

Title Page

Title: Self-Reported Behavior Change and Predictors of Engagement with a Multidomain Brain Health Intervention for Midlife and Older Adults: A Clinical Trial

Running Head: Predictors of Change in a Brain Health Intervention

Brenna Boyd, M.S.¹ Courtney McAlister, Ph.D.² and Kayela Arrotta, Ph.D.^{3,4} and Maureen Schmitter-Edgecombe, Ph.D.¹

¹Washington State University, Pullman, WA

²Mayo Clinic School of Medicine and Science, Mayo Clinic Health System, La Crosse, Wisconsin

³Neurological Institute, Cleveland Clinic, Cleveland, Ohio

⁴Department of Neurology, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Cleveland, Ohio

Brenna Boyd, Psychology Department, Johnson Tower 233, Washington State University, Pullman, WA, 99164-4820. Phone: 509-592-0631. Fax: 509-335-5043, brenna.boyd@wsu.edu

Courtney McAlister, Mayo Clinic Health System, La Crosse, WI, 54601. Phone: 608-392-9555.

Email: mcalister.courtney@mayo.edu

Kayela Arrotta, Neurological Institute, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH, 44195. Phone: 216-444-6101. Email: arrottk@ccf.org

*Maureen Schmitter-Edgecombe, Psychology Department, Johnson Tower 233, Washington State University, Pullman, WA, 99164-4820. Phone: 509-592-0631. Fax: 509-335-5043. Email: schmitter-e@wsu.edu

*corresponding author

This study utilized financial support from an H. L. Eastlick Distinguished Professorship. We would like to thank members of the Neuropsychology and Aging Laboratory for assistance in completing this work.

All authors declare no conflicts of interest.

All authors have read and approve of this manuscript.

Abstract

Objectives. This study evaluated the efficacy of a multidomain brain-health intervention on health behavior change and sought to understand whether health literacy or brain-health knowledge predicted engagement with the intervention.

Methods. One-hundred thirty midlife and older adults were assigned to one of three intervention conditions: brain fitness (B-Fit) utilizing education and goal setting, education-only, or waitlist. Questionnaires were completed at baseline and post-intervention.

Results. Both B-Fit and education-only conditions reported improvements in health behaviors over time. Although effect size for the education-only condition was moderate, only the B-Fit condition differed significantly in health behaviors from the waitlist post-intervention. Lower baseline brain-health knowledge predicted improvements in health behaviors for education-only condition.

Discussion. The multidomain brain-health intervention was successful in helping participants change their behaviors, but it was not more effective than the education-only condition. For those with lower brain health knowledge, an education-only intervention may be sufficient to encourage behavior change.

Key words: Brain health, dementia risk factors, health literacy, prevention

Trial registry name: B-Fit Intervention to Improve Brain Health (B-Fit)

URL:<https://clinicaltrials.gov/ct2/show/NCT03454074?cond=Aging&cntry=US&state=US%3A>

WA&city=Pullman&dist=100&draw=2&rank=1

Registration number: NCT03454074

Self-Reported Behavior Change and Predictors of Engagement with a Multidomain Brain Health Intervention for Midlife and Older Adults: A Pilot Clinical Trial

Alzheimer's disease (AD), a common etiology of dementia, is one of the most expensive disorders in the United States (Castro et al, 2010). Data suggest that several modifiable risk factors for dementia (e.g., hypertension, physical inactivity) exert their effects mainly during midlife (Barnes & Yaffe, 2011). An accumulating body of research also suggests that adopting preventative health behaviors in midlife and throughout older age (e.g., proper nutrition, cognitive engagement) may promote healthy brain aging and slow cognitive and physical decline (Livingston et al., 2020). Unfortunately, there is currently a gap concerning how to best disseminate knowledge about healthy brain aging behaviors and how best to assist midlife and older adults in learning to incorporate healthy brain aging behaviors into their everyday lives in a way that will lead to sustained behavior change. In this study, we assess the impact of a multidomain brain health intervention for improving engagement in preventative health behaviors in midlife and older adults. Based on prior research briefly reviewed below, seven risk factors were targeted in this multi-domain intervention: nutrition, stress, social engagement, cognitive engagement, cardiovascular risk factors (e.g., hypertension, smoking, and obesity), physical activity and sleep. We also evaluate whether baseline health literacy and brain health knowledge are predictors of who is most likely to engage in health behavior changes.

With regard to the targeted intervention risk factors, the presence of cardiovascular disease risk factors, particularly in midlife and by way of multiple, complex mechanisms, has been associated with an increased risk of developing dementia (Whitmer et al., 2005). Both physical inactivity and poor nutrition are cardiovascular risk factors that have been studied extensively in relation to dementia. Although some studies have not found a relationship between

physical activity and dementia, previous meta-analyses suggest that higher levels of physical activity likely reduce the risk of cognitive decline and dementia (Blondell et al., 2014). Proper nutrition may also reduce the risk of developing dementia by ensuring consumption of specific nutrients needed for critical brain functions (Gillette-Guyonnet, et al., 2013).

Beyond cardiovascular risk management, other behaviors may also be beneficial. For example, although the literature remains limited, a recent meta-analysis reported that poor social engagement was associated with increased risk of dementia (Penninkilampi et al., 2018). Recent research suggests that frequent engagement in focused and effortful cognitive tasks may reduce the risk of developing dementia through cognitive reserve mechanisms (Ferreira, et al., 2015; Schultz, et al., 2015). Additionally, chronic stress may increase the risk of dementia directly or indirectly through changes in the immune system, cardiovascular system, and multiple changes in the brain as a result of neurotransmitters and hormones released during stressful events (Mravec et al., 2018). Finally, a recent meta-analysis found that insufficient, excessive, or disordered sleep could elevate the risk of developing dementia (Xu et al., 2019).

In addition to these seven target risk factors, the intervention included a lesson on implementation of compensatory strategies, including assistive technologies. Research suggests that compensatory strategy use can mitigate the effects of cognitive decline on everyday task performances (Farias et al., 2020). Providing this information may improve the quality of life of older adults and assist with management of future dementia related symptoms.

