Journal of the International Neuropsychological Society (2021), **27**, 805–812

doi:10.1017/S1355617721000485

Comparative Effects of Physical Exercise and Other Behavioral Interventions on Functional Status Outcomes in Mild Cognitive Impairment

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(Received September 18, 2020; Final revision March 15, 2021; Accepted March 31, 2021; First Published Online July 26, 2021)

Abstract

Objectives: Lifestyle modifications for those with mild cognitive impairment (MCI) may promote functional stability, lesson disease severity, and improve well-being outcomes such as quality of life. The current analysis of our larger comparative effectiveness study evaluated which specific combinations of lifestyle modifications offered as part of the Mayo Clinic Healthy Action to Benefit Independence in Thinking (HABIT) program contributed to the least functional decline in people with MCI (pwMCI) over 18 months. **Methods:** We undertook to compare evidence-based interventions with one another rather than to a no-treatment control group. The interventions were five behavioral treatments: computerized cognitive training (CCT), yoga, Memory Support System (MSS) training, peer support group (SG), and wellness education (WE), each delivered to both pwMCI and care partners, in a group-based program. To compare interventions, we randomly withheld one of the five HABIT® interventions in each of the group sessions. We conducted 24 group sessions with between 8 and 20 pwMCI–partner dyads in a session. **Results:** Withholding yoga led to the greatest declines in functional ability as measured by the Functional Activities Questionnaire and Clinical Dementia Rating. In addition, memory compensation (calendar) training and cognitive exercise appeared to have associations (moderate effect sizes) with better functional outcomes. Withholding SG or WE appeared to have little effect on functioning at 18 months. **Conclusions:** Overall, these results add to the growing literature that physical exercise can play a significant and lasting role in modifying outcomes in a host of medical conditions, including neurodegenerative diseases.

Keywords: Yoga, Lifestyle, Quality of life, Neurodegenerative diseases, Activities of daily living, Cognitive dysfunction

INTRODUCTION

Mild cognitive impairment (MCI) is a syndrome that frequently represents the early stage of a neurodegenerative disease process, often Alzheimer's disease (AD; Petersen et al., 2018). Amnestic MCI is diagnosed when a person has an objectively measured memory abnormality as compared to others of similar age, yet is still functionally independent in instrumental activities of daily living (Albert et al., 2011; R. Petersen et al., 1999; GE Smith et al., 1996). These individuals are at greater risk for progressing to dementia than the general population. One of the primary distinctions between people with MCI (pwMCI) and those with dementia rests upon how independent they are in daily functioning. Indeed, it is increasingly acknowledged that forestalling functional loss, irrespective of brain disease progression and measured cognitive decline, constitutes dementia prevention (Smith, 2016). Research has shown that reductions in modifiable, lifestyle-based risk factors associated with dementia (such as obesity, high blood pressure, limited cognitive, and physical activity) could have a tremendous public health impact, potentially preventing millions of AD cases

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worldwide (Barnes & Yaffe, 2011). Thus, targeting lifestyle interventions to pwMCI has dramatically expanded in the hopes of reducing dementia risk. Particular attention has been paid to interventions that include physical exercise (Song, Yu, Li, & Lei, 2018), cognitive exercise (Barnes et al., 2009; Sherman, Mauser, Nuno, & Sherzai, 2017), diet (M. C. Morris et al., 2015), and social engagement (Fratiglioni, Paillard-Borg, & Winblad, 2004).

Increasingly, the focus has moved beyond single interventions to multicomponent programs (Blumenthal et al., 2019; Chandler, Parks, Marsiske, Rotblatt, & Smith, 2016; Ngandu et al., 2015). With multiple promising behavioral interventions being reported, a current research gap in the field is which combination of interventions is most effective for key outcomes. For over a decade we have been exploring this question, focusing on computerized cognitive training (CCT) (Smith et al., 2009), compensatory calendar training (Chandler et al., 2017; Greenaway, Duncan, & Smith, 2013), and more recently, wellness education (WE)/behavior change discussion, social support, and physical exercise. These components have been combined to form the Mayo Clinic HABIT Healthy Action to Benefit Independence and Thinking ® program. The program is a 50-hr group-based treatment program that includes compensatory calendar training, CCT, WE class, support group (SG), and physical exercise via yoga. Most recently, we have reported the primary outcome results from our Patient-Centered Outcomes Research Institute (PCORI)-funded research into the comparative effectiveness of the components of the HABIT program as they pertain to patient quality of life, self-efficacy, and mood (Chandler et al., 2019) and care partner outcomes (Amofa et al., 2021). In brief, we found that WE had more impact on quality of life and mood in comparison to CCT, and yoga had a greater effect on memory-related activities of daily living than did SGs. Here, we present the results of our comparative effectiveness study (Smith, et al., 2017) as they pertain to secondary outcomes of the study. Specifically, in this analysis, we investigated functional outcomes 18 months after intervention as assessed by the widely used functional status measures in the same cohort previously described in the Amofa et al., 2021, Chandler et al. (2019), Smith et al. (2017) citations above. Our objective was to understand which of the five Mayo Clinic Healthy Action to Benefit Independence and Thinking (HABIT®) interventions had the greatest positive impact on functional independence 18 months later. While the HABIT intervention is relatively brief (2 weeks), the purpose of the intervention is to initiate lasting behavior change (habits). Participants completed two booster sessions post-HABIT and were given materials in order to encourage ongoing behavioral change. Thus, we expected to see independent effects from each of these ongoing behaviors on functional measurements at 18 months posttreatment.

