Behavioral Interventions to Prevent or Delay Dementia

NCT02265757

08/01/2018

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Support: Research reported in this manuscript was primarily funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-1306-01897). The statements in this publication are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Trial registration: ClinicalTrials.gov Identifier: NCT02265757

IRB: Institutional Review Boards at the Mayo Clinic (14-000885) and University of Washington (49235)

Abstract

Importance: A 2017 National Academies of Sciences Engineering and Medicine (NAS) report suggests that certain behavioral interventions show promise as strategies for delaying or preventing dementia but require a stronger evidence base.

Objective: To examine five behavioral interventions' effectiveness at impacting the outcomes of highest importance to persons with mild cognitive impairment (pwMCI).

Design: Multi-site cluster randomized, multi-component comparative effectiveness trial.

Participants: Two-hundred seventy two pwMCI and their partners were enrolled. PwMCI met prevailing National Institute on Aging-Alzheimer Association for MCI with memory impairment. Partners were cognitively normal and had frequent contact with the pwMCI.

Interventions: The intervention program was modeled on the Mayo Clinic HABIT program, a 10-day, 50-hour group intervention including memory compensation training, computerized brain fitness, yoga, patient and partner support groups and wellness education. In the present comparative effectiveness study, one of 5 interventions was selected by block randomization to be withheld for each group. Dyads were followed to 12 months post-intervention with a one-day booster session occurring at 6 months.

Outcomes: Primary outcome measures were selected based on the preference rankings of previous HABIT completers. All measures were focused on pwMCI at one year of follow-up. Measures included validated scales of quality of life (QOL), mood, self-efficacy and memory based-activities of daily living (mADL).

Results: Wellness Education had the greatest estimated impact on QOL. Mood and self-efficacy were most positively impacted by a combination of wellness education, yoga, compensation based calendar training (the MSS) and supportive group therapy. Memory ADLs were most negatively affected by lack of physical exercise. All effect sizes were modest.

Conclusion and Relevance: The findings provide further support for behavioral interventions and extend our preliminary comparative effectiveness finding showing MSS to be superior to brain fitness exercises for mADLs. As might be expected, different outcomes are optimized by different combinations of interventions. The findings serve as a preliminary foundation for personalized approaches to behavioral interventions for pwMCI and that comport which each individuals priority outcomes.

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Keywords (3-6): nonpharmacological interventions; behavioral interventions; cognitive intervention; MCI, caregiver; patient preferences

Introduction

As a medical community, we are increasingly able to identify Alzheimer’s disease (AD) at an early stage, including a Mild Cognitive Impairment (MCI) stage. Approximately 15-20% of people age 65 or older have MCI and approximately a third of these individuals develop a dementia related to Alzheimer’s disease in 5 years [1]. Amnestic MCI is defined as memory abnormality beyond normal age related decline with relatively intact functional capacity, in other words, not (yet) dementia [2].

There continue to be no FDA approved medical therapies for MCI. In the absence of medical therapy, patients and families are often presented numerous recommendations regarding nonpharmacological interventions (e.g., start keeping notes, follow a physical exercise program, play computer memory games, etc.) which can be overwhelming. There is some promising evidence that such behavioral interventions can be beneficial in MCI. Namely, recent meta-analyses suggest that cognitive interventions have significant, mild to moderate effect sizes (Hedges’ g ranging from .23 to .40) for persons with MCI (pwMCI) on multiple cognitive domains, including memory, attention, and processing speed [3]. Meta-analysis of non-cognitive effects of cognitive interventions in pwMCI demonstrated small, but significant effects for activities of daily living (ADLs; Cohen’s d = 0.23), mood (d = 0.16), and metacognitive outcomes (i.e., how one thinks/feels about one’s memory; d = 0.30) [4]. Physical exercise meta-analysis outcomes in individuals over 50 have provided similar, moderate, overall effect sizes on cognition (mean effect size = .29) [5].

Only recently have enough studies been completed on individual interventions in cognitive rehabilitation, physical exercise training, or psychotherapy to allow meaningful meta-analyses like these to emerge in the literature. Still, these reviews struggle with blending an array of various approaches to such interventions, in different delivery systems, in differing “doses,” and with different measured outcomes. In other words, there still is not consensus on the best method to deliver a specific behavioral intervention. Nor is there a consensus regarding how to measure the outcomes. Yet there is increasing support for the use of multi-component interventions in dementia prevention efforts [6]. For example the Alzheimer’s Association is currently funding a $20 million study of physical exercise, diet, cognitive and social stimulation and improved self-management of health conditions (particularly blood pressure). Yet there is a dearth of literature examining the effectiveness of various behavioral interventions in comparison to each other.

Previously, we have compared outcomes for a compensatory cognitive rehabilitation intervention and computerized cognitive exercise intervention as well as no-treatment control groups in randomized trials [7, 8]. In these studies, patient memory related ADLs (mADLs) were significantly improved over no treatment in those randomized to the cognitive rehabilitation condition (but not for those completing computerized cognitive exercise), and sense of memory self-efficacy significantly improved for those trained in use of the calendar system (but not in the computerized cognitive exercise or no treatment conditions) [7, 8]. Further, partners in both treatment groups showed stable mood and anxiety while partners in the untreated group showed worsening depression and anxiety over 6 months [9]. Similarly, systematic review of the literature has supported that various computerized interventions aimed at improving cognition may have impact on reducing anxiety and depression in individuals with MCI, and those trained with therapists in compensatory strategies (like the calendar training highlighted above) show more impact on ADLs, self-beliefs about memory, and confidence [4].

