Facoltà di Medicina e Psicologia

Tesi di dottorato in "Psicologia sociale, dello sviluppo e ricerca educativa"

"The Gray Matter project: modificating lifestyles to prevent dementia"

Stefano Eleuteri
n° matricola: 1047814

Tutor:
Prof. Fabio Lucidi

anno accademico 2017/18

Index:

Introduction

Alzheimer Disease (AD) is already a public health crisis likely to get much worse with the aging of the Baby Boomer generation. AD is irreversible; there is currently no vaccine, and no cure. AD research has provided consistent evidence of significant associations between lifestyle and AD risk, above and beyond the effects of genes. A grassroots movement to engage middle-aged individuals in healthier lifestyles is crucial so that, as a society, we are doing more than just waiting for a cure to eventually be found.

Given the lack of effective pharmacological therapy, prevention interventions may represent a valid option for the treatment of these diseases.

As dementia aetiology is based on different bio-psycho-social factors, prevention strategies for dementia have recently focused on multi-domain interventions of individuals at risk and/or with a normative cognitive level, encouraging the lifestyle change through combined programs of physical activity, cognitive training, nutrition education and social activities (in chapter 1, a narrative review of these studies is presented).

Most of the multidomain intervention aimed on the prevention of cognitive disease are carried on with elderly patients with a mild cognitive decline or on at-risk adult categories.

Caregivers of patients with dementia are considered as an at-risk category. The majority of them (86%) are represented by family members (prominently women) who are also defined as “informal caregivers”. They fulfil their caring-giving role from 7 to 11 h a day on average, up to 10-15 h when clinical conditions worsen 10. Informal caregivers have to cope with physical, psychological and social stressors that affect their health conditions and quality of life negatively (Eleuteri et al., 2016). The burdens of caregiving include many things that have been shown to increase the risk of cognitive decline, including chronic stress, social isolation, depression, decreased physical activity, and a shift in eating habits toward more fast food and processed foods. Studies have shown, for example, that caregivers of Alzheimer's disease patients had lower scores on tests that measure attention, visual processing speeds, and memory than adults of the same age who were not caregivers. Studies also show that greater distress - including disturbed sleep and lack of positive experiences - appeared to account for those differences. Family caregivers have, for these reasons, been repeatedly acknowledged as a chronic stress model, even when their caregiving task finish after the death of the care recipient (Schulz et al., 2008).

For example, literature showed that caregivers partner of patients with Alzheimer’s disease have a greater BMI or gain significantly more weight compared with controls (Vitaliano et al., 1996). This could be connected with the important role that sleep plays between stress and metabolic health (Geiker et al., 2018). Being a caregiver has been found to be a factor affecting negatively sleep quality (Brummett et al., 2006).

Interventions to promote positive lifestyles are, therefore, important in order to improve the caregivers' general health and, specifically, to prevent the cognitive decline.

In the second chapter, an article recently published specifies the importance of multimodal interventions in ameliorating caregivers' health, since complex moderation and mediation effects exist between the different areas involved in the AD risk reduction.

The third chapter will, finally, describe the results of the Gray Matter Project, a multidomain pilot RCT, firstly carried out done in Cache County, Utah designed to promote positive changes in lifestyle (exercise, nutrition, cognitive stimulation, social engagement, stress management, and sleep quality), specifically for the purpose of reducing AD risk in family caregivers of elderly with dementia.

1. Preventing dementia: from the single intervention to the multidomain ones

1.1. Introduction

When it comes to prevention, it is necessary to distinguish: primary prevention, that is an intervention that seeks to reduce the occurrence or the development of a disease; secondary prevention, which points to early detection of an emerging disease, allowing for an early intervention in order to increase treatment options and to halt or to slow disease progression; and, finally, tertiary prevention which focuses on reducing negative impact of an existing disease through restoring function and reducing complications.
The primary prevention of dementia consists in a reduction of potentially modifiable risk factors in terms of lifestyle, diet and management of chronic diseases such as hypertension and diabetes; in the last ten years research has increasingly focused on the cumulative effect and the mutual interaction between genetical, biological and psychosocial risk factors and protective factors (Whalley et al, 2006; Fratiglioni & Qiu, 2009; Qiu et al., 2009).

Factors related to lifestyle represent an area of interest and particularly stimulating research for the prevention of dementia syndromes.

1.2. Interventions of individual domains

Primary prevention interventions on individual domains present a mixed picture, with some positive results but also with many studies lacking of statistical power, proving ineffective or otherwise poorly adapted to the clinical needs of the multifactorial nature of dementia (Olanrewaju et al., 2015). In the next paragraphs, just some interventions on individual domains are showed: in fact many studies have been conducted in the different areas also collected in meta-analyses (i.e. Rakesh et al., 2017; Zeng et al., 2016) and the results have been, obviously, different, based on the methodology of the intervention. The aim of these first paragraphs is, however, to highlight the difference between interventions based on single domains or on multiple ones.

1.2.1. Physical activity

The benefits of physical activity are well documented with regard to aspects related to quality of life and cognitive function in older adults (Barnett et al., 2015). Controversial results have been, however, found between exercise and decreased risk for the development of Alzheimer's Dementia (AD), with, for example, a recent longitudinal study showing a significant association (Larson et al., 2006), while others finding no significant relationships (Sink et al., 2015).

In general, the results of cross-sectional and longitudinal studies with healthy elderly, frail or suffering from cognitive impairment, stress the importance of physical activity in terms of age-related decline of prevention (Bherer et al., 2013); some extensive revisions of the scientific literature report the positive effects of specific strengthening exercises, aerobic exercises, or combinations of them on cognitive decline in older people (Angevaren et al., 2008; Carvalho et al., 2014).

The Longitudinal Aging Study Amsterdam (Visser et al., 2002) found that physical activity and a regular active lifestyle (walking outdoors, cycling, playing home activities, participating in sports activities) are associated with a slowing of cognitive and physical decline, and the resultant reduction of the disability; literature suggests that the positive effects of physical activity in older adults are not revealed only with respect to the strength, endurance, flexibility, balance (Carlson et al., 1999), but also related to the emotional well-being (Netz et al., 2005) and the prevention of disability (Spirduso & Cronin, 2001).

1.2.2. Cognitive Activity

Cognitive interventions that have been conducted in primary prevention of dementia consist of structured practices on tasks considered to be relevant for the aspects of cognitive functioning more interested in an age-related decline (Cavallini et al., 2003; McDougall et al., 2010; Ball et al., 2007; Saczynski et al., 2002); the multi-domain trainings showed greater effectiveness in the short and long term than those with a focus on the exercise of individual cognitive components (Cheng Y. et al., 2012a, Cheng Y et al., 2012b; Rapp et al., 2002; Buiza et al., 2008; Mahncke et al., 2006; Eckroth-Bucher & Siberski, 2009; Basak et al., 2008; Corbett et al., 2015).

In particular, the Advanced Cognitive Training for Independent and Vital Elderly (Jobe et al., 2001) was the first large-scale RCT to carry on a multi-domain 5/6 weeks intervention based on different skill enhancement and memory underlying strategies, reasoning and attention; the combination of 10 sessions for small groups of about 60 minutes and 4 sessions of random reinforcement was significantly valid as regards the improvement of the relative performance and the maintenance of their respective benefits five years (Wolinsky et al., 2010) and ten years later (Rebok et al., 2014).

A large amount of evidence demonstrates that this type of training in healthy and elderly adults correlates with improvements in the specific domains of verbal episodic memory, problem-solving, processing and recognition speed of visual stimuli (Ball et al., 2002), with long term effects in the execution of daily instrumental activities after 5 years (Willis et al., 2006). However, these improvements do not correlate with a significant reduction in the incidence of the disease (Unverzagt et al., 2012).

Similar results have been obtained with combined and simultaneous activities (de Bruin et al., 2013; Theill et al., 2013; Eggenberger et al., 2015; Yokoyama et al., 2015), namely the simultaneous execution of particular cognitive tasks and physical exercises; these activities resulted in significant improvements in the cognitive performance associated with executive functions, verbal and visuospatial abilities.

In general, a Cochrane review highlighted significant improvements in memory and above all in the immediate/delayed recall of both healthy elderly men and the ones with cognitive impairment, following different types of cognitive activities (Martin et al., 2011); other systematic reviews of observational studies and RCT's gave similar results (Mowszowski et al., 2010), although no direct causal relationship between cognitive activities and the reduction of risk of developing AD or dementia has been shown (Papp et al., 2009; Valenzuela & Sachdev, 2009). Moreover, the so-called 'Hawthorne Effect', due to the massive participation of the experimenter in the participants' life for a long time, may be an important factor affecting the generalisability of clinical research to routine practice (McCarney et al., 2007).

1.2.3. Social participation

Only small studies exist in scientific literature regarding the participation to socially stimulating activities as a protection factor against cognitive impairment; moreover, social tasks are most of the times combined with cognitive/physical activities (Fratiglioni et al., 2004).

Literature suggest that exist a complex network of factors where the social interaction is one of the multiple elements characterizing the individual cognitive reserve. The individual cognitive reserve is made up by the combination of intelligence, knowledge and learning assimilated over a lifetime and is also influenced by education, job satisfaction and frequency of free-time activities (Stern, 2009; Smart et al., 2014); referring to this perspective, social participation could contribute to the pathogenesis and progression of dementia contrasting with the negative effects of solitude and social isolation on the incidence of the disease (Wilson et al., 2007).

Individual studies demonstrated that the frequency of social activities connected with voluntary work (Fried et al., 2004), participative problem solving (Stine-Morrow et al., 2008), group psychosocial activities (Pitkala et al., 2011), arts in general (Noice et al., 2013) and meditation (Wahbeh et al., 2014), correlates with a better cognitive function and a reduction of the risk of developing dementia (Scarmeas et al., 2001; Karp et al., 2006); however, a coordinated analysis of four longitudinal studies on different populations did not find significant improvements in memory, semantic knowledge and reasoning, except for verbal fluence (Brown et al., 2012).

1.2.4. Diet

In the last 15 years, a large number of empirical evidence demonstrated that a high adherence to the Mediterranean diet correlates with a significant slowing in cognitive decline associated with a lower rate of conversion to AD and with the improvement in specific cognitive domains of memory (delayed recognition, long-term memory, working memory), executive functions and visuo-constructive abilities (Wengreen et al., 2013; Hardman et al., 2016).

In this field, clinical trials focused mainly on the administration of single nutrients rather than on the promotion of complex nutritional patterns (Olanrewaju et al., 2015). The latter are designed for the wider context of the prevention, for example, of cardiovascular disease; in this field, a combination of nutritional modifications, caloric restriction and physical exercise gave positive effects in terms of arterial pressure control and improvement of specific neurocognitive functions (selective attention, verbal memory, psychomotor speed) of hypertensive, sedentary and overweight adults (Smith et al., 2010).

Current epidemiological data have recognized the protective role of some micronutrients (vitamins B related to homocysteine metabolism, antioxidant vitamins C and E, flavonoids, omega-3 polyunsaturated fatty acids, vitamin D) and some macronutrients (fish) in the prevention of dementia. However, the literature is not still so convergent with the significant effect of diet in preventing dementia (Gillette-Guyonnet et al., 2013; Rathod et al., 2016). Some works have shown the positive effect that the increase of the fatty acids to omega-3 long chain have in the health enforcement of senior people functions, especially in the verbal fluency (Witte et al., 2014) and of senior people with cognitive decline (Chiu et al., 2008). Nevertheless, the results of experimental research using these nutrients were in most cases inconclusive with cognitively healthy subjects (Dangour et al., 2010), with Mild Cognitive Impairment subjects underwent nutritional interventions combined with aerobic and/or cognitive training (Kobe et al., 2016), and with frail elders undergoing nutritional interventions associated with physical and/or social training (de Jong et al., 2001).

Vitamin E supplements did not produce interesting results on the cognitive functions of senior people (Cetin et al., 2010); the same is showed for the PREDIMED-NAVARRE, nutritional intervention based on the supplementation of extra-virgin olive oil that did not find significant differences between the cognitive domains of experimental and control subjects. It was, interestingly, found a better cognitive functioning in the long term in the experimental group (Martinez-LaPiscina et al., 2013).

1.3. Multi-domain interventions

Prevention strategies for dementia have recently focused on multi-domain interventions of individuals at risk and/or with a normative cognitive level, encouraging the lifestyle change through combined programs of physical activity, cognitive training, nutrition education and social activities (Table 1). Multi-domain means that at least two different interventions in different areas have been consecutively carried out. For this reason, future models for prevention should be multimodal, characterized by a heterogeneous combination of exercises, different from each other but synergistically involved in the same dementing processes, and by the presence of a fascinating environment, stimulating and personally considered as important, able to promote the achievement of also long-term personal goals (Fissler et al., 2013).

Given the recognized multifactorial etiology of dementia, the report by the National Institutes of Health (2011) recommends to conduct Clinical Trials Randomized with multidimensional interventions on high-risk individuals; hence the growing interest in multivariate and multimodal approaches that are the focus of this work.

Recent observational studies precisely suggest that the presence of cognitive components, physical and social activities slow cognitive decline and support healthy aging (Karp et al., 2006; Paillard-Borg et al., 2009; Akbaraly et al., 2009); an active lifestyle, as difficult to theorize due to the enormous variety of its constituent elements, seems to trigger, especially in those at risk, a number of long-term changes in the global cognitive functioning and memory that significantly differ from short-term effects of training interventions on specific activities (Küster et al., 2016).

Multi-domain interventions act on more risk factors at the same time, given the complex nature of dementia and interaction with specific protective factors such as education, environmental stimulation and physical/cognitive/social activities, that in many epidemiological studies have been associated with a reduced risk of cognitive impairment (Langa et al., 2008; Schrijvers et al, 2012); these approaches aim to encourage a range of behavioral changes through the simultaneous consideration of the components that influence individual lifestyles (Lustig et al., 2009).

In recent years, two systematic reviews of the scientific literature have shown that the combination of certain physical exercises (strength, strengthening, balance) with cognitive tasks focused on specific skills (attention, executive function, working memory), produce greater cognitive benefits than those resulting from activities on just one domain (Bamidis et al., 2014; Lauenroth et al., 2016).

In particular, the study of Fabre et al. (2002) compared the effects of aerobic and mental training on cognitive function, showing the better effects in the association of the two techniques on cognitive performance of elderly subjects not suffering from any form of dementia.

The study by Oswald et al. (2006), in the same way, has found that a combined physical and cognitive treatment is accompanied by a series of long-term positive effect on cognitive physical and emotional domains. In fact, after five years, they noted substantial improvements in some cognitive functions (primary/secondary/long term memory, attention, reasoning, processing speed), in the perceived and functional autonomy levels of health status of people doing a combined cognitive and physical training, compared to the ones who have been administered a single physical and psycho-educational group training, or a physical training or a cognitive training. Other studies, by contrast, showed no significant differences between the combined or single experimental groups, even if giving evidence of the positive effects of interaction between cognitive intervention, single or combined with other physical exercises, and subsequent individual performance of non-demented elderly (Barnes et al., 2013; Legault et al., 2011; Shatil, 2013), or between physical training, single or combined with nutritional elements, and reduced risk of developing dementia (Komulainen et al., 2010).

Combined efforts of this kind have, as target group, not only cognitively healthy subjects, but also people at risk for cognitive decline and cardiovascular or metabolic comorbidities. From this perspective, a series of studies have been conducted to examine the potential benefits of encouraging healthier lifestyles of patients with mild cognitive impairment (MCI); combined training have been associated to a set of positive changes in cognitive scores at 12-months after the end of the trial and in the absence of functional improvements in the everyday autonomy (Lam et al., 2015), while in other cases there have not been significant differences in global cognition and executive function compared to other experimental groups (Singh et al., 2014).

Therefore, over the course of time, it has been outlined the need for interventions based on lifestyle change, promoting a healthy ageing in order to reduce the risk of dementia in the population; physical or cognitive tests, usually based on the involvement of limited skills for a fixed period of time, have been incorporated into a complex program of lifestyle changes.

These programs aim to involve subjects in a series of activities diversified with each other and try to integrate the behavioral changes in the life of every day, supporting them long-term and thus reinforcing the protective effect of the cognitive reserve (CR), as occurred in the trial AKTIVA (Tesky et al., 2011): in this case, participation in cognitively stimulating activities (read, play chess, play), even when combined with physical training and nutritional counseling, proved to have a crucial importance for the promotion of an active lifestyle and healthy ageing. The same study has been replicated later in patients with MCI; Results suggest that cognitive stimulation therapy is feasible for patients with MCI (Tesky et al., 2017). The AKTIVA-MCI program gives motivational support and indicates that it is never too late to start participating in (new) activities. Analysis of the daily activity protocols showed some interesting and significant behavioral modifications. However, results should be interpreted carefully because of the small sample size. Replications with a representative sample and improved methodology (eg, control group) are clearly needed.

Among the programs addressed to non-demented elderly, some interventions have sought to promote the achievement of personally meaningful goals in physical activity, cognitive activity, diet and health in general through a goal-setting approach, with or without telephone tutoring. The results have shown significant short-term improvements in memory, executive functioning, cholesterol levels in the aerobic capacity and physical agility, also confirmed at 12 months follow-up (Clare et al., 2015); other studies have relied on an employment approach, both in the study of

Pieramico and colleagues (2012) who, through the combined stimulation of cognitive (sudoku, puzzles, virtual game, listening to music), physical (dance) and social activity (discussion groups), have reported improvements in memory and information processing strategies with subsequent structural reorganization of the brain, and in the research conducted by Clark and colleagues (2012) via the protocol Lifestyle Redesign (Jackson et al., 1998). Positive effects were found on some cognitive domains (immediate/delayed recall, recognition, psychomotor speed) and on the more general state of health the elders involved.

Also the pilot study carried out by Norton and colleagues (2015) proposed a multimodal intervention for adults at risk for dementia in the context of some specific domains, including physical activity, cognitive stimulation, social engagement, diet, sleep and stress management; in this case the use of technological devices (smartphone app and Nike Fuel Band) and educational/informational materials, has proved to be useful for the promotion of a series of behavioral changes associated with preventive and healthy lifestyle.

Some interventions of health promotion and prevention of dementia have also involved the subjects with MCI in a series of cognitively, physically and socially stimulating activities, showing significant improvements in working memory and in health, in terms of body mass index reduction, and better both blood pressure and heart rate at rest/under stress (Dannhauser et al., 2014); similarly, the participation of potentially at risk individuals to on-line training programs, based on short-term achievement of specific objectives for cognitive stimulation, physical activity, social engagement, diet, chronic disease management and recognition of risk/protection factors, has proved to be effective in the increase of some healthy behaviors such as the consumption of fish and cognitive engagement, with a relative reduction of individual risk profile (Anstey et al., 2015). The Prevention of Vascular Dementia by Intensive Care (PREDIVA) can be considered the largest and long-lived randomized primary prevention of 3,526 older people from 70-78 years old and cognitively healthy (Richard et al., 2009). Elderly people were administered for six years a control treatment and monitoring of cardiovascular risk medical conditions (blood pressure, blood lipid levels and glucose) or a combined treatment of medical assessment and intervention on lifestyles (exercise, smoking, weight, diet). The results, discussed in the

Alzheimer's Association International Conference in 2016 in Toronto, reported no significant differences between the groups with respect to the incidence of AD, with the exception of a subset of people with untreated hypertension; however, clinically significant effects emerged between the groups with regard to the incidence of dementias other than Alzheimer's (van Charante et al., 2016).

The Multidomain Alzheimer Preventive Trial involved 1,680 frail elderly ≥70 years in a multi-domain intervention based on group sessions and individual interviews, which have focused on cognitive stimulation (reasoning and strategies mnemonic applicable to everyday problems), physical activity (encouragement to perform at least 150 minutes of moderately intense physical activity per week) and nutritional recommendations for healthy eating. The MAPT has investigated the effects of this intervention on their cognitive performance in 3 years, it was completed in March 2014 and provides for a follow-up at 5 years (Gillette-Guyonnet et al., 2009); the study results presented for the first time during the Clinical Trial Conference in Alzheimer's Disease (2015) in Barcelona, when the authors have reported significant improvements in the group receiving the administration of supplements of omega-3 fatty acids combined with the multi-domain intervention, both in the cognitive performance and in cerebral glucose metabolism. The results of MAPT showed no significant effects with any of the three treatment interventions compared with placebo on the primary outcomes, the 15 secondary outcomes (except for one comparison of combined intervention with placebo on the ten item Mini-Mental State Examination, p= .036), or on five of seven prespecified and exploratory subgroup analyses, which compared a multidomain intervention combined with omega 3 polyunsaturated fatty acids or placebo, or omega 3 capsules alone, against placebo capsules in old adults with memory complaints. Analyses showing significant effects favoured multidomain intervention with omega 3 versus placebo in a subgroup at high risk for dementia (based on Cardiovascular Risk Factors, Aging, and Incidence of Dementia [CAIDE] score), but with a small effect size (d= .131), and multidomain intervention (with either omega 3 or placebo) for amyloid-PET positive subgroups of 16 and 23 participants (Coley, Andrieu, 2017).

Ultimately, randomized controlled trials are critically important to assess the impact of multi-domain intervention on reducing risk factors related to impairment and cognitive decline; studies analyzed give important suggestions regarding the most effective behavioral modification strategies for dementia prevention.

This kind of interventions in pre-clinical phase proves to be low cost, low risk, and versatile for different populations; therefore, they have a huge potential in terms of health promotion mainly expressed when the regular practice of physical activity and cognitive activity takes place in a socially stimulating environment, capable of promoting the involvement and adherence to experimental programs.