Prior Interventions

Many prior studies have focused on modifying only a single risk factor. Based on the review above, it is clear that modification of only a single risk factor may not be sufficient for reducing the risk of dementia for all individuals as the etiology of dementia is heterogenous and

influenced by multiple genetic and environmental risk factors (Kivipelto, 2009; Livingston, et al., 2020). Several recent, large prevention studies (e.g., the FINGER study, the Agewell trial, and the Multidomain Alzheimer Preventive Trial (MAPT)) that assessed the impact of multidomain interventions on cognitive outcomes and/or dementia prevention (Andrieu, et al., 2017; Clare et al., 2015; Rosenberg et al., 2017), demonstrated positive benefits. However, these interventions required costly clinician input, health care provider assistance, and/or expensive treatment regimens. Furthermore, these interventions often involved highly prescriptive goals, which may not be possible for all individuals to adequately implement post-intervention. A successful intervention to delay the onset of dementia should not only yield results in the lab but be feasible to transfer into the daily lives of midlife and older adults without financial burden. Successful interventions should also capitalize on intrinsically motivating behavior change goals to sustain behavior change (Hartmann et al., 2015).

It is also important to understand for whom interventions work. Education is a necessary component of behavior change yet is rarely sufficient to initiate the behavior change process (Arlinghaus & Johnston, 2018). Prior to engaging in preventative brain health behavior change, an individual must first become knowledgeable about why a behavior is important and how to engage in the behavior. For example, one study found that, when nutrition information was tailored, those with lower education reported a greater increase in fruit and vegetable intake than those with higher education (Gans et al., 2009). Health literacy is a construct that includes health knowledge as well as the ability to acquire, understand, and appropriately apply health knowledge in a way that prevents disease (Hansen et al., 2015). Prior research indicates that poor health literacy is associated with poorer health outcomes and exercise habits, lower adherence to treatment plans, unhealthy diets and increased risk of dementia (Friis et al., 2016; Huang et al.,

2020; Miller, 2016; Oliveira et al., 2019; Park et al., 2017). However, health literacy is not static; health-literacy interventions have been shown to improve health literacy and treatment adherence (Berkman et al., 2011; Miller, 2016). Furthermore, studies have shown that health-related interventions may have a greater impact on those with lower health knowledge and health literacy (Dominick et al., 2015; Rothman, et al., 2004).

Objectives

The current study sought to evaluate the impact of a pilot multidomain brain health intervention grounded in the Self-Determination Theory (SDT) model of behavior change on preventative brain-health behaviors in midlife and older adults. According to the SDT model, individuals are more likely to be motivated to complete a goal if it is autonomously motivated, involves meaningful social interaction, and the individual feels competent to complete the goal (Edmunds et al., 2008). In line with this model, the designed group intervention focused on providing brain-health psychoeducation and a behavior-change component (B-Fit) that combines group education with autonomy-supportive individualized goal setting, group problem-solving, and social support. The following healthy brain aging behaviors were targeted: physical activity, diet, cognitive engagement, social engagement, sleep, stress management, and compensatory strategies/assistive technologies use. Participants were assigned to either the B-Fit intervention, an education-only intervention, or a waitlist control. We hypothesized that participants in the B-Fit condition would self-report engaging in more healthy brain aging behaviors following the intervention compared to both the education-only and the waitlist-control conditions. We further hypothesized that those with lower baseline health literacy and/or brain health knowledge would self-report the greatest change in healthy brain aging behaviors following the intervention.

Method

Participants

Participants were community-dwelling adults, ages 40 years and older (ages 42-85). All participants reported having 12 or more years of education (12-20 years of education).

Participants were recruited from Whitman and Spokane counties in Washington and from Latah county in Idaho in partnership with a local hospital and other community agencies. Exclusion criteria included a clinical diagnosis of dementia, inability to provide own consent, unstable or severely disabling disease (e.g., organ failure), and inability to complete assessment and intervention protocols due to communication, vision, hearing, or other medical difficulties. Prior to participation, participants were screened by phone with a medical/ health interview and the Telephone Interview of Cognitive Status (TICS; Brandt et al., 1988). Participants were excluded if they fell in the Impaired range on the TICS (score < 26) or if they met study exclusion criteria. Community dwelling midlife and older adults aged 40+ who expressed interest in the study, had the ability to attend sessions, and did not meet exclusion criteria were eligible to participate in the study.

After screening approximately 200 participants and applying the exclusion criteria along with study time commitment, 131 participants were enrolled in the study. One participant was assigned to the education-only condition but did not complete baseline testing and withdrew consent to participate in the study. The total number of participants who completed baseline testing was 130 individuals. Of these, 68 participants were allocated to the B-Fit condition, 36 to the education-only condition, and 26 to the waitlist control condition. Participants were blocked into groups based on study location and group meeting time. Groups of 8-13 participants were then randomly assigned to either the B-Fit or education-only condition in a 2:1 format. If

individuals could not get blocked into a group (e.g., group meeting time did not work) they were asked to serve as a waitlist control participant.

A total of 65 individuals participated in this pilot intervention during 2016-2017, and 65 during 2018. For the 2016-2017 cohort, the intervention lasted for 10 weeks (Session 10 was a feedback session). To truncate the 2018 intervention to 7 weeks, several related topics were discussed on the same day (i.e., exercise and cardiovascular disease; sleep and stress), and the feedback session was removed. The 2016-2017 and 2018 cohorts received the same educational information (updated where necessary) and focused on the same eight topics. A total of seven participants dropped out from the study prior to completing post-intervention testing. Of those who dropped, 4 had been assigned to the B-Fit condition and 3 to the education-only condition. See Figure 1 for the CONSORT flow diagram.

(Insert Figure 1 here).

Measures

Primary Outcome Measure

Healthy Aging Activity Engagement (HAAE) questionnaire (Schmitter-Edgecombe et al., 2019). The HAAE is a validated, 32-item scale that measures participant self-report of engagement in healthy brain aging behavior across a variety of health behaviors that fall within three domains: biological health (e.g., questions about exercise and diet), social and cognitive strategies (e.g., questions about social and cognitive engagement), and health safe guard behaviors (e.g., not smoking). The three domain subscales demonstrated excellent internal consistency (Rasch reliability .94 to .98). Test-retest reliability was acceptable with a strong correlation for the total score ($r = .83$). Participants rate their engagement in a series of health

behaviors on a scale from 1 (strongly disagree) to 5 (strongly agree). Higher scores reflect greater engagement with various healthy aging behaviors.

Predictor Variables

The Newest Vital Sign (NVS; Weiss, 2005). The NVS is a widely used screening instrument that assesses health literacy. During administration, a participant is presented with the nutritional label from an ice cream container and asked a series of six questions about the label. Total correct responses from the NVS was used as a measure of health literacy.

The Brain Health Knowledge Questionnaire (BHQ; Park et al., 2012). The BHQ is a validated, 24-item questionnaire consisting of true-false statements that measures knowledge about activities that promote brain health and reduce AD risk. Responses are scored as 0 for incorrect and 1 for correct. Higher scores indicate better knowledge regarding brain health.

