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A REVIEW OF MULTIDOMAIN INTERVENTIONS TO SUPPORT HEALTHY COGNITIVE AGEING

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Abstract: *Objective:* The risk for cognitive decline and for developing Alzheimer's disease increases with age. The aetiology is assumed to be of multi-factorial origin, and treatment opportunities are lacking. Despite the multi-factorial origin, many intervention studies focused on single factors to influence cognitive health with inconsistent findings. In this view, more and more intervention studies aim to intervene on multiple factors simultaneously to affect or slow down cognitive decline. The purpose of this paper is to give an overview of these multidomain intervention trials. *Methods:* We conducted a non-systematic literature search in Medline, Scopus, Cochrane Library, and clinical trials databases up to October 2011 to review multidomain interventions that investigated effects of combined lifestyle-related factors on cognitive decline and the progression of dementia. *Results:* Interest in multidomain interventions increased over the past years. We identified six completed and published trials and eight ongoing or not yet published studies that investigated effects on cognitive outcomes. First completed trials yielded promising results for the combination of exercise and mental training and diet and behavioural weight management. Results of ongoing multidomain trials are awaited. *Conclusions:* Some evidence suggests that strategies which target multiple factors simultaneously may prove more effective than those focusing on a single mechanism or domain. Larger high-quality randomized controlled trials are required to systematically investigate the cognitive effect of programs comprising physical and mental activity as well as nutritional aspects.

Key words: Healthy ageing, multidomain interventions, mental activity, physical activity, diet.

Over the last few years, the population aged 60 years or over has grown faster than any other age group. This increase poses a series of new challenges to our society, such as a rising demand in various forms of health and welfare care. Therefore, there is an urgent need for development of various strategies to help the elderly remain in good physical and mental health, so that they remain independent and continue to play an integral part in the family and community life. The role played by modifiable environmental factors in the prevention of cognitive decline and neurodegenerative diseases such as Alzheimer's disease and other types of dementia is not yet well understood. Yet, the cognitive deficits and behavioral abnormalities associated with this condition are the major cause of disability in the elderly (1). The potential benefit of preventive strategies to support healthy ageing is enormous. It is estimated that delaying the onset of dementia such as Alzheimer's disease by only one year would reduce its prevalence by about 25% (2).

Over the past decade, the notion that cognitive impairment and dementia may result at least in part by a lifelong cumulative effect of different risk and protective factors of genetic, biological and psychosocial origin as well as their interactions has gradually emerged (1, 3, 4). The observation that age is the strongest risk factor for dementia has largely contributed to this view. Indeed, it has been reported that the incidence rate of Alzheimer's disease increases almost exponentially with increasing age until 85 years of age (3). In the United States, Alzheimer's disease has been estimated to affect almost 50% of adults over their lifespan (5), which suggests that dementia may be an inevitable consequence of ageing.

Numerous epidemiological findings indicate that various lifestyle-related factors may play an important role in the development of cognitive impairment and dementia in elderly people. However, randomized controlled trials targeting at modifying single factors, such as cardiovascular disease factors (e.g. hypertension, hypercholesterolemia and diabetes mellitus), physical activity, mental activity, as well as diet and nutrition, often resulted in inconsistent findings or insufficient evidence (for review see for instance (6-8)). Most promising effects were reported for antihypertensive therapy (9-11), intranasal insulin (12, 13), long-term physical activity programs (> 6 months) (14-21), certain mental stimulating activities (speed of processing training and reasoning training) (22), and adherence to Mediterranean diet (23, 24).

Inconsistent findings and the difficulty to demonstrate cognitive effects in single intervention trials may be partly due to methodological limitations. Alternatively, single, isolated intervention approaches may be too simplistic with regard to the complex, multi-factorial nature of cognitive impairment. In view of that, recent observational studies suggest that leisure activities containing multiple components (e.g. mental, physical, and social) may be more beneficial than activities containing only one component (25-27). This development towards multidomain approaches to support healthy cognitive ageing or to slow down cognitive decline can also be observed in study designs of recent intervention trials. In this review, we present an overview of trials that modify simultaneously multiple lifestyle-related factors in healthy elderly subjects or

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in subjects at risk for cognitive impairment to affect cognitive performance and the risk for developing Alzheimer's disease.

