weiner MF, Cullum CM. Video Teleconference  
502 Administration of the Repeatable Battery for the Assessment of Neuropsychological Status.  


50737. Duff K, Patton D, Schoenberg MR, Mold J, Scott JG, Adams RL. Age- and education-  
508 corrected independent normative data for the RBANS in a community dwelling elderly  

51038. Duff K, Clark HJD, O’Bryant SE, Mold JW, Schiffer RB, Sutker PB. Utility of the RBANS  
511 in detecting cognitive impairment associated with Alzheimer’s disease: Sensitivity,
specificity, and positive and negative predictive powers. *Arch Clin Neuropsychol.*


Abbreviations:

AD: Alzheimer’s disease
BMI: body mass index
FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GAD-7: Generalized Anxiety Disorder scale
ITT: intention-to-treat
MCI: mild cognitive impairment
MIND-CHINA: Multimodal Intervention to Delay Dementia and Disability in Rural China
MYB: Maintain Your Brain
PHQ-9: Patient Health Questionnaire
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomized controlled trial
SCD-9: Subjective Cognitive Decline questionnaire
SINGER: Singapore Intervention Study to Prevent Cognitive Impairment and Disability
TLS: transport layer security
US POINTER: United States Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk
VC Health: virtual cognitive health study
VPC: visual paired-comparison

Acknowledgements
The authors thank all participants in the VC Health study and all of the study collaborators for their cooperation and hard work. This study was funded by Neurotrack and completed by Evidation Health. NB, CK, SK, and JLJ conceived the study and participated in its design. SK and JLJ drafted the study protocol with review and input from NB and CK. NB, JMG, and EM drafted the manuscript. JLJ and SK provided data and reviewed and edited the manuscript.

Conflicts of Interest
Neurotrack makes and owns the eye-tracking assessment and behavior change program used in this study. NB, CK, JMG, ENM, are employed by Neurotrack and receive a salary and stock options. Evidation Health collected and analyzed all study data. JLJ and SK are employed by Evidation Health and have no financial interest in Neurotrack.