Brain Fitness (B-Fit) Engagement

Self-reported Goal Completion Score. Participants in the B-Fit condition kept a record of goal progress on standardized goal tracking sheets. At the beginning of each session, participants indicated whether they made no change (0), partly met (1), completely met (2) or exceeded (3) each of their goals for the given week. For analysis, a self-reported goal completion score was computed averaging goal ratings across the intervention, such that higher scores reflected greater goal completion throughout the intervention. The self-reported goal completion score reflects engagement, or dosage, of the intervention for participants in the B-Fit condition.

Procedure

All procedures and methods were approved by the Washington State University institutional review board (#14542). All participants provided written informed consent. Prior to the start of the intervention, participants completed a brief battery of neuropsychological tests

and a questionnaire packet. Participants completed follow-up testing and questionnaires after the intervention (i.e., approximately 2.5 months later). Waitlist participants completed testing within the same time frame. Examiners gathering the assessment data were blind to participant condition and study hypotheses. Clinician educators were trained to deliver the manualized intervention (clinician manual, training meetings) and supervised closely by a licensed clinical psychologist (MSE). Fidelity of content and process was monitored via videotape.

B-Fit and Education-Only Condition

For both the B-Fit and education-only conditions, the intervention consisted of once weekly two-hour group sessions. See table 1 for side-by-side comparison of conditions. During the sessions, participants were presented with information about brain health. A bound educational booklet containing the presented material was provided to each participant. One or two learning topic(s) was covered each week. General information about each topic was discussed during specified sessions; empirical research on each topic was emphasized. Clinician educators provided information in a comprehensible manner. Care was taken to translate scientific jargon into information that all participants understood. The first session provided an overview of the brain, cognitive aging, mild cognitive impairment and dementia. After session one, a new topic or two were discussed each session in the following order: cognitive engagement, cardiovascular risk factors, physical activity, nutrition, social engagement, sleep, stress, and compensatory strategies/assistive technologies.

B-Fit Condition. During session one, an overview of the intervention and education on successful goal setting and goal monitoring was also provided. For the remaining sessions, after the educational component, participants in the B-Fit condition set an autonomous, intrinsically motivating, and manageable goal to complete during the following week that would promote

brain health. Participants also planned how to successfully integrate the goal into their daily life and problem-solved potential barriers. No goal was set during the first session. The general session format included time to socialize, a discussion of successes and challenges with goal implementation, didactics, new goal setting time, group problem solving for new and past goals, and a few minutes to socialize or ask questions at the end. Participants were expected to continue with all goals throughout the intervention such that a goal set during week 2 should be continued through the end of the intervention. As participants worked on numerous goals at the same time, they were encouraged to keep the time commitment of each goal short (approximately 5-10 minutes). Participants were provided with standardized tracking sheets to record goal progress. During the discussion of successes and challenges, participants rated their overall goal progress for the week for each goal (goal completion score).

Education-Only Condition. For the education-only condition, the general session format included time to socialize, didactics, and socializing at the end. To keep the time in session consistent between conditions, specific discussion prompts were provided during didactics to facilitate group discussion for the week's topic. For example, when discussing physical activity and cardiovascular risk factors, the clinician educator leading the group posed questions such as, "How do you feel when you exercise regularly" and "Did we discuss modifiable risk factors you were not aware of?" In this way, the additional meeting time was adequately filled without providing participants information related to goal setting or goal implementation.

Table 1: Side-by-side comparison of study conditions

	B-Fit	Education Only	Waitlist Control
Step 1: Assessment	Baseline testing	Baseline Testing	Baseline Testing
Step 2: Intervention	Group sessions	Group sessions	No intervention
	consisting of goal setting and brain health education	consisting of only brain health education	
Step 3: Assessment ^a	Follow-up testing	Follow-up testing	Follow-up testing

^aThe follow-up assessment occurred approximately 2.5 months after baseline testing

Analysis

All analyses were conducted using SPSS version 25. Prior to analysis, mean imputation at the item level was used to handle missing data for questionnaire measures (HAAE and BHQ) before computing total scores. For those who completed questionnaires, less than 1% of the questionnaire data were missing. Additionally, 8 participants in the B-Fit condition, 4 in the education-only condition, and 2 waitlist control participants did not return the HAAE T2 questionnaire and were not included in the analyses involving HAAE T2 or HAAE percent change data. The final sample for comparisons between conditions was 109. For the B-Fit condition, 56 completed and returned the information necessary to compute self-reported goal completion scores.

To examine for differential impact of the interventions on reported health behaviors, a one-way analysis of covariance (ANCOVA) was conducted using HAAE Time 2 (T2) scores as the dependent variable and HAAE T1 scores as the covariate. Demographic variables (i.e., age, education, gender) were treated as covariates if they differed between groups. Both intervention

type (B-Fit, education only, wait list) and intervention length (10-week, 7-week) were included as fixed factors. Follow-up pairwise comparisons were conducted for significant results ($p < .05$). Three paired-samples t-tests were also conducted to determine whether a significant change in HAAE scores occurred between baseline (time 1) and time 2 for each of the three conditions.

To determine whether baseline health literacy (i.e., NVS score) or brain health knowledge (i.e., BHQ) predicted who was most likely to engage in health behavior changes, multiple regression analyses were conducted for each condition. The outcome variable was a percentage change in HAAE score and was calculated using the following formula: $(\text{HAAET2} - \text{HAAET1}/\text{HAAET1}) * 100$. Bivariate correlations with the outcome variable were also conducted to identify whether age, education, or gender should be controlled for in these models.

A multiple regression analysis was also conducted to investigate whether baseline health literacy, brain-health knowledge, or engagement in health behaviors (HAEE) predicted self-reported goal completion scores in the B-Fit condition. Bivariate correlations were conducted between the self-reported goal completion score and age, gender, and education to identify whether demographic variables should be controlled for in this model.

Results

As can be seen in Table 2, one-way ANOVAs revealed that the age, $F(2,106) = 0.69, p = .51$, and education, $F(2,106) = 0.59, p = .56$, of study participants did not differ across conditions. A chi-square analysis revealed that the gender, $X^2(2, N=109) = 3.00, p = .22$, and race, $X^2(10, N=109) = 10.38, p = .41$, of study participants also did not differ across conditions. The sample was predominantly white.