There is significant debate within the field as to which outcomes to measure and how to consistently measure them. The vast majority of studies of behavioral interventions to date have focused on the impact on cognition itself for older adults or for those with MCI. However, the growing culture of patient centered care considers patients to be members of the healthcare team with an active voice in their treatment and care. There is increasing awareness of the need to ask what our patient want from an intervention. However, no trials to date have utilized the input of persons with MCI (pwMCI) or their family members in the study design and selection of outcomes. Thus, in the first aim of this larger study, we established that pwMCI and their partners rated patient quality of life (QOL), patient self-efficacy, patient mood, and memory dependent ADLs (mADLs) to be the more important target outcomes for behavioral intervention[10, 11].

In the subsequent aims, results of which are reported here, we sought to compare the effectiveness of the five behavioral interventions that compose the Mayo Clinic HABIT Healthy Action to Benefit Independence and Thinking® Program, a 50 hour behavioral intervention treatment program with 5 components in impacting those highly valued outcomes by pwMCI. The 5 components include physical exercise, computerized brain fitness, patient and family education, support group, and cognitive rehabilitation with a compensatory memory support system (calendaring system). Each of these interventions was originally chosen on a theoretical basis, because each had support individually in the literature for effectiveness when compared to no treatment controls across a variety of outcomes [e.g., cognitive functioning, QOL, mood, partner burden] [4, 12] [3, 5].

Methods

Full details of the study protocol and recruitment have been reported previously [13], and briefly summarized below.

Patient and Partner Engagement. Prior to obtaining funding we created patient/partner and stakeholder advisory groups. The patient/partner advisory group included 8 members, all of whom had completed the HABIT clinical program (described below). Each recruitment site had a patient or partner representative included. The stakeholder advisory group included representatives of the Alzheimer's Association Chapters in Minnesota and Florida, as well as a representative from the Minnesota Board on Aging. Both advisory groups reviewed our preliminary protocol. The patient and partner advisory group strongly encouraged the conduct of the comparative effectiveness protocol in such a way as to ensure that all participants received substantial treatment; they endorsed our randomized suppression of one treatment component over a design involving a no treatment control. The advisory group also provided pilot data for Aim 1 of the study as reported elsewhere [9]. The patient and partner advisory group met the principal investigators via teleconference monthly during the first year of the project and roughly quarterly thereafter to provide feedback regarding recruitment strategies and other issues. The most engaged of the advisors served as co-authors of the published protocol paper [11] and were briefed on the final results.

Participants

Dyads consisting of a pwMCI and a partner participated in the interventions. 272 such couples were recruited through clinical services at Mayo Clinic in Minnesota, Arizona, and Florida as well as University of Washington. Consecutive candidates with diagnoses of amnestic MCI (single or multi-domain) [2] were screened and if potentially eligible approached for the study. They then underwent further evaluation based upon study inclusion/exclusion criteria and enrolled in the trial. Inclusion criteria included a Clinical Dementia Rating (CDR) [14] ≤ 0.5, not taking, or stable on, nootropic medication for at least 3 months, fluent in English, and able to attend with a cognitively normal (Mini Mental Status Exam [15] >24) care partner who had at least twice-weekly contact with the pwMCI. Exclusion criteria included current participation in another treatment-related clinical trial or significant auditory, visual, or motor impairment impacting ability to participate in the program. PwMCI completed the Dementia Rating Scale-2 [14] as a measure of general cognitive function at baseline.

Intervention and Randomization:

The intervention lasted 10 days over the course of two weeks. Briefly, for group assignment, we utilized a subtraction model, randomizing groups of couples to have one of the five potential interventions withheld while receiving the other four. Block randomization was utilized to suppress one of the five components from groups of 10-20 couples in each session. Resulting randomization and allocation to each group per site can be viewed in Table 2. Each of the 4 study sites ran at least 5 sessions to allow for suppression of each component at least once at each site. In order to achieve our enrollment goals, each Mayo Clinic site ran an extra session. Components of HABIT include:

1. Yoga: Participants engaged in daily 45-60 minute sessions of yoga for physical exercise and relaxation training with certified yoga instructors. They were provided a customized DVD to encourage continued practice post-HABIT [16].
2. Brain fitness: Participants completed 45-60 minute sessions of cognitive training daily via the commercially available BrainHQ product available from Posit Science Corporation. They were provided a one year subscription to the program to encourage continued use post-HABIT.

3. Wellness education: Couples attended daily 45-50 minute lectures covering a range of health topics such as Living with MCI, Changes in Roles and Relationships, Sleep Hygiene, MCI and Depression, Nutrition, and Assistive Technology. Couples were given resources and written information to inform their choices towards incorporating the healthy behavioral changes discussed in the lectures (e.g., improving diet) into their lives post-HABIT.
4. Support groups: The pwMCI and partners met separately in support groups for 45-60 minutes each day. The pwMCI support group focused on reminiscence-focused group sessions with the opportunity for discussion of MCI related concerns as desired by the participants. The partner group was a traditional support group facilitated by a therapist around caregiving themes.
5. Cognitive rehabilitation: The pwMCI received cognitive rehabilitation daily focused on compensatory-focused memory support system (MSS) development (i.e., a calendar/note taking system). This involved training from a structured curriculum in use of a two page per day written memory book to develop compensatory written reminders for important appointments, tasks, or experiences/thoughts of the day. Both pwMCI and partners were provided the paper MSS materials in an ongoing manner to enable continued use of the system post-HABIT.

Outcome Measures:

<u>*Completed by the pwMCI:*</u>

Participant QOL was the primary outcome measure as assessed by the Quality of Life-AD (QOL-AD)[17] overall score. Participant mood was measured by the Center for Epidemiological

Studies Depression scale (CES-D)[18], and participant self-efficacy was assessed using modified, selected items from the Chronic Disease Self-Efficacy Scales[19].

Completed by the Partner:

Patient memory functional status: Participant functional memory was assessed by 8 memory-related items on the informant-based Everyday Cognition (E-Cog)[20] questionnaire.