Participating to such interventions seems to help people in decreasing depressive symptoms, modulating negative perceptions about their performance and increasing psychological wellbeing levels, especially for combined trainings (Legault et al., 2011, Shatil et al., 2013).

Lifestyle modification interventions adapt flexibly to the needs of the target population; generally, there is an alternation of individual sessions and small group sessions (group involves 6-10 people), with sessions lasting about 60 to 90 minutes for a maximum of three times a week. The theoretical discussion of specific topics is accompanied by practical activities requiring a personal, daily commitment and being, often, monitored by a telephone or technological software. Even if the most significant results were obtained in a context of cognitive trainings combined with aerobic physical component (Table 1), it is still not possible with the evidence emerged to plan the type and the duration of a protocol that can guarantee more effectiveness. Some studies have shown behavioral and morpho-functional improvements in the short term of 2-6 months (Fabre et al., 2002; Pieramico et al., 2012; Dannhauser et al., 2014; Clark et al., 2012; Anstey et al., 2015; Norton et al., 2015), others showed significant effects with longer times (Oswald et al., 2006; Tesky et al., 2011; Lam et al., 2015; Ngandu et al., 2015), others have clearly highlighted the need for larger samples or intervention service for more than six months (Legault et al., 2011; Barnes et al., 2013).

Table 1 – Overview of completed multi-domain intervention trials targeting cognition

Study	Country	Design	Sample	Intervention	Duration of intervention	Outcome measures	Follow-up	Results
Anstey et al., 2015	Australia	Randomized controlled trial	176 subjects at risk for cognitive impaiment (aged 50-60 years)	• Individual multidomain intervention (Body Brain Life: website with modules focused on physical activity, cognitive stimulation, social engagement, diet, management of chroninc conditions) • Multidomain intervention (Body Brain Life) + group sessions (discussions of the various risk factors for dementia, goal setting, and barriers to behavior change) • Control group (general informations about dementia,health and lifestyle)	12 weeks	Alzheimer's Disease Risk Index (ANU-ADRI) • Recognition of risk/protective factors for dementia (vignette)	26 weeks	Significant reduction of ANU-ADRI score in the experimental groups with relative increase of fish consumption and frequency of cognitively stimulating activities Improvement in the recognition of the risk and protective factors for dementia in both experimental groups
Barnes et al., 2013	U.S.A.	Randomized controlled trial (factorial design 2x2)	126 inactive elderly people with cognitive complaints (mean age of 73.4)	• Home-based mental activity intervention (computerized tasks) • Mental activity control group (educational lectures on art, history, and science) • Class-based exercise intervention (aerobic, stretching and toning exercise) • Exercise control group (Stretching and toning exercises)	12 weeks	• Global cognitive performance (RAVLT, verbal fluency,processing speed, executive function,attention, UFOV) • Physical performance (Senior Fitness Test)		Improvements in global cognitive performance with no evidence of difference between groups (the score in UFOV test is the only one to differ significantly between the mental activity intervention group and the related control group) No significance of difference between groups in the physical performance scores

Clare et al., 2015	United Kingdom	Randomized controlled trial	75 healthy elderly people (aged 51-84 years)	• Goal-setting intervention (behaviour change goals relating to physical, cognitive and social activity, health and nutrition) • Goal setting intervention with telephone mentoring • Control group (General informations about activities and health)	12 months	• Physical activity (PASE) and cognitive activity (FCAS) • Physical performance (SFT), cognitive performance (MoCA, immediate/ delayed recall, executive function, fluency), depression (CES-D), wellness (GSES), diet (MEDAS), health status		The two goal-setting groups, taken together increased their level of physical and cognitive activity relative to controls. The two goal-setting groups taken together achieved additional benefits compared to control in memory, executive function, cholesterol level, aerobic capacity, flexibility, balance, grip strength, and agility. In addition, the goal-setting intervention with mentoring produced further benefits compared to goal-setting alone in physical activity, body composition, global cognition and memory, but not in other domains. No significance of difference between groups in psychological well-being
Clark et al., 2012	U.S.A.	Randomized controlled trial	460 healty elderly people (aged 60-95 years)	• Occupational therapy intervention (Lifestyle Redisign protocol: behaviour change goals relating to physical, cognitive and social activity,health and everyday life) • Control group (no treatment condition)	6 months	• Cognitive performance (immediate/ delayed recall, recognition, attention, processing speed) • Health status (SF-36), life satisfaction (LSI-Z), depression (CES-D)		For mental and physical well-being, all outcomes reflected positive change; among the cognitive variables, significant pre-to-post improvement was found for immediate recall, delayed recall, recognition and psychomotor speed. Significant benefit due to the lifestyle intervention for SF-36, LSI-Z and CES-D
Coley, Andrieu, 2017	France	Randomized controlled trial	1,680 frail elderly people ≥70 years	• Integration omega-3 fatty acids • Multi-domain intervention (cognitive training, physical exercise, diet) • Integration fatty acids omega-3 and multi-domain intervention • Placebo	3 years	• Cognitive Functioning (FCRST) • Cognitive Performance (COWAT; CNT; Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised; TMT; MMSE, CDR), functional status, mood, adheren	5 years	Improvements in glucose brain metabolism in the group with integration omega-3 fatty acids and multi-domain intervention. No differences in brain volume, hippocampus, gray matter.

						ce to the program, cost/benefit ratio, functional neuroimaging		
Dannhauser et al., 2014	United Kingdom	Randomized controlled trial	70 elderly people with MCI (aged 65-81 years)	• Multi-domain intervention (ThinkingFit: doing something different, physical activity program, individual cognitive stimulation using Lumosity software and group-based cognitive stimulation) • Control (12-week assessment phase before the intervention)	24 weeks	• Cognitive performance (working memory, TMT, verbal/category fluency, digit span forwards and backwards), exercise performance (cardiovascular fitness), health status (BMI, blood pressure), quality of life	6, 12 weeks	Significant treatment effects were evident on physical health measures (decreased body mass index and systolic blood pressure), fitness measures (decreased resting and recovery heart rate), and cognition (backwards digit span). Other treatment effects showed an improvement of quality of life, letter fluency and forward digit span
Fabre et al., 2002	France	Randomized controlled trial	32 healthy elderly people (aged 60-76 years)	• Physical training (aerobic exercise) • Mental training • Mental + physical training • Control group	2 months	• Cognitive problems (BEC 96) and mnesic deterioration (WMS) • Depression, quality of life		The memory quotient obtained from the WMS was significantly improved in all trained groups, especially in the group of mental + physical training. Values in the category of functional life, such as fitness, dyspnea and tiredness, were significantly improved in the physical training group and mental + physical training group, in which the highest levels of satisfaction are shown. No significance of difference between groups in BEC96 scores
Fiataron e et al., 2014	Australia	Randomized controlled trial	132 elderly people ≥ 55 years with MCI	• Computer-based cognitive training (Cogpack: program for MCI subjects) • Cognitive control group (educational DVD on art, history, culture) • Physical training (progressive resistance exercises) • Physical control group (stretching exercises, gymnastics in the seated position) • Cognitive + physical training • Cognitive + physical control group	6 months	• Alzheimer's disease assessment scale (ADAS-Cog), functional independence (B-ADL) •Neuropsychological test (immediate/delayed memory, attention, fluency, processing speed, executive function, global cognitive domain)	18 months	Resistance training significantly improved the primary outcome ADAS-Cog at 6 months and executive function at18 months. Cognitive training only attenuated the decline in Memory Domain at 6 months. Improvement in global cognitive domain in the whole cohort over 6 months, with no group differences, and after 18 months in the physical training group
Komulainen et al., 2010	Finland	Randomized controlled trial	1335 healty elderly people (aged 57-78 years)	• Aerobic physical training • Resistance physical training • Diet (nutritional counseling)	4 years	•Neuropsychological battery for immediate/delayed memory,	2 years	No significant differences between groups in cognitive performance Secondary analyzes suggest that higher levels of exercise are associated with low risk of developing impaired delayed memory

				• Aerobic physical training + diet • Resistance physical training + diet • Control group		verbal/visual performance, MMSE (CERAD) • physical performance (MET), nutritional diary, depression (CES-D)		
Lam et al., 2015	China	Randomized controlled trial	555 elderly people ≥ 60 years with MCI with multiple-domain/single-domain deficit	• Cognitive training (board games, reading newspapers) • Physical training (aerobic, stretching, toning exercise) • Cognitive + physical training • Social activities (watching movies, group discussions) • Control group (Tai Chi)	12 months	• Dementia rating scale (CDR-SOB) • Alzheimer's disease assessment scale (ADAS-Cog), delayed recall, verbal fluency, MMSE, functional autonomy (DAD-IADL)		All experimental groups showed improvements in ADAS-Cog scale, delayed recall and verbal fluency. Secondary analyzes suggest that cognitive + physical training is associated with better performance in ADAS-Cog scale, delayed recall and verbal fluency in subjects with MCI with single-domain deficit. No change in CDR-SOB and DAD-IADL scores across time and intervention groups
Legault et al., 2011	U.S.A.	Randomized controlled trial	73 elderly people at risk for cognitive decline (aged 70-85 years)	• Cognitive training (computer exercises) • Physical training (aerobics) • Cognitive + physical training • Psychoeducational control group (Healthy Aging Education: lectures based on health education)	4 months	• Combined and specific cognitive performance (episodic memory, executive functions)		The interventions produced marked changes in cognitive and physical performance with no significant differences in composite scores of cognitive, executive, and episodic memory function. Improvements in the composite measure increased with age among participants assigned to physical activity training but decreased with age for other participants
Ngandu et al., 2015	Finland	Randomized controlled trial	1260 elderly people at risk for dementia (aged 60-78 years)	• Multi-domain intervention (cognitive training, physical exercise, social activities, diet, vascular risk monitoring) • Control group (general health advice)	24 months	• Global Cognitive Performance (mNBT) • Specific cognitive performance (executive function, processing speed, memory), incidence of AD/dementia, disability, cardio-vascular risk factors, depressive symptoms	7 years	Significant beneficial effect of the intervention for the global cognitive performance. Significant intervention effect for executive function and processing speed, BMI, dietary habits, physical activity. Risk of cognitive decline was increased in the control group compared with intervention group for NTB total score, executive functioning and processing speed
Norton et al., 2015	U.S.A.	Randomized controlled trial	146 healty people (aged 40-64 years)	• Multi-domain intervention with smartphone application, activity monitor Nike FuelBand and educational materials (physical	6 months	•Neuropsychological testing (MoCA, RAVLT, working memory, executive		Promising trend toward increases in the engagement of positive behaviors and reduction in adverse self-reports among treatment group participants

				exercise, cognitive stimulation, social engagement, food choice, sleep quality, stress management) • Control group (educational materials)		function, fluency, processing speed), biomarker (BMI), depression (CES-D), sleep (PSQI), diet (DHQ), psychological stress (PSS), motivation (SIMS), dietary pattern, metacognition, social engagement (NIH Toolbox)		
Oswald et al., 2006	Germany	Randomized controlled trial	375 healthy elderly people (aged 75-93 years)	• Cognitive Training • Physical Training (balance, coordination, flexibility) • Psychoeducational training (lectures, group discussions, role plays, problem solving) • Cognitive+ physical training • Physical + psychoeducational training • Control group (no-treatment condition)	30 weeks	• Cognitive function (processing speed, attention, reasoning, primary, secondary and long-term memory) • Cognitive impairment (SCAG) • Physical function (coordination, flexibility, agility, strength, balance) • Depression (SDS) • Independent living, health status, well-being (NAI)	5 years	Participants in the memory training experienced an improvement in cognitive function, and members of the combined physical + psychoeducational training improved in independent living and everyday competence. Participants in the cognitive + physical training experienced an improvement in cognitive function, physical function, emotional state and independent living. After 5 years: The members of the combined cognitive + physical training experienced the largest number of signicant and sustained training gains (cognitive performance, physical performance, emotional status, independent living, health and well-being). Symptoms of cognitive impairment were far less pronounced among the members of the combined cognitive and physical training than among the members of the no-treatment control group.
Pieramico et al., 2012	Italy	Randomized controlled trial	30 healty elderly people (aged 60-75 years)	• Multi-domain intervention (cognitive training, aerobic exercise, musical stimulation, fun-recreational activities) • Control group (no-treatment condition)	6 months	• Cognitive Performance (MMSE, immediate/ delayed memory, executive function, fluency, motor skills) • fMRI		The trained group showed enhanced performance in prose memory test scores and motor skills. No significance of difference between groups in cognitive performance compared to MMSE, executive function and fluency. Positive correlations between neuropsychological results and fMRI with benefits on the modulation of functional connectivity and better performance in ADL activities.
Shatil et al., 2013	U.S.A.	Randomized controlled trial	180 healthy elderly people (aged 65-	• Cognitive training (CogniFit) • Mild aerobic training (Senior	4 months	• CogniFit neuropsychological evaluation		Partecipants who received cognitive training improved on several verbal and non-verbal cognitive abilities (hand-eye coordination, working memory, long-term memory, speed of information processing, visual scanning, naming).

			93 years)	Fitness Forever Exercise Video: aerobic exercises) • Cognitive + mild aerobic training • Control group (book reading activity)		(memory, attention, executive function)		Secondary analyzes suggest that fewer significant improvements are observed in the combined intervention group.
Tesky et al., 2011	Germany	Randomized controlled trial	307 healthy elderly people (aged 65-79 years)	• AKTIVA Intervention (cognitive stimulating leisure activities) • Intervention AKTIVA + physical training (aerobic exercise, yoga) and diet (nutritional counseling) • Control group (no intervention condition)	31 weeks	• Frequency of cognitive stimulating activities • Cognitive Performance (MMSE, ADAS-Cog, CDR, TMT), depression (SDS), perceived cognitive decline (MAC-Q), quality of life	32 weeks	Participation in the group program resulted in positive effects on cognitive function and attitude toward aging for subassembly groups. AKTIVA enhanced the frequency of activities for leisure activities for subassembly groups. Secondary analyzes suggest that older persons (≥75 years) showed enhanced speed of information processing; younger participants (≤75 years) showed an improvement in subjective memory decline.
Tesky et al., 2017	Germany	Randomized controlled trial	29 people with MCI (aged 65-79 years)	• AKTIVA Intervention (cognitive stimulating leisure activities) • Intervention AKTIVA + physical training (aerobic exercise, yoga) and diet (nutritional counseling) • Control group (no intervention condition)	24 weeks	Cognition (MMSE, ADAS-Cog), mood (SDS), subjective memory decline (MAC-Q, NSL), attitude to old age (PGCMS, LBZ), feasibility of the training program (evaluation questionnaire) and the frequency of participation in cognitively stimulating activities (activity protocols)	24 weeks	Results suggest that cognitive stimulation therapy is feasible for patients with MCI. The AKTIVA-MCI program gives motivational support and indicates that it is never too late to start participating in (new) activities. Analysis of the daily activity protocols showed some interesting and significant behavioral modifications. However, results should be interpreted carefully because of the small sample size. Replications with a representative sample and improved methodology (eg, control group) are clearly needed.
van Charante et al., 2016	Netherlands	Randomized controlled trial	3526 healthy elderly people (aged 70-78 years)	• Multi-domain intervention (exercise, smoking, control weight, diet) • Medical check-up (blood pressure, glucose, lipids)	6 years	• AD incidence and disability (ALDS) • Mortality, incidence of cardiovascular events, cognitive functioning (MMSE, VAT), mood	2, 4, 6 years	No differences between groups in incidence of AD and disability No differences between groups in incidence of cardiovascular events

1.3.1. Ongoing multi-domain interventions

In the field of prevention of dementia, the most important intervention studies currently underway are: FINGER, HATICE, MIND-AD (Table 2). All these studies are testing, in elderly with normative cognitive functions, the short-term effects of multimodal interventions to encourage change in their lifestyle with combined programs of cognitive training, physical activity, nutrition education and social participation. Long-term effects like the incidence of Alzheimer's or other forms of dementia are also taken into account; among many still open questions, one of the great controversy is concerning the possible existence of a critical window to implement these measures and if specific risk factors and/or protective factors may have a different weight based on age (Sindi et al ., 2015).

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability is a multi-center study of dementia prevention of at-risk elderly who evaluated the effects of a multi-domain intervention characterized by intensive monitoring of cardiovascular risk factors, combined with computerized cognitive, physical, nutritional and social training (Kivipelto et al., 2013); individual and group sessions alternated theoretical discussions to practical experiences in the cognitive (episodic memory, working memory, executive functions, mental speed), physical (aerobic exercises, muscle strengthening, improving postural balance), nutritional (guide to a balanced diet) and social domain (participation in stimulating activities). The two-year project was completed in spring 2014 and has reported a low dropout rate (11%) with an improvement of more than 25% in the overall cognitive performance of the experimental group, compared to a risk of deterioration over 31% in the control group (Ngandu et al., 2015); currently there is an ongoing follow-up at 7 years to determine the actual incidence of long-term dementia or AD.

Based on the obvious similarities between the projects listed above, a European network called European Dementia Prevention Initiative has recently been established, which promoted collaboration between the research groups involved in different dementia prevention initiatives (Sindi et al., 2015).

The vast experience of the most important preventive RCT research team (Finger, MAPT, PreDiva) has just joined a new multinational study to be held in France, Finland and the Netherlands, to design a new strategy of Internet speech-based, functional to the prevention of cardiovascular disease and dementia; the Healthy Ageing Through Internet Counselling for the Elderly (HATICE) will have a duration of 18 months, will include approximately 2600 elderly ≥65 years at risk and will use an internet access interactive platform, in order to promote proper management of personal factors risk and adherence to lifestyle associated with a reduced incidence of dementia (Richard et al., 2016). More recently, a new experimental proposal was launched, currently funded by the Joint Programme - Neurodegenerative Disease Research (2013). The MIND-AD project is based on data collected in European clinical trials mentioned above and aims to harmonize the methods of intervention, identifying the most effective prevention strategies in the prodromal stages of dementia and then adapt them to different health systems.

Table 2 – Overview of ongoing multi-domain intervention trials targeting cognition

Study	Country	Design	Sample	Intervention	Duration of intervention	Outcome measures	Status	Follow-up	Results
FINGER	Finland	Randomized controlled trial	1260 elderly people at risk for dementia (aged 60-78 years)	• Multi-domain intervention (cognitive training, physical exercise, social activities, diet, vascular risk monitoring) • Control group (general health advice)	2 years	• Global Cognitive Performance (mNBT) • Specific cognitive performance (executive function, processing speed, memory), incidence of AD/dementia, disability, cardio-vascular risk factors, depressive symptoms	Completed, follow-up underway	7 years	Significant beneficial effect of the intervention for the global cognitive performance. Significant intervention effect for executive function and processing speed, BMI, dietary habits, psuysical activity. Risk of cognitive decline was increased in the control group compared with intervention group for NTB total score, executive functioning and processing speed.
HATICE	France, Finland, Netherlands	Randomized controlled trial	2600 at-elderly people ≥65 years at risk for dementia	• Computerized platform with interactive access and remote support of an operator • Computerized platform with basic health information	18 months	• Blood pressure, density lipoproteins, body mass index • Mortality, incidence of cardiovascular events, effects on risk factors, cognitive functioning, mood, cost / benefit ratio	Ongoing		
MIND-AD	Sweden, Finland, France, Netherlands, Germany	Randomized controlled trial	Subjects in prodromal phase of dementia	•Multi-domain computer Intervention • Control	3 years		Protocol being defined		

2. Caregiver of people with dementia lifestyles: sleep quality as predictor of BMI in the non-depressed sample

*This chapter has been modified from the article **Sleep quality as predictor of BMI in non-depressed caregivers of people with dementia** published in **Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, October 2018, Volume 23, Issue 5, pp 553–560**

2.1 Introduction

Caregivers of patients with dementia are considered an at-risk category regarding dementia. They fulfil their caring-giving role from 7 to 11 hours a day on average, up to 10-15 hours when clinical conditions worsen. Informal caregivers have to cope with physical, psychological and social stressors that affect their health conditions and quality of life negatively (Eleuteri et al., 2016).

The burdens of caregiving include many things that have been shown to increase the risk of cognitive decline, including chronic stress, social isolation, depression, decreased physical activity, and a shift in eating habits toward more fast food and processed foods. Studies have shown, for example, that caregivers of Alzheimer's disease patients had lower scores on tests that measure attention, visual processing speeds, and memory than adults of the same age who were not caregivers. Studies also show that greater distress - including disturbed sleep and lack of positive experiences - appeared to account for those differences. Family caregivers have, for these reasons, been repeatedly acknowledged as a chronic stress model, even when their caregiving task finish after the death of the care recipient (Schulz et al., 2008).

For example, literature showed that caregivers partner of patients with Alzheimer's disease have a greater BMI or gain significantly more weight compared with controls (Vitaliano et al., 1996). This could be connected with the important role that sleep plays between stress and metabolic health (Geiker et al., 2018). Being a caregiver has been found to be a factor affecting negatively sleep quality (Brummett et al., 2006).

Interventions to promote positive lifestyles are, therefore, important in order to improve the caregivers' general health and, specifically, to prevent the cognitive decline. The duration and quality of sleep are essential for a healthy weight. In recent decades, there has been increased interest in understanding the potential pathway, whereby poor sleep quality may affect obesity risk, particularly in the context of a worldwide obesity epidemic. However, the vast majority of the literature on this topic is focused on populations of children and younger adults (Norton et al., 2018). The Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society advises that adults need at least 7 hours of sleep each night. The literature clearly show that people who sleep habitually fewer than 7 hours per night have a higher obesity risk compared to people who sleep more (Kohatsu et al., 2006; Gottlieb et al., 2005). Most studies carried out on children and adolescents have found a link between short sleep duration and obesity (Chaput & Dutil, 2016), while studies on adults are not consistent, with some researches having found a correlation and others not (e.g., Pilcher et al., 1997). For example, also too much sleep in some researches has been associated with higher obesity risk (Chaput et al., 2008; Gooneratne & Vitiello, 2014), while others reported an inverse correlation (Beccuti & Pannain, 2011).

