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SYSTEMATIC REVIEW OF STRENGTHS AND LIMITATIONS OF RANDOMIZED CONTROLLED TRIALS FOR NON-PHARMACOLOGICAL INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT: FOCUS ON ALZHEIMER'S DISEASE

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Abstract: *Background:* Non-pharmacological interventions may improve cognition and quality of life, reduce disruptive behaviors, slow progression from Mild Cognitive Impairment (MCI) to dementia, and delay institutionalization. It is important to look at their trial designs as well as outcomes to understand the state of the evidence supporting non-pharmacological interventions in Alzheimer's disease (AD). An analysis of trial design strengths and limitations may help researchers clarify treatment effect and design future studies of non-pharmacological interventions for MCI related to AD. *Methods:* A systematic review of the methodology of Randomized Controlled Trials (RCTs) targeting physical activity, cognitive interventions, and socialization among subjects with MCI in AD reported until March 2014 was undertaken. The primary outcome was CONSORT 2010 reporting quality. Secondary outcomes were qualitative assessments of specific methodology problems. *Results:* 23 RCT studies met criteria for this review. Eight focused on physical activity, fourteen on cognitive interventions, and one on the effects of socialization. Most studies found a benefit with the intervention compared to control. CONSORT reporting quality of physical activity interventions was higher than that of cognitive interventions. Reporting quality of recent studies was higher than older studies, particularly with respect to sample size, control characteristics, and methodology of intervention training and delivery. However, the heterogeneity of subjects identified as having MCI and variability in interventions and outcomes continued to limit generalizability. *Conclusions:* The role for non-pharmacological interventions targeting MCI is promising. Future studies of RCTs for non-pharmacological interventions targeting MCI related to AD may benefit by addressing design limitations.

Key words: Mild cognitive impairment, Alzheimer's disease, non-pharmacologic interventions, physical activity, cognitive interventions, socialization, randomized controlled trial, CONSORT score.

Introduction

There is neither a cure nor a disease modifying drug for Alzheimer's disease. Non-pharmacological interventions are therefore essential to managing elders with this progressive, neurodegenerative disorder. Mild Cognitive Impairment (also known by the DSM-V criteria as Mild Neurocognitive Disorder) (1) is a dynamic, early clinical stage of AD, with objective neurocognitive deficits but preserved daily function. Annual conversion rates from MCI to dementia are reported between 8.1% and 6.8% (2). Persons with dementia (also known by the DSM-V criteria as Major Neurocognitive Disorder) (1) have functional deficits and require assistance with at least one activity of daily living. Once individuals reach the stage of dementia, they are more likely to be hospitalized, and each hospitalization is likely to be more costly (3). Average cost of chronic conditions such as heart failure and diabetes are higher in elders with dementia (4). These patients need caregivers, and those caregivers have a higher risk for depression and dementia than non-caregivers (5). Non-pharmacological interventions that promise to reduce the progression of MCI to dementia could improve quality of life for both patients and caregivers and reduce care costs.

Several observational longitudinal and cross-sectional studies have shown that the rate of cognitive decline towards dementia can be modified by cognitive and lifestyle factors, including cognitively engaging activities, physical exercise and socialization (6, 7). Several biologically plausible models support preservation of cognitive function with age (8-11) and similar studies have been reported in AD mouse models (12-15). Despite these observations, extension of non-pharmacological intervention clinical trials to elders with cognitive impairment is often challenging to operationalize due to multiple confounders. We have systematically reviewed the methodology of randomized clinical trials (RCTs) for non- pharmacological interventions in MCI, focusing on cognitive impairments related to underlying AD, to identify their strengths and challenges in designing clinical trials and interpreting outcomes.

Methodology and rationale for review

RCTs targeting cognitive interventions, physical activity, and socialization were the focus of this review. Cognitive training

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is the goal-oriented practice of a specific structured cognitive task with the intention of limiting deterioration in cognition and function. Physical activity and socialization are lifestyle interventions in MCI with the same purpose, to delay decline in cognition and function. Studies of dietary interventions including effects of diet and supplements were excluded due to extensive reviews in the literature on these studies. Studies of psychotherapeutic interventions (mindfulness, relaxation, stress reduction, and sleep interventions) and compensatory strategies were excluded due to known difficulties in design and evaluation due to multiple confounders, including selection bias, diffusion or imitation of intervention, experimenter expectancy, compensatory expectancy of treatments (16), the degree of subject engagement in the intervention, and the Hawthorne effect (17).

We searched PubMed, PsycINFO and SCOPUS for studies exploring the effects of the targeted non-pharmacological interventions on cognitive outcomes in MCI (including all diagnostic criteria for MCI) using search terms: 1. "cognitive intervention" or "cognitive activity" or "cognitive rehabilitation" or "cognitive exercise" 2."physical activity" or "exercise" 3. "socialization" or "social activity" AND "mild cognitive impairment". All titles and abstracts that were search hits from January 2000 until March 31, 2014 were reviewed to eliminate studies that did not pertain to our topic of interest. Reference lists were also reviewed to identify additional studies. Articles included in the final review met the following criteria: 1) The study primarily evaluated a cognitive outcome of physical activity, cognitive intervention or socialization in MCI; 2) The study was a randomized controlled trial; 3) Inclusion and exclusion criteria for MCI were specified; 4) Adequate statistical measures with effect sizes were reported ; 5) Cognitive measures were included as primary or secondary outcomes; 6) Non-pharmacological intervention was implemented as a single intervention in at least one arm of the trial. All studies were extracted and tabulated by one of the reviewers (TH) onto a standard template and reviewed by BMR and JP. Differences in opinions regarding inclusion were resolved by consensus.

The primary outcome of the systematic review was adherence of each study to the CONSORT 2010 reporting criteria (18). Higher-quality reports may be more likely to improve RCT interpretation, minimize biased conclusions, and ultimately facilitate decision making about treatment effectiveness. The CONSORT guidelines were originally published in 1996 to improve the quality of reporting results of RCTs, and have been updated periodically, most recently in 2010. We estimated adherence as a sum of individual items in the 37-item checklist contained in CONSORT 2010. Each CONSORT 2010 item was assigned a"1" if it were reported, and a "0" if it were not. The sum score was the estimated report quality measure, adapted from Huwiler-Muntener et al (19). Secondary outcomes of this systematic review were a qualitative analysis of methodological difficulties found in the design of the included trials.