METHODS

Funded as a comparative effectiveness study, shaped by stakeholder and patient and partner advisory groups, we undertook to compare evidence-based interventions with one another rather than to a no-treatment control group. The details of the recruitment methods, measures, interventions, and study protocol have been described in detail in a prior publication (Smith, Chandler, Locke, et al., 2017).

Participants

Participants were recruited as dyads made up of a partner and a pwMCI. The study sample consisted of a total of 272 dyads (for pwMCI mean (standard deviation (SD)) age of 75(8) years; 58.8% male). All participants were recruited from clinical encounters in Neurology or Neuropsychology departments at various Mayo Clinic campuses (Jacksonville, FL, Rochester, MN, Scottsdale, AZ) and the University of Washington, Seattle. Use of human subjects was performed in accord with the ethical standards of the Committee on Human Experimentation and the Helsinki Declaration with protocol approval from the Institutional Review Board at Mayo Clinic and the University of Washington. Participants were referred to the program after their clinical evaluations were completed and indicated a diagnosis of MCI. Inclusion criteria were a clinical diagnosis of amnestic (single or multi-domain), MCI, Clinical Dementia Rating (CDR) score of 0.5 or lower, fluency in English, and stable on or not taking nootropic medications for at least 3 months in the patient. A cognitively normal partner (Mini-Mental Status Examination score above 24) with whom the patient had at least twice per week contact was also required. Spouses (or live-in romantic partners) comprised 85% of study partners. Nine percent of partners were adult children, and the remainder were other family or friends. The mean age of partners was 70 (10) years. Partners served as the informants for both the Functional Activities Questionnaire (FAQ) and CDR.

Interventions

The interventions were five behavioral treatments: CCT, yoga, Memory Support System (MSS) training, peer SG, and WE, each delivered to both with pwMCI and care partners, in a group-based program, 10 times over 2 weeks and lasting 45–60 min in duration for each session. These are the components of the Mayo Clinic Healthy Action to Benefit Independence and Thinking (HABIT®). At 6 and 12 months points after the initial intervention, participants were provided with 1-day "booster" sessions intended to reinforce and remind participants of key principles/concepts for each of the four interventions in their original session. Participants completed questionnaires assessing adherence at both follow-up time points. Adherence criteria for each component led to classification of participants as "adherent," "indeterminate," or "nonadherent." Full details of adherence have been reported elsewhere (Amofa et al., 2019). Briefly, physical exercise had the highest number of participants in full adherence at 12 months, while SG had the least.

The *MSS* is a paper-based calendar/planner system that has an annual calendar, daily schedule, daily to-do list, and daily

https://doi.org/10.1017/S1355617721000485 Published online by Cambridge University Press

journal sections. Each dyad was provided with structured, individualized training on how to utilize the MSS to help compensate for memory loss. The MSS training curriculum progresses through up to three learning phases (acquisition, application, and adaptation) which each have specific target questions that are asked three times per day to help with procedural learning. For sessions randomized to include MSS, participants were encouraged throughout the program to refer to their MSS for information about their daily schedule, to write tasks on the to-do list section, and to use the journal section to take notes in. Participants were provided with the MSS calendar system for the entirety of the 18-month study (and beyond if desired) to encourage ongoing use.

Both pwMCI and partners engaged in *CCT*. This involved six select modules ("brain games") from the Posit Science product BrainHQ, which is a commercially available computerized cognitive exercise program. Each individual had their own BrainHQ account, so that they would receive customized difficulty levels based on their performance on the modules both in the moment and over time. Participants were monitored in a group while engaging in BrainHQ and provided with technical assistance as needed. Participants were provided with an ongoing subscription to the BrainHQ program to encourage continued use.

