Research Article

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Does Multidomain Intervention Reduce The Risk Of Developing Dementia In MCI Patients?

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ABSTRACT

Background: *Mild cognitive impairment (MCI) affects about 12% to 36% of older adults and the mean annual conversion rate of MCI to dementia is approximately 10%. MCI provides an optimal window in preventing the progression to dementia and a consensus has emerged about non-drug treatments being a viable alternative to drug treatments.*

Objectives: *The primary objective of this review is to quantify the overall effect of multidomain interventions on the global cognitive function in older adults with MCI; the secondary objective is to show the superiority of a multidomain intervention over single physical or cognitive intervention.*

Methods: *Databases including PubMed, Medline and the Cochrane Library were used to search for studies that reported effects of non-drug treatments in older adults with MCI. Exercise interventions, cognitive interventions, combined interventions and multidomain interventions of all selected studies were summarized and effect sizes of different interventions were calculated.*

Results: *The results showed that physical activity improved cognitive function and reduced global cognitive decline whereas cognitive interventions improved executive functioning, attention, memory and other cognitive domains. Combined interventions (physical activity + cognitive intervention) demonstrated superiority over single physical exercise on memory, global cognition and executive function and over single cognitive intervention on memory and global cognition.*

Multidomain interventions (intended as nutritional guidance, exercise, cognitive training, social stimulation and management of metabolic/vascular risk factors) reduced the risk of developing mild cognitive impairment or the composite of mild cognitive impairment and probable dementia and improved cognitive function.

Conclusion: *Multidomain interventions have demonstrated a limited superiority over the single exercise/cognitive intervention on cognitive functions. These results are encouraging but more evidence is needed to determine the optimal exposure to the multidomain intervention and whether improvements are maintained over time.*

Keywords
Mild cognitive impairment, Non-drug treatments, Physical activity, Cognitive therapy, Multidomain intervention, Dementia, Review.

Introduction
Mild cognitive impairment (MCI) has been defined as an objective cognitive impairment, reported by a patient or relative, in a person with essentially normal functional activities who does not have

dementia. It is the intermediate phase between normal age-related cognitive decline and dementia. It is estimated that about 12% to 36% of older adults have MCI [1] and, as the population of older adults increases, the prevalence of MCI will gradually increase [2]. People with MCI are clinical and neuropathological heterogeneous but it is widely known that people affected by mild cognitive impairment (MCI) are at greater risk of dementia than the general population; the mean annual conversion rate of MCI to dementia is approximately 10% [3], which is far higher than the annual incidence (1–2%) in the general population. Dementia seriously affects the quality of life and well-being of older adults and causes a heavy burden on families and society. Therefore, effective interventions are urgently needed to prevent dementia.

MCI provides an optimal window for preventing the progression to dementia and a consensus has emerged that intervention strategies must be initiated as early as possible, even before any significant symptoms begin to appear. Unfortunately, there are no curative treatments for MCI or dementia yet, but it has been estimated that 3% of the dementia cases could be prevented by increasing levels of free-living physical activity and improving nutritional status. Compared with drug treatments, non-drug treatments have no serious side effects and have thus become a viable option for treating cognitive disorders [4]. For the aforementioned reasons, a growing body of literature is focusing on the most effective intervention to prevent and eventually slow down the pathological process and dementia-related problems [5].

Cognitive impairment and dementia are complex multifactorial disorders and multidomain interventions, which target several risk factors, and disease mechanisms simultaneously could be needed for optimum preventive effects.

The primary end-point of this review is to quantify the overall effect of multidomain intervention on global cognitive function in older adults with MCI or dementia; the secondary end-point is to show the superiority of multidomain intervention over single physical or cognitive intervention.

Literature Review

The drug treatments that are currently available for cognitive disorders and dementia give poor results and do not significantly modify the natural history of neurodegenerative disease. Drugs are unable to stop the progression of the disease and they have only palliative or symptomatic effects, moreover they are often burdened by side effects that limit their possibility of use. For these reasons, in the last decade, attention has been paid to non-drug treatments that have expanded the possibilities of treatment and prevention of MCI/dementia.

Exercise interventions for MCI (Table 1)

Physical activity improves overall health and reduces the risk of many negative health outcomes, on top of that, it may also be effective in improving cognition, independent functioning and psychological health [6,7]. Therefore, physical activity should be used as a potential pathway for decreasing risk of dementia in those with mild cognitive impairment (MCI) and improving outcomes for those already diagnosed with dementia [8].