Timing.

All measures were completed at baseline, treatment end, 6 months, and 12 months post intervention. Six-months and 12 month data collection was part of a one-day booster session that included a refresher for each of the 4 interventions originally provided [13].

Adherence.

Adherence to taught program activities as well as possible treatment diffusion of the withheld intervention were assessed at 6 and 12 months post intervention by asking pwMCI and their program partners to log how much time spent in each of the 5 intervention related activities. We categorized participants into three levels of adherent: adherent, non-adherent, or indeterminate. Table 1 displays how each level of adherence was defined for each of the 5 interventions and references the standard in the literature to support each definition of adherent.

Power analysis.

We used approaches developed for this design to estimate the power to conclude that a specific HABIT® component provided benefit on the primary outcome. Data from a prior clinical sample and a matched, non-randomized, untreated control group provided initial estimates for this power estimation. We computed the expected variance of the estimated treatment effect for one HABIT® component by extracting the appropriate value from the variance-covariance matrix derived from the design matrix corresponding to the allocation of treatment groups within the study. Using this, we estimated the magnitude of the effect size (difference score divided by its standard deviation) that is detectable with 80% power using a two-sided 0.05 level test. The results of this effort suggest that we had approximately 80% power to conclude that a treatment component is efficacious if it is associated with an improvement of 0.53 standard deviation units (d = 0.53) while accounting for effects due to the other treatment components, study sites, and sessions within sites. We have observed differences larger than this in previous studies. For instance, we observed that training in the MSS improves E-cog scores by nearly 0.9 standard deviations at first follow-up in a previous study [8]. Therefore the study had sufficient power to detect meaningful changes of magnitudes that we expected.

Statistical analysis.

For analysis of the primary aim, we utilized linear mixed-effects regression models to obtain the estimated change in each of the four outcome measures (QOL, self-efficacy, mood, and functional ability) from baseline to 12 months along with 95% confidence intervals (CIs) for the 5 separate study arms. The model included the outcome measure at 4 time points (baseline, end of treatment (EOT), 6-month follow-up, and 12-month follow-up) with separate random effects for participant, session, and time point within session. Fixed effects included indicator variables for each of the 4 sites, age, sex, interactions of age and sex with each of the 3 non-baseline time points (6 parameters), and indicator variables representing each of the 5 treatments at each of the 3 non-baseline time points (15 parameters). We reported the coefficients corresponding to each of the study arms at 12 months along with the 95% profile confidence intervals and likelihood ratio test p values in addition to the coefficients corresponding to each of the study arms at EOT and 6 month follow-up. The coefficients were reported as the fitted mean change in outcome from baseline to the given time point for an individual with covariates equal to their mean values. In addition, we performed likelihood ratio tests to evaluate whether there was evidence of differences in outcome between study arms at EOT, 6 months, and 12 months. Additional sensitivity analyses were performed. Analyses were performed using R statistical software (version 3.2.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

There were 272 participants from 4 sites who were randomized as described above to one of five study arms after enrollment (Figure 1). Participant baseline characteristics are described in Table 2 according to study arm. There were no meaningful differences in demographics or general cognitive status across sites or samples. Participants in the no support group arm were slightly more likely to be taking memory medications. Two hundred eleven of these participants completed the study. Two participants died over the course of follow-up, 42 participants formally withdrew (predominantly due to health concerns of participant or partner, or because of time commitments) and 17 participants were lost to follow-up.

Outcome Measures

Results by suppression group for QOL, mADLs, mood, and self-efficacy are displayed in Table 3.

Quality of Life

All 5 study arms showed improvement in QOL-AD overall score from baseline to EOT with the fitted mean change from baseline ranging from 1.10 (no support groups) to 1.55 (no wellness education) (all $p \leq 0.049$), but these changes were not sustained through 6-month or 12-month follow-up. There was no evidence of a difference between study arms in change in QOL-AD from baseline at EOT (p=0.98), 6-month follow-up (p=0.38), or 12-month follow-up (p=0.21). In comparative effectiveness analysis at 12 months, and in the context of treatment which also includes MSS, support groups, and yoga, replacing BF with wellness education appeared to have significant positive impact on QOL (effect size = 0.34, p = .02). See Figure 2a.

Self-efficacy

At EOT there were improvements in self-efficacy from baseline for the arm with no support group, no MSS training, and no yoga. At 6 months, the arm with no yoga had statistically significant worsening of self-efficacy, though there were no significant within group changes by 12 months. There were no statistically significant differences between study arms in change in self-efficacy from baseline at EOT (p=0.58), 6-month follow-up (p=0.19), or 12-month follow-up (p=0.23). In comparative effectiveness analysis at 12 months, and in the context of treatment which also includes MSS, wellness, and yoga, replacing BF with support group had a significant positive impact on self-efficacy (effect size = 0.31, p = .04. See Figure 2b.

Mood

Three of the five arms (no MSS, no BF, and no yoga) showed an improvement in mood from baseline to EOT. The remaining two arms showed change in the direction of improvement, but were not statistically significant. At 6-month follow-up there was no evidence of a change from baseline for any of the 5 arms. At 12-month follow-up the arm with no BF training showed an improvement in mood, while the arm with no wellness education showed a significant worsening in mood. A likelihood ratio test detected overall differences between the 5 study arms in change in mood from baseline to 12-months and the confidence intervals in Table 3 suggest these differences are between the arm with no wellness education (mean fitted change 95% CI: 0.50 to 4.33) and no computerized brain fitness training (mean fitted change 95% CI: -3.79 to 0.00). In the context of multicomponent treatment involving four interventions, replacing BF with another intervention appeared to have significant positive impact on mood as follows: replace with wellness education (effect size = 0.53, p = .001), replace with yoga (effect size = 0.34, p = .035), and replace with MSS calendar training (effect size = 0.34, p = .04). These findings suggest only support groups were not statistically better than BF in terms of impact on patient mood. See Figure 2c.