Table 2: Demographics and Baseline Data of Participants by Condition

	Condition		
	B-Fit (N = 56)	Education-only (N = 29)	Waitlist (N = 24)
Age (in years)	63.57 (8.86)	64.41 (8.94)	66.29 (11.54)
Education (in years)	16.11 (2.43)	16.52 (1.99)	15.88 (1.96)
% Female	67.86%	62.07%	83.33%
% White/Not Hispanic or Latino	89.23%	89.66%	100.00%
TICS Average	35.17 (2.93)	34.68 (3.24)	35.25 (3.12)
NVS T1 Average	4.82 (1.32)	4.64 (1.42)	4.83 (1.09)
BHQ T1 Average	21.89 (1.30)	22.07 (1.31)	22.09 (1.48)

Notes. TICS = Telephone Interview of Cognitive Status; NVS = Newest Vital Signs; BHQ = Brain Health Knowledge Questionnaire. Standard deviations in parentheses.

HAAE Group Analysis. Although not significantly different between groups, gender was controlled for in the model given the notably higher percentage of females in the waitlist control condition. The one-way ANCOVA revealed a significant difference between the three conditions on self-reported healthy aging behaviors after controlling for baseline healthy aging behaviors and gender, $F(2, 101) = 3.43, p = .036, \eta^2_p = .06$. There was no main effect of intervention length, $F(1, 101) = .04, p = .84$, and no condition by intervention length interaction, $F(2, 101) = 2.11, p = .13$. Pairwise comparisons revealed that the B-Fit condition ($M_{adj} = 124.47$), $M_D = 6.37, SE = 2.45, p = .01, d = .63, 95\% CI [1.51, 11.24]$ reported significantly greater engagement in healthy aging behaviors post-intervention compared to the waitlist controls ($M_{adj} = 118.10$).

There was no significant difference in healthy aging behaviors between the B-Fit and education-only condition ($M_{adj} = 123.36$), $M_D = 1.11$, $SE = 2.33$, $p = .64$, $d = .11$, 95% CI [-3.52, 5.74]. Although the difference did not reach statistical significance, there was a medium effect size, $M_D = 5.26$, $SE = 2.82$, $p = .07$, $d = .52$, 95% CI [-0.34, 10.86], consistent with higher engagement in healthy brain aging activities post-intervention by the education-only condition than by the waitlist controls.

Moreover, paired-samples t-tests examining for change over time (see Table 3) revealed a significant difference between baseline (time 1) and post-intervention (time 2) engagement in healthy brain aging behaviors for both the B-Fit condition, $M_D = 9.45$, $t(56) = 5.58$, $p < .001$, 95% CI [6.05, 12.83], and the education-only condition, $M_D = 8.41$, $t(29) = 3.87$, $p = .001$, 95% CI [3.96, 12.87]. In contrast, the waitlist condition did not show a difference in their engagement in brain health behaviors across time, $M_D = 2.33$, $t(24) = 1.68$, $p = .11$, 95% CI [-.54, 5.20].

Table 3: Descriptive Statistics for HAAE by Intervention Condition

	Intervention Condition		
	B-Fit (N = 56)	Education-only (N = 29)	Waitlist (N = 24)
T1 HAAE	115.54 (17.31)	113.34 (13.70)	117.50 (12.86)
T2 HAAE	124.98 ^a (16.09)	121.76 (11.36)	119.83 (12.68)

Notes. HAAE = Healthy Aging Activity Engagement questionnaire. Standard deviation in parentheses; ^adiffered from waitlist control group at $p < .05$

HAAE Percent Change Analyses. Correlations between HAAE percent change and demographic variables were small and non-significant for the B-Fit ($r = -.03$ to $.15$), education-only ($r = -.11$ to $.29$), and waitlist control ($r = -.02$ to $.21$) conditions. There were no concerns with multicollinearity between predictors; the correlation between brain-health knowledge and health literacy was not significant for the education-only, $r(26) = .11, p = .57$, nor control, $r(20) = .39, p = .07$, conditions. Although the correlation was significant for the B-Fit condition, $r(63) = .25, p = .05$, the tolerance value was $.87$ and VIF was 1.15 , which both indicate no multicollinearity concerns.

For the B-Fit condition, the two predictors did not account for significant variability in percent change in brain-health behaviors, $F(2, 53) = .99, p = .38$. Neither brain-health knowledge, $\beta = .10, t(53) = .67, p = .50, 95\% \text{ CI } [-1.73, 3.52]$, nor health literacy, $\beta = .13, t(53) = .90, p = .37, 95\% \text{ CI } [-1.42, 3.75]$, emerged as a significant predictor (see Table).

For the education-only condition, the two predictors explained a significant 54.87% of the variability in percent change in brain-health behaviors, $F(2, 25) = 15.20, p < .001$. Although baseline brain-health knowledge was a significant predictor of percent change in brain-health behaviors, $\beta = -.74, t(25) = -5.50, p < .001, 95\% \text{ CI } [-8.81, -4.01]$, health literacy was not, $\beta = .15, t(25) = 1.07, p = .30, 95\% \text{ CI } [-1.08, 3.42]$, (see Table 4).

For the control condition, the two predictors did not account for significant variability in percent change in brain-health behaviors, $F(2, 19) = .46, p = .64$. Neither brain-health knowledge, $\beta = .23, t(19) = 0.96, p = .35, 95\% \text{ CI } [-1.11, 2.99]$, nor health literacy, $\beta = -.11, t(19) = -.44, p = .67, 95\% \text{ CI } [-3.34, 2.18]$, were significant predictors (see Table 4).

Table 4: HAAE Regression Analyses by Condition

Predictor	Condition		
	B-Fit (N = 56)	Education Only (N = 28)	Waitlist Control (N = 22)
Brain Health Knowledge	$\beta = .10, t = .67$	$\beta = -.74, t = -5.50^*$	$\beta = .24, t = .96$
Health Literacy	$\beta = .13, t = .90$	$\beta = .15, t = 1.07$	$\beta = -.11, t = -.44$
Total R^2	.036	.549	.046
F for R^2	.99	15.20*	.64

Note. HAAE = Healthy Aging Activity Engagement questionnaire. β presented for predictors. * $p < .001$

Goal Completion Score Analysis for the B-Fit Condition. Bivariate correlations showed no significant relationship between self-reported goal completion and age, $r(54) = .19$, and gender, $r(54) = .02$, for the B-Fit condition. The correlation between education and self-reported goal completion was negative and significant, $r(54) = -.33, p = .01$. The correlations between baseline brain health-knowledge and health literacy, $r(61) = .25, p = .046$, was significant; however, the correlation was not large enough to lead to significant multicollinearity.