The existing literature that examines the effectiveness of physical activity in patients with MCI and dementia shows conflicting findings [9,10]. Several studies reported that exercise interventions improved cognitive function [11,12], memory [13] and psychological outcomes [14] among older adults with MCI and reduced global cognitive decline and behavioural problems [5]. Its benefits on cognitive function are mainly due to its effects on working memory.

Physical activity interventions targeting older adults with MCI have included a wide variety of programs, including aerobic exercise (e.g., walking), resistance training [15], yoga [16], and tai chi [17], and there is some support for each of these forms of activity having a positive impact on healthy aging. In order to better understand the effects of the physical activity there are several studies presenting those beneficial effects by exercise type [18]. The most pronounced effect on global cognitive ability and memory, among older adults with MCI, appears to arise from aerobic exercise at moderate or greater intensity with at least 24 hours of total training time and resistance exercise. The effect appeared to be more pronounced in those with moderate-grade dementia relative to those at an earlier stage. It remains controversial whether or not the effect of exercise on cognitive function could be lasting until after the termination of exercise [5]. The existing literature that shows no effects or small positive effects [19,20] on cognitive outcomes in older adults with MCI is the minority; studies are of moderate quality, inconclusive and most of them had a medium or small term intervention length (usually six months or less), which may constitute a methodological limitation since persistent relevant changes in cognitive function may require a longer time period, in particular for older people.

Cognitive interventions for MCI (Table 2)

Many systematic reviews and meta-analyses have shown that cognitive interventions are effective for improving cognitive function in older adults with MCI.

There exist different kinds of cognitive therapies demonstrating their effectiveness in improving the cognitive ability in patients diagnosed with MCI: computerized cognitive training (CCT), group-cognitive stimulation (CS), memory rehabilitation. There are mixed results about which cognitive intervention is relatively the best for MCI [21]: cognitive stimulation (CS) and cognitive training (CT) have a significant improvement in cognitive ability and CS seems to be the best cognitive intervention to improve cognitive function in MCI patients.

These cognitive interventions do not only address the problem of a decreasing cognitive function but also have a prominent effect on executive functioning, attention, memory and other cognitive domains. In recent years, some studies have shown that memory-focused interventions (e.g., memory training or other related strategies) effectively defer cognitive or memory function decline and improve cognitive function and motor skills [4]. Memory-focused interventions were proven effective in improving memory-related performance with a medium-to-large effect size in the people with cognitive disorders. The results indicated that memory performance improvement was more profound with memory interventions which implemented a memory training type, an individual training format, and shorter and more sessions.

Few studies evaluated long-term outcomes however, from the results of previous studies; the duration does not seem the longer the better. When the duration reaches 24 weeks, the benefit on global cognitive function appears to be preserved over extended follow-up periods [22].

Although there is extensive research available on the effectiveness of various cognitive interventions associated with MCI, the results are highly controversial thus resulting in a necessity for more studies.

Combined interventions for MCI: cognitive intervention + physical exercise (Table 3)

The existing literature has shown that cognitive interventions or physical exercises are effective for improving cognitive function in older adults with MCI; if combined they may yield additive and synergistic effects on cognitive functions in MCI patients. The combined intervention resulted in cognitive benefits in older adults with MCI and exhibited limited superiority over the single cognitive intervention and the single physical exercise on cognitive subdomains. Combining a single cognitive intervention with a single physical exercise intervention would greatly increase the likelihood of cognitive benefit [23].

A recent study found that compared to a group that underwent only cognitive intervention and a group that underwent only physical exercise, the combined intervention significantly improved memory but did not significantly improve global cognition or executive function [24].

Another new study showed positive effects of combined intervention on global cognition and executive function compared to a group that underwent only physical exercise [25]; moreover, other studies have indicated that the combined intervention positively affects global cognition compared to no cognitive intervention or physical exercise in older adults with MCI. However, some studies did not observe the positive effect of the combined intervention on global cognition in older adults with MCI [23,26]. These conflicting results are due to the large methodological heterogeneity of intervention characteristics and to the short follow-up; future studies with strictly defined intervention characteristics and long-term follow-up are needed to better investigate the effects of combined interventions in patients with MCI or dementia.

Multidomain interventions for MCI (Table 4)

As cognitive impairment/dementia has a multifactorial aetiology, resulting from interactions between both genetic and environmental factors, multidomain intervention, which combines interventions for multiple risk factors and controls for many other factors, could be considered as the most effective non-drug treatment in patients with MCI/dementia [27].