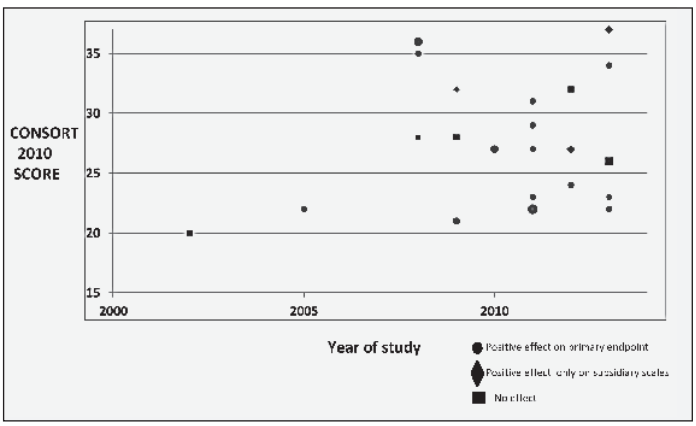
Results

Twenty-three studies met our inclusion criteria. Of these studies, eight studies focused on physical activity (20-27), fourteen incorporated cognitive interventions (28-41), and one explored the effects of socialization (42). The details of the studies are in Tables 1-3.

Figure 1 depicts the CONSORT scores for all studies since 2000. Most studies demonstrate a positive effect compared with control. As depicted in Figure 2, the mean CONSORT reporting quality score for physical activity interventions, 31.5(SD 5.2), was statistically higher than the mean quality score for cognitive interventions, 25.4(SD 3.5) ($p < .013$, Independent samples t-test, equal variances not assumed). The overall mean, including the one socialization study, was 27.7 out of 37 (range: 20 to 37, SD 5). Separating the CONSORT scores by intervention, Figure 3 demonstrates an improvement in CONSORT quality scores since 2000 among physical activity interventions, but not, as in Figure 4, in cognitive interventions. In both the cognitive and physical activity interventions, there was an overall improvement in enrollment of larger pool of subjects and longer duration of intervention and follow-up. However, the cognitive domains (executive, delayed recall, attention) chosen as outcomes were inconsistent across studies even when studies within a single modality of intervention (cognitive or physical) were analyzed.

Figure

Survey of physical, cognitive and socialization interventions. The number of subjects in each study relates to log circumference of point size



Given the difference in pattern of CONSORT scores, we analyzed each type of intervention separately.

Physical activity interventions

The mean reporting score was higher for physical activity interventions compared with cognitive interventions. The physical activity interventions tested included different degrees

Table 1
Physical activity interventions

Study	CONSORT 2010 score:	Population	Intervention/ groups	Length of study	Outcomes measured	Results related to cognitive measures	Comments
Scherder, et al. (2005) (21)	22	43 MCI (MCI defined by Peterson criteria)	3 times per week; 30 minute sessions in walking group, 15 minute sessions in the hand/face exercise group Walking vs. hand/face exercises vs. control group	6 week intervention, 6 week follow-up	- Category Naming - Trail Making A and B - Digit Span and Visual Memory Span from the Wechsler Memory Scale-Revised - Verbal Learning and Memory Test: List A (V LMT) - Face Recognition and Picture Recognition from the Rivermead Behavioural Memory Test (RBMT)	- Exercise groups analyzed together compared to control performed better in Category Naming; performance was significantly better in the walking group compared to hand/face exercise group (ES was 0.16 for the walking group, 0.12 for the hand/face exercise group); these results were not sustained in the f/u analyses - Non-significant trend toward better Trail Making A & B score in the treatment groups compared to control; the hand/face group performed significantly better after intervention on these tests compared to control (ES 0.19); there were no significant differences in performance on these tests after delay - There were no significant differences in scores on Digit Span, Visual Memory, RBMT Faces and Pictures, and the VLMT	- Hand/face exercises were chosen because many elderly individuals are limited in their physical abilities and these activities stimulate the frontal lobe - 38 of the 43 participants were female
Lautenschlager, et al. (2008) (22)	35	170 adults (mean age ~68) - 85 amnestic MCI - 17 non-amnestic MCI - 68 subjective memory complaints (MCI defined as scores of 1.5 or more SD below the mean for age and sex-matched controls on Cognitive Battery of the CERAD subtests for verbal fluency, object picture naming, word list immediate and delayed recall and praxis)	Intervention group: 150 minutes of physical activity per week or add 50 minutes if they exercised this amount at baseline; 60 minutes were spent with a trained staff member to design a home-based intervention ; periodic contact via phone, newsletter, workshops and manuals to increase adherence Control group: received material about health issues that did not pertain to exercise	24-week intervention 18 months follow-up	Primary: - ADAS-Cog Secondary: - Cognitive Battery of the CERAD - Digit-Symbol Coding Test - Delis-Kaplan Executive Function Battery - Clinical Dementia Rating	- Better ADAS-Cog scores in the intervention group (1.3 points higher at 6 months, 0.69 points higher at 18 months) - Difference in ADAS-Cog score remained significant when just MCI patients were analyzed - When all participants were analyzed, the intervention group had better delayed recall and lower CDR scores at the end of the study	- Participants self-reported physical activity on the CHAMPS survey, wore a pedometer and kept an activity diary for baseline, 6-, 12- and 18-month assessments - Walking/aerobic exercise and/or strength training activities were the most common physical activities performed - Intervention ultimately resulted in an average of 142 minutes more physical activity compared to control
Van Uffelen, et al. (2008) (23)	36	152 community-dwelling adults aged 70-80 with MCI (MCI defined by Peterson criteria)	Group-based hourly sessions twice weekly 1. Walking program + vitamin B12/B6/folic acid 2. Walking program + placebo pill 3. Vitamin supplementation + placebo exercise program 4. Placebo only	1 year	- Auditory Verbal Learning Test (AVLT) - Verbal Fluency Test (VFT) - Digit Symbol Substitution Test (DSST) - Abridged Stroop Color Word Test (SCWT-A)	- No significant effect of exercise or vitamin intervention on cognition in intention to treat analyses - AVLT was improved in men who attended at least 75% of the exercise sessions - AVLT and Stroop scores were directly related to attendance in women	Gender was analyzed and found to be an effect modifier
Baker, et al.	27	33 sedentary	45-60 minutes per day, 4 days	6 months	- Symbol-Digit Modalities	- Aerobic exercise group	- Small study (may not have