The *SG* component involves separate, simultaneous peer SGs for pwMCI and their program partners. The MCI group is facilitated by a clinical psychologist using a structured approach based on reminiscence therapy principles. The partner group is less directed and more driven by the needs of the particular group of partners, but still facilitated by a trained member of the team, who encouraged emotion processing and validation of feelings in the group, suggested topics for discussion when needed, and provided specific tips for improving communication between partners and pwMCI.

WE discussions involve a brief lecture on a topic important for brain health (e.g., nutrition, sleep, physical exercise, cognitive exercise, social engagement, and mood/stress management) followed by a group discussion focused on goal-setting, predicting and planning on overcoming obstacles for behavior change, and outlining concrete steps to achieving specific changes.

The *physical exercise* component of the program involved *Hatha yoga* as it was suited to the constrained space and the different levels of baseline physical activity of our participants and partners. Hatha yoga as a group-based physical exercise intervention is highly adaptable to the varied capabilities of older adults. We were able to adapt the yoga practice as needed so that deconditioned participants or those with imbalance could sit on chairs for some asana (poses) and use the chair for support for balance during other standing poses and for other parts of the sequence. The HABIT® (yoga) intervention was intended to initiate and sustain a schedule rather than a type of physical activity. Because most clinical trials of yoga include group classes supported by home practice, we provided a customized DVD as a supplement for continued use and practice after the program to those that opt to continue yoga. The DVD included sections on the following: poses, modifications, benefits, breathing, and meditation practices. However, our primary goal post-programming was for participants and partners to maintain a schedule of 150 min of their preferred physical exercise per week. Post-program, we considered yoga, swimming, walking, running, or exercise programming (water aerobics, resistance training, etc.) to count equivalently towards this total. The sessions used an armless, sturdy chair placed on top of a sticky yoga mat. HABIT® yoga also incorporated breathing and meditation. Our instructors had at least 200 hr of training and were certified. The appropriately sequenced HABIT® yoga practice met the American College of Sports Medicine recommendation for older adults for muscle strengthening and flexibility.

Design

To compare interventions, we employed a fractional factorial study design (Collins, Dziak, Kugler, & Trail, 2014) wherein we randomly suppressed (withheld) one of the five HABIT® interventions in each of the group sessions. In other words, this was a cluster-randomized design where four included interventions were delivered in a session. In the end, we conducted 24 group sessions with between 8 and 20 pwMCI–partner dyads in a session. Randomization was performed by a statistician and conditions were blinded to personnel and participants delivering treatments until recruitment of a session was finalized. Additional outcome raters were kept delivery blinded to the make-up of the sessions. Each site ran each condition once, and some sites ran additional select conditions to achieve recruitment goals and equalize the number of subjects receiving each combination of interventions as much as possible. The Consolidated Standards of Reporting Trials (CONSORT) diagram is included in supplement 1.

Outcome Measures

Functional ability outcomes were the focus of the present study and included the FAQ total score and the Clinical Dementia Rating-Sum of Boxes (CDR-SOB) score. Both measures are routinely collected in large-scale dementia trials, including contributors to the National Alzheimer's Coordinating Center (NACC).

The FAQ (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) informant rating includes 10 questions measuring the patient's ability to perform routine activities of daily living. Each of the 10 items is scored as 0 = normal, 1 = has difficulty but does by self, 2 = requires assistance, and 3 = dependent. The FAQ total score is calculated by summing the 10 items with a possible range of 0–30. If more than two items were skipped or marked as "not applicable," then the total score was not calculated. This measure was collected at baseline, completion of treatment, 6 months posttreatment, 12 months posttreatment, and 18 months posttreatment. The CDR (J. C. Morris, 1993) was collected only at baseline and 18 months. It consists of six subscales (memory, orientation, judgment and problem-solving, community affairs,

Table 1. Baseline FAQ and CDR by study arm

	No yoga	No CCT	No wellness education	No support groups	No MSS
Characteristic	(*n* = 56)	(*n* = 54)	(*n* = 52)	(*n* = 53)	(*n* = 57)
FAQ score, mean (SD)[a]	6.04 (5.70)[9]	7.40 (6.04)[7]	7.00 (5.12)[8]	6.35 (4.93)[9]	7.76 (5.50)[8]
CDR-SOB score, mean (SD)	1.92 (1.10)	2.47 (1.02)	2.03 (1.17)	1.68 (1.04)	1.84 (1.09)

Abbreviations: CCT, computerized cognitive training; MSS, Memory Support System; FAQ, Functional Activities Questionnaire; CDR-SOB, Clinical Dementia Rating-Sum of Boxes.
[a] Superscripts indicate the number of patients with missing FAQ scores.

home and hobbies, and personal care) and one global scale. The global scale and each subscale are rated as 0 = none (meaning not demented), 0.5 = questionable (possible dementia), 1 = mild, 2 = moderate, or 3 = severe. The CDR-SOB score was calculated by summing the six subscales with possible values ranging from 0 to 18.