This is the point on which "The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)" focuses. The multidomain intervention consisted of nutritional guidance, exercise, cognitive training, social stimulation and intensive monitoring and management of metabolic and vascular risk factors. It provided four intensive lifestyle-based strategies (diet, exercise, cognitive training and vascular management) to over 600 people, aged over 60, who were at high risk of dementia according to their age, sex, education, systolic blood pressure, total cholesterol and physical activity. This highly intensive research study was conducted with health professionals and trainers over a period two years. The primary end-point was cognitive performance measured by a battery of neuropsychological tests and the secondary end-points were: dementia (after extended follow-up), disability, depression symptoms, vascular risk factors and outcomes, life quality, use of health resources and neuroimaging measures.

Participants showed a mean improvement in a composite measure of cognition on executive function and processing speed, but not memory. Despite the intervention's intensity, the effect was small, although this demonstrates the potential of lifestyle modification to improve cognition function in people at risk of dementia. The FINGER intervention was effective regardless of the characteristics of the participants and can therefore be implemented in a large elderly population at increased risk of dementia.

Another multidomain trial is "The Prevention of Dementia by Intensive Vascular Care (preDIVA)" that studied how to prevent dementia by reducing vascular risk factors [28] in a six-year follow up. The primary outcomes were the incidence of dementia and the disability score (Academic Medical Center Linear Disability Score [ALDS]); the main secondary outcomes were incident cardiovascular disease and mortality. The results showed no significant difference in dementia incidence between the intervention group and usual care group; this may be related to the relative lack of cardiovascular risk factors in the study population, reducing the possibility of risk reduction, or to the high standards of usual care. Future studies should assess the efficacy of such interventions in selected populations.

Furthermore there is the recently published SPRINT-MIND that is a pre-planned sub-study of the SPRINT trial [29]. The Systolic Blood Pressure Intervention Trial (SPRINT) showed that intensive systolic blood pressure (BP) control reduces cardiovascular disease outcomes and mortality largely than treatment to standard systolic BP target in people with hypertension. The SPRINT Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study tested whether aiming at the lower systolic BP target reduced the risk of developing the incidence of probable dementia,

Table 1: Exercise Intervention: Study Characteristics.

Authors, year	Study design	Participants and Mean age	Intervention and Duration	Outcome measures
Stanley Colcombe et al. (2003)	meta-analytic study (18 intervention studies published between 1966 and 2001)		Exercise intervention	Outcome measures: cognitive processes identified by the four theoretical positions (speed, visuospatial, controlled processing, and executive control).
Nicola Gates et al. (2013)	meta-analysis (14 randomized controlled trials)	1695 subjects Age: 65–95 years	Exercise intervention	Outcome measures: cognitive performance.
Guohua Zheng et al. (2016)	systematic review (10 studies)	394 subjects	Exercise intervention	Primary outcome: global cognitive ability. Secondary outcomes: memory, attention, visuospatial ability, verbal fluency, language, execution and processing speed.
Paul D. Loprinzi et al. (2018)	systematic review and meta-analysis (11 randomized controlled trials)		Exercise intervention	Outcome measures: memory function.
Dan Song et el. (2018)	systematic review and meta-analysis (11 randomized controlled trials)	956 subjects	Exercise intervention	Primary outcome: global (i.e. domain general) cognition. Secondary outcomes: domain-specific cognition (e.g. memory, executive function), depression and HRQoL.
Yu-chai Chang et al. (2012)	systematic review (10 randomized controlled trials)		Exercise intervention	Outcome measures: cognitive and executive function.
Guohua Zheng et al. (2016)	systematic review and meta-analysis (11 randomized controlled trials)	1497 subjects (female: 932) Mean age: 74.1 years	Exercise intervention	Outcome measures: global cognitive ability, memory, attention, executive ability, verbal fluency and visuospatial function.
Chun-Kit Law et al. (2020)	systematic review and meta-analysis (50 randomized controlled trials)	age: 68-86 years	Exercise intervention	Outcome measures: cognitive functions and behavioural problems.
Carol E. Rogers et al. (2009)	systematic review (36 randomized controlled trials)	3799 subjects (Female: 71.97%)	Exercise intervention	Outcome measures: balance and falls, cardiovascular health, physical function, psychological outcomes and disease outcomes.
B. S. Oken et al. (2004)	randomized controlled trial	69 subjects	Exercise intervention 6 months	Outcome measures: cognitive measures focused on attention, physiologic measures of alertness, Profile of Mood States, State-Trait Anxiety Inventory, Multi-Dimensional Fatigue Inventory (MFI) and Short Form (SF)-36 health-related quality of life.
J. Lee et al. (2020)	systematic review and meta-analysis (14 randomized controlled trials)	1178 subjects	Exercise intervention	Outcome measures: cognitive function, blood pressure, body mass index and handgrip strength.
Yael Netz et al. (2005)	meta-analysis (36 studies)		Exercise intervention	Outcome measures: anger, anxiety, confusion, depression, energy, overall well-being, life satisfaction, physical symptoms, positive effects, self-efficacy and view of self.
Philipe de Souto Barreto et al. (2018)	systematic review and meta-analysis (5 randomized controlled trials)	2878 subjects age: 60+	Exercise intervention	Outcome measures: dementia onset, mci onset, other clinically meaningful cognitive decline and any of these three outcomes combined.
E. G. A. Karssemeijer et al. (2017)	single-blind, randomized controlled trial		Exercise intervention 24 weeks	Primary outcome: objective executive functioning measured with a neuropsychological assessment. Secondary outcomes: objective cognitive functioning in other domains, physical functioning, physical activity levels, activities of daily living, frailty, mood and quality of life.