Magee and colleagues (2010) have found both short and long sleep being associated with a greater obesity risk, suggesting a U-shaped association. A recent narrative review suggested also that a U-shaped pattern is often reported in researches considering the association between obesity and sleep duration in older adults (Norton et al., 2018).

Between the possible for the U-shaped association, we can enumerate comorbidities with other psychiatric disorders or the presence of depressive mood that could in different ways influence the association between obesity and sleep duration (Lombardo et al., 2015). Zimmerman and colleagues (2013), in their study, have found significant correlations between sleep onset and maintenance, BMI, abdominal obesity, symptoms of anxiety and depression. Hormones like cortisol, ghrelin, leptin, and orexin produce a suggestion of the moderating role of depression and stress in the link between sleep and weight. Leptin, for example, decreases appetite and increases energy expenditure (Knutson & Lauerdale, 2007). Decreased leptin levels are expected to facilitate weight gain, because high leptin levels signal satiety. Low leptin levels, observed in some depressed individuals (Jow et al., 2006; Kraus et al., 2001; Lu, 2007), might be associated with weight gain, increased REM sleep and increased sleep fragmentation.

The objective of this chapter is to evaluate the effect of sleep on BMI in a sample of caregivers of people with dementia. Sleep and feeding were chosen as two of the possible habits connected to the lifestyles of the caregivers of people with dementia that could influence the possible onset or worsening of cognitive deficits. Considering the importance that depression has in the association between sleep problems and BMI, we firstly considered whether depressive symptoms might be one of the factors influencing BMI.

Secondly, to test for the hypothesis that depressive symptoms could act as moderators, we evaluated the relationship between sleep and obesity, considering separately caregivers with high and low depressive symptoms. Inserting this chapter in this dissertation is important because it clearly highlights the complex relationship of moderation between the variables, also not strictly connected between them like depression, BMI and sleep, involved in the AD risk reduction. These complex and intricate relationships between variables importance of multimodal interventions in ameliorating caregivers' health, since complex moderation and mediation effects exist between the different areas

2.2. Methods

117 subjects took part in the study using a purposive sampling method, even if some of them did not answered to all of the questions. Participants were or had recently been primary caregivers of people with dementia. Eligibility criteria included the following: (1) age between 40 and 64, (2) fluency in the Italian language, (3) residency in Italy. Dementia, unmanaged diabetes and/or untreated major depression have been considered as exclusionary medical conditions. Although a diagnosis of dementia in the

caregiver was exclusionary, mild cognitive impairment was not. 6 interviewed possible participants were excluded for the following reasons: age not in the range (3), dementia (2), diabetes (1). The participants were recruited between the 27th of September 2016 and the 9th of February 2017. This cross-sectional study was approved by the Institutional Review Board of the Psychology Department, Sapienza University of Rome.

Questionnaires were administered in a private setting. Data are taken from the baseline questionnaires of the Gray Matters Project (for more details see chapter 3). Participants took approximately 75 min to complete the questionnaires. They were informed that participation in the study was voluntary and that their responses would be treated confidentially. Participants were encouraged to answer honestly and to ask questions if they had any doubts about the instructions or the items. They had the right to withdraw from the study at any moment.

A set of questionnaires were administered to the subjects (please see chapter 3 for the full details of the measurement tools).

The measurement tools analyzed in this specific chapter are the following:

- Sociodemographic Questionnaire: The items included were age, gender, marital status, income level, and self-reported height and weight were used to compute BMI.
- The Pittsburgh Sleep Quality Index (Curcio et al., 2013; PSQI): This index is an instrument used to measure the patterns and relative quality of sleep in adults. It measures 7 seven areas (components) in order to differentiate between “poor” and “good” sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. This tool consists of 19 items, producing one overall score, and takes 5–10 min to complete. Higher scores on the PSQI and in the individual component scores imply poorer sleep.
- The Eating Behavior Questionnaire (Panagiotakos et al., 2006; adapted to Italian dietary habits by Alberti and colleagues 2004, 2009): This tool aims at detecting eating habits over the previous 6 months in terms of daily, weekly and monthly frequency, evaluating adherence to the Mediterranean diet. The

questionnaire assesses the consumption of the following food groups in the diet score: non-refined cereals (wholemeal bread, pasta, rice, other grains, biscuits, etc.), fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, full-fat dairy products (like cheese, yogurt, and milk), olive oil and alcohol intake. Individual ratings (from 0 to 5 or the reverse) are assigned to each of the 11 food groups according to their position in the Mediterranean diet pyramid. For the consumption of items presumed to be close to this pattern (i.e., those suggested on a daily basis or more than 4 servings/week; non-refined cereals, fruits, vegetables, legumes, olive oil, fish, and potatoes) the authors assigned a score of 0 when someone reported no consumption, a score of 1 when they reported consumption of 1–4 servings/month, a score of 2 for 5–8 servings/month, a score of 3 for 9–12 servings/month, a score of 4 for 13–18 servings/month and a score of 5 for more than 18 servings/month. Thus, the score ranges from 0 to 55. Higher values for this score indicate greater adherence to the Mediterranean diet.

- The Center for Epidemiologic Studies-Depression (Radloff, 1997; CES-D): This scale is a self-report measurement tool for depressive symptoms. Twenty items inquiring about depressive symptoms over the preceding week compose it. The respondents are asked to choose among four possible responses in a Likert format, where “0” indicates “rarely or none of the time (less than 1 day)”, and “4” is “almost or all of the time (5–7 days)”. Cronbach’s alpha is 0.80 or above, with a test–retest correlation being moderate (0.40 or more).

Hierarchical linear regression models were computed considering BMI as the outcome variable, in order to examine the association between sleep problems and obesity,

Three different models were assessed. The first step of each regression model entered gender and diet quality data, the second step entered data regarding depressive symptoms and sleep problems. In the first model, the total PSQI score was assessed, in the second model the seven different subcomponents. The third model included all the variables used in the first model standardized and last the product between the PSQI Total Score and the CES-D Total Score.

To better understand the moderation effects, we divided the sample into two groups: caregivers with low (CES-D total < 16) and high symptoms of depression (CES-D total ≥ 16).

To reduce the chances of obtaining false-positive results, due to multiple comparisons, a Benjamini–Hochberg correction was used; the Benjamini–Hochberg corrected the alpha level corresponding to an alpha level of 0.037. Therefore, all p values lower or equal to 0.037 were considered significant.

In Fig. 1 and 2 we explain the models we computed.

Fig. 1
Hierarchical regressions model

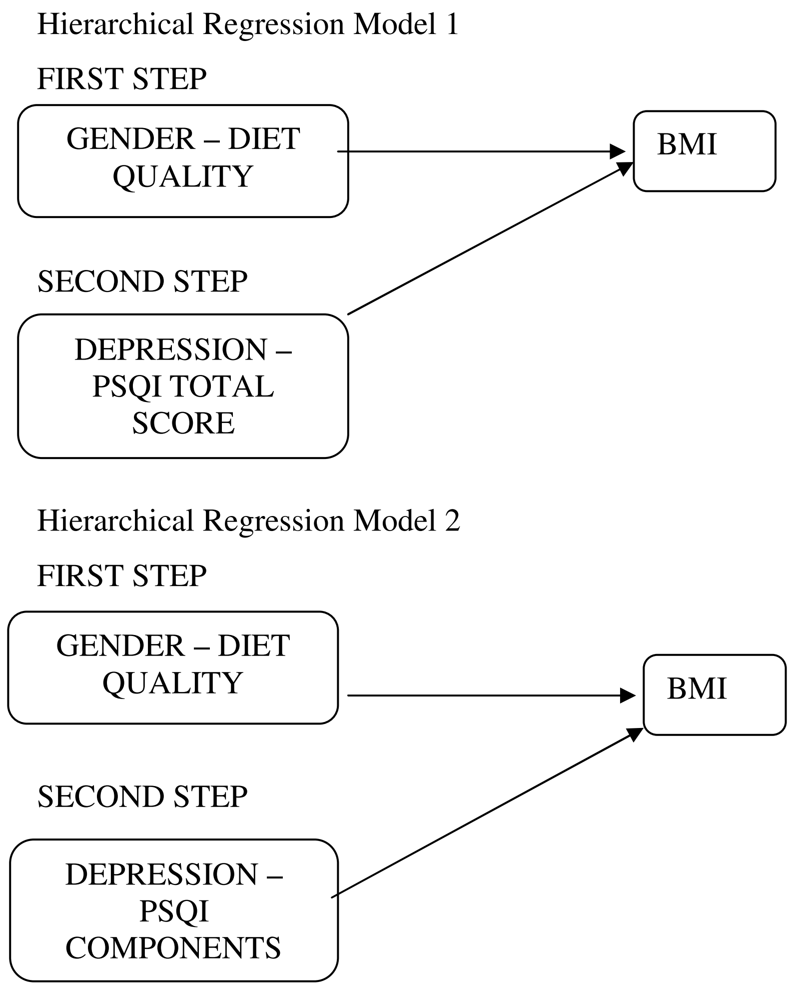
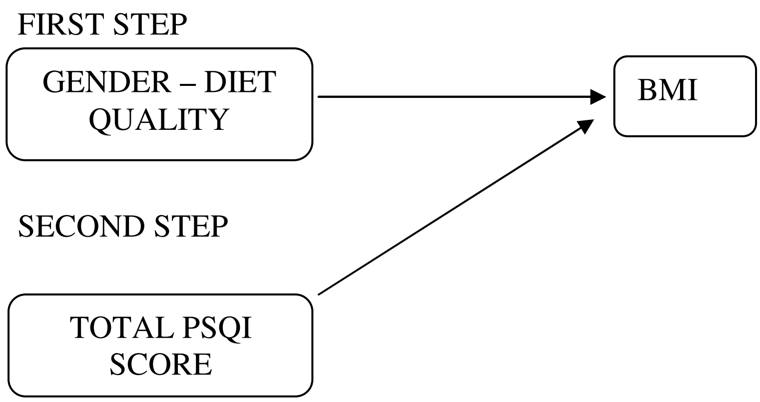


Fig. 2
Moderation Model Divided into Low Depressive Symptoms and High Depressive Symptoms subgroups



2.3. Results

Table 1 provides a demographic summary of the final sample, for high or low depressive symptoms separately, as well as for the total sample. In the total sample, the minimum BMI was 17 and the maximum was 35, with a mean score of 24.61 and a SD of 3.7. Females were more likely to have depressive symptoms than males ($p = 0.049$ Fisher's Exact test), while educational attainment ($p = 0.862$), income level ($p = 0.628$), and marital status ($p = 0.062$) were unrelated to depressive status (Chi-square test of independence for the latter 3 variables).

Table 1
Demographic summary of the final sample, with low and high depressive symptoms examined separately ($n = 117$)

Categorical variables	**Low depressive symptoms, *N* (%)**	**High depressive symptoms, *N* (%)**	**Total, *N*(%)**
Gender			
Male	30 (44.1%)	14 (28.6%)	44 (37.6)*
Female	38 (55.9%)	35 (71.4%)	73 (62.4%)
Continuous variables	**Low depressive symptoms, mean (SD)**	**High depressive symptoms mean (SD)**	**Total, mean (SD)**
Age	54.38 (5.9)	53.55 (7.1)	54.03 (6.4)
BMI	24.63 (3.6)	24.58 (3.9)	24.61 (3.7)
Adherence to the Mediterranean diet	31.78(5.1)	31.53 (5.2)	31.67 (5.2)
PSQI score	5.35 (4.1)	8.47(3.7)	6.79 (4.0)**

*$p < 0.05$, **$p < 0.001$

Furthermore, mean levels of age ($p = 0.464$), BMI ($p = 0.924$), and diet quality ($p = 0.770$) did not differ according to depression status; however, there were significantly more sleep problems reported by participants with high depressive symptoms ($M = 8.47$, SD = 3.7) than by participants with low depressive symptoms ($M = 5.35$, SD = 4.1; $p < 0.001$).

Tables 2 and 3 summarize the hierarchical regression models, showing separately results for each model-building step. Female gender was positively associated with lower BMI, while in the first model higher diet quality was positively associated with lower BMI, marginally.

Table 2
Hierarchical regression models of BMI regressed on gender, diet quality, depression, and sleep problems—as total score ($n = 117$)

Predictor variable	Model 1 **β, *p* value**	Model 2 **β, *p* value**
Female gender	− 2.96 ($p < 0.001$)	− 3.06 ($p < 0.001$)
Diet quality	− 0.12 ($p = 0.057$)	− 0.13 ($p = 0.044$)
Depressive symptoms		− 0.02 ($p = 0.614$)
Sleep problems: PSQI total score		0.16 ($p = 0.048$)
Sleep quality		
Sleep latency		
Sleep duration		
Sleep efficiency		
Sleep disturbances		
Sleep medication use		
Daytime dysfunction (sleepiness)		
Model R^2	0.177	0.206
ΔR^2 from simpler model; *p* value	0.177 ($p < 0.001$)	0.029 ($p = 0.140$)

In the first hierarchical regression, depressive symptoms did not act as significant regressors, but the total PSQI score was associated with higher BMI, and there was a positive trend toward higher diet quality linking to lower BMI. However, the power analysis revealed that model 2 of this regression presented just a power of 0.42, and we could not take into consideration the results. Replacing the sleep problems score with its seven-component scores (Table 3), results for gender, diet quality and depressive symptoms remained unchanged, but just one of the sleep components, in particular "sleep disturbances", was as a significant factor positively influencing BMI.

Table 3
Hierarchical regression models of BMI regressed on gender, diet quality, depression and sleep problems—as 7-component scores ($n = 117$)

Predictor variable	Model 1 ***β, p* value**	Model 2 ***β, p* value**
Female gender	− 2.96 ($p < 0.001$)	− 3.43 ($p < 0.001$)
Diet quality	− 0.12 ($p = 0.057$)	− 0.12 ($p = 0.049$)
Depressive symptoms		− 0.02 ($p = 0.565$)
Sleep problems: PSQI total score		
Sleep quality		0.25 ($p = 0.686$)
Sleep latency		− 0.19 ($p = 0.647$)
Sleep duration		− 0.43 ($p = 0.437$)
Sleep efficiency		0.25 ($p = 0.583$)
Sleep disturbances		1.72 ($p = 0.014$)
Sleep medication use		0.36 ($p = 0.240$)
Daytime dysfunction (sleepiness)		0.23 ($p = 0.671$)
Model R^2	0.177	0.306
ΔR^2 from simpler model; p value	0.177 ($p < 0.001$)	0.111 ($p = 0.05$)

In the third model, the interaction effect was non-significant ($\beta = -0.118$; $p = 0.186$); however, as we wanted to test the moderation hypothesis, suggested by previous literature, we repeated the first hierarchical regression model separating the sample in a subgroup with low depressive symptoms and a subgroup with high depressive symptoms (Table 4).

Table 4
Hierarchical regression models of BMI regressed on gender, diet quality, and sleep problems total score, rated separately for participants with low depressive symptoms ($n = 68$) and with high depressive symptoms ($n = 49$) subsamples

Predictor variable	Low depressive symptoms (CESD < 16)		High depressive symptoms (CESD ≥ 16)	
	Model 1 β, *p* value	Model 2 β, *p* value	Model 1 β, *p* value	Model 2 β, *p* value
Female gender	− 2.60 ($p = 0.002$)	− 2.59 ($p = 0.002$)	− 3.90 ($p = 0.002$)	− 3.91 ($p = 0.002$)
Diet quality	− 0.17 ($p = 0.037$)	− 0.16 ($p = 0.040$)	− 0.04 ($p = 0.671$)	− 0.04 ($p = 0.665$)
Sleep problems: PSQI total score		0.21 ($p = 0.027$)		0.02 ($p = 0.911$)
Model R^2; R^2 change from simpler model; *p* value	0.183 0.183 ($p = 0.002$)	0.245 0.063 ($p = 0.027$)	0.206 0.206 ($p = 0.006$)	0.206 0.000 ($p = 0.911$)

Table 4 shows the results. In caregivers with low depressive symptoms, diet quality and female gender were both significant regressors of BMI, both in model 1, and then in model 2 upon addition of the sleep problems total score, also appearing a significant influencing factor, revealing once again that the greater the sleep problems to the higher BMI. On the contrary, in caregivers with high depressive symptoms, female gender was the only factor significantly influencing BMI, while diet quality and sleep problems did not show any relationship with BMI. The power analysis revealed that the model in the depressed caregivers had a power of 0.05, so that we could not take these results into consideration.

2.4. Discussion

The objective of this research was to evaluate if depressive symptoms could influence the association between sleep problems and BMI in a population of caregivers of people with dementia, using adherence to Mediterranean diet as a control variable and investigating possible gender differences. As described in the literature (e.g., Vaatainen et al., 2013), we also found in our sample that females were more likely to report depressive symptoms than males. Depressive status, in our study, was not found to be different based on educational attainment, income level, marital status, average age, BMI, and diet quality. Moreover, caregivers presenting more depressive symptoms reported to have also more sleep problems than the ones with lower symptoms; also this finding is consistent with the previous studies (i.e. Baglioni et al., 2011).

Regarding the main aim of the study, our results show that depressive symptoms do not directly influence BMI. Sleep problems, together with female gender, were, however, significant regressors of BMI, among caregivers with low depressive symptoms, while they did not act as influencing factors on BMI among participants with higher depressive symptoms. This is a novel finding, which may provide a new interpretative factor to already existing studies on the relationship between sleep and BMI. Different researches, in fact, have, investigated the role of depression in the link between short sleep duration and BMI (Ohayon & Vecchierini, 2005; Gildner et al., 2014; Norton et al., 2018); however, to the best of our knowledge, they only have assessed the direct effects of depression on BMI, without testing the possible moderating role of depressive symptoms. Another important strength is the fact that our data throw light on the other variables that may explain why the association between poor sleep and obesity in adults is debated in existing literature. An interesting and practically novel finding is that diet quality influences BMI only in caregivers with low depressive symptoms; Elder and colleagues (2012) suggested that sleep duration was a predictor of weight loss, with weight loss significantly correlating with declines in depression ($p = 0.035$). Moreover, they found a correlation between weight loss and depression. This factor could be taken into account when projecting programs to change lifestyles in caregivers. Data on caregivers with high depressive symptoms should be, however, taken into careful consideration, given the low power of the analysis in this subsample. Table 2 suggests, besides, that the "sleep disturbances" component was the only PSQI component acting as a significant predictor of BMI, above and beyond all the other 6 components. Future studies should focus on the fact that disturbances during sleep may be much more important than subjective sleep quality, latency, efficiency, and other areas concerning sleep. These data might also suggest the importance of focusing on sleep disorders when planning programs to reduce BMI in caregivers.

Several limitations should be also acknowledged. First, all our data are self-reported, even if Lombardo and colleagues (2011) have found that BMI calculated according to objective data gathered at the moment of the clinical interview and the self-reported data obtained through the DEQ questionnaire have been found to be positive and statistically significant ($r = 0.95$; $p < 0.001$). We can conclude, therefore, that this is an acceptable practice for our study, especially because the aim of the intervention was to implement lifestyles, so that participants had no reasonable need to underreport their weight. Furthermore, we also lacked severely obese participants, with only one person being classed as II obese and fewer than 10% of the sample being classed as obese I. These limit the generalizability of our results and their application to possible interventions extendible to the clinical population. It is also possible that self-reported height and weight may have led to underestimated BMI scores. Although we found that sleep problems are significant factors influencing BMI only among people with low depressive symptoms, this should be interpreted with caution (due to the non-significant results obtained for the interaction test and to the low power of the analysis in the other subsample) and will require further studies. Moreover, the power analysis of model 2 for the first hierarchical regression presented just a power of 0.42, so that we could not take into consideration the emerging results. Future studies may also address these relationships by measuring objectively height and weight, and by evaluating additional biomarkers potentially linked to obesity, such as a lipid panel, glucose, insulin, and c-reactive protein. The mixing of current and past caregiver status could complicate even further the results;

however, Shulz and colleagues (2008) suggested that family caregivers have been repeatedly acknowledged as a model of chronic stress even when their caregiving task finished, after the death of the care recipient. A psychiatric evaluation is also lacking: some major psychiatric diagnoses may have been missed, jeopardizing the reliability of the study results.

2.5. Conclusions

Our findings confirm some of the results provided by earlier studies and additional results that, if they will be confirmed by future research, may contribute to explain why in adults the relationship between poor sleep and obesity is still a matter of debate. The present study actually investigated the role of depressive symptoms in the relationship between sleep disorders and BMI, controlling for gender and quality of diet. Depressive symptoms are greater in women than in men, while no differences between depressed and non-clinical depressed were found for caregivers based on their educational achievement, income level and marital status, age, BMI and adherence to Mediterranean diet. Only within caregivers with low depressed symptoms, sleep disturbances have been found to be a factor influencing BMI. Probably this result can be explained with the fact that depressive symptoms themselves are connected with BMI at a greater level than sleep problems, so the effect of sleep problems disappear in caregivers with depressive symptoms.

The variables that seem to play a pivotal role in explaining high BMI values are female gender, sleep problems, and diet quality in caregivers with low depressive symptoms, while only female gender predicted BMI in the high depressive symptoms caregivers.