Methods

We conducted a non-systematic literature search with no specific criteria for quality assessment in Medline, Scopus, Cochrane Library, and ClinicalTrials databases up to October 2011 to review interventions that investigated lifestyle-related factors and their effects on cognitive performance. Trials were considered appropriate if they included cognitive outcomes, investigated healthy or cognitively impaired older adults and if non-pharmacological interventions aimed at modifying several lifestyle-related factors simultaneously, such as mental stimulation plus physical activity or physical activity plus a nutritional intervention and so on. Search terms were exclusively used in English and comprised for instance "mental health", "cognitive decline", "cognition", "physical activity", "cognitive training", "nutrition", "diet", "social engagement" "lifestyle", "elderly", and combinations thereof.

The search procedure was not systematic and cannot be considered as comprehensive.

Results

Following our literature search, we identified 6 completed and published, non-pharmacological multidomain intervention studies (table 1) as well as 8 ongoing or not yet published, non-pharmacological multidomain intervention studies (table 2) to investigate cognitive effects in elderly people. Hereafter we present a short description of the trials.

Completed Multidomain Trials

Three of the completed multidomain trials investigated physical exercise and cognitive training either alone or in combination. In the SimA study conducted in Germany, 375 healthy elderly subjects aged 75-93 years were assigned into 6 different groups: psychoeducational training, cognitive training, physical training, psychoeducational and physical training, cognitive and physical training, or control group (28, 29). The psychoeducational training focused on various needs (e.g., technical aids in the household, problem solving in everyday life, etc.). The cognitive training focused on information processing speed, attention and memory functions. The physical training consisted in training of balance, perceptual and motor coordination, and flexibility. The training occurred every week over 9 months, and each session lasted between 45-135 minutes depending on the group assignment. Participants were followed up to 5 years. Various domains of outcomes were measured, such as cognitive function (information processing speed, attention, primary and secondary memory, long-term memory and reasoning), physical function, emotional status, independent living, and health status. The authors reported that participants in the combined cognitive and physical training displayed sustained improvements in most domains as compared to the control group. Among the best improvements were those seen in cognitive functions, cognitive impairment, health status and depression. Interestingly, the cognitive outcome measures in the combined cognitive and physical training group appeared to be better than in the single cognitive training group. Similar findings were reported from a small study in France (30). Thirty-two healthy elderly subjects aged 60-76 years were allocated into four different groups: aerobic training, mental training, combined aerobic and mental training, and a control group. The authors reported that 2 months of combined aerobic and mental training provided greater effects on memory scores than either treatment alone. The third cognition and exercise trial, the Seniors Health and Activity Research Program Pilot (SHARP-P), investigated the effect of a 4 month training program in 73 community-dwelling older people aged 70-85 years and at risk for cognitive decline (31). Participants received cognitive training, physical activity sessions or both. The cognitive training consisted of 2 computer-based sessions per week, 40-45 minutes each, and targeted at improving memory and executive functions. The physical activity sessions aimed on aerobic and flexibility training for 150 minutes per week, including 2 centre-based sessions of 60 minutes each and additional home-based training. Participants of the combined intervention received both trainings on the same day. The control intervention comprised weekly health education lectures. Outcome measures included executive functioning, episodic memory, and physical function. No treatment led to statistically significant differences in 4-month changes in cognitive outcomes. For data interpretation it should be considered that the trial was a pilot trial and designed to obtain information on required sample sizes.

Another three completed trials identified for this review included diet-related interventions; two studies in frail elderly people, one in overweight or obese older people with high blood pressure. In a Dutch study, De Jong et al. (32) randomized elderly people aged 70 years and older and at risk of suboptimal micronutrient status, functional decline, and neurological disorders to a 17-week intervention of enriched foods plus a social program, regular foods plus exercise, enriched foods plus exercise, or regular foods plus a social program. In the nutrition condition of enriched foods participants were asked to consume 2 products daily in addition to their regular diet: one fruit-based product and one dairy product. These products delivered 100% of the Dutch recommended dietary allowance of several vitamins and minerals. The exercise program emphasized on muscle strength, coordination, flexibility and speed and lasted 45 minutes, twice a week. The social program focused on creative and social activities. It served as a control for the exercise program and lasted 90 minutes every other week. Outcome measures included psychomotor speed and biochemical indexes. While enriched foods showed positive effects on

Table 1
Overview of completed multidomain intervention trials targeting cognition

