Ann Ist Super Sanità 2016 | Vol. 52, No. 2: 240-248
DOI: 10.4415/ANN_16_02_16



# Mild cognitive impairment, from theory to practical intervention: "Camminando e leggendo… ricordo" (Walking and reading… I remember), an action plan. The Treviso Dementia (TREDEM) Registry

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**Abstract**
Dementia is one of the most disabling health conditions in older people. Increasing attention is paid to the preclinical phase of dementia and to the prevention programs to reduce the number of patients in the future. Aims of the current study are: a) to present Mild Cognitive Impairment (MCI) as a heterogeneous risk factor and to expose the relationship between cognitive impairment and lifestyles such as physical activity, Mediterranean diet, reading and socialization; b) to present a model, called "Camminando e leggendo… ricordo" (CLR), as a practical experience of secondary prevention aimed at MCI older people. The CLR model is composed of a program of physical and reading activities in group to promote healthy lifestyles. Here we present a protocol to evaluate the effectiveness of our intervention model. A multidimensional geriatric assessment will be carried out. A questionnaire for the detection of frailty, disability and for the adherence to the Mediterranean diet will be administered. The Psychological General Well-Being Index (PGWBI) will be used to assess the quality of life. CLR is an intervention model for secondary prevention in MCI subjects. It is the description of a practical proposal aimed at improving lifestyles and reducing the risk of dementia.

**Key words**
- Mild Cognitive Impairment (MCI)
- Cognitive Frailty (CF)
- physical activity
- TREDEM

## INTRODUCTION

Population aging is accompanied by an increase in the incidence of chronic diseases, including dementia, and healthcare costs [1-3]. Incidence of dementia in Italy paralleles that in most industrialized countries. In Italy, today, there are at least 1 million and 200 000 dementia patients [4] with 150-180 000 new cases each year [5, 6]. Alzheimer's disease is the most common form of dementia (over 60%) and affects at least 700 000 people, of which more than 85% are fully assisted by the family. In reference to the population over 65 years of age, the prevalence of dementia in the territory of the Local Health Authority n. 9 (LHA9) of Treviso is about 6700 cases, while the incidence is of 1700 new cases/year [4-6]. The population of Italy is among the oldest in the world, and the number of affected individuals is expected to grow. Increasing attention is therefore paid to the preclinical phase of the chronic diseases and to the prevention programs to reduce the number of patients in the future [7, 8]. As regards the topic of dementia, in

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recent years, much interest has been given to the initial stages of cognitive decline such as Mild Cognitive Impairment (MCI) [9-15] and Subjective Cognitive Impairment (SCI) [16, 17], and to hypotheses about the mechanisms underlying the onset of memory loss. In this context, an emerging interest has focused on the relationship between frailty and cognitive decline and on the recent concept of Cognitive Frailty (CF) [18-21].

Frailty is a multidimensional construct characterized by an age-related increased vulnerability to stressors due to reduced capacity of different physiological systems. Frailty is closely associated with adverse health outcomes, especially in older people, including falls, disability, hospitalizations, and mortality. The most common definition of frailty was developed by Fried *et al*. on the basis of work in the Cardiovascular Health Study (CHS) [22] and the Women's Health and Aging Studies (WHAS) [23]; this definition of frailty is limited to physical aspects.

Even though the frailty construct, introduced by Fried *et al.* [22], is widely used and accepted by the scientific community, there is evidence of the importance of considering other common age-related conditions such as cognitive impairment.

In recent years, there has been growing attention to the relationship between the physical and cognitive domains of the aging individual [24-30].

Recently, a consensus panel has proposed the identification of the so-called "cognitive frailty" as an heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and cognitive impairment. The key factors defining such a condition include the presence of physical frailty and cognitive impairment (Clinical Dementia Rating Scale, CDR = 0.5) and the exclusion of concurrent AD dementia or other dementias. In particular Kelaiditi *et al.* [18] underline that physical impairment is often responsible for increasing sedentary behavior and social isolation in older persons and that these two factors concur at determining a vicious cycle detrimental to the physical domain but may also explain a cognitive decline produced by factors independent of a neurodegenerative condition.