Depressive symptoms, therefore, should be evaluated to identify the risk of obesity (a major risk of dementia), and to differentiate clinical interventions at least in a population that chronically experiences the stress of caregiving. These complex and intricate relationships between variables predicting the AD risk highlight the importance of multimodal interventions that could address all the possible factors involved.

3. The Gray Matters randomized trial: a multidomain lifestyle intervention to improve brain health in middle-aged persons to reduce later Alzheimer's disease risk.

3.1. Introduction

Dementia, in its many forms, is a worldwide need in terms of public health; disappointing results from recent drug trials for Alzheimer's disease (AD) medications, including bapineuzumab (Salloway et al., 2014) and solanezumab (Doody et al., 2014) and the absence of an effective pharmacological cure resulted in the emerging importance of prevention as a priority on the global agenda of WHO for the coming years and have led to the development of preventive interventions that complement the pharmacological search for a cure (Norton et al., 2015). The observation that common genetic variants may account for roughly 30% of variance in risk for AD implies that a substantial portion of risk may be the result of modifiable "environmental factors" (Ridge et al., 2013).

Some factors were proved to have a protective role reducing the risk for AD: involvement in cognitively activities (Stern & Munn, 2010), physically (Larson et al., 2006) and socially stimulating (Verghese et al., 2006; Karp et al, 2006; Seeman et al, 2011) activities like reading, drawing, playing chess, rating a crossword, visiting a museum, playing an instrument and dancing. These activities affect individual cognitive reserve and prevent a potential cognitive decline, as opposed to all those activities involving a passive lifestyle (Lindstrom et al., 2005). Physical activity, in particular, has been linked to better cognitive function (Baker et al., 2010) and lower AD risk (Boyle et al., 2009), potentially via neuroprotection through increased neurogenesis and the enhancement of brain cytoarchitecture (Rolland et al., 2008). Additionally, healthy diet and good nutrition are linked to lower dementia risk, including dietary patterns rich in fruits, vegetables, whole grains, and low fat dairy (Wengreen et al., 2013). The use of extra virgin olive oil as the principal fat, a high intake of fresh/dried fruits, vegetables and legumes, associated with moderate consumption of fish and a low consumption of dairy products, meat and sugar; strict adherence to a Mediterranean diet and the assumption of small amounts of alcohol (Peters et al., 2008; Anstey et al., 2009; Neafsey & Collins, 2011) has been shown to be protective against dementia (Lourida et al., 2013; Psaltopoulou et al., 2013; Morris et al., 2015), especially with regard to serum levels of fatty acids (Morris et al., 2003; Solfrizzi et al., 2006), folate and B vitamins (Quadri et al., 2004), antioxidant vitamins (von Arnim et al., 2012). Sleep disturbances may influence the development of AD via the modulation of biochemical processes that influence AD neuropathology (Di Meco et al., 2014), and greater social engagement has been associated with lower rates of incident dementia (Fratiglioni et al., 2000; Saczynski et al., 2006).

Midlife health has implications for later dementia as obesity (Anstey et al., 2011), hypertension (Launer et al., 2000), and serum cholesterol (Solomon et al., 2009) have been linked to higher dementia risk in late life. Because of the multidimensional risk factors for AD and a strong evidence of a long presymptomatic phase (Fagan et al., 2014), multidomain preventive interventions are critically needed in midlife (and earlier) to maximize the effect on AD risk reduction (Imtiaz et al., 2014).

Encouraging individuals to change multiple domains of their lifestyle has inherent challenges (Berra et al., 2010); however, a variety of intervention modalities may be useful and successful. In a recent study of 80 middle-aged persons, King and colleagues (2013) demonstrated that participants using three different smartphone apps focusing on (1) goal setting/monitoring, (2) social comparisons and supports, or (3) operant conditioning, each showed increases in physical activity levels. Smith Di Julio and Anderson (2009) implemented a multimodal lifestyle cardiovascular risk intervention in 60 middle-aged women in Australia, finding that subjects were generally continuing healthy behaviors in a 5-year follow-up survey. Anstey and colleagues have conducted a multidomain health education RCT in Australia (2015). Similarly, multidomain prevention trials are being conducted among older adults at higher AD risk, emphasizing exercise and nutritional advice (Cyarto et al., 2012) in combination with cognitive training (Kipivelto et al., 2013) or medical treatment of risk factors (Richard et al., 2009). A detailed analysis of previous multimodal intervention to prevent cognitive deficits could be read in the previous chapter.

In summary, a number of RCTs designed to lower AD risk via lifestyle behavioral change have commenced in recent years; however, nearly all these studies focus on older adults or on middle-aged persons at higher risk for AD. Indeed, none were found that targeted the general population of middle-aged individuals, and none have taken a holistic approach to encourage positive lifestyle changes in as many domains as the study reported herein.

Gray Matters is a multidomain pilot RCT, firstly carried out done in Cache County, Utah designed to promote positive changes in lifestyle (exercise, nutrition, cognitive stimulation, social engagement, stress management, and sleep quality), specifically for the purpose of reducing AD risk in healthy

middle-aged adults. Based on this study, we have designed a multidomain pilot RCT, adapting the content to the Italian language and culture and adding one lifestyle, the smoke habit, as it is diffuse in our culture and because of its connections with AD risk (Cataldo et al., 2010).
The transtheoretical model of behavior change (Prochaska & DiClemente, 2005) provides a theoretical foundation for the intervention, guiding the assessment of individuals' motivation and readiness to change, alongside the measurement of behavioral and health outcome change. The goal for each domain is to introduce evidence-based associations explaining AD risk and encourage positive changes.

3.2. Methods

Study design

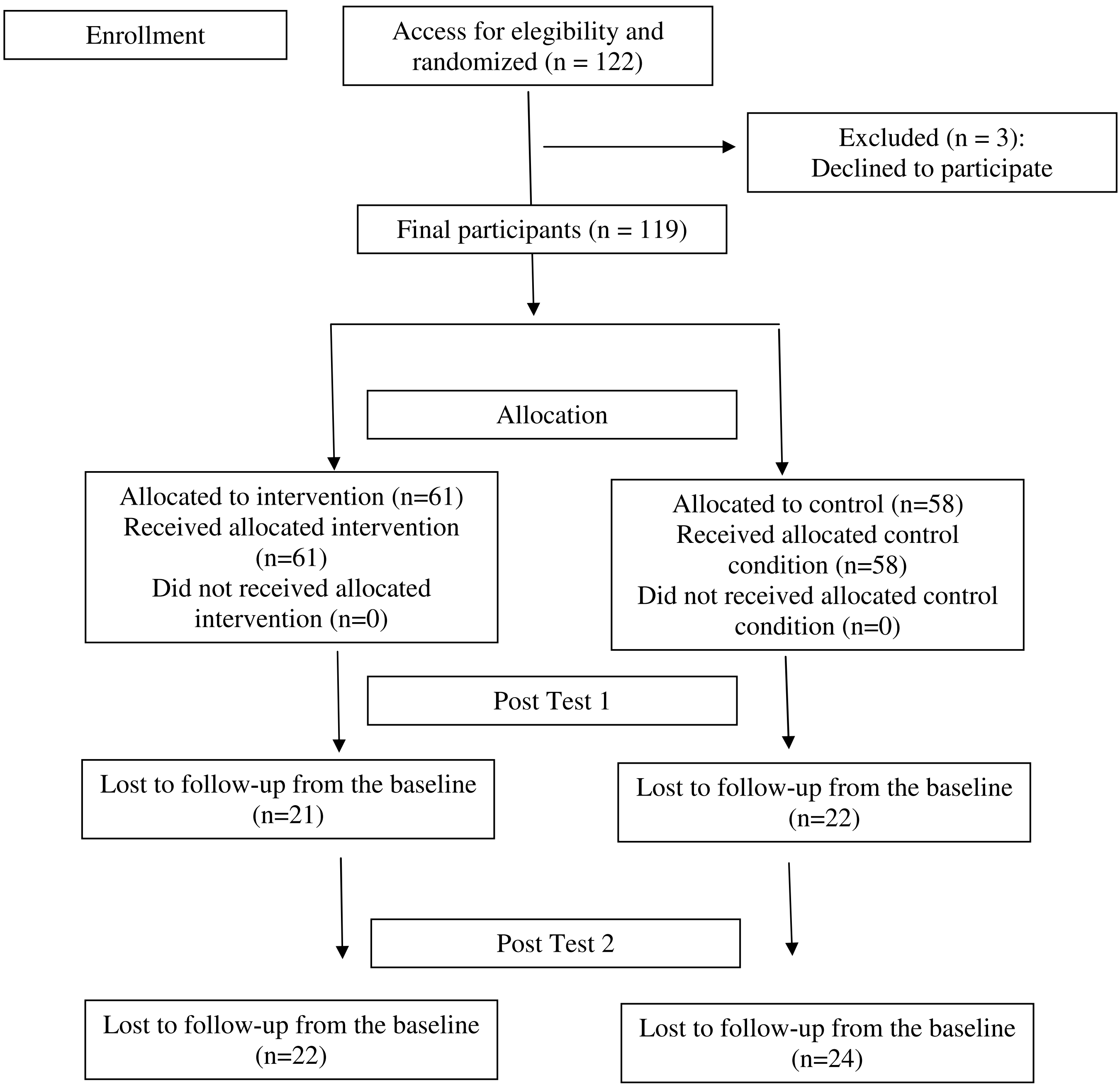
This pilot study is an RCT; subjects were randomly assigned into treatment or control condition. Hence, half of the sample was randomized to treatment and half to control. The intervention was delivered over a 6-month period (starting September 2016) with posttest data collection planned at 4 and 8 months.

Participants

The study used a convenience sampling approach. Recruitment efforts included caregivers of patients in Sant'Andrea Hospital and other services for the elderly in Rome and in the neighborhood. We enrolled the first 122 persons who met eligibility criteria (61 for each group). 3 of the participants randomized in the control group did not came neither in the first appointment, so the final sample included 119 participants (61 in the experimental group and 58 in the control one). The participants were recruited between the 27th of September 2016 and the 9th of February 2017. This cross-sectional study was undertaken at Rome's Sapienza University and funded by the University itself, with the approval of the Institutional Review Board of the Psychology Department, Sapienza University of Rome.

A flowchart depicting recruitment, enrollment, randomization, and follow-up throughout the study appears in Fig. 1.

Fig. 1. Flow diagram of participant recruitment, enrollment, randomization, and follow-up in the Gray Matters Alzheimer's Disease Prevention Study



Eligibility criteria included the following: (1) age between 40 and 64, (2) fluency in the Italian language, (3) residency in Italy, and (4) non-presentation with any of the following exclusionary medical conditions: dementia, unmanaged diabetes, or untreated major depression. Although a diagnosis of dementia in the caregiver was exclusionary, mild cognitive impairment was not.

Procedure

After permission was received from each patient, questionnaires were administered to the subjects in a private setting. They took approximately 75 minutes to complete. The caregivers were informed that participation in the study was voluntary and that their responses would be treated confidentially. They were encouraged to answer honestly and to ask the doctor questions if any doubts about the instructions or the items arose. The participants had the right to withdraw from the study at any moment.

Measurement Tools

A set of questionnaires were administered to the subjects. The measurement tools used to collect data for the present study were:

- Sociodemographic Questionnaire: The items included were age, gender, marital status, income level, while current height and weight were used to compute BMI.
- Cognitive tests: Global cognitive ability was assessed with the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005), episodic memory was assessed with the Rey Auditory Verbal Learning Test (Strauss et al., 2006), and verbal fluency and lexical heritage was assessed with the Verbal Phonemic Fluency Test (Splinner, Tognoni, 1987) and Semantic Verbal Fluency Test (Novelli et al., 1986).
- Surveys: The Pittsburgh Sleep Quality Index (PSQI; Curcio et al., 2013) was used to measure the quality and patterns of sleep in adults. It differentiated between "poor" and "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. International Physical Activity Questionnaire (IPAQ) was used to measure the type and amount of physical activity. It was divided into four survey areas intense activity, modern activity, walking time and sitting time (Craig et al., 2003). Current depressive symptoms were measured with the 20-item Center for

Epidemiologic Studies—Depression scale (CESD; Radloff, 1997). Psychological stress was measured with the 10-item Perceived Stress Scale (PSS; Cohen et al., 1983). Functional metacognitive state was measured with Brief Metacognition Questionnaire for the Elderly (BMQE, Buckley et al., 2010), a set of seven items (each scored from 1 much better to 5 much worse), comparing current memory to how it was 3 years ago.. Fagerström Test for Nicotine Dependance investigated habits related to smoke (Fagerström 1991). The Eating behavior Questionnaire (adapted to Italian dietary habits by Alberti et al. 2004, 2009) was used to assess habits over the previous 6 months in terms of daily, weekly and monthly frequency, evaluating adherence to the Mediterranean diet. The questionnaire assesses the consumption of the following food groups in the diet score: non-refined cereals (wholemeal bread, pasta, rice, other grains, biscuits, etc.), fruit, vegetables, legumes, potatoes, fish, meat and meat products, poultry, full-fat dairy products (like cheese, yoghurt, and milk), as well as olive oil and alcohol intake. The 10-item General Self-Efficacy Scale (GSES) evaluated the sense of self-efficacy (each scored from 1 not at all true to 4 totally true; Sherer et al., 1982). The Lubben Social Network Scale (LSNS) was used to measure social engagement including family and friends (Lubben 1988, 2006) and the 12-item Multidimensional Scale of Perceived Social Support (MSPSS) was used to evaluate perceived social support in three different areas (Family, Friends, and Significant Other; Zimet et al 1988). Intrinsic motivation was measured with 16 item Situational Intrinsic Motivational Scale (SIMS; Guay, 2000). The subjects had to express the level of agreement (each scored from 1 completely disagree to 7 totally agree). It was designed to assess the construct of intrinsic motivation, identified regulation, external regulation, and amotivation. The positivity scale was used to evaluate personal and interpersonal orientation towards life and the future (Caprara et al., 2012).

Data analysis

To examine the effect of Time (month 0 vs. month 8) overall, then an interaction between Group x Time (to determine whether the amount of change over time is equal for Treatment and Control groups), General linear model (GLM) repeated measures models were conducted. As the next step, a 3-level group variable (control, low compliance treatment, and high compliance treatment) has been

created. Low compliance treatment was defined as having participated to 0 seminar and to have used the smartphone app less than 80 days, while the high compliance was defined having participated to more than one seminar and to have used the smartphone app more than 80 days. GLM repeated measures models were conducted again for the three new groups: control group, low compliance treatment and high compliance treatment. In these first two models, participants who attended all the evaluations were included (39 for the experimental group, 34 for the control group).
We have then inserted the middle (month 4) data point and re-run these first as linear mixed models (LMM) with up to 3 time values, testing for a possible different pattern of change between the two different post-test evaluation, including all the participants to the project, attending even just one evaluation (see Fig.1 for the participants number). To see if sociodemographic factors can influence in the outcome of the intervention, GLM repeated measures models were conducted again separating the dataset for age.

Intervention program

The intervention provides evidence-based information linking lifestyle behaviors and cognitive decline or risk for AD or other dementia. Seven behavioral domains associated with AD risk were targeted: physical activity, healthy food choices, social engagement, cognitive stimulation, stress management, sleep quality and smoking behavior.

Educational components

A series of 4 “seminars” were delivered over the 8-month intervention period. Seminars were designed to emphasize the link between a behavioral domain and AD risk and to give participants experiential opportunities to try example behaviors, the overall behavioral domain being promoted, rather than specific activities. For example, individual nutrients or food items were not promoted, rather, a healthy overall dietary pattern rich in fruits, vegetables, whole grains, fish and lean meats, akin to the Mediterranean diet. Seminars have been focused respectively on: diet, physical activity, stress management and sleep behavior.

Smartphone application

Participants were given an app adapted for this project and designed to work on Apple iOS and Android OS smartphones and tablets. This technology included three primary functions.

- Information: Tapping a “daily fact” produced a full reference from the lifestyle/AD literature and concrete suggestions for adoption (e.g. “Lack of physical activity is a risk factor for AD. Try taking a walk during your lunch break.”).

- Accountability: Subjects were asked daily to respond to a set of 13 behavioral questions, taking 3 minutes/day total to complete. The 13 questions enquired about physical activity level (moderate and vigorous), consumption of fruits/vegetables, whole grains, legumes/nuts, cognitively stimulating activities, novel information processing activities, sleep improvement efforts, social engagement, stress reduction efforts and smoke reduction efforts. Data entry took the form of a user-friendly horizontal “slider.”
- Feedback: The app provided a progress report with two graphical displays (1–5 stars daily and histogram weekly).

Personal coach

A team of 5 trainees were “personal coaches” and were trained in motivational interviewing and the transtheoretical model. Coaches provided a monthly emails, phone call or text messages exchange with their “clients” to provide emotional support and encouragement for lifestyle change goals, keeping a log monitored by the researchers, who provided assistance in resolving any questions or issues.

Study website

A website was adapted from the website of the pilot study and shared with participants, providing intervention content in the seven domains. The website provided links to other resources, a phone to contact daily and an email portal for submitting questions to the research team. The study website is the only intervention resource available also for control participants.

Procedures

The Institutional Review Board at Sapienza University approved this research, and written informed consent was collected from all participants.

Participants completed a 1 and half-hour battery of paper-pencil cognitive and psychological tests administered by trained psychologists. It is hypothesized that significantly greater gains in healthy lifestyle behaviors and both subjective and objective outcomes will be observed in the treatment group, compared with control group, over the 8-month intervention period.

3.3 Results

Table 1 provides a demographic summary of the final sample with results for the test to compare the experimental and control groups. As it is possible to see, participants of the two groups did not significantly differ in most of the demographic characteristics, nor in the scores of most of the surveys assessed (Table 2.)

Table 1. Chi-square to compare baseline socio-demographic characteristics of experimental and control subsample

Variable	**Experimental (n=61)**	**Control (n=58)**	**Significance test (chi-square for categorical or Fisher' Exact for 2x2)**
Marital Status	Single (16.7%) Married (57.4%) Divorced (22.2%) Widowed (3.7%)	Single (17.3%) Married (63.5%) Divorced (15.4%) Widowed (3.8%)	.794
Gender	Female (53.7%) Male (46.3%)	Female (67.3%) Male (32.7%)	.066
Education	None (1.8%) Elementary school (24.1%) Middle school (38.9%) High school (31.5%) University or post-university (3.7%)	None (1.9%) Elementary school (17.3%) Middle school (53.8%) High school (17.3%) University or post-university (9.7%)	.238
Occupation	Employee (31.5%) Freelance professional (31.5%) Entrepreneur (5.6%) Worker (7.4%) Housewife (9.3%) Retired (5.6%) Other (9.1%)	Employee (33.3%) Freelance professional (5.9%) Entrepreneur (7.9%) Worker (7.8%) Housewife (27.5%) Retired (11.8%) Other (5.8%)	.029
Have any children?	No (26.2%) Yes (73.8%)	No (19%) Yes (81%)	.234
Children co-	No (30.4%)	No (40.4%)	.303

residing?	Yes (69.6%)	Yes (59.6%)	
Income level	< 10.000 € (10%) 10.000 - 20.000 € (20%) 20.000 - 40.000 € (36%) > 40.000 € (34%)	< 10.000 € (11.8%) 10.000 - 20.000 € (33.3%) 20.000 - 40.000 € (45,1%) > 40.000 € (9,8%)	.013
Any grandchildren?	No (90.2%) Yes (9.8%)	No (69.6%) Yes (30.4%)	.005
Do you smoke?	No (68.6%) Yes (31.4%)	No (56.8%) Yes (43.2%)	.041
Take antihypertensives?	No (76.3%) Yes (23.7%)	No (74.2%) Yes (25.8%)	.426
Take cholesterol meds?	No (80%) Yes (20%)	No (74.6%) Yes (25.4%)	.200
Have diabetes?	No (100%) Yes (0%)	No (89%) Yes (11%)	.020
Self-rated general health	Excellent (5.6%) Good (64.8%) Fair (25.9%) Poor (3.7%)	Excellent (1.9%) Good (55.8%) Fair (34.6%) Poor (7.7%)	.628
Sleep medication frequency/month	M=3.6 (SD=0.9)	M=3.4 (SD=0.9)	.287
Age	M=53.6 (SD=6.6)	M=54.3 (SD=6.5)	.345
Family size (# persons in nuclear family)	M=2.8 (SD=1.2)	M=2.8 (SD=1.3)	.735
# of children	M=1.6 (SD=.9)	M=2.0 (SD=.9)	.039
# of grandchildren	M=1.6 (SD=1.5)	M=2.4 (SD=1.3)	.244

Table 2. Chi-square to compare baseline clinical, lifestyles and psychological characteristics of experimental and control subsample

Variable	**Experimental (n=61)**	**Control (n=58)**	**Significance test (independent samples t-tests)**
Weight (kg)	M=71 (SD=13.6)	M=67 (SD=12.7)	.319
Physical activity frequency/week	M=2.4 (SD=1.0)	M=1.7 (SD=1.0)	.001
Moderate intensity PA minutes/week	M=190.8 (SD=357.5)	M=257.8 (SD=377)	.192
Vigorous intensity PA minutes/week	M=62.4 (SD=93.8)	M=96.4 (SD=261)	.410
Walking minutes/week	M=171 (SD=231)	M=302 (SD=585)	.333
PSQI (sleep problems)	M=6.3 (SD=3.4)	M=7.2 (SD=4.3)	.086
MOCA (cognitive assessment)	M=25.3 (SD=2.6)	M=25.4 (SD=2.9)	.517
Dietary Adherence score	M=31.8 (SD=5.2)	M=31.5 (SD=5.2)	.735
GSES (self-efficacy score)	M=29.9 (SD=4.1)	M=29.4 (SD=5.2)	.615
MSPSS (perceived social support)	M=16.4 (SD=4.4)	M=15.9 (SD=5.0)	.742

PSS (perceived stress)	M=16.6 (SD=5.8)	M=15.8 (SD=5.8)	.113
BMQE (metacognitive concerns)	M=3.1 (SD=0.4)	M=3.2 (SD=0.5)	.132
CES-D (depression symptoms)	M=16.3 (SD=9.5)	M=14.3 (SD=8.7)	.220
SIMS-IM (intrinsic motivation)	M=17.2 (SD=6.7)	M=16.5 (SD=5.6)	.118
SIMS-ID (identified regulation)	M=22.1 (SD=6.7)	M=22.1 (SD=5.9)	.116
SIMS-ER (external regulation)	M=6.3 (SD=4.6)	M=5.9 (SD=3.6)	.559
SIMS-AM (amotivation)	M=6.8 (SD=4.3)	M=7.0 (SD=4.1)	.287
Lubben (social network score)	M=31.1 (SD=7.2)	M=30.9 (SD=8.7)	.925

To examine the effect of Time (month 0 vs. month 8) overall, then an interaction between Group x Time (to determine whether the amount of change over time is equal for Treatment and Control groups), General linear model (GLM) repeated measures models were conducted. The only significant finding is the Total Cholesterol that decreased in the experimental group while increase in the control one ($F=4618$, $p = 0.043$).