Completed Trials							
Study	**Country**	**Design**	**Population**	**Intervention**	**Duration of intervention**	**Outcome measures**	**Results**
SimA	Germany	Randomized controlled trial	Healthy elderly (n = 375)	Psychoeducational training; Cognitive training; Physical training; Psychoeducational and physical training; Cognitive and physical training; Control group	9 months	Cognition; Physical function; Emotional status; Independent living; Health status	Combined physical training and cognitive training improved psychomotor performance and reduced symptoms of dementia which neither treatment alone achieved
Fabre et al.	France	Randomized controlled trial	Healthy elderly (n = 32)	Aerobic training; Mental training; Both combined; Control group	2 months	Physiological measures; Cognition	Combined aerobic and mental training provided greater effects on memory scores that either treatment alone
SHARP-P	US	Randomized controlled pilot trial	Elderly people at risk for cognitive decline (n =73)	Physical training; Cognitive training; Physical and cognitive training	4 months	Cognition; Physical function; Attendance rate	Attendance rates higher in cognitive training groups than in physical training alone; No significant change from baseline in cognition among treatments
De Jong et al.	Netherlands	Randomized controlled trial	Frail elderly (n = 130)	Enriched foods plus social program; Regular foods plus exercise; Enriched foods plus exercise; Regular foods plus social program	17 weeks	Cognition; Biochemical indexes	No effect of either intervention on cognitive measures
Cetin et al.	Turkey	Randomized controlled trial	Elderly people living in retirement homes (n = 43)	Vitamin E supplementation; Exercise; Vitamin E plus exercise; Control group	6 months	Cognitive function (EEG)	Shortened P3 latency values found in both exercise groups with no additive effect of vitamin E supplementation; P3 amplitude values unaltered among all groups
Smith et al.	US	Randomized controlled trial	Overweight/obese elderly with high blood pressure (n = 124)	DASH (Dietary Approaches to Stop Hypertension) diet; DASH diet plus weight management (exercise plus behavior modification); Control group	4 months	Cardiovascular measures; Cognition	Combined DASH diet plus weight management improved executive function, memory, learning measures relative to control group, while the DASH diet alone group did not improve compared to control; Combined DASH diet plus weight management and DASH diet alone improved psychomotor speed measures relative to control group

homocysteine and methylmalonic acids, no significant effects on the neuropsychological tests were yielded for either intervention. The study focused on lowering homocysteine and methylmalonic acid rather than on cognition. Therefore, it may have been underpowered for detecting changes in cognitive functions. A study by Cetin et al. (33) randomized 57 elderly people aged 60 to 85 years and living in retirement homes to vitamin E supplementation, exercise, vitamin E under exercise, or a sedentary control program. The vitamin E dose was 300 mg in capsules, three times a day for 6 months. The aerobic exercise program consisted of 3 walking sessions per week. Cognitive outcome measures were based on event-related brain potentials (ERPs) and included P3 latency which is associated with cognitive function. The authors report P3 latency improvement over baseline in the exercise group. And in the vitamin E plus exercise group, reduced mean P3 latencies were found compared to the control group. The authors therefore conclude that the effect resulted from the exercise component of the program rather than from the vitamin E intake. No additive effect of a combined intervention was demonstrated. A third nutritional intervention trial was conducted in the US. The Dietary Approaches to Stop Hypertension (DASH) diet study investigated a subgroup from the Exercise and Nutrition Interventions for Cardiovascular Health (ENCORE) study of 124 overweight people with elevated blood pressure (34). Participants received the DASH diet intervention or the DASH diet plus behavioural weight management intervention including exercise and caloric restriction for a period of 4 months. Usual care served as control. The DASH diet conditions required participants to follow dietary instructions to meet DASH guidelines. The weight management program consisted of aerobic exercise sessions of 30 minutes each, three times a week, as well as of weekly group counselling sessions. The latter delivered behavioural strategies to lose weight. The cognitive outcomes comprised a variety of tests focusing on executive function, memory, learning and psychomotor speed. The study results showed improved executive function-memory-learning results for DASH plus weight management relative to the control group, while the DASH diet alone group did not improve compared to control. A direct comparison of the DASH diet alone group and the combined group revealed similar improvements for executive function-memory-learning results. Both groups furthermore improved psychomotor speed relative to control. Again, they showed similar improvements when compared directly to one another.