According to these considerations, there is a growing consensus to include cognitive impairment as a significant component of the operational definitions of frailty [26].

Aims of the current study are: a) to present MCI as a heterogeneous risk factor and to expose the relationship between cognitive impairment and lifestyles such as physical activity, Mediterranean diet, reading and socialization; b) to present a model as a practical experience of secondary prevention aimed at MCI older people.

In the analysis of the literature, we considered the manuscripts published in journals with impact factor and peer reviewers, preferring the most recent and most relevant ones in the PubMed free search engine.

## MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is defined as cognitive decline greater than expected for an individual's age and education level, which does not interfere notably with activities of daily life [9, 31]. In people aged 70 years and older, the reported prevalence of MCI ranges from 14 to 18% and the progression rate to dementia is 5-15% per year [32, 33]. MCI is widely considered a transition stage between normality and dementia [9], however not all patients with MCI convert to dementia: several studies reported that about 60% of these patients remains cognitively stable in a time range of about 2-3 years [34-36]. Furthermore, in other studies it was determined that 40% of MCI subjects returned cognitively normal at further follow-ups [37, 38]. Also MCI represents an extremely heterogeneous condition. MCI may represent the clinical manifestation of an incipient neurodegenerative process, thus constituting the early stage of AD and other dementias. However, it may also represent the "cognitive" expression of other underlying pathological conditions, not confined to the brain and cognitive domain. In this case, the progression of MCI to dementia is not obvious nor unavoidable [39]. The heterogeneous aspects of MCI and the different trajectories in the evolution of this situation suggest that it may be sustained also by non-neurodegenerative factors such as cognitive frailty. The concept of cognitive frailty may provide useful insights for better exploring the complex construct of early stages of cognitive impairment.

Boyle *et al.* [40] notice a relation between physical frailty and an increased risk of MCI and a more rapid rate of cognitive decline in aging. In their study physical frailty was associated with a greater decline in global cognition and in five specific cognitive systems. These data may suggest that physical frailty and cognitive impairment share a common underlying pathogenesis. For example, many risk factors for cardiovascular disease such as inflammation, hypertension, diabetes, dyslipidemia, and hyperhomocysteinemia are possibly responsible for brain damage and are strongly associated with frailty [18]. Regular physical activity, nutrition, social contacts and cognitively stimulating activities such as reading, have been individually correlated to cognitive status [41-44]. In particular, these activities play a protective role against both the onset and the progression of MCI to dementia.

Most available observational studies have shown that such activities are associated with a reduced risk of dementia. Nevertheless, there are still only few studies, with RCT design, that have shown that physical and cognitive interventions may actually prevent dementia or MCI progression.

Further studies are therefore required to develop prevention programs, at the intermediate stage between normality and pathology, with the goal of delaying the onset of dementia.

## PHYSICAL ACTIVITY AND COGNITIVE IMPAIRMENT

Some evidence indicates that motor and cognitive systems are both likely to be influenced by processes, both developmental and degenerative, which regulate CNS function; this suggestion has been termed the "common cause" hypothesis [45, 46]. Sustaining this hypothesis is the evidence that both cognitive and

physical performance can be negatively influenced in parallel by factors such as chronic disease, sedentary lifestyles and poor socioeconomic conditions [47-52]. Many studies demonstrated that poor baseline physical performance results in cognitive impairment or dementia [26, 27, 42, 52-63]. Two of our recent studies are in line with these findings, in fact good physical performance seems to play as a protective factor against cognitive decline [64-65].