Functional Memory Ability

The study arm with no support group was the only group to have a significant improvement in everyday memory from baseline to EOT. There was no evidence of change in any group for everyday memory from baseline to 6-month follow-up. By 12-month follow-up, all of the groups had a significant worsening of everyday memory function with the exception of the arm with no support groups. There were no statistically significant differences between study arms in change in everyday cognition from baseline at EOT (p=0.10), 6-month follow-up (p=0.90), or 12-month follow-up (p=0.07). See Figure 2d.

Impact of Ongoing Adherence

Adherence at 12 months to the various components had minimal impact on QOL or mood outcomes. Adherence to exercise broadly was positively associated with self-efficacy outcomes ($p < .05$, $d = .29$) and mADLs outcomes ($p < .05$, $d = .26$). Wellness adherence was positively associated with mADL outcomes as well ($p < .05$, $d = .22$). Adherence impact on outcome variables is presented in Table 4.

Discussion

In 2017, the National Academies of Sciences Engineering and Medicine (NAS) released its report evaluating strategies aimed at preventing or delaying normal age related cognitive decline, MCI, or Alzheimer's-type dementia[21]. That report concludes that the data do not currently support a widespread public health campaign for any particular prevention strategy. However, they report promising results with one medical intervention (blood pressure management) and two behavioral interventions: cognitive training and physical activity. In this study, we sought to examine the comparative effectiveness of behavioral interventions, including cognitive training through either the MSS compensation system or computerized BF training and physical activity through yoga, as well as the impact of wellness education and supportive group therapy on individuals with MCI.

This study was a patient-centered comparative effectiveness outcome study. Thus, our methodology and results were guided by former behavioral intervention program participants and patient/partner focus groups (see full protocol[13]). As a consequence, the primary outcomes were defined by our former patients as QOL, self-efficacy, mood, and mADLs[11]. Further, we were prompted to forgo the traditional “additive” approach of clinical trials of randomly adding participants to one intervention at a time, to undertake a novel, “subtractive” approach of randomly withholding one intervention at a time. This assured that all participants would receive substantial interventions while still permitting comparison of the components. This design inverts the typical interpretation of intervention studies. Rather than looking to associate the best outcomes with the presence of an intervention, this design requires consideration which groups has the poorest outcomes associated with a missing intervention.

Treatment End

Immediately after the intervention, all combinations of behavioral intervention resulted in reports of improved QOL. Thus, each of our interventions actually may positively impact QOL in the short run. It could be argued that simply participating in an intensive group intervention leads to a sense of better QOL immediately following the group, regardless of what the intervention is, simply because the act of doing *something* rather than nothing fosters an improved sense of QOL. On the other hand, meta-analysis of cognitive interventions in MCI have not previously been shown to significantly impact on QOL[4], suggesting mere contact alone may not produce improved QOL.

All groups except those missing BF showed statistically significant improvements in self-efficacy by treatment end. This suggests that not participating in BF may have some cost in terms of improved self-efficacy. The findings regarding self-efficacy are in keeping with an overall positive effect size of d = .30 for meta-cognitive variables such as sense of self-efficacy reported in a prior meta-analysis of cognitive interventions for MCI[4]. However, our finding stands in contrast to prior studies showing computerized training interventions did not impact beliefs about one's memory ability confidence [22, 23].

Mood improved significantly by treatment end for the no MSS, no BF, and no yoga groups, but did not improve for the no support group or no wellness education groups. Thus, support group and wellness education may be more important in mood improvement than MSS, BF, or yoga at treatment end. Improvement in mADLs at treatment end was only observed for those not receiving support group. Thus, support group did not appear to play a significant role in improving mADLs in the near term or conversely, the combination of MSS, BF, yoga and wellness was most potent at improving near term mADLs.

12 Month Follow-Up

We were particularly interested in the lasting effects of these interventions over time, after the initial "honeymoon" period of participation subsided. By 12 months post intervention, the group that did not have computerized BF training had the best reported QOL whereas the group that did not receive wellness education had the lowest QOL and was the only group with worsening QOL relative to baseline. This would suggest that in terms of QOL there was no cost to withholding BF but that there was significant cost to QOL for withholding wellness education. More specifically, a combination of MSS training, support group, wellness education, and yoga had the best outcomes on QOL and replacing wellness with brain fitness elevated that benefit. The 12-month outcomes for mood followed a similar pattern as QOL with the exception that the benefits of retaining yoga and MSS over brain fitness were also statistically supported.

The group that did not have computerized brain fitness training also showed the best improvement of the groups at 12 months post intervention in self-efficacy. As such, the combination of MSS training, support group, wellness education, and yoga may have the best outcomes for self-efficacy. The group that did not receive support group had a decline in self-efficacy suggesting that support group may be a key component to positively impact self-efficacy.

Previous work suggests that those who adhere better to the interventions of a study in the long run also are likely to have better outcomes [8, 24]. In this study, adherence to exercise broadly improved self-efficacy, and adherence to exercise and wellness improved mADLs. There is much still to be determined about the impact on adherence to outcomes. For example, of the interventions, the physical exercise component (broadly defined) had the most individuals still adherent at one year (55%) compared to the other variables (BF = 25%, wellness = 23%, MSS = 12%, and support group 9%), giving more power to detect significant differences in the physical exercise component for adherent and non-adherent groups. Further, our grading of adherence is not equivalent across interventions. For example we required strict use to our particular calendar and brain fitness programs to be considered adherent to those components but accepted any form of physical exercise towards adherence to the physical exercise component. This makes it difficult to compare impact of adherence across components in this study design. Most behavioral interventions in this area are intended not as one time treatments, like a course of antibiotics but more as life-style modifications intended to persist as long as possible. Research on efficacious and cost-effective ways to optimize adherence is needed.