As the next step, a 3-level group variable (control, low compliance treatment, and high compliance treatment) has been created. Again, no many significant results emerged, but the graphs show a more positive change for high compliance treatment group compared to both low compliance treatment and control groups in the CES-D, SIMS (Fig. 1), PSS (Fig. 2), MSPSS (Fig. 3), PS (Fig. 4), GSES (Fig. 5), Total Cholesterol (Fig. 6), Systolic Blood Pressure (Fig. 7), MOCA (Fig. 8). The control group had a significant major improvement in the IPAQ score compared to the treatment groups ($F=3967$, $p=0.031$).

Fig 1. Estimated marginal means of SIMS between the 3 different groups

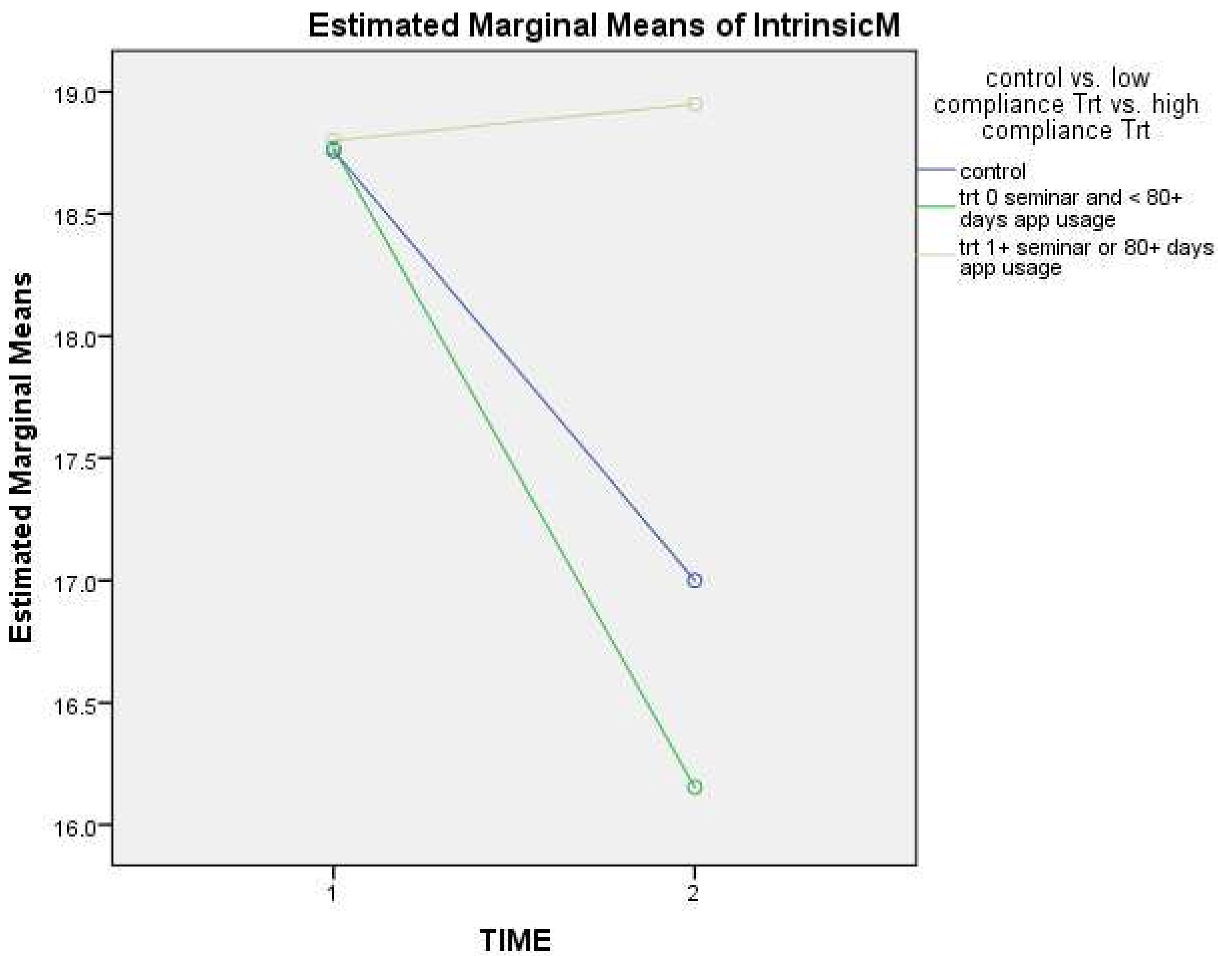


Fig 2. Estimated marginal means of PSS between the 3 different groups

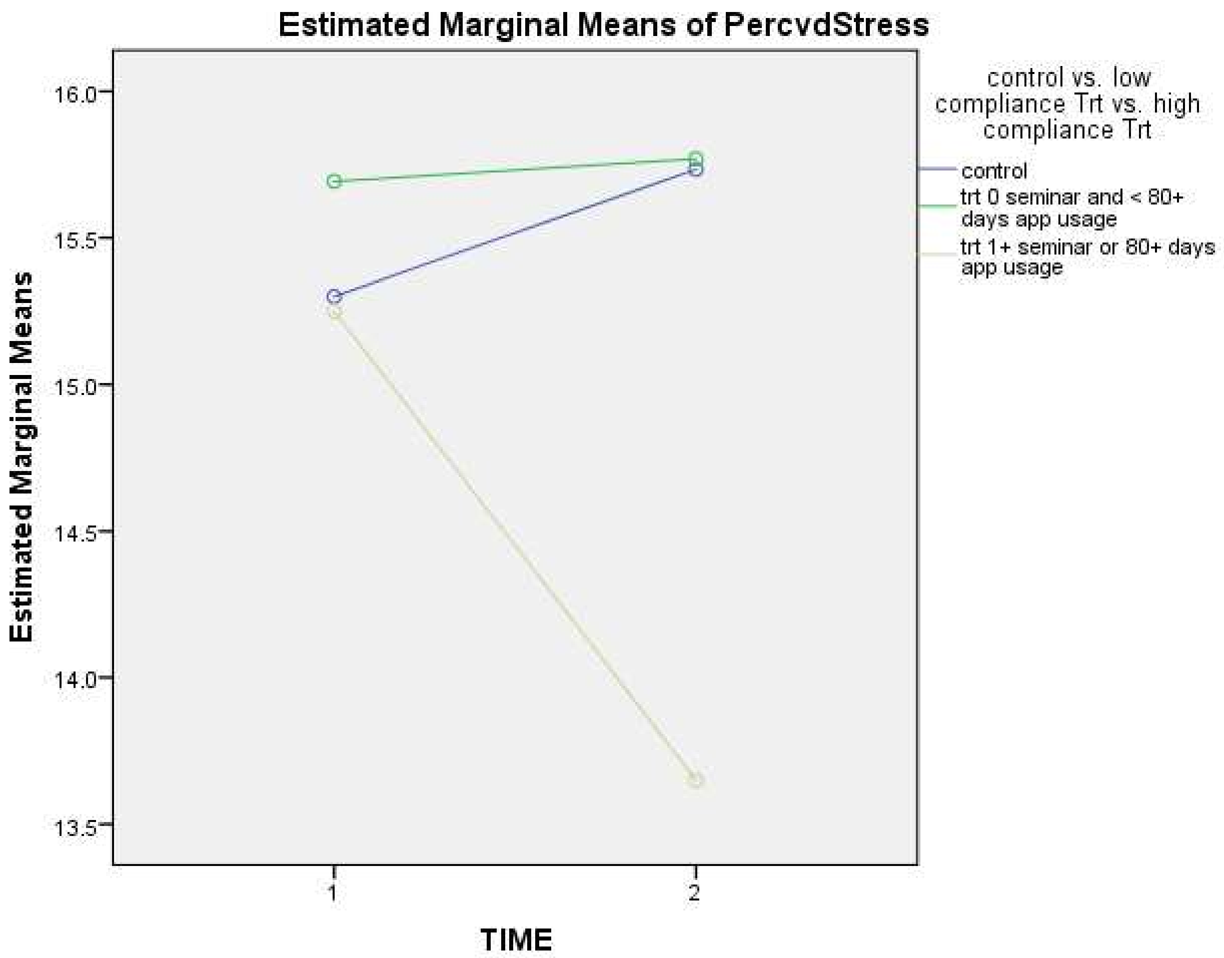


Fig 3. Estimated marginal means of MSPSS between the 3 different groups

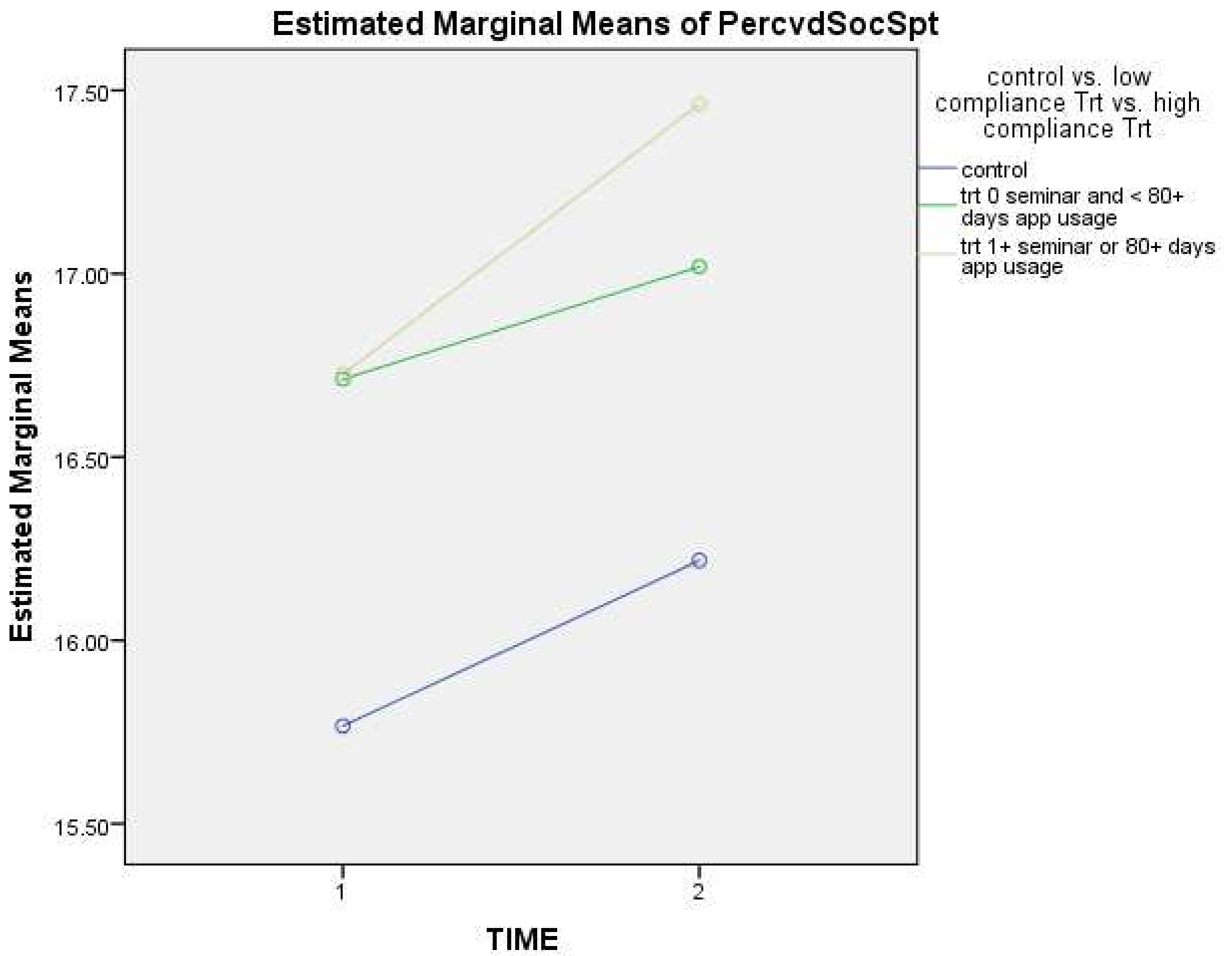


Fig 4. Estimated marginal means of PS between the 3 different groups

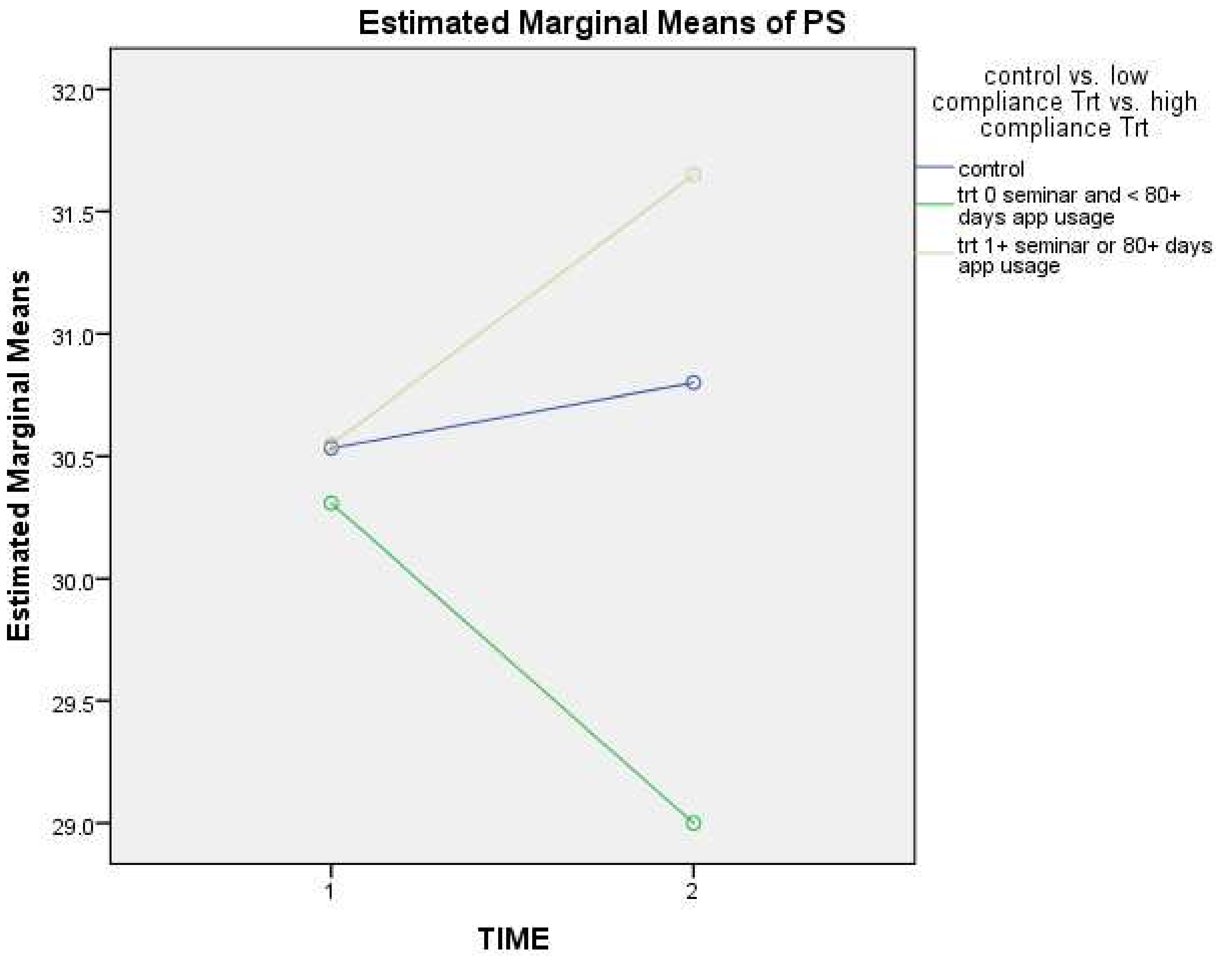


Fig. 5. Estimated marginal means of GSES between the 3 different groups

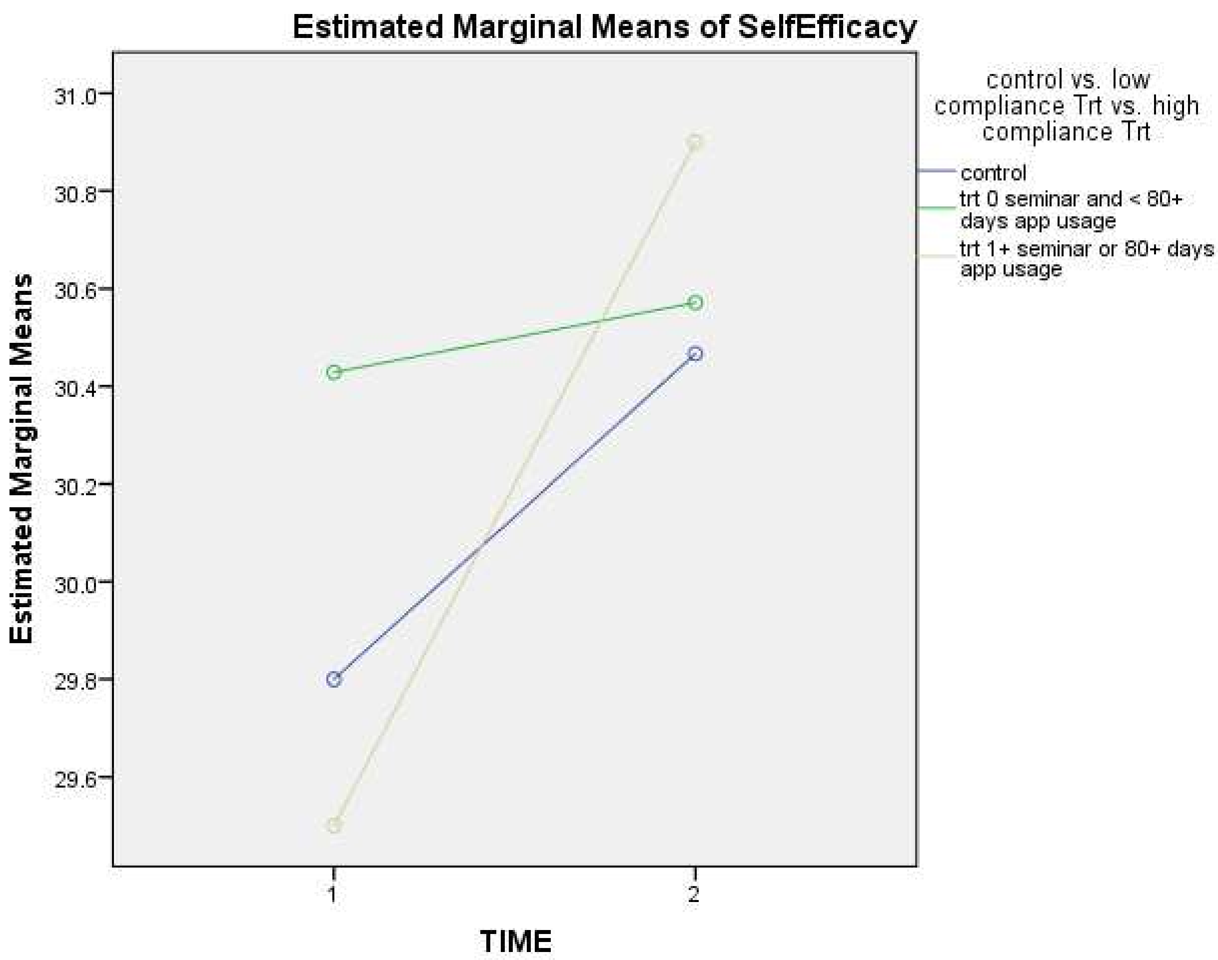


Fig. 6. Estimated marginal means of Total Cholesterol between the 3 different groups