Increasing evidence indicates, through prospective studies, that regular exercise is able to reduce the risk of MCI and dementia [66]. Among patients with dementia or MCI, RCTs and cross-sectional studies show improvement in cognitive scores after 6 months-1 year of exercise, increase in volume of the hippocampus and improved spatial memory [67-69]. Neuroimaging studies of cognitive networks also show that regular exercise improves connectivity and increases neuroplasticity which translates into better learning skills [70]. Aerobic exercise was the training regimen in most of the trials showing significant improvement in global cognitive function. Isolated resistance training was studied in trials and produced significant effects on memory [71]. While it is still unclear what type of exercise is most beneficial and at what age it has to start, much more research seems to be required to understand dose response linkages between exercise and cognitive effects. Currently, the American College of Sports Medicine recommends that exercise programs for older adults include both aerobic and non-aerobic physical activities, such as resistance training, balance training, and stretching for optimal general health (www.acsm.org/docs/current-comments/exerciseandtheolderadult.pdf). Older adults can benefit a lot from a combination of exercise that can build strength, maintain bone density, improve balance, coordination and mobility, reducing the risk of falling and helping maintain independence in performing activities of daily life. Even moderate exercise can improve the health of people who are frail or who have diseases associated with aging.

Several explanations for the protective effect of physical activity on cognitive functions have been suggested. Possible mechanisms underlying the relationship between physical activity and cognition are indirect, through the positive effect of physical activity on brain vascularity (pressure reduction, improvement of the lipoprotein profile, increased perfusion) and direct on the brain through the preservation of the neuronal structure and major changes in plasticity in the hippocampus [72]. Furthermore, physical activity reduces cardiovascular risk factors (diabetes, hypertension, obesity, dyslipidaemia) and the incidence of cardiovascular and cerebrovascular injuries, with global haemodynamic benefits [73]. Finally, it has been reported that an active lifestyle with regular physical exercise may prevent distress, reducing cortisol levels, which in turn can positively influence cognitive function [74].

## MEDITERRANEAN DIET AND COGNITIVE IMPAIRMENT

The term "Mediterranean diet" has not always been universally appreciated sometimes expressing marked differences not only between countries, but also within countries overlooking the Mediterranean Sea. In 1989 Ferro wrote: "It appears that currently there is insufficient material to give a proper definition of what the Mediterranean diet is or was in terms of well defined chemical compounds or even in terms of foods... The all embracing term "Mediterranean diet" should not be used in scientific literature..." [75]. This view was not shared by the majority of researchers in the following years and the term has spread as an expression of healthy eating, also thanks to tools that have defined the quantity and frequency of intakes [76].

The most widespread model of healthy eating is therefore the Mediterranean diet (MeDi), generally characterized by high consumption of plant foods (vegetables, fruits, legumes, and cereals), high intake of olive oil as the principal source of monounsaturated fat, moderate intake of fish, low intake of dairy products, low consumption of meat and poultry, and wine consumed in low to moderate amounts, normally with meals.

Adherence to a Mediterranean dietary pattern has been associated with longer survival, reduced risk of cardiovascular or cancer mortality, and reduced risk of neurodegenerative disease.

One of our recent works shows an association between a high adherence to a MedDi and a higher physical performance [77].

A MeDi might also have protective effects against cognitive decline in older individuals, because it combines several foods and nutrients potentially protective against cognitive dysfunction or dementia, such as fish, monounsaturated fatty acids, vitamins B12 and folate, antioxidants (vitamin E, carotenoids, flavonoids) and moderate amounts of alcohol. Higher levels of accordance with the MeDi has been linked to slower cognitive decline, reduced risk of AD and of transition from MCI to AD, and decreased mortality in AD patients. Therefore, higher adherence to the MeDi may affect the risk of both MCI and AD, probably influencing also disease progression [78, 79].

## READING AND COGNITIVE IMPAIRMENT

As we know, there are not many studies that have evaluated the effect of the habit of reading in older people on the changes in the cognitive profile. Uchida *et al.* [80] introduced a new cognitive intervention program for healthy aged people, and demonstrated that a daily training program involving reading and arithmetic problems was effective for the improvement of cognitive functions of community-dwelling elderly. Jefferson *et al.* [81] showed cross-sectional findings suggesting that education and reading ability are the most robust proxy measures of cognitive reserve in relation to late-life cognition. Nouchi *et al.* [82] used simple training tasks (reading aloud and simple calculation) to reveal the beneficial effects of learning therapy on a wide range of cognitive functions in elderly people. Our previous works showed that reading habits may play a protective role against cognitive decline [64, 65]. Public health programs that promote the diffusion of reading, even in old age, could reduce the incidence of cognitive impairment.