Table 2: Cognitive Intervention: Study Characteristics.

Authors, Year	Study Design	Participants and Mean Age	Intervention and Duration	Outcome Measures
Verena C Buschert et al. (2012)		24 subjects	Cognitive intervention Study period: 2 years Intervention period: 6 months	Primary outcome: change in cognitive function. Secondary outcomes: changes in specific cognitive and noncognitive functions and conversion to Alzheimer's disease.
Jing-Hong Liang et al. (2019)	meta-analysis (13 randomized controlled trials published from 2007 to 2018)	1333 subjects	Cognitive intervention	Primary outcome: change in cognitive function.
Hui-Ling Yang (2018)	systematic review and meta-analysis (27 randomized controlled trials)	2177 subjects Mean age: 75.80 years	Cognitive intervention	Primary outcome: objective memory (learning and memory function, immediate recall, delayed recall, and recognition). Secondary outcomes: subjective memory performance, global cognitive function and depression.

Table 3: Combined Intervention: Study Characteristics.

Authors, Year	Study Design	Participants and Mean Age	Intervention and duration	Outcome measures
Lawla L. F. Law et al. (2019)	four-arm, single-blind (rater-blinded) randomized controlled trial	59 subjects Age 60+	Combined intervention Study period: 1 year	Primary outcomes: cognitive function, memory and executive function. Secondary outcomes: functional status and the caregiver's burden.
Imran Amjad et al. (2019)	randomized controlled trial	44 subjects	Combined intervention 14 months	Outcome measures: the mini-mental state examination (MMSE), Montreal cognitive assessment scale (MoCA), trail making test (TMT) A and B, slowness and complexity of EEG.
Michael Schwenk et al. (2016)	open-label pilot randomized controlled trial	22 subjects Mean age: 78.2 years	Combined intervention 3 months	Outcome measures: balance, gait, fear of falling and cognitive performance.
Qiuyan Meng et al. (2022)	meta-analysis (16 randomized controlled trials)	Female: 57.82% Mean age: 73.33 years	Combined intervention	Outcome measures: global cognition, memory, and executive function/attention.
E. G. A. Karssemeijer et al. (2017)	meta-analysis (10 randomized controlled trials)		Combined intervention	Primary outcome: global cognitive function. Secondary outcomes: performance on the domains of memory and executive function/attention, ADL and mood.

Table 4: Multidomain Intervention: Study Characteristics.