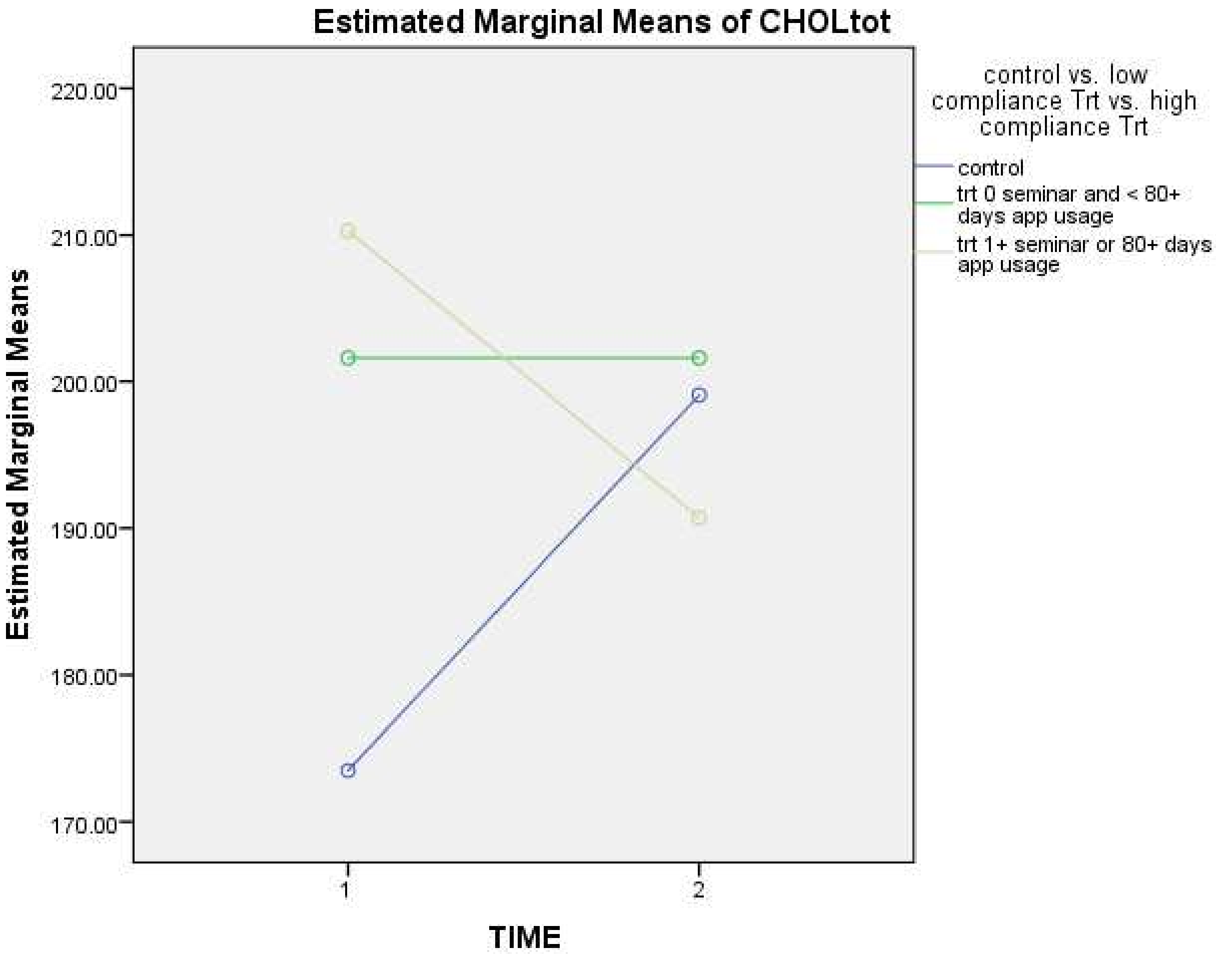


Fig. 7. Estimated marginal means of Systolic Blood Pressure, between the 3 different groups

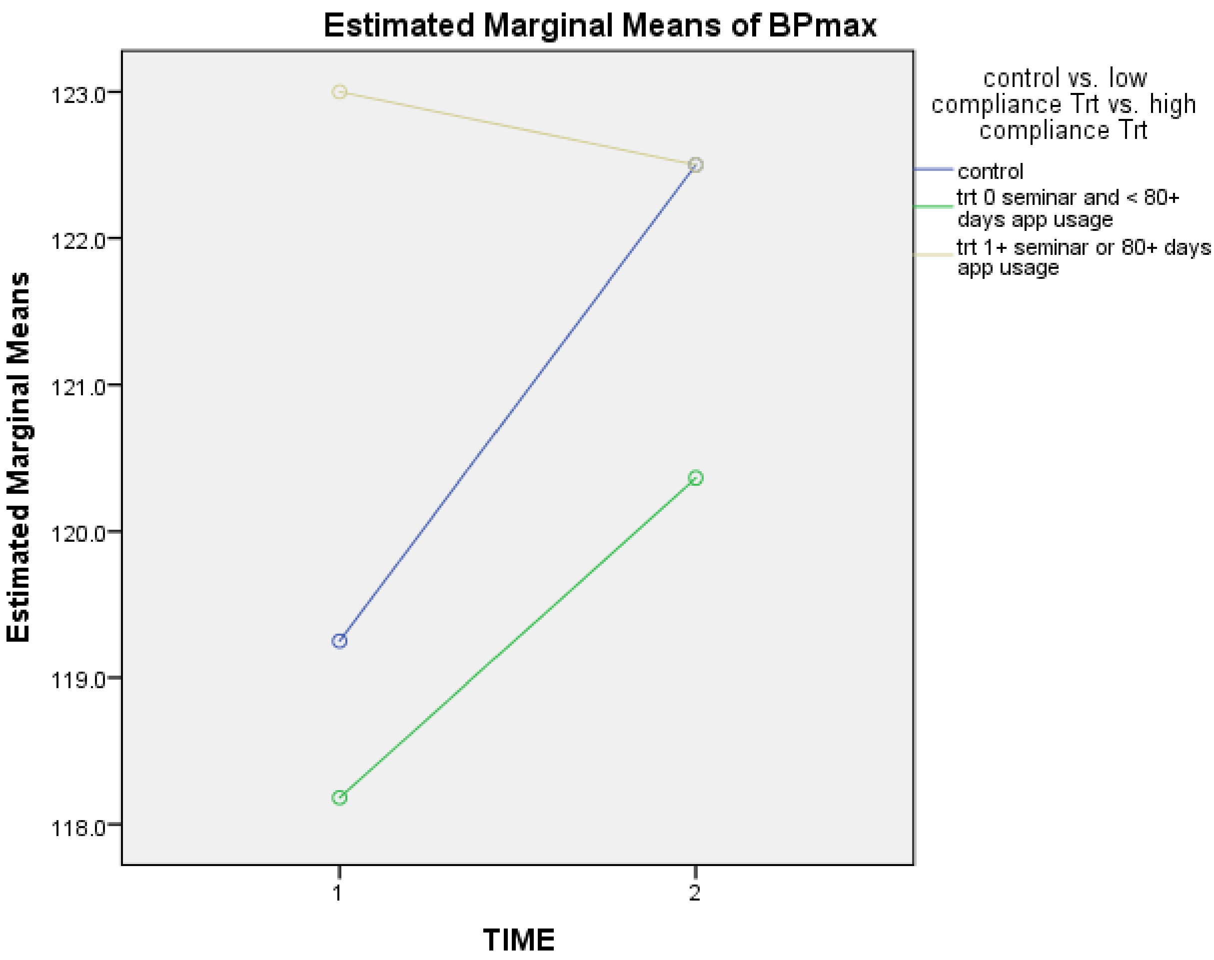
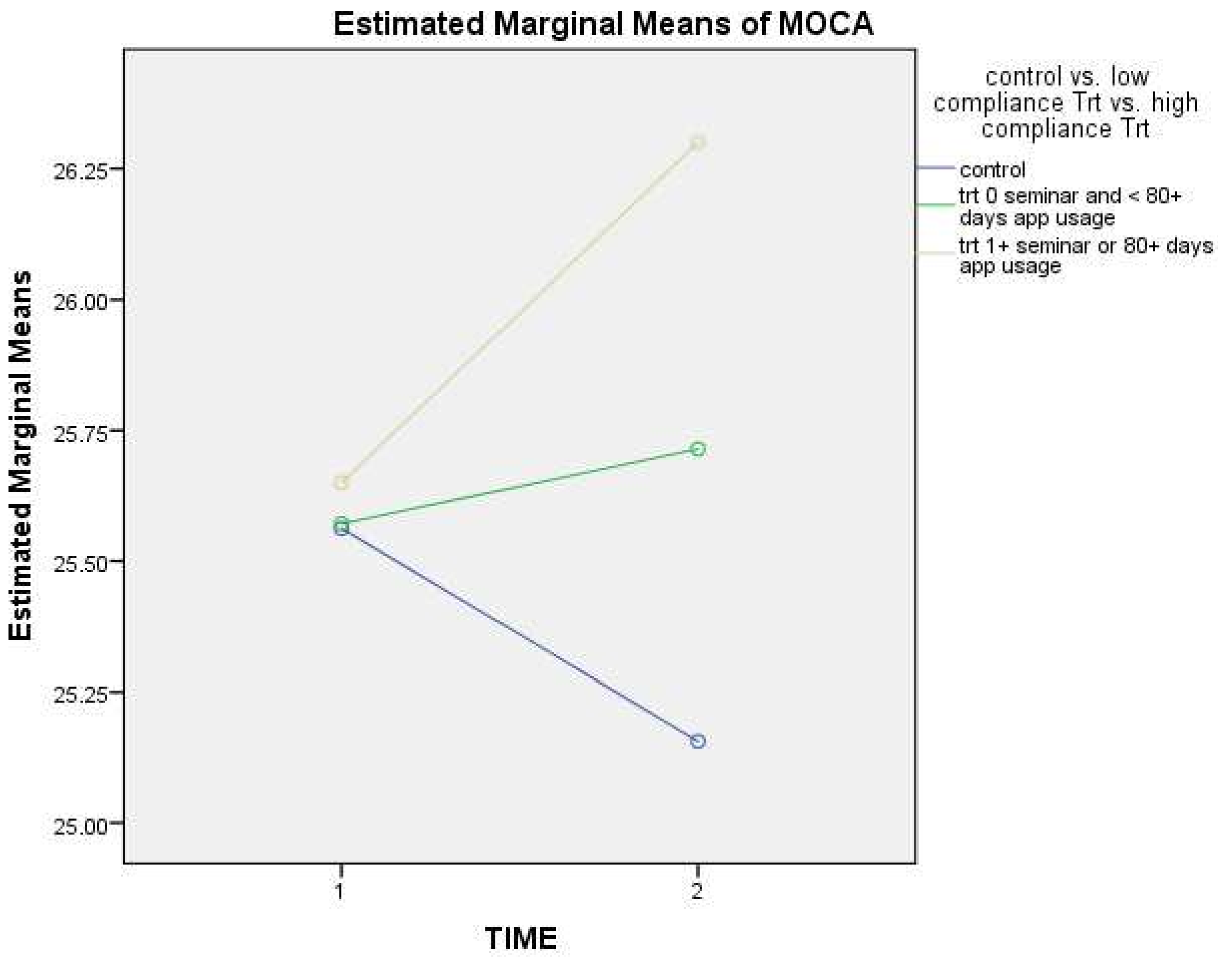


Fig. 8. Estimated marginal means of MOCA, between the 3 different groups

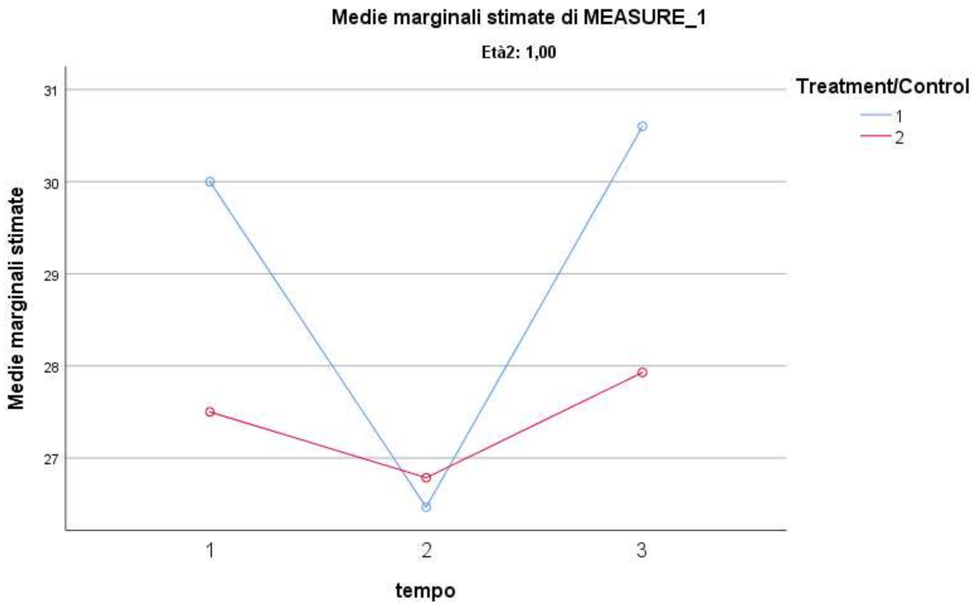


We have then inserted the middle (month 4) data point and re-run these first as linear mixed models (LMM) with up to 3 time values, testing for a possible different pattern of change between the two different post-test evaluation, including all the participants to the project, attending even just one evaluation. Also using the 3 evaluation points, it is confirmed that the control group had a significant major improvement in the IPAQ score compared to the treatment group ($F=4091$, $p=0.018$). The experimental group had a major improvement in the CESD score compared to the control group ($F=3881$, $p=0.023$),

We have re-run the middle (month 4) data point and re-run these first as general mixed models (GMM) with up to 3 time values, testing for a possible different pattern of change between the two different post-test evaluation, including all the participants to the project, attending even just one evaluation (see Fig.1 for the participants number). To see if sociodemographic factors can influence in the outcome of the intervention, GLM repeated measures models were conducted again separating the dataset for age.

Regarding age, interestingly it has been found a significantly quadratic effect for the LSNS score (Figure 9), with the experimental group with the lowest age (40-54) scoring lower than the control group in the 4-months evaluation and than significantly higher in the 8-months one ($F= 5497$, $p= 0.025$) while a similar effect was not found in the eldest participants (55-64).

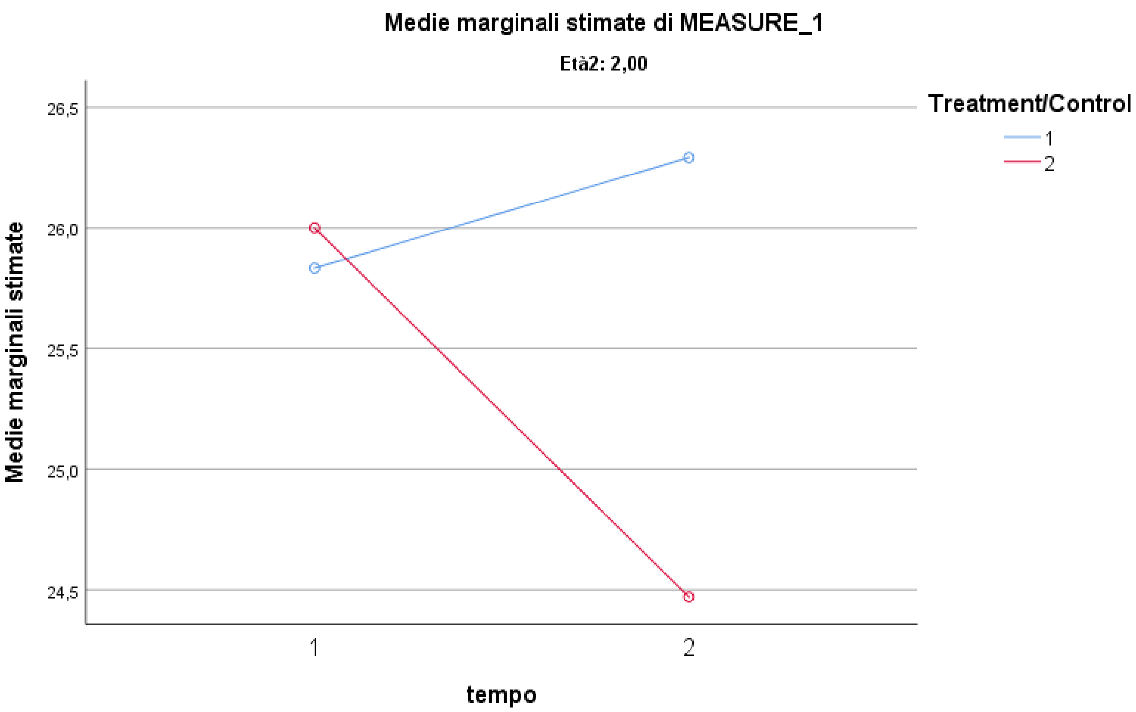
Fig. 9. Estimated marginal means of LSNS, between the experimental and control groups in the youngest participants



Moreover, a significantly linear effect for the MOCA score has been found (Figure 10), with the experimental group with the highest age improving more than the control group of the same age in the 8-months one (F= 4700, p=

0.037) while a similar effect was not found in the youngest participants.

Fig. 10. Estimated marginal means of LSNS, between the experimental and control groups in the youngest participants



Discussion

The Gray Matters study uses a multidomain healthy lifestyle intervention to promote positive behavioral changes that are associated with lower AD risk, with the goal to increase participants' knowledge, intrinsic motivation, and sense of empowerment to make such changes. The pilot study had the aim to relieve the types of activities that are most popular and effective, and the extent to which participants engaged in meaningful and sustained behavioral change (Norton et al., 2015). The mobile phone app provided a novel method to remotely monitor participants in a behavior change intervention, while also facilitating the delivery of intervention material. Our data showed that participants in the experimental group, after the 8-months intervention, reported decreased Total Cholesterol and decreased depressive symptoms. Regarding Total Cholesterol, it is supported by strong epidemiological and control trial data that the Mediterranean diet, included in the project as suggestion, is suggested to decrease its levels (Rosenthal, 2000). Also the feasibility of providing a multimodal treatment to decrease depression was already been proved in another study (Mohr et al., 2010). However, the novelty of our study is the fact that, with the aim to decrease AD incidence, we gave the patients a lot of input in different lifestyles.

Adherence to Internet treatments is a problem generally (Eysenbach, 2005). We have, in fact, found a different outcome pattern in participants with a high or low compliance to the suggested treatment. No many significant results emerged (and this may be due to the small size of our sample), but the graphs show a more positive change for high compliance treatment group compared to both low compliance treatment and control groups in the cognitive domain, in some psychological traits (motivation, stress, self-efficacy, social support, depressive symptoms) and in the reported total level of cholesterol and systolic blood pressure. In this new analyses, the control group had a significant major improvement in the physical activities compared to the treatment groups. However, in the baseline we noted that there was a significant difference in the report physical activity frequency, were participants in the experimental group were more likely to say to do it 2-3 times/week or daily while ones in the control group were more likely to say never or once/week. So, most of the people in the experimental group already had a good lifestyle connected to the physical activity. We also know that the experimental group reported a better trend connected to systolic blood pressure and cholesterol levels.

Maybe the mixing of these data can suggest that control group are more likely to overreport their changes, probably as they do not have daily stimuli to change, while the experimental sample can underreport their improvement as they are daily exposed to stimuli that suggest them they can always improve their behaviour.

Social support decrease with age (Weiner et al., 2016). The fact that we have found that youngest participants had a major increase in the social support may be due to the fact that they are engaged in a biggest social network, so they could have major opportunity to put into practice our suggestions. The oldest participants reported a major increase in the cognitive results: this datum may be interpreted with the generally lower engagement in cognitive activities in the older adults, when our intervention could be more helpful.

A review of the literature showed an increased awareness of the importance of multicomponent AD risk-lowering interventions as well as the need for allowing individuals to actively identify what they need in terms of health behavior improvement and what they are willing/able to do (Olanrewaju et al., 2015). In our study, each treatment group participant was asked to self-prioritize the seven behavioral domains. However, due to the limited number of our sample, we were not able to study the influence of the prioritization in the outcome. A future study could evaluate how much the intervention would be effective in the specific domains that were more highly prioritized at the individual participant level. Future analyses should, then, test whether greater behavioral change in each given behavioral domain occurred within the subset of participants who prioritized that domain and whether the independent variables might influence participants' level of intervention utilization.

The racially and culturally homogeneous current sample and the so-called 'Hawthorne Effect' may limit the generalizability of study findings. Nevertheless, contextual variables which might otherwise confound results are generally absent and thus, internal validity is increased. Moreover, the website provided also for the control group should limit the 'Hawthorne Effect' in the experimental group. Instead, we can imagine that the presence of the experimenter also in the control participants' life for a long time may be a factor affecting the difficulty in finding significant differences between experimental and control group results in some of the results. Future studies could test the efficacy of this intervention in a more ethnically and socioeconomically diverse sample, mindful of the need for cultural sensitivity. In addition, the small size of the sample increases the likelihood that the sample is not representative of the population from which we recruited.