The regression results indicated that the three-predictor model explained a significant 20.46 % of the variability in self-reported goal completion, $F(3, 52) = 4.46, p = .007$. Both baseline engagement in health behaviors, $\beta = .36, t(52) = 2.90, p = .006, 95\% \text{ CI } [0.003, 0.02]$, and baseline health literacy, $\beta = -.25, t(52) = -2.01, p = .050, 95\% \text{ CI } [-0.16, 0.00]$, were significant predictors of self-reported goal completion. Baseline brain-health knowledge was not a significant predictor, $\beta = .01, t(52) = 0.08, p = .94, 95\% \text{ CI } [-0.09, 0.09]$. When education was added in the first step of the model, education accounted for a significant 10.88% of the variability in self-reported goal completion, $\beta = -.33, t(54) = -2.57, p = .01$. The addition of the

baseline predictors explained an additional 25.27% of variance, $\Delta R^2 = .14$, $\Delta F(3, 51) = 3.27$, $p = .03$. For the four-predictor model, only baseline engagement in health behaviors emerged as a significant predictor of self-reported goal completion, $\beta = .31$, $t(51) = 2.51$, $p = .015$, 95% CI [0.002, 0.02]. Neither health literacy, $\beta = -.22$, $t(51) = -1.79$, $p = .08$, 95% CI [-0.15, 0.01], nor education, $\beta = -.23$, $t(51) = -1.81$, $p = .08$, 95% CI [-0.09, 0.005], reached significance. Brain health knowledge, $\beta = .03$, $t(51) = .27$, $p = .79$, 95% CI [-0.08, 0.10], was not a significant predictor (See Table 5).

Table 5: Regression Analysis for Self-Reported Goal Completion Score for B-Fit Condition

Model Statistics				
	R^2	F	p	
	.25	4.31	.004	
Predictor Statistics				
	β/b	SE	t	p
Brain Health Knowledge	.03/.01	.04	.27	.79
HAAE	.31/.01	.003	2.51	.02
Health Literacy	-.22/-.07	.04	-1.79	.08
Education	-.23/-.04	.02	-1.81	.08

Note. HAAE = Healthy Aging Activity Engagement questionnaire

Discussion

Primary Findings

Consistent with our hypotheses, participants in the B-Fit condition self-reported engaging in more preventative brain-health behaviors post-intervention (i.e., time 2) compared to the

waitlist control condition. Furthermore, there was an increase in the number of self-reported preventative brain-health behaviors being engaged in at post-testing compared to baseline for participants in both the B-Fit and education-only conditions, but not the waitlist condition. These findings add to the small but growing body of literature on the benefits of designing and implementing multidomain brain health interventions. Furthermore, the data suggests that in some instances an education intervention may successfully support promotion of health behavior change.

Of the three prior multidomain brain-health interventions, the FINGER study and Agewell trial methodologies were most similar to the current study. FINGER participants were randomly assigned to either a multidomain intervention condition or a control condition that received information and health advice at baseline (Rosenberg et al., 2018). Participants in the intervention condition reported significantly greater improvements on outcome measures compared to controls. For the Agewell trial, participants were randomly assigned to either a goal setting intervention, goal setting and mentoring condition, or an information condition (Clare et al., 2015). Both goal setting conditions reported greater improvement in physical activity and cognitive activity compared to the information control condition.

Although education is not typically sufficient to initiate the behavior-change process (Arlinghaus & Johnston, 2018), certain factors may have increased the likelihood of education being effective in this study. For example, tailored health messages that are personally relevant to a participant command greater attention and are likely to be processed more intently (Lustria, et al., 2013). The education content in our intervention was tailored toward midlife and older adults, and dementia prevention was personally relevant for many of the participants. Also, notable for participants in the education-only condition, we found that participants with lower

brain-health knowledge at baseline self-reported higher levels of behavior change. This may suggest that, for those individuals who lacked important information about how preventative behaviors impact brain health and lower dementia risk, the education-only condition may have been sufficient to promote new behavior change. Finally, the education-only condition was a fairly active control condition that engaged in multiple face-to-face sessions, benefitting also from social support. The education-only condition for this study appeared much more involved than the education/information control conditions in the FINGER and Agewell studies, which could help to explain the discrepancy in results.

Secondary Findings

Although lower-brain health knowledge at baseline was predictive of greater change in healthy brain-aging behaviors for the education-only condition, this was not found in the B-Fit condition. As such, it is possible that, regardless of prior brain-health knowledge, the B-Fit condition provided the necessary elements that encouraged participants to initiate new health-behavior change. Lower levels of health literacy along with higher baseline brain-health behaviors were also found to predict higher levels of self-reported goal-completion by B-Fit participants. Furthermore, when education was the only variable in the model, education itself was a significant predictor of goal completion scores. As such, individuals within the B-Fit condition with lower education and lower baseline health literacy seemed to benefit the most from the intervention based on self-reported higher rates of goal completion. However, in the full model, only the baseline brain-health behaviors score was a significant predictor such that higher baseline brain-health behaviors predicted higher levels of goal completion. This may suggest that B-Fit participants who were already engaging in healthy brain aging behaviors prior to the start of the intervention obtained the greatest success with implementing new behaviors. It is possible

that prior success with health-behavior change results in greater self-efficacy for creating new behavior change, and self-efficacy has been associated with behavior-change success (Cramer et al., 2013; Purdie & McCrindle, 2002).

Lower education and health literacy have been linked to poorer health behaviors and poorer treatment adherence in medical settings (Friis et al., 2016; Huang et al., 2020). Presently, a small body of research suggests that individuals with lower education or health literacy may more strongly benefit from health-related behavior-change interventions compared to those with higher education and health literacy (Dominick et al., 2015; Gans et al., 2009; Rothman et al., 2004). This may be particularly true when the intervention is tailored to an individual's needs and works to improve health literacy (Miller, 2016; Rothman et al., 2004). As such, the data linking lower education and lower health literacy to greater improvement for the education-only participants and higher self-reported goal completion scores for the B-Fit participants fits well within this literature. Therefore, the results of the current study add to this body of work and, consistent with precision medicine, support the importance of understanding person-specific variables which may impact interventions.

Strengths and Limitations

This study possesses a number of important strengths. Only a few studies have previously assessed the impact of multidomain behavior-change interventions that target risk factors for dementia. Outside of the FINGER, MAPT, and Agewell studies, most prior interventions focused on modification of only a single risk factor, which is likely not sufficient to adequately reduce risk for dementia. Furthermore, our pilot intervention was specifically designed to be completed at low cost, with no expensive equipment, or costly clinician involvement. As such, this pilot intervention could be taken from a laboratory setting and implemented for the general

public without a great financial burden. For example, the PowerPoint slides created for the B-Fit condition and information about running the group could be provided to other health care providers or agencies that would wish to promote healthy brain aging.