(2010) (24)		individuals with amnestic MCI (mean age 70) (MCI defined by Peterson criteria)	per week Aerobic intervention group vs. stretching control group		- Verbal Fluency - Stroop - Trails B - Task Switching - Story Recall - List Learning - Blood levels of insulin, cortisol, BDNF, IGF-1, amyloid	improved on Symbol-Digit Modalities, Verbal , Fluency Trails B, and Task Switching; when further analyzed by gender, men in the intervention group improved only on Trails B, while women improved in all of these tests - In women, increased fitness level was associated with improved executive function - Women in the intervention and not control group showed improvement in Stroop test; the same was not seen in men	been powered to properly detect smaller effect sizes) - Strict exclusion criteria could limit generalizability
Varela, et al. (2011) (25)	29	48 residents of care homes for the elderly with a diagnosis of MCI (mean age 78.3) (MCI defined by the Spanish Society of Geriatrics and Gerontology criteria)	Three 30-minute sessions per week 1. Aerobic exercise at 40% max heart rate reserve 2. Aerobic exercise at 60% max heart rate reserve Recreational activity control	3 month intervention followed by 3 month follow-up period	- Spanish-adapted version of the MMSE - Timed Up and Go	- Non-significant increase in MMSE score and decrease in Timed Up and Go in the aerobic exercise groups - No significant differences in outcome measures were seen among groups at any point	- In order to make groups comparable, participants were allocated to groups based on whether or not they were taking AChE inhibitor therapy - Authors note suspicion that some participants may have already had dementia
Lam, et al. (2012) (26)	32	389 individuals with MCI from community centers or residential homes for the elderly (mean age 77-78) (MCI defined as CDR of 0.5 or subjective memory complaints + memory impairment with reference to delayed recall of list learning test at >/= 1.5 SD below education and age matched subjected with CDR 0)	Intervention had 2 phases: 1. weekly instruction sessions for 4 to 6 weeks at a center 2. participants received a video with the exercise program and practice sessions were arranged (sessions were at least 30 minutes per day, 3 days per week + monthly refresher sessions) Tai Chi (intervention) group vs. stretching and toning (control) group	1 year	Primary: rate of conversion to dementia Secondary: - The Cornell Scale for Depression in Dementia - The Chinese Neuropsych Inventory - The Berg Balance Scale	- Rate of progression to dementia was less in the intervention vs. control group (4.3% vs. 16.6%); there was a non-significant decreased risk of progression to dementia when controlling for education (this was statistically significant when only participants who completed the study were analyzed) - The intervention group had lower CDR sum of boxes at the end of the study	Higher default rate observed in the Tai Chi group
Nagamatsu, et al. (2013) (27)	34	86 women with subjective memory complaints (noted as probable MCI with mean MMSE of 27.2) ("Probable MCI" based on scores of >/= 24 on MMSE, <26 on MoCA, subjective memory complaints, >/= 6 on Lawton and Brody IADL and did not have a dx of dementia)	60-minute classes held twice per week a. Resistance training b. Aerobic training c. Control (balance and tone exercises)	26 weeks	- Rey Auditory Verbal Learning Test (RAVLT) - Spatial memory	- The only significant between group difference at endpoint in tasks of the RAVLT was in loss after interference between the aerobic and control groups - Reaction times for spatial memory were improved more in the aerobic and resistance groups than in the control group but there was no difference in accuracy	- This study analyzed secondary data from a previous study - Study was not powered to detect differences between the resistance and aerobic training groups
Suzuki, et al. (2013 ([28)	37	100 community-dwelling adults with MCI, 50 of which were sub-classified as amnestic MCI (MCI defined by Peterson criteria)	5. Multi-component exercise intervention group (90 minute group sessions, twice per week, 40 times in 6 months) vs. education control group (2 sessions total)	6 months	- MMSE - ADAS-Cog - Wechsler Memory Scale-Revised - Brain MRI (voxel-based specific regional analysis system for AD) - Serum biomarkers – T-cho, HbA1C, BDNF, VEGF, receptor 1	- In all participants, there were no significant main effects of group and group x time interactions for outcomes on the cognitive tests - In those with aMCI, there was a benefit in MMSE and WMS-immediate recall associated with exercise	There was a component of cognitive stimulation incorporated into several of the exercise sessions, which could confound results