Conclusion

A cure for AD may still be years or even decades away, and even when discovered may have contraindications for universal application. Although genetics are largely non modifiable, interventions that assist individuals with making and sustaining lifestyle behavioral changes that lower AD risk are urgently needed as a complement to pharmacologic therapies. Extensive research supports associations between poorer lifestyle behaviors and cardiovascular risk, and interventions to improve lifestyle behaviors have shown promise. To date, research has established associations between poorer lifestyle behaviors and reduced cognitive performance in late life and/or AD risk (Norton et al., 2015). The prevailing theme of this paper has been to express the benefit of using a mobile phone app as a core component of a behavior change intervention—to yield the advantages offered by the pervasive nature of the mobile phone within an individual's daily life and routines. In this study, the mobile phone offered the opportunity for clinical effect to occur through behavior change. The app excelled as a delivery platform for the intervention, enabling the dissemination of educational intervention material, while simultaneously monitoring and encouraging positive behavior change. Although the interesting effect of behavior change in midlife, observed during the 8-month RCT, based on the restricted size of our sample was not possible to reach a statistical significance, and the effect on future AD risk is still relatively unclear. It is evident that participants in the treatment group had favorable improvements across numerous psychological and physiological domains, suggesting that a sustained effort would yield superior outcomes in the future.

The delivery of these interventions to middle-aged persons, decades before likely disease onset, may alter cognitive health trajectories (Norton et al., 2015). Due to the differences found between the low and high adherence to the treatment sub-groups, feedback and supports to assist these individuals to maintain healthy lifestyle choices should be importantly considered in future interventions.

Conclusions

The literature, summarized in chapter 1, underlines the importance of multi-domain interventions on reducing risk factors connected to cognitive decline; studies analyzed give important suggestions regarding the most effective behavioral modification strategies for dementia prevention.

Lifestyle modification interventions have to be flexible, as different are the needs of the target population; generally, in the studies analyzed there is an alternation of individual sessions and small group sessions (group involving 6-10 people), with sessions lasting about 60 to 90 minutes for a maximum of three times a week. The theoretical discussion of specific topics is accompanied by practical activities requiring a personal, daily commitment and being, often, monitored by a telephone or technological software. Even if the most significant results were obtained in a context of cognitive trainings combined with aerobic physical component, it is still not possible with the evidence emerged to plan the type and the duration of a protocol that can guarantee more effectiveness. Some studies have shown behavioral and morpho-functional improvements in the short term of 2-6 months, others showed significant effects with longer times, others have highlighted the need for larger samples or intervention service for more than six months. Most of the multidomain intervention aimed on the prevention of cognitive disease are carried on with elderly patients with a mild cognitive decline or on at-risk adult categories.

Literature clearly showed that the burdens of caregiving of people with dementia include many aspects that could increase the risk of cognitive decline, including chronic stress, social isolation, depression, decreased physical activity, and a shift in eating habits toward more fast food and processed foods. In the second chapter, selecting some of the lifestyles studied in the literature as influencing dementia, we tried to evaluate if depressive symptoms could influence the association between sleep problems and BMI in a population of caregivers of people with dementia, using adherence to Mediterranean diet as a control variable and investigating possible gender differences. The variables that emerged to play a pivotal role in explaining high BMI values were female gender, sleep problems, and diet quality in caregivers with low depressive symptoms, while only female gender predicted BMI in the high depressive symptoms caregivers. Our results, therefore, confirm that the complex and intricate relationships between variables predicting the AD risk highlight the importance of multimodal interventions that could address all the possible factors involved.

Based on these premises, and on the Gray Matters multidomain pilot RCT, firstly carried out done in Cache

County, Utah, we we have designed a multidomain pilot RCT designed to promote positive changes in lifestyle (exercise, nutrition, cognitive stimulation, social engagement, stress management, and sleep quality), specifically for the purpose of reducing AD risk in caregivers of people with dementia. We have adapted the content to the Italian language and culture and added one lifestyle, the smoke habit, as it is diffuse in our culture and because of its connections with AD risk (Cataldo et al., 2010).

The prevailing theme of the third chapter has been to express the benefit of using a mobile phone app as a core component of a behavior change intervention—to yield the advantages offered by the pervasive nature of the mobile phone within an individual's daily life and routines. In our study, the mobile phone offered the opportunity for clinical effect to occur through behavior change. The app excelled as a delivery platform for the intervention, enabling the dissemination of educational intervention material, while simultaneously monitoring and encouraging positive behavior change. Our data showed that participants in the experimental group, after the 8-months intervention, reported decreased Total Cholesterol and decreased depressive symptoms. Although the interesting effect of behavior change in participants, observed during the 8-month RCT, based on the restricted size of our sample was not possible to reach a statistical significance, and the effect on future AD risk is still relatively unclear. It is evident that participants in the treatment group had favorable improvements across numerous psychological and physiological domains, suggesting that a sustained effort would contribute to better outcomes in the future. Due to the differences found between the low and high adherence to the treatment sub-groups, feedback and supports to assist these individuals to maintain healthy lifestyle choices should be importantly considered in future interventions. Moreover, in our study, each treatment group participant was asked to self-prioritize the seven behavioral domains. However, due to the limited number of our sample, we were not able to study the influence of the prioritization in the outcome. A future study could evaluate how much the intervention would be effective in the specific domains that were more highly prioritized at the individual participant level and try to monitor the interventions in order to increase participants' compliance.

REFERENCES

Akbaraly, T. N., Portet, F., Fustinoni, S., Dartigues, J. F., Artero, S., Rouaud, O., Touchon, J., Ritchie, K., & Berr, C. Leisure activities and the risk of dementia in the elderly results from the Three-City Study. Neurology. 2009; 73(11), 854-861.

Alberti-Fidanza, A., & Fidanza, F. (2004). Mediterranean adequacy index of Italian diets. *Public Health Nutrition,* 7, 937–941.

Alberti, A., Fruttini, D., & Fidanza, F. (2009). The mediterranean adequacy index: further confirming results of validity. *Nutrition, Metabolism and Cardiovascular Diseases, 19*, 61–66.

Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*, *3*(3).

Anstey, K. J., Bahar-Fuchs, A., Herath, P., Kim, S., Burns, R., Rebok, G. W., & Cherbuin, N. (2015). Body brain life: A randomized controlled trial of an online dementia risk reduction intervention in middle-aged adults at risk of Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, 1*(1), 72-80.

Anstey, K.J., Cherbuin, N., Budge, M., Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obesity Reviews, 12,* e426–37.

Anstey, K. J., Mack, H. A., & Cherbuin, N. (2009). Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. *The American Journal of Geriatric Psychiatry*, *17*(7), 542-555.

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., …. & Riemann, D. (2011) Insomnia as a predictor of depression: a met a-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders, 135*, 10–19.

Baker, L.D., Frank, L.L., Foster-Schubert, K., Green, P.S., Wilkinson, C.W., McTiernan, A. (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of Neurology, 67*, 71–79.

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., ... & Unverzagt, F. W. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama*, *288*(18), 2271-2281.

Ball, K., Edwards, J. D., & Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *62*(Special Issue 1), 19-31.

Bamidis, P. D., Vivas, A. B., Styliadis, C., Frantzidis, C., Klados, M., Schlee, W., & Papageorgiou, S. G. A review of physical and cognitive interventions in aging. Neuroscience & Biobehavioral Reviews. 2014; 44, 206-220.

Barnes, D. E., Santos-Modesitt, W., Poelke, G., Kramer, A. F., Castro, C., Middleton, L. E., & Yaffe, K.The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. JAMA Internal Medicine. 2013; 173(9), 797-804.

Barnett, J., Bahar-Fuchs, A., Cherbuin, N., Herath, P., & Anstey, K. (2015). Intervention to prevent cognitive decline and dementia in adults without cognitive impairment: A systematic review. *J Prevent Alzheimers Dis*, *2*, 38-44.

Basak, C., Boot, W. R., Voss, M. W., & Kramer, A. F. (2008). Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychology and Aging*, *23*(4), 765.

Beccuti, G., Pannain, S. (2011). Sleep and obesity. *Current Opinion in Clinical Nutrition and Metabolic Care*, 14, 402–412.

Berra, K. (2010). Challenges of changing lifestyle to reduce risk for cardiovascular disease. *Journal of Cardiovascular Nursing*, 25, 223–227.

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *Journal of Aging Research*, *2013*, 1-8.

Boyle, P.A., Buchman, A.S., Wilson, R.S., Leurgans, S.E., Bennett, D.A. (2009). Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Archives of Neurology* , 66, 1339–1344.

Brown, C. L., Gibbons, L. E., Kennison, R. F., Robitaille, A., Lindwall, M., Mitchell, M. B., ... & MacDonald, S. W. (2012). Social activity and cognitive functioning over time: a coordinated analysis of four longitudinal studies. *Journal of Aging Research*, *2012*.

Brummett, B.H., Babyak, M.A., Siegler, I.C., Vitaliano, P.P., Ballard, E.L., Gwyther, L.P., & Williams, R.B. (2006) Associations among perceptions of social support, negative affect, and quality of sleep in caregivers and noncaregivers. *Health Psychology*, *25*(2), 220–225.

Buckley, T., Norton, M. C., Deberard, M. S., Welsh-Bohmer, K. A., & Tschanz, J. T. (2010). A brief metacognition questionnaire for the elderly: comparison with cognitive performance and informant ratings the Cache County Study. *International journal of geriatric psychiatry, 25*(7), 739-747.

Buiza, C., Etxeberria, I., Galdona, N., González, M. F., Arriola, E., de Munain, A. L., ... & Yanguas, J. J. (2008). A randomized, two-year study of the efficacy of cognitive intervention on elderly people: the Donostia Longitudinal Study. *International Journal of Geriatric Psychiatry*, *23*(1), 85-94.

Caprara, G.V., Alessandri, G., Eisenberg, N., Kupfer, A., Steca, P., Caprara, M.G., ….. & Abela, J. (2012) The positivity scale. *Psychological Assessment*, *24*(3):701-12.

Carlson, J. E., Ostir, G. V., Black, S. A., & Markides, K. S. (1999). Disability in older adults 2: physical activity as prevention. *Behavioral Medicine*, *24*(4), 157.

Carvalho, A., Rea, I. M., Parimon, T., & Cusack, B. J. (2014). Physical activity and cognitive function in individuals over 60 years of age: a systematic review. *Clin Interv Aging*, *9*, 661-82.

Cataldo, J.K., Prochaska, J.J., Glantz, S.A. (2010). Cigarette smoking is a risk factor for Alzheimer's Disease: an analysis controlling for tobacco industry affiliation. *Journal of Alzheimer's disease, 19*(2), 465-80.

Cavallini, E., Pagnin, A., & Vecchi, T. (2003). Aging and everyday memory: the beneficial effect of memory training. *Archives of Gerontology and Geriatrics*,*37*(3), 241-257.

Cetin, E., Top, E. C., Şahin, G., Özkaya, Y. G., Aydin, H., & Toraman, F. (2010). Effect of vitamin E supplementation with exercise on cognitive functions and total antioxidant capacity in older people. *The Journal of Nutrition, health & aging*, *14*(9), 763-769.

Chaput, J.P., Despres, J.P., Bouchard, C., & Tremblay, A. (2008). The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. *Sleep, 31*, 517–523

Chaput, J.P., & Dutil, C. (2016). Lack of sleep as a contributor to obesity in adolescents: impacts on eating and activity behaviors. *International Journal of Behavioral Nutrition and Physical Activity*, *13*, 103.

Cheng, G., Huang, C., Deng, H., & Wang, H. (2012a). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Internal Medicine Journal*, *42*(5), 484-491.

Cheng, Y., Wu, W., Feng, W., Wang, J., Chen, Y., Shen, Y., ... & Li, C. (2012b). The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. *BMC medicine*, *10*(1), 1.

Chiu, C. C., Su, K. P., Cheng, T. C., Liu, H. C., Chang, C. J., Dewey, M. E., ... & Huang, S. Y. (2008). The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(6), 1538-1544.

Clare, L., Nelis, S. M., Jones, I. R., Hindle, J. V., Thom, J. M., Nixon, J. A., ... & Whitaker, C. J. The Agewell trial: a pilot randomised controlled trial of a behaviour change intervention to promote healthy ageing and reduce risk of dementia in later life. BMC Psychiatry.2015; 15(1), 1-19.

Clark, F., Jackson, J., Carlson, M., Chou, C. P., Cherry, B. J., Jordan-Marsh, M. & Wilcox, R. R. (2012). Effectiveness of a lifestyle intervention in promoting the well-being of independently living older people: results of the Well Elderly 2 Randomised Controlled Trial. *Journal of Epidemiology and Community Health*. *66*(9), 782-790.

Clinical Trials on Alzheimer's Disease (2015). *Health Interventions Boost Cognition - But Do They Delay Dementia?*. Available from: http://www.alzforum.org/news/conference-coverage/health-interventions-boost-cognition-do-they-delay-dementia

Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*, 386–96.

Coley, N., Andrieu, S., & MAPT Study Group (2017). Lessons from the Multidomain Alzheimer Preventive Trial - Authors' reply. *The Lancet Neurology, 16*(8):586..

Corbett, A., Owen, A., Hampshire, A., Grahn, J., Stenton, R., Dajani, S., ... & Ballard, C. (2015). The effect of an online cognitive training package in healthy older adults: an online randomized controlled trial. *Journal of the American Medical Directors Association*, *16*(11), 990-997.

Craig, C.L., Marshall, A.L., Sjostrom, M. (2003) International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise, 35,* 1381-95.

Curcio, G.G., Tempesta, D., Scarlata, S., Marzano, C., Moroni, F., Rossini, P.M., ….. & De Gennaro, L. (2013) Validity of the Italian version of the Pittsburgh sleep quality index (PSQI). *Neurological Sciences*, 34, 511–519.

Cyarto, E., Lautenschlager, N., Desmond, P.M., Ames, D., Szoeke, C., Salvado, O. (2012). Protocol for a randomized controlled trial evaluating the effect of physical activity on delaying the progression of white matter changes on MRI in older adults with memory complaints and mild cognitive impairment: the AIBL Active trial. *BMC Psychiatry, 12,* 167.

Dangour, A. D., Allen, E., Elbourne, D., Fasey, N., Fletcher, A. E., Hardy, P., ... & Uauy, R. (2010). Effect of 2-yn– 3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *The American Journal of Clinical Nutrition*, *91*(6), 1725-1732.

Dannhauser, T. M., Cleverley, M., Whitfield, T. J., Fletcher, B. C., Stevens, T., & Walker, Z. A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment–ThinkingFit: pilot and feasibility study for a randomized controlled trial. BMC Psychiatry.2014; 14(129), 1-9.

de Bruin, E. D., van Het Reve, E., & Murer, K. (2013). A randomized controlled pilot study assessing the feasibility of combined motor–cognitive training and its effect on gait characteristics in the elderly. *Clinical Rehabilitation*, *27*(3), 215-225.

de Jong, N., Paw, M. J. C. A., de Groot, L. C., Rutten, R. A., Swinkels, D. W., Kok, F. J., & van Staveren, W. A. (2001). Nutrient-dense foods and exercise in frail elderly: effects on B vitamins, homocysteine, methylmalonic acid, and neuropsychological functioning. *The American Journal of Clinical Nutrition*, *73*(2), 338-346.

Di Meco, A., Joshi, Y., Pratico, D. (2014). Sleep deprivation impairs memory, tau metabolism and synaptic integrity of a mouse model of Alzheimer's disease with plaques and tangles. *Neurobiology of Aging*, *35,* 1813–1820.

Doody, R., Thomas, R., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *New England Journal of Medicine, 370,* 311–321

Eckroth-Bucher, M. C., & Siberski, J. (2009). Preserving cognition through an integrated cognitive stimulation and training program. *American Journal of Alzheimer's Disease and other dementias*, *24*(3), 234-245.

Eggenberger, P., Schumacher, V., Angst, M., Theill, N., & de Bruin, E. D. (2015). Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. *Clinical Interventions in Aging*, *10*, 1335.

Elder, C.R., Gullion, C.M., Funk, K.L., Debar, L.L., Lindberg, N.M., Stevens, V.J. (2012). Impact of sleep, screen time, depression and stress on weight change in the intensive weight loss phase of the LIFE study. *International Journal of Obesity*, *36*, 86–92.

Eleuteri, S., Bellanti, G., Falaschi, P. (2016). Hip fracture: preliminary results supporting significative correlations between the psychological wellbeing of patients and their relative caregivers. *Journal of Gerontology & Geriatrics, 64,* 104-111.

Eysenbach, G. (2005). The law of attrition. *Journal of Medical Internet Research, 7*, e11.

Fabre, C., Chamari, K., Mucci, P., Masse-Biron, J., & Prefaut, C.Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. International Journal of Sports Medicine. 2002; 23(06), 415-421.

Fagan, A.M., Xiong, C., Jasielec, M.S., Bateman, R.J., Goate, A.M., Benzinger, T.L. (2014). Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. *Science Translational Medicine, 6,* 226ra30.

Fagerstrom, K.O., & Schneider, N.G. (1989). Measuring nicotine dependence: A review of the Fagerstrom Tolerance Questionnaire. *Journal of Behavioral Medicine*, *12*(2):159-82.

Fiatarone Singh, M. A., Gates, N., Saigal, N., Wilson, G. C., Meiklejohn, J., Brodaty, H., ... & Baker, M. K.The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. Journal of the American Medical Directors Association. 2014; 15(12), 873-880.

Fissler, P., Küster, O., Schlee, W., & Kolassa, I. T. Novelty interventions to enhance broad cognitive abilities and prevent dementia: synergistic approaches for the facilitation of positive plastic change. Progress in Brain Research. 2013; 207, 403-434.

Fratiglioni, L., Paillard-Borg, S., & Winblad, B. (2004). An active and socially integrated lifestyle in late life might protect against dementia. *The Lancet Neurology*, *3*(6), 343-353.

Fratiglioni, L., & Qiu, C. (2009). Prevention of common neurodegenerative disorders in the elderly. *Experimental gerontology*, *44*(1), 46-50.

Fratiglioni, L., Wang, H.-X., Ericsson, K., Maytan, M., Winblad, B. (2000). Influence of social network on occurrence of dementia: a communitybased longitudinal study. *Lancet*, *355,* 1315–1319.

Fried, L. P., Carlson, M. C., Freedman, M. M., Frick, K. D., Glass, T. A., Hill, M. J., ... & Wasik, B. A. (2004). A social model for health promotion for an aging population: initial evidence on the Experience Corps model. *Journal of Urban Health*, *81*(1), 64-78.

Geiker, N.R.W., Astrup, A., Hjorth, M.F., Sjödin, A., Pijls, L., & Markus, C.R. (2018). Does stress influence sleep patterns, food intake, weight gain, abdominal obesity and weight loss interventions and vice versa? *Obesity Reviews, 19*, 81–97.

Gildner, T.E., Liebert, M.A., Kowal, P., Chatterji, S., & Josh Snodgrass, J. (2014). Sleep duration, sleep quality, and obesity risk among older adults from six middle-income countries: findings from the study on global ageing and adult health. American Journal of Human Biology, *26*, 803–812.

Gillette-Guyonnet, S., Secher, M., & Vellas, B. (2013). Nutrition and neurodegeneration: epidemiological evidence and challenges for future research. *British Journal of Clinical Pharmacology*, *75*(3), 738-755.

Gottlieb, D.J., Punjabi, N.M., Newman, A.B., Resnick, H.E., Redline, S., Baldwin, C.M., & Nieto, F.J., (2005) Association of sleep time with diabetes mellitus and impaired glucose tolerance*. Archives of Internal Medicine, 165*, 863–867.

Gooneratne, N.S., & Vitiello, V.M. (2014) Normative changes, sleep disorders and treatment options. *Clinics in Geriatric Medicine, 30*, 591–627.

Guay, F., Vallerand, R. J., & Blanchard, C. (2000). On the assessment of situational intrinsic and extrinsic motivation: The Situational Motivation Scale (SIMS). *Motivation and emotion, 24*(3), 175-213.

Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., & Pipingas, A. (2016). Adherence to a Mediterranean-Style Diet and Effects on Cognition in Adults: A Qualitative Evaluation and Systematic Review of Longitudinal and Prospective Trials. *Frontiers in Nutrition*, *3*, 22.

Imtiaz, B., Tolppanen, A.M., Kivipelto, M., Soininen, H. (2014). Future directions in Alzheimer's disease from risk factors to prevention. *Biochemical Pharmacology, 88*, 661–70.

Jobe, J. B., Smith, D. M., Ball, K., Tennstedt, S. L., Marsiske, M., Willis, S. L., ... & Kleinman, K. (2001). ACTIVE: A cognitive intervention trial to promote independence in older adults. *Controlled Clinical Trials*, *22*(4), 453-479.

Joint Programme - Neurodegenerative Disease Research (2013). *Results of the 2013 JPND Transnational call for "European research projects for pilot studies on preventive strategies related to Neurodegenerative Diseases*. Available from: http://www.neurodegenerationresearch.eu/initiatives/annual-calls-for-proposals/closed-calls/preventive-strategies-2013/preventive-strategy-pilot-projects/

Jow, G.M., Yang, T.T., & Chen, C.L. (2006). Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *Journal of Affective Disorders, 90*, 21–27.

Karp, A., Paillard-Borg, S., Wang, H. X., Silverstein, M., Winblad, B., & Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders*, *21*(2), 65-73.

Kivipelto, M., Solomon, A., Ahtiluoto, S., Ngandu, T., Lehtisalo, J., Antikainen, R., ... & Lindström, J. (2013). The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): study design and progress. *Alzheimer's & Dementia*, *9*(6), 657-665.

Knutson, K.L., & Lauderdale, D.S. (2007). Sleep duration and overweight in adolescents: self-reported sleep hours versus time diaries. *Pediatrics, 119*, e1056–e1062.

Köbe, T., Witte, A. V., Schnelle, A., Lesemann, A., Fabian, S., Tesky, V. A., ... & Flöel, A. (2016). Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. *NeuroImage*, *131*, 226-238.

Kohatsu, N.D., Tsai, R., Young, T., Vangilder, R., Burmeister, L.F., Stromquist, A.M., & Merchant, J.A. (2006) Sleep duration and body mass index in a rural population. *Archives of Internal Medicine, 166*, 1701–1705.