In this type of behavioral intervention treatment diffusion is also a problem. In drug trials it is generally difficult to get the experimental medication unless your are randomized to it. But here participants could freely engage in the behaviors that had been suppressed in their intervention arm. For example, 82% of the physical exercise suppressed group met physical exercise adherence guidelines at 10 months, which is nominally higher that the overall average. After intervention, reported participation in support groups was equally likely in the no support group arm as any other arm. No one would wish for participants to avoid activities that could benefit them but this does produce confounds perhaps unique to behavioral research that can diminish the ability to detect treatment differences.

We should expect that the comparative effectiveness of different behavioral interventions for MCI is dependent upon the specific outcome targeted. Unsurprisingly, the interventions a pwMCI should pursue likely depend on which outcomes are most important to the individual. We acknowledge that in this study, interpretation of the impact of NOT getting an intervention component was counter to the design of most clinical trials who report the impact of receiving an intervention. However, maximizing the number of interventions received was of great import to our patient advisors in designing this trial [13]. To try to help simplify the explanation of the results, we also sought to statistically examine the impact of receiving each component by comparing each intervention to the intervention found to have the minimal overall impact: brain fitness. When viewed in this manner, wellness education appears to be most important to QOL at one year post intervention; wellness education, yoga, and MSS calendar training were important for mood outcomes; support group had a positive impact on self-efficacy, and yoga was most beneficial to mADLs. Thus, for participants who share the same opinions as our former HABIT alumni in choosing outcomes of most importance (patient QOL, self-efficacy, mood, and functional ability[11], the most benefit would be found in the long term of participating in a program that included wellness education, yoga, MSS calendar training, and support group. The same alumni group also ranked the importance of our interventions overall as 1) MSS, 2) support group, 3) wellness education, 4) yoga, and 5) brain fitness [11], further supporting the importance of these top four interventions. Though these findings are preliminary, they provide a start on the development of 'personalized' intervention protocols wherein the interventions are tailored to the outcomes of greatest importance to the pwMCI and his or her support network. Other outcomes including pwMCI cognition, time to dementia diagnosis and partner QOL, mood and burden, are available to us as secondary outcomes and will be reported elsewhere.

For the time being however, the urgency of dementia and an individual and public health concern is great[21]. Under the circumstances it is reasonable to pursue all possible behavioral approaches in multiple components programs as studied here and deployed in the World Wide Fingers network (wwfingers.com).

While we utilized our particular version of these interventions, similar behavioral interventions (therapy based cognitive rehabilitation, computerized brain training programs, physical exercise, psychotherapy/group therapy, and education programs for memory loss) are being offered in various combinations in medical and research centers around the world[4]. While our exact conclusions may not generalize to other forms of the behavioral intervention (e.g., resistance training as physical exercise versus yoga), we offer these results as a starting point in the literature to begin these sorts of comparative effectiveness trials. Future research thus can look at the nuances of different types of physical exercise compared to different types of therapist based cognitive rehabilitation, etc., and combinations thereof. The recruited cohort was ultimately not diverse and was highly educated. It is not clear how results might change in more representative samples or in specific underrepresented populations.

Conclusions: Wellness education had the most impact on our highest patient ranked outcome of QOL by one year post intervention. Psychological outcomes of mood and self-efficacy were most positively impacted at one year by participating in a combination of wellness education, yoga, compensation based calendar training (the MSS) and supportive group therapy. When functional independence was considered as the outcome, a combination of MSS training, computer BF, wellness education, and yoga appeared to be of most benefit in maintenance of mADLS, with particular decline if yoga was not included.

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Table 1. Classifications of Adherence at 12 month Follow-Up

	Adherent	Non-Adherent
MSS Calendar	Compliance score ≥ 7[25]	Less than daily
Computerized BF	40 hours post program (2 hours per week for 6 months)[24]	Less than 1 hour per week
Physical Activity	150 minutes a week[26]	Less than 60 minutes per week
Supportive Therapy	Activity Log participating in individual or group therapy	"Not at all"
Wellness Education	Activity Log answer of "once, twice or more than twice in past 2 weeks"	"Not at all"

Note. MSS = Memory Support System, BF = Brain Fitness. Rationale for the cut-off adherence standard is referenced as applicable. Non-adherent fell far lower than those standards. All responses not falling into the adherent or non-adherent categories were labeled as "indeterminate."