Table 2
Overview of ongoing multidomain intervention trials targeting cognition

Ongoing Trials/Unpublished Results							
Study	**Country**	**Design**	**Population**	**Intervention**	**Duration of intervention**	**Outcome measures**	**Status**
Dr's EXTRA	Finland	Randomized controlled trial	Healthy elderly (n ~ 1500)	Aerobic exercise; Resistance exercise; Diet; Aerobic exercise and diet; Resistance exercise and diet ; Control group	4 years	Endothelial function; Atherosclerosis; Cognitive function; Inflammatory status; Metabolic risk factors; Cardiovascular risk factors	Study completed; No results published yet regarding intervention effects on cognitive function
Passport to Brain Wellness	US	Randomized trial	Healthy elderly (n ~ 60)	Guided behavioral intervention (targets lifestyle factors related to cognitive health, physical and social activities, nutrition); Self-directed behavioral intervention	4 months	Feasibility; Physical activity; Cognition; Social integration; Nutrition	Study completed
Fit Bodies, Fine Minds	Australia	Randomized controlled trial	Healthy elderly (n ~ 99)	Exercise; Exercise and cognitive training; Control group	16 weeks	Cognition; Physical function; Physiological measures; Mood and well-being	
FINGER	Finland	Randomized controlled trial	Elderly people at increased risk for cognitive decline and dementia (n ~ 1200)	Multi-domain (nutritional guidance, exercise; cognitive training, reduction of vascular risk factors); Control group	2 years	Cognitive impairment; Disability, Quality of Life; Vascular and metabolic risk factors; Dietary biomarker level	Currently recruiting; Estimated primary completion date: December 2013
MAX	US	Randomized controlled trial	Elderly people with self-reported memory complaints (n ~ 200)	Aerobic exercise; Mental activity; Aerobic exercise and mental activity; Control (stretching/ educational DVD)	12 weeks	Cognition	Ongoing; Estimated study completion date: December 2011
MAPT	France	Randomized controlled trial	Frail elderly (n ~ 1200)	Omega-3 supplementation; Omega-3 and multi-domain i ntervention (physical exercise, cognitive training, social activities); Placebo; Placebo and multi-domain intervention	3 years	Cognition; Functional capacities	Ongoing; Estimated study completion date: February 2014
SMART	Australia	Randomized controlled trial	Elderly people at risk for cognitive decline (n ~ 132)	Cognitive training; Progressive resistance training; Both combined; Control (stretching/ video quiz)	6 months	Cognition; Independence of function; Brain morphology and biochemistry; Inflammatory markers; Insulin resistance; Physical function; Quality of life	Ongoing
ASPIS	Austria	Randomized controlled trial	Older adults after Ischemic stroke (n ~ 200)	Motivation and lifestyle intervention (medication compliance control, blood pressure checks, diet changes, physical activity); Control group (standard stroke care)	2 years	Cognitive decline; Vascular events; Functional capacities; Quality of life	Ongoing; Estimated study completion date: April 2014

Ongoing Multidomain Trials

Ongoing trials or completed but not yet fully published trials were identified through trial register databases. We identified 8 trials that plan to investigate cognitive outcomes (see table 2).

The Dose-Response to EXercise TRAining (DR's EXTRA) study (ISRCTN45977199), the Passport to Brain Wellness study (ClinicalTrails.gov identifier: NCT00979446), and the Fit Bodies, Fine Minds study (Australian Clinical Trial Register: ACTRN012607000151437) (35) target healthy elderly people with durations of intervention of 4 years, 4 months and 16 weeks, respectively. Planned sample sizes vary between 60 and 1500 participants. The DR's EXTRA study is completed and several results have been published. However, results concerning effects on cognitive functions are still awaited. It was shown from the baseline data of this study that low plasma levels of Brain-Derived Neurotrophic Factor (BDNF) were associated with impaired memory and general cognition in elderly women. As BDNF appears to be increased by various lifestyle factors such as physical exercise and cognitive activity, this finding supports the notion that neurotrophic factors, such as BDNF, may play an important role in the prevention of cognitive decline (36).

Four further trials will investigate multidomain intervention effects in frail elderly or older people at risk for cognitive decline: The Finnish Geriatric Intervention Study to Prevent Cognitive impairment and Disability (FINGER; ClinicalTrials.gov identifier: NCT01041989) study, the Mental Activity and eXercise Trial for Seniors (MAX; ClinicalTrials.gov identifier: NCT00522899) study, the Omega-3 Fatty Acids and/or Multi-domain Intervention in the Prevention of Age-related Cogntive Decline (MAPT; ClinicalTrials.gov identifier: NCT00672685) study and its 2-

year extension of follow-up (MAPT-PLUS; ClinicalTrials.gov identifier:NCT01513252), as well as the Study of Mental Activity and Regular Training (SMART; ANZCTRN12608000489392) (37). Intervention duration varies between 12 weeks (MAX) and 3 years (MAPT), and studies will include between 130 (SMART) and 1200 participants (MAPT, FINGER).