Authors, Year	Study Design	Participants and Mean Age	Intervention and Duration	Outcome Measures
B. Vellas et al. (2014)	study is a phase III, multi-centered (n=13), randomized, placebo- controlled trial	1680 subjects (Female: 64.8 %) Mean age: 75.3 years	Multidomain intervention 3 years	Primary outcome: change in memory function after 3 years follow up. Secondary outcomes: other cognitive performances, physical function, frailty syndrome, depression, tolerability to the omega-3 supplementation and adherence to the multidomain intervention.
Edo Richard et al. (2016)	multinational, multi-centre, prospective, randomized, open-label blinded end point (PROBE) trial	2600 subjects Age 65+	Multidomain intervention 18 months	Primary outcome: composite score based on the average z-score of the difference between baseline and 18 months follow-up values of systolic blood pressure, low-density-lipoprotein (LDL) and body mass index (BMI). Secondary outcomes: the difference between baseline and month 18 on the individual components of the primary outcome, the difference in lifestyle-related risk factors, the difference in estimated 10-year cardiovascular disease risk based on the Framingham cardiovascular disease risk score (measured at 18 months), cardiovascular risk factors, aging and dementia risk-score (CAIDE), incident cardiovascular disease, mortality, disability, cognitive functioning, incident dementia, physical fitness, mood and cost-effectiveness.
Eric P. Moll van Charante et el. (2016)	pragmatic, multisite, cluster-randomized, open-label trial	3526 subjects (Female: 55%) Mean age: 74.5 years	Multidomain intervention 6 years	Primary outcomes: cumulative incidence of dementia and disability score (ALDS) at 6 years of follow- up. Secondary outcomes: incident cardiovascular disease and cardiovascular and all-cause mortality, cognitive decline, symptoms of depression, blood pressure, body-mass index (BMI), blood lipid concentrations, and glucose concentration.
J.D. Williamson et al. (2019)	single-blind randomized controlled trial	9361 subjects (Female: 35.6%) Mean age: 67.9 years	Multidomain intervention Average intervention period: 3.34 years. Average follow-up period: 5.11 years.	Primary outcome: the incidence of probable dementia. Secondary outcomes: mild cognitive impairment and the composite of mild cognitive impairment and probable dementia.
Tiia Ngandu et al. (2015)	multi-center, randomized, controlled trial	1200 subjects Age: 60-77 years	Multidomain intervention Screening period: 2 years Intervention period: 2 years	Primary outcome: cognitive performance. Secondary outcomes: dementia (after extended follow-up), disability, depressive symptoms, vascular risk factors and outcomes, life quality, use of health resources and neuroimaging measures.
I.M.Nasrallah et al. (2019)	randomized clinical trial	670 subjects (Female: 40.4%) Mean age: 67.3 years	Multidomain intervention Average intervention period: 3.40 years Follow-up period: 4 years	Primary outcome: change in total white matter lesion volume from baseline. Secondary outcome: change in total brain volume.

mild cognitive impairment (MCI) and a composite outcome of MCI or probable dementia. The intensive lowering of blood pressure did not result in a significant reduction of the incidence of probable dementia, compared with standard management of blood pressure (the primary outcomes in SPRINT MIND). However, mild cognitive impairment and the composite of mild cognitive impairment and probable dementia (the secondary outcomes in SPRINT MIND) were significantly reduced in the intensive lowering group compared with the standard treatment group. Some caution should be used in interpreting this result, both because MCI was not the primary cognitive outcome of the trial and because it is not clear what this effect may imply for the longer-term incidence of dementia.

A subset of participants in SPRINT-MIND took part in the magnetic resonance imaging (MRI) brain study [30], which evaluated changes in total white matter lesion (WML) volume and total brain volume (TBV) during the active treatment and passive follow-up phases of the trial. The results showed that intensive BP lowering prevents increases in WML volume and that is consistent with the finding of reductions in MCI and in the combined outcome of MCI and probable all-cause dementia in the intensive treatment group. Two other studies (The Multidomain Alzheimer Preventive Trial in France (MAPT) [31] with multidomain lifestyle interventions and The Healthy Ageing Through Internet Counselling in the Elderly (HATICE)) [32] investigated the effectiveness of multidomain intervention but they had inconclusive results [33]. These results are encouraging but more evidence is needed to determine the optimal exposure to the multidomain intervention and whether improvements are maintained over time.

Conclusion

The present review aims at providing a summary of research on non-drug treatments in MCI/dementia that has been conducted over the last decade.

Previous single-domain prevention trials for cognitive impairment and dementia have yielded mixed results; some positive associations with cognition were reported for physical activity, cognitive training or both in smaller and shorter intervention studies.

Combined interventions demonstrated superiority over single exercise intervention on memory, global cognition and executive function and superiority over single cognitive intervention on memory and global cognition whereas multidomain interventions (intended as nutritional guidance, exercise, cognitive training, social stimulation and management of metabolic/vascular risk factors) reduced the risk of developing mild cognitive impairment or the composite of mild cognitive impairment and probable dementia and improved cognitive function.

Studies show a large methodological heterogeneity in intervention characteristics and a short-term follow up, despite these methodological limitations the current review illustrates the importance of multidomain interventions to help delay the progression of MCI or dementia.

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