Table 2: Participant baseline characteristics by study arm

Table 1 Participant baseline characteristics by study arm

	No Brain Fitness (N=54)	No MSS (N=57)	No Support Group (N=53)	No Wellness (N=52)	No Yoga (N=56)	p value
Age						0.64[2]
N	54	57	53	52	56	
Mean (SD)	75.8 (8.0)	74.3 (8.1)	75.1 (7.3)	76.5 (7.2)	74.3 (7.3)	
Median	75.0	75.0	75.0	76.0	74.5	
Q1, Q3	71.0, 82.0	69.0, 80.0	71.0, 80.0	72.0, 80.0	70.0, 80.5	
Range	(53.0-95.0)	(56.0-91.0)	(57.0-88.0)	(59.0-94.0)	(58.0-87.0)	
Gender						0.95[1]
Male	33 (61.1%)	31 (54.4%)	32 (60.4%)	30 (57.7%)	34 (60.7%)	
Female	21 (38.9%)	26 (45.6%)	21 (39.6%)	22 (42.3%)	22 (39.3%)	
Years of education						0.37
N	53	57	53	52	56	
Mean (SD)	16.0 (2.7)	15.8 (3.0)	16.1 (3.0)	15.8 (2.6)	16.6 (2.8)	
Median	16.0	16.0	16.0	16.0	16.5	
Q1, Q3	14.0, 18.0	14.0, 18.0	14.0, 19.0	14.0, 18.0	16.0, 19.0	
Range	(12.0-20.0)	(6.0-20.0)	(10.0-20.0)	(12.0-20.0)	(9.0-20.0)	
Race,						0.36[1]
Non-white	1 (1.9%)	5 (8.8%)	2 (3.8%)	1 (1.9%)	3 (5.4%)	
White, non-hispanic	53 (98.1%)	52 (91.2%)	51 (96.2%)	51 (98.1%)	53 (94.6%)	
DRS Total Raw Score						0.25[2]
N	54	55	53	51	49	
Mean (SD)	127.5 (9.3)	129.7 (8.8)	130.9 (7.6)	128.2 (8.0)	127.7 (18.7)	
Median	129.5	132.0	132.0	129.0	131.0	
Q1, Q3	122.0, 135.0	124.0, 136.0	127.0, 136.0	122.0, 135.0	124.0, 138.0	
Range	(97.0-142.0)	(100.0-143.0)	(110.0-141.0)	(108.0-141.0)	(14.0-143.0)	
Partner						0.13[1]
Missing	0	4	0	0	0	
Adult Child, sibling, other	10 (18.5%)	12 (22.6%)	5 (9.4%)	8 (15.4%)	4 (7.1%)	
Spouse	44 (81.5%)	41 (77.4%)	48 (90.6%)	44 (84.6%)	52 (92.9%)	

Table 1 Participant baseline characteristics by study arm

	No Brain Fitness (N=54)	No MSS (N=57)	No Support Group (N=53)	No Wellness (N=52)	No Yoga (N=56)	p value
Current memory medications						0.02[1]
Missing	0	4	0	3	1	
No	30 (55.6%)	31 (58.5%)	42 (79.2%)	33 (67.3%)	28 (50.9%)	
Yes	24 (44.4%)	22 (41.5%)	11 (20.8%)	16 (32.7%)	27 (49.1%)	

(report generated on 20JUL2018)

[1]Chi-Square [2]Kruskal Wallis

Table 3: Fitted mean change from baseline in QOL, mADL, mood, and self-efficacy.

Outcome	Study Arm	Change BL to EOT (95% CI)	Change BL to 6 months (95% CI)	Change BL to 12 months (95% CI)
QOL	No Wellness	1.55 (0.40, 2.69)**	0.55 (-0.64, 1.72)	-0.85 (-2.06, 0.33)
	No MSS	1.31 (0.22, 2.41)*	0.22 (-1.02, 1.49)	-0.01 (-1.19, 1.19)
	No Support	1.10 (0.01, 2.25)*	0.47 (-0.71, 1.67)	0.36 (-0.82, 1.59)
	No Yoga	1.52 (0.45, 2.57)**	-0.84 (-1.95, 0.28)	0.61 (-0.53, 1.73)
	No Computer	1.33 (0.24, 2.43)*	0.51 (-0.65, 1.67)	1.07 (-0.11, 2.26)†
mADL	No Wellness	-0.36 (-1.38, 0.67)	0.38 (-0.68, 1.44)	1.15 (0.08, 2.22)*
	No MSS	0.48 (-0.50, 1.45)	0.47 (-0.66, 1.59)	1.29 (0.24, 2.35)*
	No Support	-1.34 (-2.32, -0.37)**	0.21 (-0.86, 1.29)	0.42 (-0.66, 1.49)
	No Yoga	-0.35 (-1.30, 0.59)	0.36 (-0.64, 1.35)	2.52 (1.52, 3.53)***
	No Computer	0.09 (-0.88, 1.06)	0.91 (-0.12, 1.94)†	1.09 (0.03, 2.14)*
Mood	No Wellness	-1.75 (-3.58, 0.08)†	1.22 (-0.66, 3.10)	2.42 (0.50, 4.33)**
	No MSS	-3.68 (-5.44, -1.93)***	-0.52 (-2.52, 1.47)	0.87 (-1.03, 2.76)
	No Support	-1.02 (-2.76, 0.72)	-0.54 (-2.45, 1.36)	-1.00 (-2.94, 0.93)
	No Yoga	-2.47 (-4.17, -0.77)**	0.34 (-1.46, 2.13)	0.86 (-0.96, 2.68)
	No Computer	-3.47 (-5.21, -1.72)***	-1.62 (-3.48, 0.25)	-1.90 (-3.79, 0.00)*
SE	No Wellness	2.79 (-0.12, 5.69)†	0.47 (-2.51, 3.46)	-0.74 (-3.78, 2.30)
	No MSS	4.83 (2.05, 7.62)***	1.66 (-1.54, 4.85)	1.09 (-1.92, 4.10)
	No Support	4.91 (2.14, 7.69)***	1.4 (-1.61, 4.42)	-2.48 (-5.52, 0.56)
	No Yoga	3.66 (0.97, 6.36)**	-2.86 (-5.70, -0.02)*	-1.82 (-4.70, 1.05)

	No Computer	2.26 (-0.52, 5.04)	-0.23 (-3.19, 2.73)	1.82 (-1.18, 4.83)

Note. BL = baseline; EOT = end of treatment; MSS = Memory Support System; QOL = Quality of Life; mADL = memory related activities of daily living; SE = self-efficacy. A positive change from baseline indicates and improvement in quality of life and self-efficacy. A negative change from baseline indicates and improvement in mADL and mood. Fitted mean change from baseline to each of the three time points was estimated from a linear mixed-effects regression model (see statistical analysis section for details) for a hypothetical average participant.