Statistical Analysis

Baseline FAQ total score and CDR-SOB were summarized with the mean and SD separately according to study arm. Baseline differences in these scores between study arms were evaluated using linear mixed effects regression models with fixed effects for study arm and random effects for site and group session. For the primary analysis, a longitudinal mixed effects regression model was used to compare FAQ total score at 18 months between the five study arms. The analysis used data from baseline (BL), end of treatment, and follow-up at 6, 12, and 18 months. Baseline FAQ total score was modeled with fixed effects for age, sex, and site. The mean change in FAQ total score was modeled with fixed effects for age, sex, and study arm (no yoga, no CCT, no WE, no SGs, and no MSS). The multiple measurements over time were accounted for in the model with person-specific random effects. Pairwise differences in study arm effects on FAQ total score at 18 months were of primary interest. We additionally examined the fitted trajectories of FAQ total score over time for each of the five study arms. Statistical tests were performed using likelihood ratio tests, and corresponding 95% confidence intervals were estimated using the profile likelihood method. Two-sided $p < 0.05$ was considered to be statistically significant. The effect size (ES) for FAQ total score at 18 months was calculated as the fitted mean difference between study arms at 18 months divided by the baseline SD of FAQ total score. For the analysis of CDR-SOB, we used the same analytical approach as we used for FAQ total score; however, CDR-SOB was only collected at baseline and 18 months and those were the only two time points included in the model. Analyses were performed using R statistical software, version 3.2.3 (R Foundation for Statistical Computing).

RESULTS

An analysis evaluating associations between study arm and baseline values of FAQ and CDR revealed no statistically significant associations of study arm with either baseline FAQ (chi-square = 6.18, df = 4, overall $p = 0.19$) or baseline CDR (chi-square = 8.18, df = 4, overall $p = 0.09$). (Table 1). The comparative incremental effects on FAQ total score and CDR-SOB are shown in Table 2. As expected, given the likelihood that most pwMCI have a neurodegenerative disease process as the primary etiology, participants in all study arms show a negative trend in CDR and FAQ scores from baseline to 18 month follow-up. However, with respect to our hypothesis that we would see independent, incremental effects of each intervention, there were statistically significant differences ($p = .032$) and moderate ESs (greater than 0.6) on CDR-SOB in groups that had yoga withheld and replaced with WE or SG, with worse functioning in those who had yoga withheld. In addition, trends were observed, with moderate ESs (~0.55), for poor functioning in those who had MSS or CCT withheld and replaced with WE or SG. Figure 1 shows the ESs by study arm. Thus, withholding yoga, and possibly CCT or MSS training, led to more progression of functional impairments as measured by the CDR-SOB than did withholding WE or SG. For the FAQ, the pattern was similar. PwMCI who did not receive yoga appear to fare worse at 18 months than those that did not receive WE or SG, with statistically significant differences (p = .011–.026), but slightly smaller effects sizes (.44–.53) than found on the CDR-SOB. There were also nonsignificant trends with mild to moderate ESs for a negative impact on FAQ scores for those who did not receive MSS training, followed by those who did not receive CCT (.26–.40). Overall, those who received yoga, especially in combination with CCT and MSS, had a lesser rate of decline in functional ability than those in which one those interventions were left out.

DISCUSSION

The present report is an extension of our prior comparative effectiveness studies (Amofa et al., 2021, Chandler et al., 2019) of the HABIT® program developed at Mayo Clinic. We compared the impact of combinations of the HABIT® behavioral interventions including MSS, CCT, SG, WE, and yoga. We found that withholding yoga resulted in the steepest declines in functional status, while including yoga with CCT and MSS training yielded the lowest rate of decline. This finding at 18 months is not only consistent across two separate but related functional measures but also consistent with our previous finding (Chandler et al., 2019) on a separate measure, the Everyday Cognitive Function (Farias et al., 2008) Memory subscale assessed at 12-months.