Table 2
Cognitive interventions

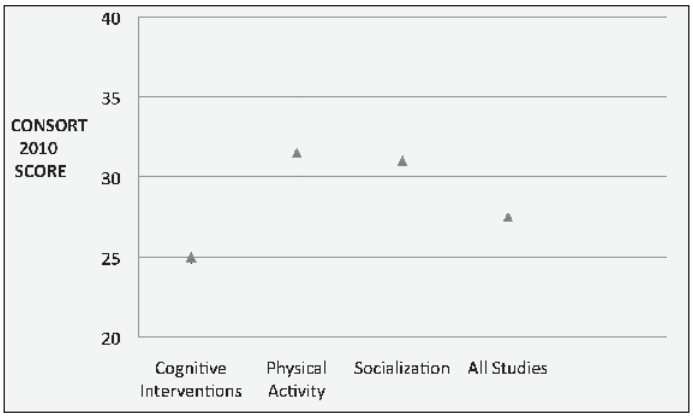
Study	CONSORT 2010 score:	Population	Intervention/ groups	Components of intervention	Outcomes measured	Results related to cognitive measures	Comments
Rapp, et al. (2002) (29)	20	19 community-dwelling adults with MCI (MCI defined by Peterson criteria)	6 weekly group sessions for 2 hours vs. no-treatment control	Education on memory loss, relaxation training, memory skills training, cognitive restructuring for memory-related belief	- CERAD Neuro-psychological Battery - MMSE - Memory performance on 4 memory tasks - Memory Functioning Questionnaire - Memory Controllability Inventory - Profile of Mood States	- No significant difference between groups on measures of memory - Trained group perceived memory ability to be significantly better after intervention– this was sustained after 6 months - Intervention improved belief in ability to control memory- not sustained at 6 months - Perceived impact of memory problems was not different between groups after intervention	Assessments were performed at baseline, 2-weeks post completions of the interventions and 6 months later
Troyer, et al. (2008) (30)	28	54 amnestic MCI (MCI defined by Peterson criteria)	10 two-hour sessions over 6 months + home assignments vs. waitlist control	Sessions included presentation of information regarding a lifestyle factor that can affect memory function, focused memory intervention training or review of information and outcome testing	- Memory Toolbox Questionnaire - Self-reported memory strategy use - Multifactorial Metamemory Questionnaire (MMQ) – strategy, contentment, ability subscales - Impact Rating Scale - Lifestyle Importance Questionnaire - Memory tests created by the investigators to measure face-name learning, number learning and wordlist learning	- Significant group by time interaction for measures of strategy use and knowledge favoring the intervention after training and 3 month post-training - No group by time interaction for measures of memory-related affect/ thought or objective memory measures	- 2 pilot programs were conducted (1st with 4 individuals, 2nd with 5 individuals) to analyze and modify the training program - Testing occurred prior to the training, after training and 3 months post-training - At baseline the control group scored higher on the MMSE, BVMT immediate and delayed recall and Digit Span
Barnes, et al. (2009) (31)	28	47 MCI (MCI defined "using standardized clinical criteria")	Home-based cognitive intervention for 100 minutes per day, 5 days per week for 6 weeks vs. control computer program for 90 minutes per day, 5 days per week	Computer-based training program: exercises designed to improved processing speed and accuracy in the auditory cortex Control group: computer-based exercises including listening to audio books, reading online newspapers, or playing a visuo-spatially oriented computer game	Primary: Repeatable Battery for Assessment of Cognitive Status (RBANS) Secondary: - 5 RBANS index scores - California Verbal Learning Test II - Controlled Oral Word Association Test - Boston Naming Test - California Trails Making Test - Design Fluency Tests from the Delis-Kaplan Executive Function Scale - Spatial Span test	- No difference in RBANS scores - Significant difference in Spatial Span Test in favor of the intervention	The effect size seen with RBANS scores suggests that a larger sample size is needed to detect a significant difference between groups
Kinsella, et al. (2009) (32)	32	54 amnestic-MCI and their family partners (MCI defined by IWG criteria)	5 week memory rehabilitation group (5 weekly hour and a half sessions) vs. waitlist control	Problem-solving approach to common everyday memory problems with special focus on external memory aids, organizational and attention skills, memory strategies and coping strategies	- Reminding Task (adapted from the Rivermead Behavioral Memory Test) - Envelope Task - Multifactorial Metamemory Questionnaire (Ability, Strategy and Contentment Subscales) - Strategy Knowledge Repertoire	- Intervention group performed better on prospective memory indices and strategy knowledge - No difference in self-reported memory ability - Family participants in the intervention group performed significantly better than control group on strategy knowledge at 2-week follow-up	- Assessments performed at baseline, 2 weeks post-intervention, and 4 months post-intervention; however, 4-month follow-up analysis was not performed for family participants due to decline in participation - The mean age of the intervention group was higher than the control group; therefore, age was used as a covariate in all analyses
Kurz, et al. (2009) (33)	21	30 MCI, 10 with mild severity Alzheimer's dementia (MCI defined by IWG criteria)	4-week structured group program intervention (22 hours per week) vs. wait list control	Problem solving, self-assertiveness training, relaxation techniques, and stress management	- California Verbal Learning Test (CVLT) - Rey Complex Figure (RCF) - Bayer-ADL Scale (BADL) - Beck Depression Inventory (BDI)	- MCI in the intervention group had significant improvements in all cognitive tests, mood and ADLs - Control group had a slight increase in depressive symptoms, no change in ADLs, and a re-test effect noted on the episodic verbal learning section of the CVLT	Cognitive and functional outcomes were felt to be independent of changes in depressive symptoms

						- No significant differences in outcome measures in those with mild dementia - Significant effect for ADAS-Cog and MMSE scores in MCI patients; mainly secondary to stabilization of scores in the intervention group and decline in the control group - Main effect seen for treatment for MMSE scores in MCI - MCI control group exhibited significant attenuated decline in FDG uptake in the left anterior temporal pole and left anterior cingulate gyrus, while the MCI intervention group had no decline	
Forster, et al. (2011) (34)	27	24 MCI, 15 mild AD dementia (MCI defined by IWG criteria)	Weekly 120 minute group sessions for 6 months vs. active control (monthly meetings with self-study assignments)	Cognitive intervention was based on the theory of cognitive reserve and focused on global cognitive functioning, mood and quality of life; the control group's sessions focused on isolated, sustained attention tasks	- MMSE - ADAS-Cog - Montgomery Asberg Depression Scale - FDG-PET imaging to determine the pattern of cerebral glucose metabolism		PET imaging and cognitive testing was performed at baseline and after 6 months
Kwok, et al. (2011) (35)	23	31 MCI (MCI defined as a CMMSE score of 20-25)	30 minute sessions, 5 sessions per week for 8 weeks vs. control	Intensive training in Chinese calligraphy	- Chinese version of the MMSE (CMMSE)	- Significant interaction effect of time and intervention - Increase in global CMMSE score and in domains of orientation, attention and calculation after intervention	- Cognitive test performed at baseline and after training intervention - Calligraphy is felt to incorporate visual perception, spatial structuring, cognitive planning and maneuvering of the brush
Tsolaki, et al. (2011) (36)	22	176 MCI (MCI defined by Peterson criteria)	Weekly visits to a center for 3 separate group sessions per day of 90 minutes for a total of 60 sessions vs. waitlist control	Cognitive training (focused on attention and executive function), cognitive stimulation (focused on memory) and psycho-therapeutic techniques	- Rivermead Behavioral Memory Test (RBMT) - Rey Auditory Verbal Learning Test (RAVLT) - Rey-Osterrieth Complex Figure Test-Delayed Recall (ROCFT) - MoCA - Test of Everyday Attention (TEA) - Digit Symbol (Wais-R) - Functional Cognitive Assessment Scale (FUCAS) - Trail Making B - Verbal Fluency Test (FAS) - Boston Naming Test - Boston Diagnostic Aphasia Examination - ROCFT - Clock Drawing Test - Functional Rating Scale of Symptoms of Dementia (FRSSD) - MMSE	- At 6 months intervention group significantly better on measures of general cognitive performance (MMSE, MoCA), executive function (FUCAS), verbal memory (MoCA), visual-constructive abilities (ROCFT, MoCA) and daily functioning (FRSSD) - Intervention group improved in within-group analyses in general cognitive performance, attention, language, verbal memory, executive function, visual perceptions and daily functioning between time points, while the control group declined in daily functioning	Cognitive assessments performed at baseline and 6 months
Buschert, et al. (2012) (37)	27	24 amnestic MCI (MCI defined by Peterson criteria)	Crossover design with 6 months intervention in each group - Intervention consisted of weekly 2 hour sessions; control group received paper-and-pencil exercises for self-study	Cognitive activities, including mnemonic memory techniques and activities to foster cognitive and social engagement	Primary: - MMSE - ADAS-Cog Secondary: - Conversion to Alzheimer's disease - Repeatable Battery for the Assessment of Neuro-psychological Status (RBANS) Trail Making Test A & B - MADRS (Montgomery Åsberg Depression Rating Scale) - Quality of Life-AD scale	- ADAS-Cog and RBANS scores improved in Group A with intervention and remained significantly improved from baseline through the remainder of the assessments (ADAS- Cog increased at 8 months, RBANS increased at 15 months) - Group A showed improvement on MADRS and a near - significant improvement in MMSE and TMT with intervention, but these findings did not remain on further follow-up analyses - Group B showed decline in cognitive measures at 8 months and subsequently did not show any significant effects from the intervention	- Assessments were performed at baseline, 8 months, 15 months and 28 months - Intervention was designed with a large social component, while the control exercises were done without social engagement - Group A displayed significantly better baseline cognition, immediate and delayed recall prior to the intervention (baseline for Group A, 8 month testing for Group B)