Both a limitation and study strength was the individualized goal setting afforded to B-Fit participants. Allowing participants to set small, intrinsically motivating, and realistic goals that could be easily assimilated into their everyday life means the designed intervention is likely to be more transmissible to the general public and sustainable after the intervention. However, measuring the reported behavior change and comparing this to the education-only and control conditions created some challenges. Although we could compare HAAE data across all three conditions, it may not have accurately captured all the behavior changes engaged in and reported by the B-Fit participants. The goal sheets may have more accurately captured the behavior change reported by participants, but we could not compare this data to the other two conditions.

A potential limitation is the lack of external validation of self-reported behavior change. As with any self-report measure, it is possible participants did not accurately report their behaviors on the HAAE. However, participants did appear willing to acknowledge during B-Fit sessions when they struggled to complete goals; therefore, it is possible participants were equally vigilant when reporting behavior changes on the HAAE. As previously stated, the intervention length, but not the material covered, changed between the 2016-2017 and 2018 cohorts. However, intervention length did not emerge as a significant variable in the primary outcome analysis. Additionally, characteristics of the sample itself may have influenced the results. The study was composed of a non-clinical, predominately white, and well-educated population. Given these characteristics, we may expect less variability between conditions on measures of health literacy, brain health knowledge, and engagement in healthy brain aging behaviors.

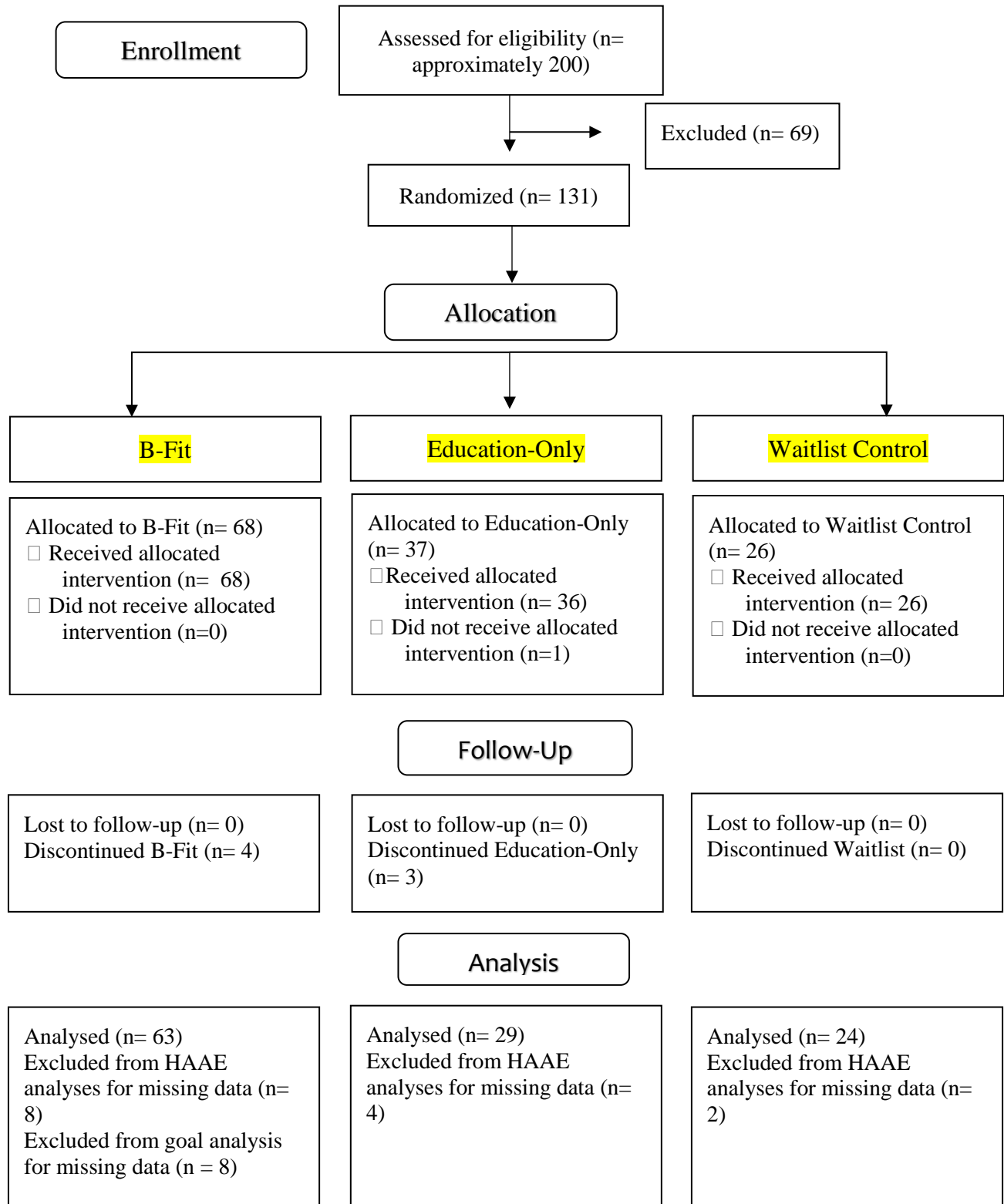
Future Directions

Future work will be necessary to demonstrate whether the health behavior changes can be sustained and to identify whether the changes have any significant impact on cognition, everyday functioning, or onset of dementia. Future work is also needed to understand under what conditions (e.g., person factors, educational materials) an education only intervention may promote health behavior change. Additionally, future studies may benefit from more objective measures of behavior change to remove any concerns regarding accurate reporting. For example, participants could wear smart watches that track physical activity and sleep. In general, more research is needed to determine the best ways to design a multidomain brain-health intervention (e.g., length of intervention, number of risk factors to target, type of educational material provided, etc.) and consider which person-factors and population characteristics may impact outcomes.

Conclusion

In sum, the designed multidomain brain-health intervention was effective at helping midlife and older adults increase their engagement in healthy brain-aging behaviors. Furthermore, individuals with higher baseline healthy brain-aging behaviors reported greater success in meeting their designated health goals. The results also suggested that the B-Fit intervention may have been especially successful in assisting those with lower education and lower health literacy in meeting their designated health goals. Finally, the significant change in health behaviors reported by the active education-only control condition suggests that education, when provided in this format, may spur on the behavior change process. Moreover, individuals with lower-brain health knowledge were found to especially benefit from an education-only condition.