* = $p < .05$, ** $p < .01$, *** = $p < .001$, † = $p = .06$ to .08

Table 4. Impact of Adherence by 12 month Follow Up on Outcomes

Adherence to	**QOL**	**Mood**	**Self-Efficacy**	**mADLs**
Wellness	0.12 (-0.10,0.33)	-0.01 (-0.25, 0.23)	-0.05 (-0.27, 0.18)	0.22* (0.00, 0.45)
MSS	0.00 (-0.28, 0.27)	0.05 (-0.25, 0.36)	0.16 (-0.12, 0.44)	0.08 (-0.20, 0.35)
Support	0.06 (-0.24, 0.37)	-0.27 (-0.61, 0.07)	0.22 (-0.09, 0.53)	-0.30 (-0.62, 0.01)
Yoga/Exercise	0.10 (-0.09, 0.29)	0.07 (-0.14, 0.28)	0.29* (0.09, 0.49)	0.26* (0.05, 0.46)
Computerized Brain Fitness	0.00 (-0.21, 0.21)	0.01 (-0.22, 0.25)	0.02 (-0.20, 0.23)	0.14 (-0.07, 0.36)

Note. QOL = Quality of Life; mADLS – Memory Related Activities of Daily Living; MSS = Memory Support System.

Adherence is defined here as: adherent at both 6 and 12 months (considered non-adherent if indeterminate or missing at 6 or 12 months). Estimates and 95% confidence intervals for the change in outcome scores from baseline to 12 months are given as standardized effect sizes. Estimates result from linear mixed effects models with stratification by adherence at 6 and 12 months to the given HABIT intervention. * = $p < .0$

Figure 1.

Figure 1. Recruitment Consort Chart

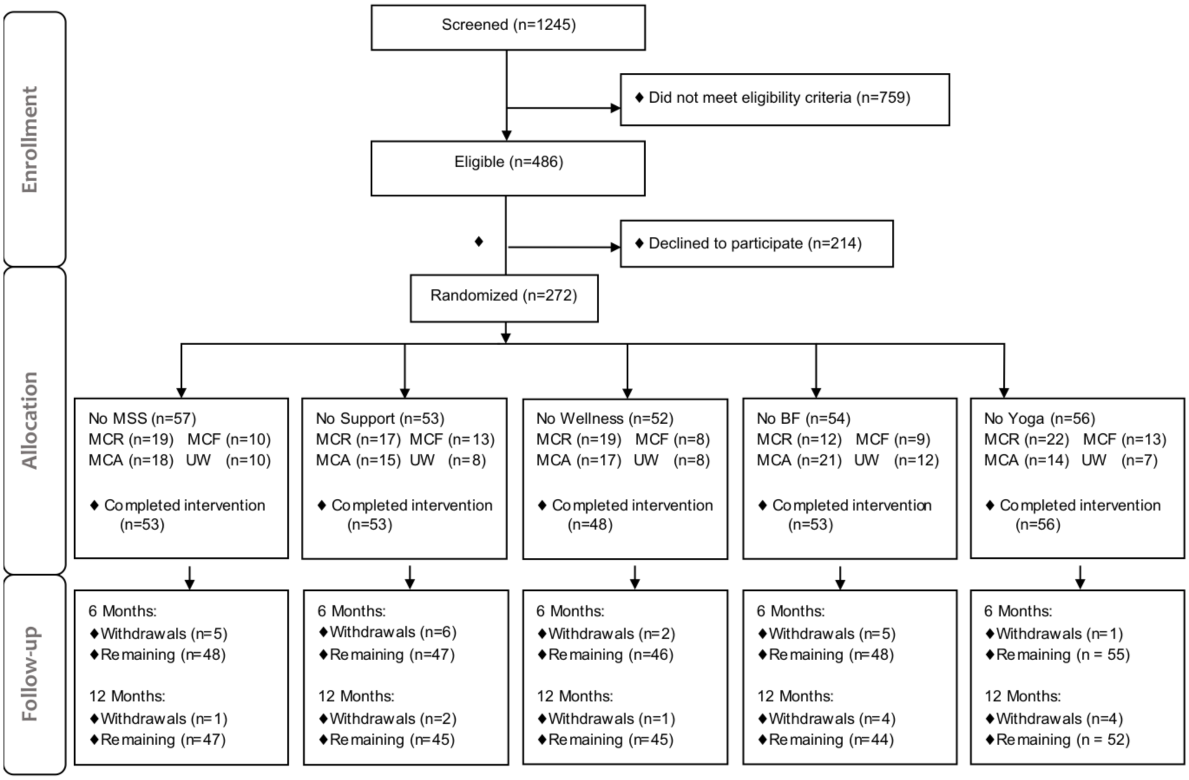
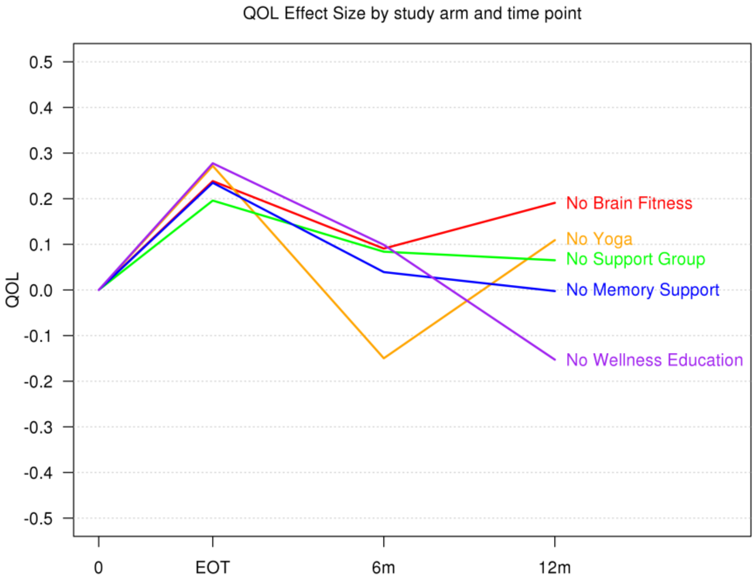
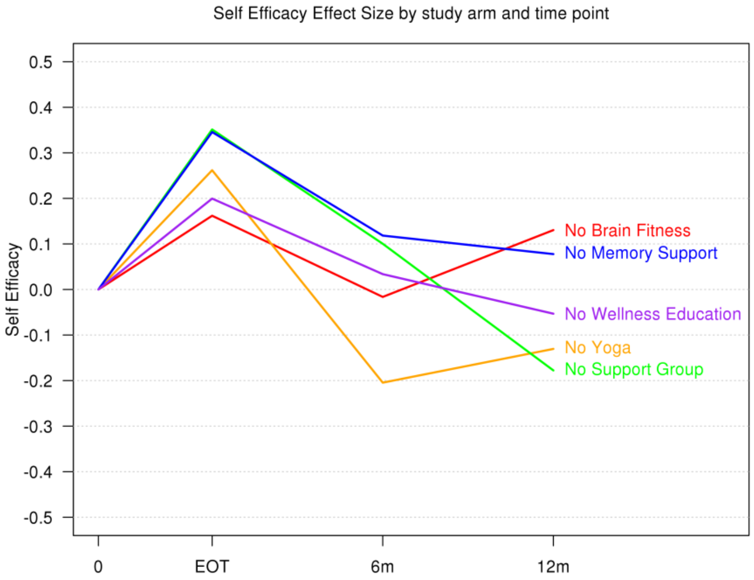