Greenaway, et al. (2012) (38)	24	40 amnestic MCI (MCI defined by Peterson criteria)	Intervention group (12 one-hour sessions over 6 weeks) vs. control group (given calendar and encouraged to use it without training)	Memory Support System / (MSS) – calendar Notebook rehabilitation intervention that provides orientation, modeling, practice and notebook	- DRS-2 - MMSE - Everyday Cognition (ECog) memory subscale - CES-Depression - QoL-AD - Self-Efficacy in MCI - Caregiver Burden Questionnaire - Adherence Assessment	- 6 individuals progressed to AD – all from Group B - No changes in DRS-2 or MMSE scores at any time point - Improvement in ADLs based on ECog with intervention at immediate post-intervention and 8-weeks but NOT significant at 6-months - Improvement in sense of memory self-efficacy with intervention	Outcome measures assessed at baseline, immediately post-intervention, 8 weeks after intervention and 6 months after intervention
Moro, et al. (2012) (39)	27	30 amnestic MCI (MCI defined by Peterson criteria)	Crossover design with 6 months intervention in each group Training consisted of 3 individual sessions per week for 1 month, followed by weekly sessions for 5 months and encouragement that each participant use the techniques at home with his/her caregiver	Rehabilitative training program focusing on memory enhancement strategies and metacognitive abilities and individualized to the needs of each participant	- Bell Test - Attentional matrices - Trial Making A & B - Bourdon Test - Verbal Span - Auditory Verbal Learning Test (immediate and delayed recall) - Omissions Test - False Recognitions - Listening Span Test - Story Recall - Verbal Fluency - Tower of London - Analogies - Stroop Test	- Overall, positive impact on delayed recall memory; (1) both the groups improved their performance as an effect of training; (2) in the interval without intervention, performance of group B worsened and (3) group A has maintained their results over time. - Tests of executive function did not reveal any significant effects	- Participants were placed into either group A or B based on individual preferences - All 30 participants completed the 12-month study - Caregivers were involved in the training sessions
Olchik, et al. (2013) (40)	23	47 MCI, 65 Normal controls (MCI defined by Gauthier and Touchon criteria)	Memory training group (8 twice weekly group sessions of 90 minutes) vs. educational intervention group (8 twice weekly group sessions of 90 minutes) vs. control group	- Memory training consisting of mnemonic strategies and attention/ executive function tasks - Educational sessions s consisting of content only, no task	- FAS Verbal Fluency Test - Verbal Fluency – animal category - Rey Auditory Verbal Learning Test (RAVLT) - Rivermead Behavioral Memory Test (RBMT)	- Greater impact on RAVLT immediate and delayed recall and RBMT scores for MCI participants than for those without cognitive impairment for both intervention groups - Animal verbal fluency and RAVLT improved more with memory training than education alone	- Practice/retest effects were seen in FAS and RBMT scores
Rojas, et al. (2013) (41)	26	46 MCI (MCI defined by Peterson criteria)	2 hour sessions, twice per week for 6 months vs. wait-list control	Cognitive stimulation training sessions, cognitive training, use of external aids	Primary: - MMSE - CDR stage Secondary: - The QoL Questionnaire - Neuropsych Inventory Efficacy Measures: - Signoret's Memory Battery - Boston Naming Test - Verbal Fluency - Wechsler Abbreviated Scale of Intelligence - Similarities and Matrix reasoning - Block Design - Trail Making A & B - Wechsler Adult Intelligence Scale III	- MMSE, recognition and semantic fluency, and CDR differences after intervention - Significant improvement in semantic fluency and Boston Naming Test score in the intervention group with no significant changes on other tests - Conversion to dementia was 26.66% in the control vs. 6.66% in the intervention	Cognitive measures were tested at baseline, 6 months and 12 months
Carretti, et al. (2013)	22	20 individuals with amnestic MCI (MCI defined by Petersen criteria)	Training program (5 sessions of 30 to 90 minutes over two weeks) vs. control group (received educational activities on memory also over 5 sessions in 2 weeks)	Working Memory training program	- Categorization Working Memory Span Test (CWMS) - Dot Matrix Task - Digit Span Forward and Backward - Pattern Comparison Task - Intrusion errors in the CWMS - The Cattell Task (Culture Fair Test) - List Recall Task	- Benefit index was higher for the group that underwent the training program compared to the control for the primary CWMS measure (Effect size >2.0) - No differences between groups in Dot Matrix, Digit Span, CWMS Intrusions, Pattern Comparison - Benefit index was higher for the intervention for Cattell Test	- Assessments performed at the first and fifth sessions

of exertion from walking, aerobic exercise, stretching and resistance training. No consistent pattern of cognitive domains improved was noted regardless of specific physical activity tested (e.g. aerobic exercise). Among cognitive domains most effected, prominent executive function benefits but not memory was noted in one (23) while small benefits related to memory but not executive function were noted in others (22, 27).