Komulainen, P., Kivipelto, M., Lakka, T. A., Savonen, K., Hassinen, M., Kiviniemi, V., ... &

Rauramaa, R. (2010). Exercise, fitness and cognition–A randomised controlled trial in older individuals: The DR's EXTRA study. *European Geriatric Medicine*, *1*(5), 266-272.

Kraus, T., Haack, M., Schuld, A., Hinze-Selch, D., & Pollmacher, T. (2001). Low leptin levels but normal body mass indices in patients with depression or schizophrenia. *Neuroendocrinology, 73*, 243–247.

Lam, L. C. W., Chan, W. C., Leung, T., Fung, A. W. T., & Leung, E. M. F. (2015). Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial*. PloS One*, *10*(3), e0118173.

Langa, K. M., Larson, E. B., Karlawish, J. H., Cutler, D. M., Kabeto, M. U., Kim, S. Y., & Rosen, A. B. (2008). Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimer's & Dementia*, *4*(2), 134-144.

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine*, *144*(2), 73-81.

Lauenroth, A., Ioannidis, A. E., & Teichmann, B. (2016). Influence of combined physical and cognitive training on cognition: a systematic review. *BMC Geriatrics*, *16*(1), 141.

Launer, L.J., Ross, G.W., Petrovitch, H., Masaki, K., Foley, D., White, L.R. (2000). Midlife blood pressure and dementia: the Honolulu–Asia Aging Study. *Neurobiology of Aging, 21*, 49–55.

Legault, C., Jennings, J. M., Katula, J. A., Dagenbach, D., Gaussoin, S. A., Sink, K. M., & Espeland, M. A. (2011). Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. *BMC Geriatrics*, *11*(1),1.

Lombardo, C., Battagliese, G., Venezia, C., Salvemini, V. (2015). Persistence of poor sleep predicts the severity of the clinical condition after 6 months of standard treatment in patients with eating disorders. *Eating Behaviors, 18*, 16–19.

Lombardo, C., Cuzzolaro, M., Vetrone, G-, Mallia, L., Violani, C. (2011). Concurrent validity of the Disordered Eating Questionnaire (DEQ) with the Eating Disorder Examination (EDE) clinical interview in clinical and non clinical samples. *Eating and Weight Disorders*, *16*(3), e188–e198.

Lourida, I., Soni, M., Thompson-Coon, J., Purandare, N., Lang, I. A., Ukoumunne, O. C., & Llewellyn, D. J. (2013). Mediterranean diet, cognitive function, and dementia: a systematic review. *Epidemiology*, *24*(4), 479-489.

Lu, X.Y. (2007) The leptin hypothesis of depression: a potential link between mood disorders and obesity? *Current Opinion in Pharmacology, 7*, 648–652.

Lubben, J., Blozik, E., Gillmann, G., Iliffe, S., von Renteln Kruse, W., Beck, J. C., & Stuck, A. E. (2006). Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *The Gerontologist*, *46*(4), 503-513.

Lustig, C., Shah, P., Seidler, R., & Reuter-Lorenz, P. A. (2009). Aging, training, and the brain: a review and future directions. *Neuropsychology Review*, *19*(4), 504-522.

Mahncke, H. W., Connor, B. B., Appelman, J., Ahsanuddin, O. N., Hardy, J. L., Wood, R. A., ... & Merzenich, M. M. (2006). Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proceedings of the National Academy of Sciences*, *103*(33), 12523-12528.

Magee, C.A., Caputi, P., & Iverson, D.C. (2010). Is sleep duration associated with obesity in older Australian adults? *Journal of Aging and Health*, *22*, 1235–1255.

Martin, M., Clare, L., Altgassen, A. M., Cameron, M. H., & Zehnder, F. (2011). Cognition-based interventions for healthy older people and people with mild cognitive impairment. *The Cochrane Library*, 1.

Martinez-Lapiscina, E. H., Clavero, P., Toledo, E., San Julian, B., Sanchez-Tainta, A., Corella, D., ... & Martinez-Gonzalez, M. A. (2013). Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *The Journal of Nutrition, health & aging*, *17*(6), 544-552.

McCarney, R., Warner, J., Iliffe, S., van Haselen, R., Griffin, M., & Fisher, P. (2007). The Hawthorne Effect: a randomised, controlled trial. *BMC Medical Research Methodology,* 7, 30.

McDougall, G. J., Becker, H., Pituch, K., Acee, T. W., Vaughan, P. W., & Delville, C. L. (2010). The SeniorWISE study: Improving everyday memory in older adults. *Archives of psychiatric nursing*, *24*(5), 291-306.

Mohr, D.C., Duffecy, J., Jin, L., Ludman, E.J., Lewis, A., Begale, M., McCarthy, M. Jr. (2010).

Multimodal e-mental health treatment for depression: a feasibility trial. *Journal of Medical Internet Research*, *12*(5):e48.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Wilson, R. S., ... & Schneider, J. (2003). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Archives of Neurology*, *60*(7), 940-946.

Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Bennett, D. A., & Aggarwal, N. T. (2015). MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimer's & Dementia*, *11*(9), 1007-1014.

Mowszowski, L., Batchelor, J., & Naismith, S. L. (2010). Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *International Psychogeriatrics*, *22*(04), 537-548.

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ……. & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*, 695–699.

Neafsey, E. J., & Collins, M. A. (2011). Moderate alcohol consumption and cognitive risk. *Neuropsychiatric Disease and Treatment*, *7*, 465.

Netz, Y., Wu, M. J., Becker, B. J., & Tenenbaum, G. (2005). Physical activity and psychological well-being in advanced age: a meta-analysis of intervention studies. *Psychology and Aging*, *20*(2), 272.

National Institutes of Health (2011). *NIH State-of-the-Science Conference: Preventing Alzheimer's Disease and Cognitive Decline*. Disponibile da https://consensus.nih.gov/2010/alzstatement.htm

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., ... & Lindström, J.A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet. 2015; 385(9984), 2255-2263.

Noice, T., Noice, H., & Kramer, A. F. (2013). Participatory arts for older adults: A review of benefits and challenges. *The Gerontologist*, *54*(5), 741-753..

Norton, M. C., Clark, C. J., Tschanz, J. T., Hartin, P., Fauth, E. B., Gast, J. A., ... & Lefevre, M. (2015). The design and progress of a multidomain lifestyle intervention to improve brain health in middle-aged persons to reduce later Alzheimer's disease risk: The Gray Matters randomized trial. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *1*(1), 53-62.

Norton, M.C., Eleuteri, S., Cerolini, S., Ballesio, A., Conte, S.C., Falaschi, P., & Lucidi, F. (2018). Is poor sleep associated with obesity in older adults? A narrative review of the literature. *Eating and Weight Disorders, 23*(1), 23-38.

Novelli, G., Papagno, C., Capitani, E., & Laiacona, M. (1986). Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. *Archivio di psicologia, neurologia e psichiatria, 47*(4), 477-506.

Ohayon, M.M., & Vecchierini, M.F. (2005). Normative sleep data, cognitive function and daily living activities in older adults in the community. *Sleep, 28*, 981–989.

Olanrewaju, O., Clare, L., Barnes, L., & Brayne, C. (2015). A multimodal approach to dementia prevention: A report from the Cambridge Institute of Public Health. *Alzheimer's & Dementia: translational research & clinical interventions*, *1*(3), 151-156.

Oswald, W. D., Gunzelmann, T., Rupprecht, R., & Hagen, B. (2006). Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. *European Journal of Ageing*, *3*(4), 179-192.

Paillard-Borg, S., Fratiglioni, L., Winblad, B., & Wang, H. X. (2009). Leisure activities in late life in relation to dementia risk: principal component analysis. *Dementia and Geriatric Cognitive Disorders*, *28*(2), 136-144.

Panagiotakos, D.B., Pitsavos, C., Stefanadis, C. (2006) Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutrition, Metabolism and Cardiovascular Diseases*, *16*, 559–568.

Papp, K. V., Walsh, S. J., & Snyder, P. J. (2009). Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. *Alzheimer's & Dementia*, *5*(1), 50-60.

Pieramico, V., Esposito, R., Sensi, F., Cilli, F., Mantini, D., Mattei, P. A., & Romani, G. L. (2012). Combination training in aging individuals modifies functional connectivity and cognition, and is potentially affected by dopamine-related genes. *PLoS One*, 7(8), e43901.

Pilcher, J.J., Ginter, D.R., & Sadowsky, B. (1997) Sleep quality versus sleep quantity: relationships between sleep and measures of health, well-being and sleepiness in college students. *Journal of Psychosomatic Research, 42*, 583–596.

Pitkala, K. H., Routasalo, P., Kautiainen, H., Sintonen, H., & Tilvis, R. S. (2011). Effects of socially stimulating group intervention on lonely, older people's cognition: a randomized, controlled trial. *The American Journal of Geriatric Psychiatry*, *19*(7), 654-663.

Prochaska, J.O., & DiClemente, C.C. (2005). The transtheoretical approach. In: Norcross JC, Goldfried MR, eds. Handbook of psychotherapy integration. 2nd ed. New York: Oxford University Press, p. 147–71.

Psaltopoulou, T., Sergentanis, T. N., Panagiotakos, D. B., Sergentanis, I. N., Kosti, R., & Scarmeas, N. (2013). Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Annals of Neurology*, *74*(4), 580-591.

Qiu, C., Kivipelto, M., & von Strauss, E. (2009). Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci*, *11*(2), 111-128.

Quadri, P., Fragiacomo, C., Pezzati, R., Zanda, E., Forloni, G., Tettamanti, M., & Lucca, U. (2004). Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. *The American Journal of Clinical Nutrition*, *80*(1), 114-122.

Radloff, L.S. (1997). The CES-D scale: a self report depression scale for research in the general population. Applied Psychological Measurement, *1*, 385–401.

Rakesh, G., Szabo, S.T., Alexopoulos, G.S., & Zannas A.S. (2017). Strategies for dementia prevention: latest evidence and implications. *Therapeutic Advances in Chronic Disease*, *8*(8-9): 121–136.

Rapp, S., Brenes, G. M. A. P., & Marsh, A. P. (2002). Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. *Aging & Mental health*, *6*(1), 5-11.

Rathod, R., Kale, A., & Joshi, S. (2016). Novel insights into the effect of vitamin B 12 and omega-3 fatty acids on brain function. *Journal of Biomedical Science*, *23*(1), 17.

Rebok, G. W., Ball, K., Guey, L. T., Jones, R. N., Kim, H. Y., King, J. W., ... & Willis, S. L. (2014). Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *Journal of the American Geriatrics Society*, *62*(1), 16-24.

Richard, E., Jongstra, S., Soininen, H., Brayne, C., van Charante, E. P. M., Meiller, Y., ... & Ngandu, T. (2016). Healthy Ageing Through Internet Counselling in the Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment. *BMJ Open*, *6*(6), e010806.

Richard, E., Van den Heuvel, E., van Charante, E. P. M., Achthoven, L., Vermeulen, M., Bindels, P. J., & Van Gool, W. A. (2009). Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. *Alzheimer Disease & Associated Disorders*, *23*(3), 198-204.

Ridge, P.G., Mukherjee, S., Crane, P.K., Kauwe, J.S.K. (2013). Alzheimer's disease: analyzing the missing heritability. *PLoS One*, *18*, e79771.

Rolland, Y., van Kan, G.A., Vellas, B. (2008). Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives. *Journal of the American Medical Directors Association, 9*, 390–405.

Rosenthal, R.L. (2000). Effectiveness of altering serum cholesterol levels without drugs. *Baylor University Medical Center Proceedings, 13*(4): 351–355.

Saczynski, J. S., Willis, S. L., & Warner Schaie, K. (2002). Strategy use in reasoning training with older adults. *Aging, Neuropsychology, and Cognition*, *9*(1), 48-60.

Saczynski, J.S., Pfeifer, L.A., Masaki, K., Korf, E.S., Laurin, D., White, L. (2006). The effect of social engagement on incident dementia. The Honolulu– Asia Aging Study. *American Journal of Epidemiology, 163*, 433–440.

Salloway, S., Sperling, R., Fox, N.C., Blennow, K., Klunk, W., Raskind, M. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. New England Journal of Medicine, 370, 322–33.

Scarmeas, N., Levy, G., Tang, M. X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. *Neurology*, *57*(12), 2236-2242.

Schrijvers, E. M., Verhaaren, B. F., Koudstaal, P. J., Hofman, A., Ikram, M. A., & Breteler, M. M. (2012). Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology*, *78*(19), 1456-1463.

Schulz, R., Hebert, R., Boerner, K. (2008). Bereavement after caregiving. *Geriatrics*, *63*(1), 20–22.

Seeman, T. E., Miller-Martinez, D. M., Merkin, S. S., Lachman, M. E., Tun, P. A., & Karlamangla, A. S. (2011). Histories of social engagement and adult cognition: midlife in the US study. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *66*(suppl 1), i141-i152.

Shatil, E. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. Frontiers in Aging Neuroscience. 2013; 5, 8.

Sherer, M., Maddux, J. E., Mercandante, B., Prentice-dunn, S., Jacobs, B., & Rogers, R. W. (1982). The Self-efficacy Scale: Construction and validation. *Psychological Reports, 51*(2), 663-671.

Sindi, S., Mangialasche, F., & Kivipelto, M. (2015). Advances in the prevention of Alzheimer's disease. *F1000prime reports*, 7-50.

Sink, K. M., Espeland, M. A., Castro, C. M., Church, T., Cohen, R., Dodson, J. A., ... & Lopez, O. L. (2015). Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. *JAMA*, *314*(8), 781-790.

Singh, M. A. F., Gates, N., Saigal, N., Wilson, G. C., Meiklejohn, J., Brodaty, H., ... & Baker, M. K. (2014). The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *Journal of the American Medical Directors Association*, *15*(12), 873-880.

Smart, E. L., Gow, A. J., & Deary, I. J. (2014). Occupational complexity and lifetime cognitive abilities. *Neurology*, *83*(24), 2285-2291.

Smith, P. J., Blumenthal, J. A., Babyak, M. A., Craighead, L., Welsh-Bohmer, K. A., Browndyke, J. N.... & Sherwood, A. (2010). Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension*, *55*(6), 1331-1338.

Solfrizzi, V., Colacicco, A.M., D'Introno, A., Capurso, C., Del Parigi, A., … & Capurso, S.A. (2006). Dietary polyunsaturated fatty acids intakes and rate of mild cognitive impairment. The Italian Longitudinal Study on Aging. *Experimental Gerontol*ogy, *41*, 619-627.

Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J., Whitmer, R. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dementia and Geriatric Cognitive Disorders, 28*, 75–80.

Spinnler, H., Tognoni, G. (1987). "Standardizzazione e Taratura Italiana di Test

Neuropsicologici," *The Italian Journal of Neurological Sciences, 6*(S8):44-46.

Spirduso, W. W., & Cronin, D. L. (2001). Exercise dose–response effects on quality of life and independent living in older adults. *Medicine & Science in Sports & Exercise*, *33*(6), S598-S608.

Stine-Morrow, E. A., Parisi, J. M., Morrow, D. G., & Park, D. C. (2008). The effects of an engaged lifestyle on cognitive vitality: a field experiment. *Psychology and Aging*, *23*(4), 778.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015-2028.

Stern, C., & Munn, Z. (2010). Cognitive leisure activities and their role in preventing dementia: a systematic review. *International Journal of Evidence-Based Healthcare*, *8*(1), 2-

Strauss, E., Sherman, E., & Spreen, O. (2006). Rey Auditory Verbal Learning Test. Compendium of Neuropsychological Tests (3rd Edition), Oxford University Press, 776-807.

Tesky, V. A., Köbe, T., Witte, A.V., Flöel, A., Schuchardt, J.P., Hahn, A., & Pantel, J. (2017) Feasibility and first results of a group program to increase the frequency of cognitively stimulating leisure activities in people with mild cognitive impairment (AKTIVA-MCI). *Clinical Intervention in Aging*, *12*(12), 1459-1469.

Tesky, V. A., Thiel, C., Banzer, W., & Pantel, J. Effects of a group program to increase cognitive performance through cognitively stimulating leisure activities in healthy older subjects: The AKTIVA study. GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry. 2011; 24(2), 83.

Theill, N., Schumacher, V., Adelsberger, R., Martin, M., & Jäncke, L. (2013). Effects of simultaneously performed cognitive and physical training in older adults. *BMC Neuroscience*, *14*(1), 1.

Unverzagt, F. W., Guey, L. T., Jones, R. N., Marsiske, M., King, J. W., Wadley, V. G., ... & Tennstedt, S. L. (2012). ACTIVE cognitive training and rates of incident dementia. *Journal of the International Neuropsychological Society*, *18*(04), 669-677.

Vaatainen, S., Tuomilehto, H., Saramies, J., Tuomilehto J., Uusitalo, H., Hussi, E., ……. & Martikainen, J. (2013). The health-related quality-of-life impact of nocturnal awakenings in the middle-aged and older Finnish population. *Quality of Life Research, 22*, 2737–2748.

Valenzuela, M., & Sachdev, P. (2009). Can cognitive exercise prevent the onset of dementia?

Systematic review of randomized clinical trials with longitudinal follow-up. *The American Journal of Geriatric Psychiatry*, *17*(3), 179-187.

van Charante, E. P. M., Richard, E., Eurelings, L. S., van Dalen, J. W., Ligthart, S. A., Vanpre Bussel, E. F., ... & van Gool, W. A. (2016). Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *The Lancet*, *388*(10046), 797-805.

Verghese, J., LeValley, A., Derby, C., Kuslansky, G., Katz, M., Hall, C., ... & Lipton, R. B. (2006). Leisure activities and the risk of amnestic mild cognitive impairment in the elderly. *Neurology*, *66*(6), 821-827.

Visser, M., Pluijm S.M., Stel V.S., Bosscher R.J., Deeg D.J., Longitudinal Aging Study Amsterdam (2002). Physical activity as a determinant of change in mobility performance: the Longitudinal Aging Study Amsterdam. *Journal of the American Geriatric Society, 50(11)*, 1774-81.

Vitaliano, P.P., Russo, J., Scanlan, J.M., Greeno, C.G. (1996). Weight changes in caregivers of Alzheimer's care recipients: psychobehavioral predictors. *Psychology and Aging*, 11, 155–63.

von Arnim, C. A., Herbolsheimer, F., Nikolaus, T., Peter, R., Biesalski, H. K., Ludolph, A. C., ... & Nagel, G.

(2012). Dietary antioxidants and dementia in a population-based case-control study among older people in South Germany. *Journal of Alzheimer's Disease*, *31*(4), 717-724.

Wahbeh, H., Goodrich, E., & Oken, B. S. (2016). Internet mindfulness meditation for cognition and mood in older adults: a pilot study. *Alternative therapies in health and medicine*, *22*(2), 44-53.

Whalley, L. J., Dick, F. D., & McNeill, G. A life-course approach to the aetiology of late-onset dementias. The Lancet Neurology. 2006; 5(1), 87-96.

Weiner, M.R., Monin, J.K., Mota, N., Pietrzak, R.H. (2016). Age Differences in the Association of Social Support and Mental Health in Male U.S. Veterans: Results From the National Health and Resilience in Veterans Study. *American Journal of Geriatric Psychiatry, 24*(4):327-36

Wengreen, H., Munger, R. G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., ... & Welsh-Bohmer, K. A. (2013). Prospective study of Dietary Approaches to Stop Hypertension–and Mediterranean-style dietary patterns and age-related cognitive change: the Cache County Study on Memory, Health and Aging. *The American Journal of Clinical Nutrition*, *98*(5), 1263-1271.

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., ... & Wright, E. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *Journal of the American Medical Association*, *296*(23), 2805-2814.

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., ... & Bennett, D. A. (2007). Loneliness and risk of Alzheimer disease. *Archives of general psychiatry*, *64*(2), 234-240.

Witte, A. V., Kerti, L., Hermannstädter, H. M., Fiebach, J. B., Schreiber, S. J., Schuchardt, J. P., ... & Flöel, A. (2014). Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cerebral Cortex*, *24*(11), 3059-3068.

Wolinsky, F. D., Mahncke, H., Vander Weg, M. W., Martin, R., Unverzagt, F. W., Ball, K. K., ... & Tennstedt, S. L. (2010). Speed of processing training protects self-rated health in older adults: enduring effects observed in the multi-site ACTIVE randomized controlled trial. *International Psychogeriatrics*, *22*(03), 470-478.

Yokoyama, H., Okazaki, K., Imai, D., Yamashina, Y., Takeda, R., Naghavi, N., ... & Miyagawa, T. (2015). The effect of cognitive-motor dual-task training on cognitive function and plasma amyloid β peptide 42/40 ratio in healthy elderly persons: a randomized controlled trial. *BMC Geriatrics*, *15*(1), 1.

Zeng, Z., Deng, Y.H., Shuai, T., Zhang, H., Wang, Y., & Song, G.M. (2016). Effect of physical activity training on dementia patients: A systematic review with a meta-analysis, *Chinese Nursing Research, 3*(4), 168-175.

Zimet, G.D., Dahlem, N.W., Zimet S.G., & Farley, G.K. (1988). The Multidimensional Scale of Perceived Social Support, *Journal of Personality Assessment, 52*(1), 30-41.

Zimmerman, M.E., Bigal, M.E., Katz, M.J., Derby, C.A., & Lipton, R.B. (2013). Are sleep onset/maintenance difficulties associated with medical or psychiatric comorbidities in nondemented community-dwelling older adults? *Journal of Clinical Sleep Medicine*, *9*, 363–369