Table 2. Comparative incremental effects on patient outcomes at 18 months for pairs of HABIT components when added to the remaining three components of HABIT

Comparison[a]	Difference in effect size at 18 months (95% CI), baseline SDs	*p*
FAQ total score		
Yoga-WE	0.528 (0.123, 0.933)	0.011*
Yoga-SG	0.440 (0.052, 0.828)	0.026*
MSS-WE	0.399 (−0.030, 0.828)	0.068
CCT-WE	0.344 (−0.067, 0.754)	0.10
MSS-SG	0.311 (−0.102, 0.725)	0.14
CCT-SG	0.256 (−0.140, 0.652)	0.21
Yoga-CCT	0.184 (−0.203, 0.571)	0.35
Yoga-MSS	0.129 (−0.276, 0.534)	0.53
SG-WE	0.088 (−0.325, 0.500)	0.68
MSS-CCT	0.055 (−0.357, 0.467)	0.79
CDR-SOB		
Yoga-WE	0.686 (0.058, 1.313)	0.032*
Yoga-SG	0.641 (0.057, 1.227)	0.032*
CCT-WE	0.596 (−0.036, 1.229)	0.065
CCT-SG	0.551 (−0.05, 1.156)	0.072
MSS-WE	0.408 (−0.249, 1.064)	0.22
MSS-SG	0.364 (−0.25, 0.979)	0.25
Yoga-MSS	0.278 (−0.327, 0.883)	0.37
CCT-MSS	0.187 (−0.433, 0.811)	0.55
Yoga-CCT	0.09 (−0.501, 0.68)	0.76
SG-WE	0.044 (−0.591, 0.678)	0.89

Abbreviations: CI, confidence interval; WE, wellness education; CCT, computerized cognitive training; SG, support group; MSS, Memory Support System.
[a] To ease interpretation, the two components compared are ordered such that the first component listed has a higher effect size than the second component.
*Significant at $p < .05$.

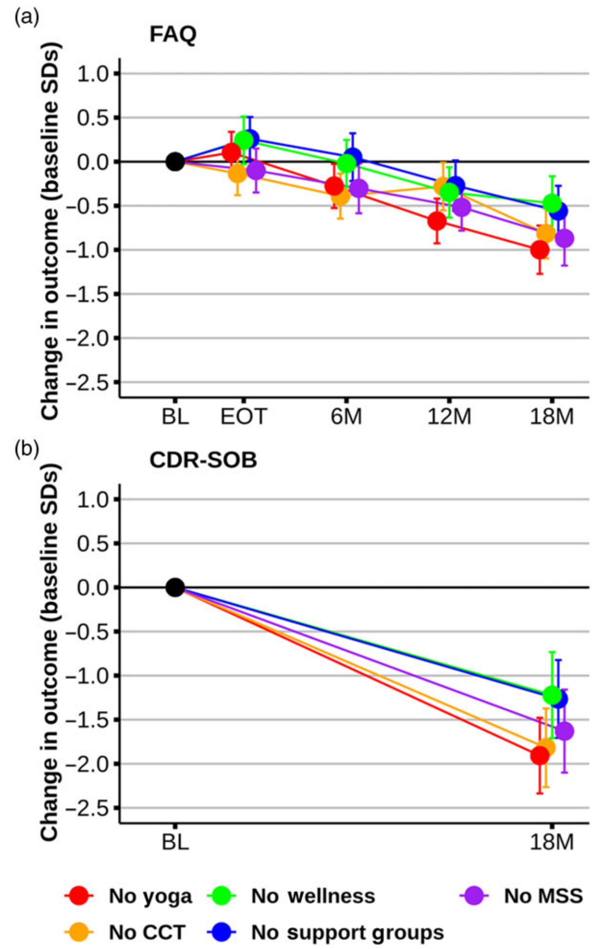

Figure 1. Effect sizes by study arm.

Note that in the report (Chandler et al., 2019), yoga combined with MSS, WE, and SG interventions associated with better quality of life and mood outcomes. For these patient-wellness variables, CCT was expendable relative to WE.

Reduction in dementia risk and cognitive decline through participation in physical exercise has been well documented (Song et al., 2018) and is recounted elsewhere in this this *JINS* Special Section. Arguably physical exercise, the strongest evidence base for all behavioral interventions, intended to preventing cognitive decline. Our finding that yoga had the most impact on functional status at 18 months is consistent with the notion that physical exercise can mitigate cognitive decline in MCI. The current findings expand on current knowledge about the relative impact of physical exercise by being among the first to assess this association within a comparative effectiveness framework. These findings suggest that physical exercise is not only helpful, but more helpful than certain other behavioral interventions, specifically WE and SGs in these analyses. This is not merely because those are inert, "active control" interventions. We have shown elsewhere (Amofa, et al., 2021, Chandler, et al., 2019) that each of these is a potent intervention for other outcomes. Rather, improving physical exercise levels likely impacts modifiable risk factors such as inactivity, obesity, and high blood pressure which associate with the functional declines associated with dementia (Barnes & Yaffe, 2011).