Figure 2
Mean and Standard deviation of CONSORT 2010 rating across all three intervention types



Cognitive interventions

Cognitive interventions were again quite variable in their details; strategy training, mnemonics, calligraphy, and computer based training. Some studies noted at least immediate benefit on different cognitive test indices (31, 37, 39-41). Interventions targeting metacognition and mnemonic strategies were more common than computer based cognitive training. There was striking variability on the main cognitive domains significantly improved after intervention; executive function (35), working memory (30, 38, 41), delayed recall predominant effects in some (31, 35, 38, 39), improvement in global cognition (33-37) or no improvement of intervention groups (28, 29) in others. It was further unclear among the cognitive intervention studies, 1) if the positive outcome would continue to hold after accounting for the multiple confounding factors, 2) if uneven quality of studies could account for differences in outcomes, 3) if some interventions listed under cognitive training were more effective than others.

Socialization intervention

The one RCT study published on socialization was promising in its outcome, noting improvement in cognitive and functional domains (42).

MCI subjects with a high probability of underlying AD

Studies that targeted amnestic MCI (aMCI) subjects were more recent studies (2008 and later) and were expected to target MCI from underlying AD pathology. Among this subgroup of aMCI subjects most studies noted improvement in cognition for both physical activity (3 of 3 aMCI studies) and cognitive interventions (5 of 6 aMCI studies). The cognitive interventions in the aMCI studies were all focused on improving memory strategies and metacognition and were notable for being effective. But the specific cognitive domains that were most improved were again not consistent even within this subgroup of aMCI studies. A small study by Förster et al (33) targeting cognitive intervention reported use of functional biomarkers in identifying their MCI subjects as more likely from underlying AD and also noted stabilization of ADAS-Cog scores after intervention compared to controls.

A summary of methodological problems identified among the MCI studies are listed in Table 4. Specific comments include the following:

1. Defining of MCI and its subtypes. The definition of MCI has evolved over the years, making it difficult to compare trials. MCI was defined most commonly by the Peterson and International Working Group (IWG) criteria. However, some studies used Gauthier and Touchon criteria, Spanish Society of Geriatrics and Gerontology criteria; while others used cutoffs on MMSE, CDR and scores on CERAD subtests. This contributes significantly to the variability in the degree of cognitive deficits in the MCI state across different studies.

Additionally, distinguishing subtypes of MCI were not always of concern among the studies. Categorization of impairment into amnestic MCI (21, 23, 27, 29, 31, 36-38, 41) and thereby more likely related to AD pathology (43) were specified in some RCTs. The use of AD biomarkers in MCI (43, 44) could serve to enrich trials with patients who have an early symptomatic form of AD and help to overcome some of the challenges of previous MCI randomized control trials..

2. Capturing cognitive subdomains of MCI in outcomes: The RCTs reviewed often considered different cognitive subdomains and functional scales as outcomes, resulting in difficulty in comparing outcomes between trials. A simple comparison of effect sizes across studies therefore fails to capture the variability in 1) quality of studies and accounting for confounders, 2) cognitive tests used and 3) differences in cognitive and functional outcomes.

Furthermore, differential rate of decline across cognitive domains has been well characterized among MCI subjects. Identifying MCI subtypes that have different natural histories of progression also helps decrease heterogeneity in rate of progression and improve our capability in assessing effectiveness of interventions (45). For instance MCI subjects in the Religious Orders Study declined significantly faster on measures of episodic memory, semantic memory, and perceptual speed, but not on measures of working memory or visuospatial ability compared to cognitively normal-for-age subjects (46). Studies reviewed were therefore not easily generalizable regarding the effectiveness of interventions when MCI populations are incompletely characterized as to their underlying etiology, the degree of cognitive deficits at baseline and their subsequent expected differences in the rate of

Table 3
Socialization intervention

Study	CONSORT 2010 score:	Intervention	Population	Outcomes measured	Length of study	Results	Comments
Pitkala, et al. (2011) (42)	31	Social intervention group (activities for 6 hours per day, 1 day per week for 3 months) vs. control	235 >75 years old subjects with self-reported loneliness; either cognitively intact or diagnosed with MCI or mild dementia	- ADAS-Cog - 15D (measure of health-related QoL and mental function)	1 year	- Significant improvement in ADAS-Cog - Significant improvement QOL as measured by the 15D	- Patients enrolled in the study were allowed to voice their interests and were then placed into one of three social groups based on these interests (physical activity, art or writing) - ADAS-Cog performed at baseline and 3 months - 15D measured at baseline and 1 year

progression.

3. Considering stage of disease and rate of cognitive decline: Studies have noted that initial stage of disease at the beginning of the observation period («how far») is an important predictor of subsequent decline («how fast») (47, 48). RCTs reviewed here did not attempt to take into consideration stage of MCI and related rate of cognitive decline for individual subjects to assess effectiveness of intervention. This omission is important due to the differences in the rate of decline of cognition in early MCI compared with later MCI.

4. Capturing lifestyle, medication use, and comorbidities: Accounting for treatable etiologies of the MCI syndrome that influence rate of progression was not accounted for clearly in some of the studies reviewed. This omission is important due to the impact of smoking, nutrition, alcohol use, head trauma, hypertension, diabetes, heart failure and sleep disorder, on the rate of decline of cognition. Medications with cognitive side effects also influence performance of cognitive and functional measures (49).