## SOCIALIZATION, EXPERIENTIAL FACTORS AND COGNITIVE IMPAIRMENT

Some reports have examined the relation of various aspects of social engagement to measures of cognitive and dementia status [83]. A study used data from 89 participants in the Rush Memory and Aging Project to investigate the potential protective effect of social networks [84]. Social networks were assessed by standard questions regarding the number of children, family and friends with whom the participant feels close to and how often they interacted with them. Social networks strongly modified the relation of both amyloid and tangles to cognition proximate to death such that amyloid and tangles had little effect on cognition in the presence of a large network. Another report examined the relation of loneliness, a measure of perceived social isolation, to cognitive outcomes [85]. The authors used data from more than 800 participants who completed a loneliness scale and found that loneliness was related to the development of incident AD and to rate of cognitive decline. The finding was robust and persisted after checking for numerous confounders including social networks, cognitive and physical activities, disabilty and depressive symptoms. One of our previous works examined the interaction of lifestyle factors and confirmed their positive effects on cognitive functions: physical activity, socialization and reading were associated with better cognitive performance and these correlations remained significant after adjusting for confounding factors, such as comorbidity and hearing function [64]. Another of our recent manuscripts shows that being married and not living alone affect the cognitive status and the response to long-term cholinesterase inhibitors therapy [86]. Emerging data suggest that psychological and experiential factors are associated with risk of Alzheimer disease (AD). Purpose in life, the psychological tendency to derive meaning from life's experiences and to possess a sense of intentionality that guides behaviour, has long been hypothesized to protect against adverse health outcomes [87-90]. In particular greater purpose in life is associated with a reduced risk of AD and MCI in community-dwelling older persons [91].

## AN ACTION PLAN

To elucidate the relationships between the concepts of MCI and healthy lifestyles in the light of the recent literature would be a fruitless exercise without resulting in practical initiatives. For this reason, we present a practical initiative of secondary prevention conducted in Treviso and aimed at MCI subjects and a protocol to evaluate the effectiveness of our intervention model.

The Local Health Authority n. 9 (LHA9) of Treviso and in particular the Department of Prevention is engaged in the organization of "Lasciamo il segno" (Let's leave our footprints), a local network for physical activity in accordance with the "Toronto Charter" [92] that currently involves 180 multisectorial partners (institutions, sports organizations, schools, private agencies) whose involvement can support health enhancing physical activity for all.

"Camminando e leggendo… ricordo" (CLR) (Walking and reading… I remember) is also an action in the framework of "Lasciamo il segno" aimed at MCI subjects and was built by the Cognitive Impairment Center and the Department of Prevention of LHA9. Our elderly MCI have practiced very little physical activity in their lives and have read even less due to their low education and their often low social and cultural level. So the biggest challenge was precisely the creation of a group of people who agreed to adhere to new, and for them unusual, activities.

The CLR physical exercise program we propose is composed of a two-phase group training with 30 minutes of walking at moderate intensity on a dirt path (1 to 2 miles, depending on participants' physical efficiency) and 30 minutes of exercises for balance, flexibility and joint mobilization; resistance training with small equipment and weights; gait training with rapid changes of direction (forward, backward, step crossover) and speed variation. Each session ends with 7 minutes of stretching. The subjects who enrol in this multicomponent program group, participate in the activities for 2 days/week under the supervision of a physical therapist and personal trainer; they are also encouraged to add more time walking or doing other aerobic activity at the week end. Consistently with the evidence about the association of physical activity, socialization and reading with better cognitive performance in particular among people who read novels and non-fiction [62], a bi-monthly "reading group activity", led by experienced trainers, has also been added.