We contend that for pwMCI, physical exercise interventions should nevertheless be embedded in multicomponent programs. There is supporting evidence herein that the MSS has an additional decelerating impact on functional decline, consistent with our observations in preliminary research (Greenaway, Duncan & Smith, 2013). The MSS is specifically designed as a memory compensation tool to help pwMCI remain functional despite their memory loss. CCT using BrainHQ from Posit Science has been shown to positively impact working memory and processing speed, with some evidence that this translates to improved functional ability (Smith et al., 2009; Barnes et al., 2009). More broadly, evidence on which combinations of interventions are associated with better functioning over time is relevant for the entire scientific and clinical community who are working to help pwMCI delay or avoid progression to dementia.

Limitations

The primary objective of our comparative effectiveness studies is to tease out which behavioral interventions of a multicomponent intervention for MCI have the largest impact on the outcomes of importance to pwMCI and their partners (Smith, Chandler, Fields, Aakre, & Locke, 2018). Comparing within-group trajectories must be interpreted cautiously, as there was no untreated control group in our comparative effectiveness study. Further, trying to interpret the cost of not receiving an intervention component is counter to the design of most clinical trials where the incremental benefit of adding an intervention is considered. In an attempt to simplify the explanation of the results, we used pairwise comparisons. However, focusing on the absence of any one intervention ignores the probable synergy or interaction between the remaining interventions.

Our exact conclusions may not generalize to other forms of the physical exercise (e.g., resistance training, more intense aerobic exercise, etc.). Additionally, we cannot exclude the possibility that the more meditative components of yoga as opposed to the physical exertion are responsible for the observed effects. The recruited cohort was ultimately highly educated and not diverse. This limits potential generalizability of the results. The sample may have been biased by at least two major factors: education and socioeconomic status (SES). First, highly educated people may be more likely to pursue active coping approaches to manage chronic illness like MCI. Although we have previously reported that time and distance were primary reasons that eligible candidate might not enroll in this type of intervention (Locke et al., 2014), we did not have that information for all participants in this trial. However, the intensive nature of the program, requiring participants and partners to dedicate 40 hr per week over 2 weeks to the program, including daily travel to and from the program, and in some cases requiring self-funded hotel stays to participate, also likely biased the sample to higher SES.

In addition, although this is a large cohort relative to other behavioral intervention trials in MCI, we were only powered to detect within-group change over time but underpowered to detect pairwise differences between arms of the study. We used data from a prior clinical sample of participants in the full five-component HABIT and an untreated control group from a prior randomized clinical trial to inform statistical power. Estimated standard errors (SEs) were extracted from the fitted models from which we could estimate SEs for different sample size scenarios. We originally determined a study sample size of 300 participants with 10% attrition would be powered (80% at 5% significance level) to detect an effect of 0.53 baseline SDs of any one of the five interventions on quality of life at 12 months. However, subsequent analysis proved this sample size to be an underestimate. Our study had a novel statistical design, and our initial statistical power assessment was unrealistic. Further, we should have considered that comparative effectiveness trials, especially with cluster randomization, will generate smaller ESs than placebo-controlled studies (Sox & Goodman, 2012). We subsequently have determined that for pairwise comparisons, we were powered (80% power at the 5% significance level) to detect differences with effects sizes of 0.72 or higher, while accounting for multiple testing adjustment. Thus, the study was not sufficiently powered for these pairwise comparisons. Given this finding, we thought it important to also list pairwise comparisons with moderate ESs that were significant without multiple analysis adjustments because a future, better-powered study could demonstrate those ESs to be statistically significant. However, we acknowledge that there is a possibility of a type I error (i.e., false-positive finding) in our current study owing to the multiple tests performed.

The interpretation challenges notwithstanding, we offer these results to encourage more multicomponent and comparative effectiveness trials in pwMCI. As noted at the outset, there is emerging evidence to justify multiple component interventions and thankfully large-scale trials are now underway (cf. Baker et al., 2019). Perhaps 60%–80% of pwMCI have a degenerative disease as the cause of cognitive decline, mostly commonly AD (Petersen et al., 2013). It seems to us that offering pwMCI multiple component interventions is a rational response to the significant morbidity they face. Not only do multiple component comparative trials avoid the ethical dilemma of offering no treatment to some participants, but they bring the best current hope of benefit to pwMCI. We also note that our work included only pwMCI. It would also be beneficial to evaluate the effectiveness of nonpharmacological interventions in multicomponent programs in cognitively normal older adults as well.