Figure 1 CONSORT flow diagram



References

- Albert, M., Blacker, D., Moss, M. B., Tanzi, R., & McArdle, J. J. (2007). Longitudinal change in cognitive performance among individuals with mild cognitive impairment. *Neuropsychology, 21*(2), 158–169. <https://doi.org/10.1037/0894-4105.21.2.158>
- Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., Bories, L., Cufi, MN., Dantoine, T., Dartigues, JF., Desclaux, F., Gabelle, A., Gasnier, Y., Pesce, A., Sudres, K., Touchon, J., Robert, P., Rouaud, O., Legrand, P., ... & Vellas, B. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomized, placebo-controlled trial. *The Lancet Neurology, 16*(5), 377-389. [https://doi.org/10.1016/S1474-4422\(17\)30040-6](https://doi.org/10.1016/S1474-4422(17)30040-6)
- Arlinghaus, K. R., & Johnston, C. A. (2018). Advocating for behavior change with education. *American Journal of Lifestyle Medicine, 12*(2), 113-116. <https://doi.org/10.1177/1559827617745479>
- Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology, 10*(9), 819-828. [https://doi.org/10.1016/S1474-4422\(11\)70072-2](https://doi.org/10.1016/S1474-4422(11)70072-2)
- Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., Viera, A., Crotty, K., Holland, A., Brasure, M., Lohr, K., Harden, E., Tant, E., Wallace, I., & Viswanathan, M. (2011). Health literacy interventions and outcomes: An updated systematic review. *Evidence Report/Technology Assessment (Full Report), 199* (1), 1-941.
- Blondell, S. J., Hammersley-Mather, R., & Veerman, J. L. (2014). Does physical activity prevent

- cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC public health*, *14*(1), 510. <https://doi.org/10.1186/1471-2458-14-510>
- Bourassa, K., & Sbarra, D. A. (2017). Body mass and cognitive decline are indirectly associated via inflammation among aging adults. *Brain, Behavior, and Immunity*, *60*, 63-70. <https://doi.org/10.1016/j.bbi.2016.09.023>
- Brandt, J., Spencer, M., & Folstein, M. (1988). The telephone interview for cognitive status. *Neuropsychiatry Neuropsychology Behavioral Neurology*, *1*(2), 111-117.
- Brookmeyer R, Johnson E, Ziegler-Graham K, & Arrighi HM. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia*, *3*, 186–19. <https://doi.org/10.1016/j.jalz.2007.04.381>
- Castro, D. M., Dillon, C., Machnicki, G., & Allegri, R. F. (2010). The economic cost of Alzheimer's disease: Family or public health burden? *Dementia & Neuropsychologia*, *4*(4), 262–267. <https://doi.org/10.1590/S1980-57642010DN40400003>
- Clare, L., Nelis, S. M., Jones, I. R., Hindle, J. V., Thom, J. M., Nixon, J. A., Cooney, J., Jones, C. L., Tudor Edwards, R., & Whitaker, C. J. (2015). The Agewell trial: A pilot randomized controlled trial of a behaviour change intervention to promote healthy ageing and reduce risk of dementia in later life. *BMC Psychiatry*, *15*(1), 25. <https://doi.org/10.1186/s12888-015-0402-4>
- Cramer, H., Lauche, R., Moebus, S., Michalsen, A., Langhorst, J., Dobos, G., & Paul, A. (2014). Predictors of health behavior change after an integrative medicine inpatient program. *International Journal of Behavioral Medicine*, *21*(5), 775-783. <https://doi.org/10.1007/s12529-013-9354-6>
- Dominick, G.M., Dunsiger, S.I., Pekmezi, D.W. Larsen, B., Marquez, B., Nodora, J., Gans,

- K.M., & Marcus, B.H. (2015). Moderating effects of health literacy on change in physical activity among Latinas in a randomized trial. *Journal of Racial and Ethnic Health Disparities*, 2(3), 351–357. <https://doi.org/10.1007/s40615-014-0080-9>
- Edmunds, J., Ntoumanis, N., & Duda, J. L. (2008). Testing a self-determination theory-based teaching style intervention in the exercise domain. *European Journal of Social Psychology*, 38(2), 375-388. <https://doi.org/10.1002/ejsp.463>
- Farias, S., Gravano, J., Weakley, A., Schmitter-Edgecombe, M., Harvey, D., Mungas, D., Chan, M., & Giovannetti, T. (2020). The Everyday Compensation (EComp) questionnaire: Construct validity and associations with diagnosis and longitudinal change in cognition and everyday function. *Journal of the International Society of Neuropsychology*, 26(3), 303-313. <https://doi.org/10.1017/S135561771900119X>
- Ferreira, N., Owen, A., Mohan, A., Corbett, A., & Ballard, C. (2015). Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline. *International Journal of Geriatric Psychiatry*, 30(4), 422-430.
- Freedman, V. A., Kasper, J. D., Spillman, B. C., Agree, E. M., Mor, V., Wallace, R. B., & Wolf, D. A. (2014). Behavioral adaptation and late-life disability: A new spectrum for assessing public health impacts. *American Journal of Public Health*, 104(2), e88-e94.
- Friis, K., Vind, B. D., Simmons, R. K., & Maindal, H. T. (2016). The relationship between health literacy and health behaviour in people with diabetes: A Danish population-based study. *Journal of Diabetes Research*. <https://doi.org/10.1155/2016/7823130>
- Gans, K., Risica, P., Strolla, L., Fournier, L., Kirtania, U., Upegui, D., Zhao, J., George, T., & Acharyya, S. (2009). Effectiveness of different methods for delivering tailored nutrition

education to low income, ethnically diverse adults. *The International Journal of Behavioral Nutrition and Physical Activity*, 6(1), 24–24. <https://doi.org/10.1186/1479-5868-6-24>

Gillette-Guyonnet, S., Secher, M., & Vellas, B. (2013). Nutrition and neurodegeneration: Epidemiological evidence and challenges for future research. *British Journal of Clinical Pharmacology*, 75(3), 738-755. <https://doi.org/10.1111/bcp.12058>

Gitlin, L. N., Winter, L., & Stanley, I. H. (2017). Compensatory strategies: Prevalence of use and relationship to physical function and well-being. *Journal of Applied Gerontology*, 36(6), 647-666. <https://doi.org/10.1177/0733464815581479>

Gottesman, R. F., Schneider, A. L., Albert, M., Alonso, A., Bandeen-Roche, K., Coker, L., Coresh, J., Knopman, D., Power, M. C., Rawlings, A., Sharrett, A. R., Wruck, L. M., & Mosley, T. H. (2014). Midlife hypertension and 20-year cognitive change: The atherosclerosis risk in communities neurocognitive study. *JAMA neurology*, 71(10), 1218-1227. <https://doi.org/10.1001/jamaneurol.2014.1646>

Hansen, H., Shneyderman, Y., & Belcastro, P. (2015). Investigating the association of health literacy with health knowledge and health behavior outcomes in a sample of urban community college undergraduates. *American Journal of Health Education*, 46(5), 274–282. <https://doi.org/10.1080/19325037.2015.1055016>