Table 4
Limitations of randomized controlled trials of nonpharmacological interventions for MCI

Variable definitions implemented for MCI
Inconsistent reporting of MCI subtype
Small sample size
Short intervention periods with limited follow up beyond completion of intervention
Variable cognitive tests used for outcome measures
Highly variable interventions
- Duration of intervention
- Frequency of intervention
- Setting in which the intervention is conducted
- Content of the intervention
Multiple confounding factors
Variable control groups (waitlist control vs. active control)
Practice effects/test familiarization due to repeated administration of cognitive tests
Inconsistent reporting of and controlling for comorbidities, lifestyle factors and affective state

5. Capturing cognitive improvement: Most MCI clinical trials involved repeated trials of cognitive testing to characterize the degree of change in particular measures of interest. When testing a study population, test familiarization or practice effects could persist into the treatment phase and impair accurate characterization of the effects and the effect size. This is well-studied in the field of psycho-pharmacology, where five practice sessions before treatment trials is a rule of thumb (50). But all tests do not follow convenient heuristics, including digit span which is known to be markedly affected by practice (51) and improvement has been noted to continue over more than 50 practice sessions (50, 52). Several of the MCI cognitive intervention trials reviewed failed to detail how the subjects were familiarized to their tests before pre-post differences were calculated, potentially missing a major confounding effect.

6. Capturing functional improvement: An MCI diagnosis draws attention to cognitive changes not severe enough to warrant the diagnosis of dementia and therefore subjects are functionally independent. Enrolling a population with objective cognitive deficits who declare themselves to be without functional impairment may be hampered by differences in patients or informants threshold of functional independence. Furthermore, most studies captured functional improvement using scales that depended upon the patient or informant report. Although validated in crossectional studies, these scales incorporate a fair amount of subjectivity in tracking subtle longitudinal changes over the period of an RCT.

7. Adequate sample sizes: The number of subjects in the RCTs reviewed range from 19 to 389. The median number of subjects among RCTs was 47. AD clinical trials typically use a detection threshold of 25% or 50% reduction in mean rate of decline on the standard cognitive outcome with a minimum 6-month assessment interval. Calculations in the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set using these measures have consistently estimated sample sizes of over 100 MCI subjects per arm of the study, although reported sample size estimates for each measure are more often larger and widely divergent (53-58). Use of enrichment strategies calculated to decrease the sample sizes are implemented quite frequently (59, 60). Non-pharmacological trials for cognitive intervention in MCI have subjects in far lower numbers than needed but they have been improving with time. Many studies looking into physical activity in MCI are of higher quality in this respect. Moreover, additional factors, including

study subject dropout or lack of engagement in interventions to be done without supervision and loss to follow-up also have to be taken into consideration in design of future non-pharmacological interventions.

Figure 3
CONSORT 2010 rating in physical intervention studies across years. The number of subjects in each study relates to log perimeter of marker size

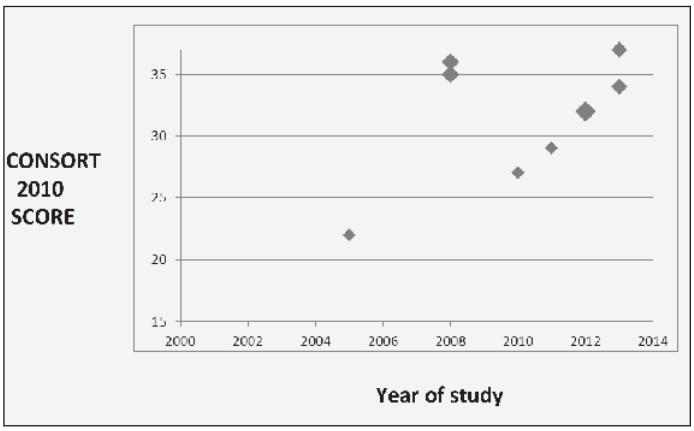
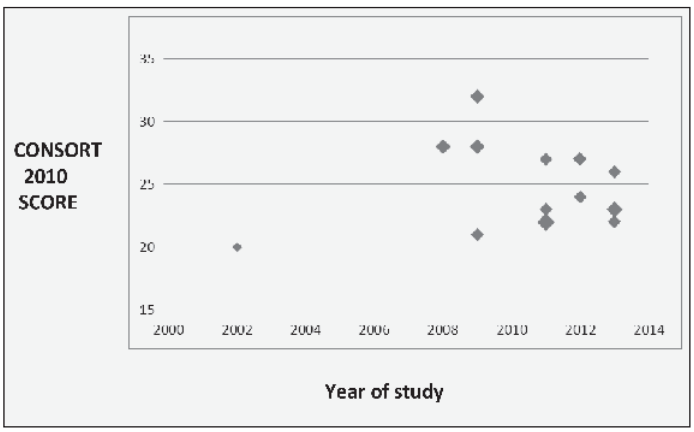


Figure 4
CONSORT 2010 rating in cognitive intervention studies across years. The number of subjects in each study relates to log perimeter of marker size



Discussion

In our study, the CONSORT reporting quality score as well as qualitative assessment of methodological areas suggests that methodology of studies of non-pharmacological interventions have improved from earlier studies over a decade ago. Strengths of our study include a systematic approach to reviewing the studies, and both a quantitative measure and a qualitative assessment to analyze the methodologies. Our quantitative measure, the sum score of the CONSORT 2010 checklist, has face and content validity. A weakness of our study is that this reporting tool has not been validated in previous studies exactly as used; we adapted it from Huwiler-Muntener et al (19) inorder to take advantage of the updated CONSORT checklist to assess the methodology of RCTs reviewed. Another weakness is that reporting quality is a surrogate as opposed to a direct measure of quality of the study methodology. However, CONSORT checklist has become so widely accepted that its use has gone beyond the original intent (to improve reporting quality). Reporting guidelines for extending CONSORT for social and psychological intervention RCTs have been proposed (61). Nonpharmacological interventions among MCI subjects fall within this rubric. By pointing out gaps in reporting, CONSORT can focus attention on the quality of methodology. Hence we felt it was appropriate to use the CONSORT checklist over other quality assessment tools such as Chalmerset al. (62) and Jadad et al (63).