Conclusion

The noted limitations of this study notwithstanding, there was a statistically significant finding that physical exercise in the form of chair-based yoga muted declines in functional status at 18 months post-intervention, across two independent measures. This is especially true when the physical exercise was paired with intensive training in a calendar-based memory compensation system and engagement in CCT. This is meaningful, especially as there are few treatment options for pwMCI. This finding should encourage the continued recommendation of physical exercise as a component of potentially beneficial multicomponent lifestyle interventions for pwMCI. Additional work on expanding access to such programs for older adults with and without MCI could contribute to improving public health.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617721000485

FINANCIAL SUPPORT

The institutions that employ the authors generate revenue from the HABIT clinical programs; the authors do not derive any direct financial benefit. Research reported in this manuscript was partially 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 PCORI, its Board of Governors, or Methodology Committee.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., . . . Phelps, C.H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, *7*(3), 270–279. doi: 10.1016/j.jalz.2011.03.008

Amofa, PA, DeFeis, B, De Wit, L, O'Shea, D, Mejia, A, Chandler, M, . . . Smith G. (2019). Functional ability is associated with higher adherence to behavioral interventions in mild cognitive impairment. *The Clinical Neuropsychologist*, 1–19. doi: 10.1080/13854046.2019.1672792. [Epub ahead of print] PubMed PMID: 31608773.

Amofa, P.A., Locke, D., Chandler, M., Crook, J.E., Ball, C.T., Phatak, V., & Smith, G. (2021). Comparative effectiveness of behavioral interventions to prevent or delay dementia: one-year partner outcome. (Manuscript accepted for publication). *Journal of Prevention of Alzheimer's Disease*, *1*(8), 33–40.

Baker, L.D., Beavers, D.P., Cleveland, M., Day, C.E., Decarli, C., Espeland, M.A., . . . Carrillo, M.C. (2019). O4–11–03: U.S. Pointer: study design and launch. *Alzheimer's & Dementia*, *15*(7S_Part_24), P1262–P1263. doi: 10.1016/j.jalz.2019.06.4802

Barnes, D.E., Yaffe, K., Belfor, N., Jagust, W.J., DeCarli, C., Reed, B.R., & Kramer, J.H. (2009). Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. *Alzheimer Disease and Associated Disorders*, *23*(3), 205–210. doi: 10.1097/WAD.0b013e31819c6137

Barnes, DE & Yaffe K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology*, *10*(9), 819–828. doi: 10.1016/S1474-4422(11)70072-2. Epub 2011 Jul 19. PMID: 21775213; PMCID: PMC3647614.

Blumenthal, J.A., Smith, P.J., Mabe, S., Hinderliter, A., Lin, P.H., Liao, L., . . . Sherwood, A. (2019). Lifestyle and neurocognition in older adults with cognitive impairments: a randomized trial. *Neurology*, *92*(3), e212–e223. doi: 10.1212/WNL.0000000000006784

Chandler, M.J., Locke, D.E., Crook, J.E., Fields, J.A., Ball, C.T., Phatak, V.S., . . . Smith, G.E. (2019). Comparative effectiveness of behavioral interventions on quality of life for older adults with mild cognitive impairment: a randomized clinical trial. *JAMA Network Open*, *2*(5), e193016. doi: 10.1001/jamanetworkopen.2019.3016

Chandler, M.J., Locke, D.E.C., Duncan, N.L., Hanna, S.M., Cuc, A.V., Fields, J.A., . . . Smith, G.E. (2017). Computer versus compensatory calendar training in individuals with mild cognitive impairment: functional impact in a pilot study. *Brain Sciences*, *7*(9). doi: 10.3390/brainsci7090112

Chandler, M.J., Parks, A.C., Marsiske, M., Rotblatt, L.J., & Smith, G.E. (2016). Everyday impact of cognitive interventions in mild cognitive impairment: a systematic review and meta-analysis. *Neuropsychology Review*, *26*(3), 225–251. doi: 10.1007/s11065-016-9330-4

Collins, L.M., Dziak, J.J., Kugler, K.C., & Trail, J.B. (2014). Factorial experiments: efficient tools for evaluation of intervention components. *American Journal of Preventive Medicine*, *47*(4), 498–504. doi: 10.1016/j.amepre.2014.06.021

Farias, S.T., Mungas, D., Reed, B.R., Cahn-Weiner, D., Jagust, W., Baynes, K., & Decarli, C. (2008). The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology*, *22*(4), 531–544. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18590364