Hartmann, C., Dohle, S., & Siegrist, M. (2015). A self-determination theory approach to adults' healthy body weight motivation: A longitudinal study focusing on food choices and recreational physical activity. *Psychology and Health*, 30(8), 924-948. <https://doi.org/10.1080/08870446.2015.1006223>

Huang, C. L., Yang, S. C., & Chiang, C. H. (2020). The associations between individual

- factors, eHealth literacy, and health behaviors among college students. *International Journal of Environmental Research and Public Health*, 17(6), 2108.
<https://doi.org/10.3390/ijerph17062108>
- Kivipelto, M. (2009). Lifestyle related factors in stroke and dementia. *Journal of the Neurological Sciences*, 283(1), 242–243. <https://doi.org/10.1016/j.jns.2009.02.018>
- Knickman, J. R., & Snell, E. K. (2002). The 2030 problem: Caring for aging baby boomers. *Health services research*, 37(4), 849–884. <https://doi.org/10.1034/j.1600-0560.2002.56.x>
- Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S. Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. S., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413-446. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6)
- Lustria, M. L. A., Noar, S. M., Cortese, J., Van Stee, S. K., Glueckauf, R. L., & Lee, J. (2013). A meta-analysis of web-delivered tailored health behavior change interventions. *Journal of Health Communication*, 18(9), 1039-1069. <https://doi.org/10.1080/10810730.2013.768727>
- Miller, T. A. (2016). Health literacy and adherence to medical treatment in chronic and acute illness: A meta-analysis. *Patient Education and Counseling*, 99(7), 1079-1086.
<https://doi.org/10.1016/j.pec.2016.01.020>
- Mravec, B., Horvathova, L., & Padova, A. (2018). Brain under stress and Alzheimer's

disease. *Cellular and Molecular Neurobiology*, 38(1), 73-84.

<https://doi.org/10.1007/s10571-017-0521-1>

Oliveira, D., Bosco, A., & di Lorito, C. (2019). Is poor health literacy a risk factor for dementia in older adults? Systematic literature review of prospective cohort

studies. *Maturitas*, 124, 8-14. <https://doi.org/10.1016/j.maturitas.2019.03.010>

Park, A., Eckert, T. L., Zaso, M. J., Scott-Sheldon, L. A., Venable, P. A., Carey, K. B., Ewart, C.

K., & Carey, M. P. (2017). Associations between health literacy and health behaviors among urban high school students. *Journal of School Health*, 87(12), 885-893.

<https://doi.org/10.1111/josh.12567>

Park, C. S., Troutman-Jordan, M., & Nies, M. A. (2012). Brain health knowledge in community-dwelling older adults. *Educational Gerontology*, 38(9), 650-657.

<https://doi.org/10.1080/03601277.2012.686838>

Penninkilampi R, Casey A., Singh M., & Brodaty H. (2018). The association between social engagement, loneliness, and risk of dementia: A systematic review and meta-

analysis. *Journal of Alzheimer's Disease*, 66(4),1619-1633. <https://doi.org/10.3233/JAD-180439>

Purdie, N., & McCrindle, A. (2002). Self-regulation, self-efficacy and health behavior change in

older adults. *Educational gerontology*, 28(5), 379-400. <https://doi.org/10.1080/03601270290081353>

Rose, K. C., Gitlin, L. N., & Dennis, M. P. (2010). Readiness to use compensatory strategies

among older adults with functional difficulties. *International Psychogeriatrics*, 22(8),

1225. <https://doi.org/10.1017/S1041610210001584>

Rosenberg, A., Ngandu, T., Rusanen, M., Antikainen, R. Bäckman, L., Havulinna, S., Hänninen,

- T., Laatikainen, T., Lehtisalo, J., Levälähti, E., Lindström, J., Paajanen, T., Peltonen, M., Soininen, H., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Solomon, A., & Kivipelto, M. (2018). Multidomain lifestyle intervention benefits a large elderly population at risk for cognitive decline and dementia regardless of baseline characteristics: The FINGER trial. *Alzheimer's & Dementia*, *14*(3), 263–270. <https://doi.org/10.1016/j.jalz.2017.09.006>
- Rothman, R. L., DeWalt, D. A., Malone, R., Bryant, B., Shintani, A., Crigler, B., Weinberger, M., & Pignone, M. (2004). Influence of patient literacy on the effectiveness of a primary care-based diabetes disease management program. *The Journal of the American Medical Association*, *292*(14), 1711–1716. <https://doi.org/10.1001/jama.292.14.1711>
- Schmitter-Edgecombe, M., Lamb, R., McAlister, C., Vo, T., & Robertson, K. (2019). Development and psychometric properties of the Healthy Aging Activity Engagement Scale (HAAE). *Aging & Mental Health*, *23*(3), 357-364. <https://doi.org/10.1080/13607863.2017.1414147>
- Schultz, S. A., Larson, J., Oh, J., Kosciak, R., Dowling, M. N., Gallagher, C. L., Carlsson, C. M., Rowley, H. A., Bendlin, B. B., Asthana, S., Hermann, B. P., Sterling, C. J., Sager, M., LaRue, A., & Okonkwo, O. C. (2015). Participation in cognitively-stimulating activities is associated with brain structure and cognitive function in preclinical Alzheimer's disease. *Brain Imaging and Behavior*, *9*(4), 729–736. <https://doi.org/10.1007/s11682-014-9329-5>
- Schulz, D. N., Kremers, S. P. J., Vandelanotte, C., van Aichen, Mathieu J. G., Schneider, F., Candel, M. J. J. M., & de Vries, H. (2014). Effects of a web-based tailored multiple-lifestyle intervention for adults: A two-year randomized controlled trial comparing

sequential and simultaneous delivery modes. *Journal of Medical Internet Research*, 16(1), 48-65. <https://doi.org/10.2196/jmir.3094>

Weiss, B. D., Mays, M. Z., Martz, W., Castro, K. M., DeWalt, D. A., Pignone, M. P., Mockbee, J., & Hale, F. A. (2005). Quick assessment of literacy in primary care: The newest vital sign. *The Annals of Family Medicine*, 3(6), 514-522. <https://doi.org/10.1370/afm.405>

Whitmer, R.A., Sidney, S., Selby, J., Johnston, S.C., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*, 64(2), 277-281. <https://doi.org/10.1212/01.WNL.0000149519.47454.F2>

Xu, W., Tan, C. C., Zou, J. J., Cao, X. P., & Tan, L. (2020). Sleep problems and risk of all-cause cognitive decline or dementia: An updated systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*, 91(3), 236-244. <https://doi.org/10.1136/jnnp-2019-321896>