Lastly, the Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke (ASPIS; ClinicalTrials.gov identifier: NCT01109836) investigates a motivation and lifestyle intervention in about 200 adults with symptomatic ischemic stroke. The intervention period is 24 months.

All trials comprise a physical exercise component, 6 out of 8 trials include a cognitive training component (FINGER, MAX, MAPT, SMART, Passport to Brain Wellness, Fit Bodies Fine Minds), and 5 trials have a nutritional or diet change component (DR's EXTRA, FINGER, MAPT, Passport to Brain Wellness, ASPIS).

Discussion

In summary, the complex and multifactorial nature of cognitive decline and dementia led a number of researchers to initiate multidomain interventions to investigate potential additive or synergistic effects of lifestyle-related factors on cognitive performance. While overall findings look promising for lifestyle intervention effects on cognitive performance, additive or synergistic effects could not yet clearly be demonstrated. From 6 completed trials that were included in our review, 4 trials showed positive effects on their cognitive outcomes. Amongst them 3 trials yielded promising results for multidomain interventions, suggesting combined exercise and mental training in healthy elderly for at least 2 months and diet plus weight management in overweight elderly for 4 months to provide positive effects on cognitive outcomes relative to control (28-30). However, based on these findings, no conclusions can be drawn regarding additive or synergistic effects of multiple, simultaneously modified lifestyle factors. Only 2 trials included direct comparisons of multidomain versus single domain interventions. Their findings suggest a greater effects for combined aerobic and mental training than either treatment alone (30), but similar improvements for combined diet plus behavioral weight management and diet alone (34). Future studies to investigate this further would be desirable.

Furthermore, some methodological limitations need to be raised. Various non-standardized programs have been described, differing in duration and possibly in intensity which makes it difficult to compare. In addition, most trials comprise small sample sizes per intervention group. The SHARP-P study was designed to provide benchmarks to calculate required sample sizes for a full scale trial over 4 years. Depending on the outcome and based on their statistical assumptions, the authors projections indicate a minimal randomization of n = 290 per group in a two-armed trial to be required (31). Thus, most of the presented trials in this review may not have been powered to detect cognitive changes. This seems particularly true for those trials that were originally designed to provide information on other, not cognition-related outcomes. Future studies that are statistically adequately powered are needed.

Ongoing multidomain trials presented in this review focus on interventions between 12 weeks and 4 years in healthy elderly participants (50 years or above), frail elderly participants or those with memory complaints. Interestingly, all ongoing trials included in this review consist of a physical exercise component. The registered trials seem to be promising with respect to their sample sizes. The complexity of the multidomain interventions will increase in some of the trials, combining nutritional, cognitive, physical components and including vascular factors or social activities. To detect synergistic or additive effects, direct comparisons of multidomain versus single factor interventions and thus double-controlled trials (single intervention, no intervention) will be of most interest. Results are keenly awaited.

As mentioned previously by several researchers (38), there are many challenges to multidomain interventions. First, subjects willing to modify multiple lifestyle factors are likely to have a higher level of education and better overall health. In these subjects, an effect of the intervention may be difficult to demonstrate. Secondly, it is difficult to define an appropriate control group, especially for physical and cognitive interventions. Third, double blind conditions cannot be maintained with such interventions. Last, if the intervention is based on lifestyle recommendations the behavioural changes cannot be evaluated precisely.

Conclusion

There are currently no curative treatments for cognitive impairment and dementia. Support for roles played by lifestyle factors in the development of such chronic diseases is growing, however large, long-duration, well-designed randomized controlled trials assessing causality are still lacking in this field. Investigating changes in various lifestyle habits simultaneously represents an attractive strategy for the prevention of diseases of multi-factorial origin. This is certainly a challenging task and changing lifestyle habits durably needs considerable individual efforts. Yet, it is important to take up the challenge now in order to be able to delineate clear recommendations in the future for a cost-effective, safe and sustainable solution.

Conflict of Interest: No conflict of interest to declare

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