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology*, *3*(6), 343–353. doi: 10.1016/S1474-4422(04)00767-7

Greenaway, M.C., Duncan, N.L., & Smith, G.E. (2013). The memory support system for mild cognitive impairment: randomized trial of a cognitive rehabilitation intervention. *International Journal of Geriatric Psychiatry*, *28*(4), 402–409. doi: 10.1002/gps.3838

Locke, D.E., Greenaway, M.C., Duncan, N., Fields, J.A., Cuc, A.V., Snyder, C.H., . . . Smith, G.E. (2014). A patient-centered analysis of enrollment and retention in a randomized behavioral trial of two cognitive rehabilitation interventions for Mild Cognitive Impairment. *The Journal of Prevention of Alzheimer's Disease*, *1*(3), 143–150. doi: 10.14283/jpad.2014.27

Logsdon, R.G., Gibbons, L.E., McCurry, S.M., & Teri, L. (2002). Assessing quality of life in older adults with cognitive impairment. *Psychosomatic Medicine*, *64*(3), 510–519. doi: 10.1097/00006842-200205000-00016

Morris, J.C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–2414. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8232972

Morris, M.C., Tangney, C.C., Wang, Y., Sacks, F.M., Bennett, D.A., & Aggarwal, N.T. (2015). MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement*, *11*(9), 1007–1014. doi: 10.1016/j.jalz.2014.11.009

Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., . . . Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*, *385*(9984), 2255–2263. doi: 10.1016/S0140-6736(15)60461-5

Petersen, R., Smith, G., Waring, S., Ivnik, R., Tangalos, E., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology*, *56*(3), 303–308.

Petersen, R.C., Aisen, P., Boeve, B.F., Geda, Y.E., Ivnik, R.J., Knopman, D.S., . . . Jack, C.R. (2013). Mild cognitive impairment due to alzheimer disease in the community. *Annals of Neurology*, *74*(2), 199–208. doi: 10.1002/ana.23931

Petersen, R.C., Lopez, O., Armstrong, M.J., Getchius, T., Ganguli, M., Gloss, D., . . . Rae-Grant, A. (2018). Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*, *90*(3), 126–135. doi: 10.1212/WNL.0000000000004826

Pfeffer, R.I., Kurosaki, T.T., Harrah, C.H., Jr., Chance, J.M., & Filos, S. (1982). Measurement of functional activities in older adults in the community. *J Gerontol*, *37*(3), 323–329. doi: 10.1093/geronj/37.3.323

Radloff, L.S. (1977). The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401.

Sherman, D.S., Mauser, J., Nuno, M., & Sherzai, D. (2017). The efficacy of cognitive intervention in Mild Cognitive Impairment (MCI): a meta-analysis of outcomes on neuropsychological measures. *Neuropsychology Review*, *27*(4), 440–484. doi: 10.1007/s11065-017-9363-3

Song, D., Yu, D., Li, P., & Lei, Y. (2018). The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. *International Journal of Nursing Studies*, *79*, 155–164. doi: 10.1016/j.ijnurstu.2018.01.002

Smith, G., Chandler, M., Locke, D.E., Fields, J., Phatak, V., Crook, J., . . . Cochran, D. (2017). Behavioral interventions to prevent or delay dementia: protocol for a randomized comparative effectiveness study. *JMIR Research Protocols*, *6*(11), e223. doi: 10.2196/resprot.8103

Smith, G., Petersen, R., Parisi, J., Ivnik, R., Kokmen, E., Tangalos, E., & Waring, S. (1996). Definition, course and outcome of mild cognitive impairment. *Aging, Neuropsychology, and Cognition*, *3*, 141–147.

Smith, G.E. (2016). Healthy cognitive aging and dementia prevention. *The American Psychologist*, *71*(4), 268–275. doi: 10.1037/a0040250

Smith, G.E., Chandler, M., Fields, J.A., Aakre, J., & Locke, D.E.C. (2018). A survey of patient and partner outcome and treatment preferences in mild cognitive impairment. *Journal of Alzheimer's Disease*, *63*(4), 1459–1468. doi: 10.3233/JAD-171161

Smith, G.E., Housen, P., Yaffe, K., Ruff, R., Kennison, R.F., Mahncke, H.W., & Zelinski, E.M. (2009). A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *Journal of the American Geriatrics Society*, *57*(4), 594–603. doi: 10.1111/j.1532-5415.2008.02167.x

Sox, H.C. & Goodman, S.N. (2012). The methods of comparative effectiveness research. *Annual Review of Public Health*, *33*, 425–445. doi: 10.1146/annurev-publhealth-031811-124610