Specific areas of concern in methodology for future studies

1. Targeting AD within a population with MCI subjects. MCI may be regarded as a syndrome that is often (but not always) associated with Alzheimer pathology and has variable outcomes. Zanetti et al. (64), in a longitudinal study note that MCI subjects classified with amnestic MCI (aMCI) after 3 years were more likely to progress to AD dementia while those MCI subjects displaying multiple impaired cognitive domains with prominent executive deficits (multidomain MCI) had more vascular comorbidity and had progressed to vascular dementia (VaD). Absence of amyloid positivity among MCI subjects was associated with stability in overall cognition and improvement in verbal memory in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study (65). Thus, interventions may have a differential effect on MCI subtypes, diluting (or enhancing) the impact of an intervention.

In addition to familial AD, cognitively normal people with a very high risk of developing AD dementia include carriers of two copies of the APOE ε4 allele. The field of AD genetics is moving rapidly in identifying additional risk factors in pre-dementia subjects. In 2013 researchers identified 11 new susceptibility loci for AD (66) including inflammation related gene, *TREM2* (67). The field of exome sequencing linked with RNA expression is growing, suggesting that in the future, genetic and epigenetic information could guide individual subject selection among clinical trials.

The use of amyloid imaging, functional imaging (fMRI and FDG PET), and AD biomarkers in MCI (44) now, and genetic-epigenetic information in the future, could help overcome some of the challenges of previous MCI randomized control trials. Availability of a better characterized' subject pool would help in the design of effective non-pharmacological interventions in AD.

2. Enrollment of subjects in the same stage of disease. MCI is a dynamic stage in AD and may last for a few months or for many years. The rate of decline changes during the disease course and may be faster at the time that MCI is identified, compared with later follow-up. In the Rush Memory and Aging

Project, persons with MCI showed an increased average rate of decline of more than 500% in the first year of follow-up and an increase of nearly 200% in the second year of follow-up compared to persons without cognitive impairment; this difference decreased as the duration of follow-up increased (68). Non-pharmacological interventions in the MCI population have to overcome the limitations of the expected natural rate of cognitive decline depending on the stage of the underlying disease in designing RCTs.

3. Enrollment of subjects with similar lifestyle and comorbidities. If the intervention and control groups in a MCI RCT differ in lifestyle, medication use, and comorbidities, cognitive decline may progress differently between the groups, affecting the impact of the interventions. Variability in lifestyle, medication use, and comorbidities within each group may also dilute the effect of an intervention.

4. Variability in the rate of decline among different cognitive subdomains in MCI. MCI subjects in the Religious Orders Study declined significantly faster on measures of episodic memory, semantic memory, and perceptual speed, but not on measures of working memory or visuospatial ability compared to cognitively normal-for-age subjects (46). Preservation of working memory, but not episodic memory, in MCI and early dementia stages relates to slower rate of functional decline among autopsy confirmed AD subjects (69).

These results open the possibility that within MCI, targeting working memory among Aβ positive subjects could help slow rate of functional decline rather than nonspecific interventions across all cognitive domains with different rates of decline.

5. Surrogate methods for capturing cognitive change. Functional imaging has been used to characterize neuroplasticity related changes in multiple neurological conditions and in normal aging (70-72).

An early functional MRI study by Belleville et al. (73), found that strategy memory training increased activation in brain regions involved in memory (but not in the hippocampus) and in the right inferior parietal lobe. Relative to healthy older adults, a number of brain regions that were dysfunctional before training were no longer different compared to healthy elders following training. In two slightly different studies, the same group reported increased activation in the default-mode network and hippocampal activation following training in MCI populations (74, 75). A small study by Rosen et al, reported increased left hippocampal activation among trained persons with MCI (76).

FDG PET is promoted as a promising tool for developing surrogate marker in the assessment of an AD treatment's ability to improve clinical outcome and modify disease progression (77). A single FDG-PET study in MCI and early AD participants after a 6-month multicomponent cognitive training program was found to reduce decline in brain glucose metabolism. However, there was no correlation between measured cognitive improvement and changes in glucose metabolism in that study (33).

6. Alternative methods for capturing functional improvement. Information and Communication Technologies (ICTs) and use of embedded devices to capture 'everyday cognition' is promising from the perspective of developing tools that could be useful among culturally and socially diverse populations with pre-dementia. ICTs are becoming recognized as a potential way to help stage cognitive impairment (78). By using technology to observe individuals in real-life scenarios, it may be possible to stage baseline function and observe changes in function over time during a cognitive intervention study.

Conclusion

A new generation of studies targeting MCI based on underlying etiology is likely to be seen in the near future. Early studies including Förster et al (33) are providing insights into the effectiveness of 'targeted to etiology' interventions. The use of functional neuroimaging, amyloid imaging and AD biomarkers in non-pharmacological interventions in MCI due to AD is important primarily as an enrichment tool to identify the target population in a comparable stage of disease and to reduce heterogeneity of results from confounding etiologies of MCI as well as differential rates of decline. Over time, genetic and epigenetic information about subjects will improve the enrichment potential and reduce sample size and duration of study, improving effective measures of tracking cognitive changes and this could reduce overall cost in care of AD patients.

The field of AD therapeutics, after a spate of recent disease-modifying trial failures, is regrouping. Similarly, the field of non-pharmacological interventions has to tackle complex issues, before non-pharmacological interventions that will prevent or defer the onset of cognitive impairment in AD can be confidently recommended to MCI due to AD patients. Once the sample of subjects is more uniform; lifestyle, polypharmacy, and comorbidities are identified and addressed; a broader array of tools for measuring cognitive and functional outcomes are incorporated, non-pharmacological trials can be designed to answer more specific questions.

1. Are there outside influences on cognition during an RCT, other than the natural progression of disease and the intervention? (Placebo, Hawthorne effect)

2. How long are the effects sustainable post-trial?

3. Are there surrogate marker changes that correlate with the modifying effect of intervention and underlie time duration of effects noted?

4. Are specific cognitive sub domains like executive function and working memory more amenable to training?

5. Are behavioral outcomes affected during and after the trial by the intervention?

6. How does burden of white matter changes impact benefit from non-pharmacological interventions among MCI subjects?

It is likely that with the ready availability and utilization of AD specific biomarkers in clinical settings, recruitment and

targeting of patients with MCI due to AD specific diagnosis will be feasible in future clinical trials of non-pharmacological interventions. A higher standardization of the methods needs to be agreed upon by the field to allow comparability and generalizability of the findings to overcome the variability in trial design for non-pharmacological interventions.

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