Figure 2

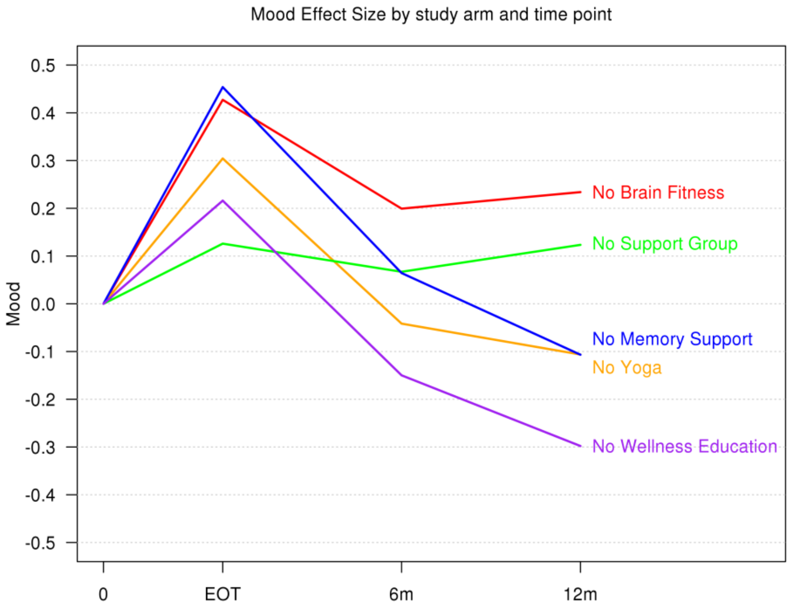
a.


QOL Effect Size by study arm and time point
QOL
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0
EOT
6m
12m
No Brain Fitness
No Yoga
No Support Group
No Memory Support
No Wellness Education

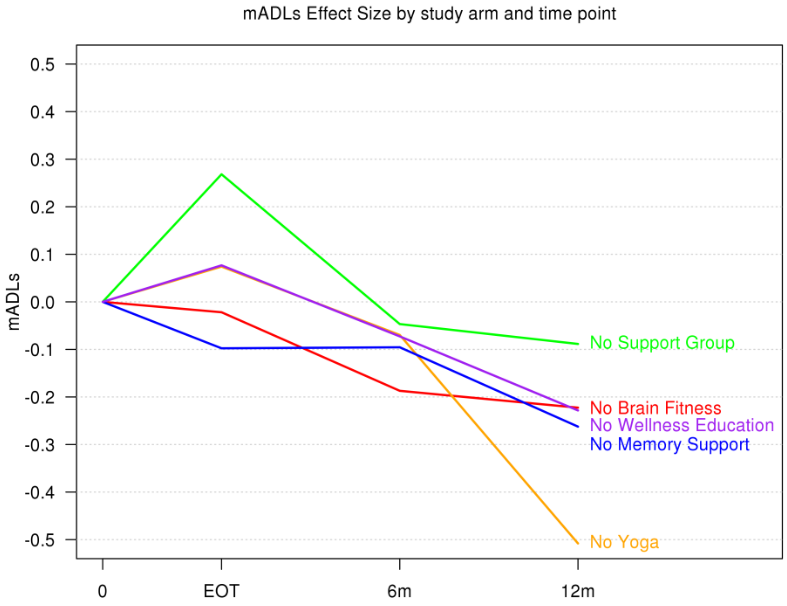
b.


Self Efficacy Effect Size by study arm and time point
Self Efficacy
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0
EOT
6m
12m
No Brain Fitness
No Memory Support
No Wellness Education
No Yoga
No Support Group

c.


Mood Effect Size by study arm and time point
Mood
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0
EOT
6m
12m
No Brain Fitness
No Support Group
No Memory Support
No Yoga
No Wellness Education

d.


mADLs Effect Size by study arm and time point
mADLs
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
0
EOT
6m
12m
No Support Group
No Brain Fitness
No Wellness Education
No Memory Support
No Yoga