This practice has the purpose of ensuring a cognitive stimulation: subjects are invited to comment on the readings and complete them at home. The combination of the two activities, always carried out in group, also offers an important opportunity for socialization. Most importantly, interventions such as these, that combine physical exercise and socialization with cognitive stimulation, are often more enjoyable for patients, leading the participants to adhere more closely to the whole program. During the physical activity and reading meetings the trainers often recommend adherence to healthy lifestyles, to the MeDi and quitting smoking, promoting a virtuous cycle of healthy behaviors.

Participants are raving about the proposed activities and they require the continuation and strengthening of the initiative. Given the success of this initiative and in the light of the evidence in the international literature, we have decided to monitor over time the participants together with a control group to carry out a pilot prospective observational study to support our model with scientific evidence. We also received funding from the "Center for the Control of Chronic Diseases" of the Italian Ministry of Health to assess the results, effectiveness and transferability of our model to other Italian regions.

We propose, therefore, to assess the promotion of physical activity, reading and healthy lifestyles in MCI subjects, to evaluate: 1) the rate of conversion to dementia compared to that of the control group; 2) the level of functional autonomy over time in the conduct of basal and instrumental activities of daily living (ADL, IADL) [93, 94]; 3) the quality of life of MCI subjects detected with ad hoc questionnaire such as "The Psychological General Well-Being Index" [95, 96].

All participants are outpatients attending the Cognitive Impairment Center and undergo a multidimensional assessment consisting of socio-demographic and clinical (cognitive, behavioral, neurological, functional, physical) evaluation as already described in TREDEM Study [97-100] and Registry [86]. All subjects undergo standard laboratory and instrumental workup for cognitive impairment (including assessment of thyroid-stimulating hormone, vitamin B12, folate, and homocysteine concentrations, as well as brain CT scan).

Among other scales and questionnaires, a questionnaire for the detection of frailty and disability realized by Cesari *et al.* [101] is administered to the participants to detect the characteristics of physical disability and frailty of the subjects participating in the CLR. The questionnaire consists of seven different questions. The first two questions, composing the "disability domain" of the questionnaire, are specifically aimed at identifying individuals with motor disability. Five additional questions are aimed at assessing signs, symptoms, or conditions commonly considered as possible components of the frailty syndrome [22].

We also propose to calculate the "Mediterranean-Style Dietary Pattern Score (MSDPS)" [102] to assess the conformity of an individual's diet to a traditional Mediterranean-style diet.

The local Ethic Committee approved the entire TREDEM Study and Registry protocol and the present study design. When formulating diagnosis to MCI subjects, the adhesion to the CLR group is proposed. Consensus criteria for the diagnoses of MCI [103] are adopted.

## CONCLUSIONS

MCI should be considered the manifestation of a global homeostatic disorder and should not be exclusively thought of as the prelude to unavoidable future dementia, but as a condition presenting potential for being reversed to normality [104]. Such framework may find support in the effectiveness of interventions targeting specific domains of the health status such as physical activity, social engagement etc., capable of produce more systemic benefits to the individual, including cognitive function [105]. In this context, the CLR intervention model is placed.

It is the description of a practical proposal aimed at improving lifestyles and reducing the risk of cognitive decline, which is the central part of the project "Implementation of an integrated model for the management of patients with dementia: from prevention to care" supported by the Italian Ministry of Health's National Center for the Prevention and Control of Diseases. This practical proposal is applied to MCI subjects. The Cesari's Questionnaire may be a useful risk index of cognitive frailty to identify those subjects most at risk of becoming demented and on which to concentrate all possible interventions.

There is a lack of observational studies of outcome research that can address policy decisions with the aim of slowing down the progression of cognitive impairment to dementia in the early stages of the disease. Several evidences cited in the literature show associations and not causal relationships also due to the large number of potential confounders, particularly in observational studies.

The CLR action plan goes towards the assessment tools to discriminate between MCI subjects that are likely to become demented and those that can potentially return to a state of normality. The early identification of these categories of persons may be useful in terms of saving money and suffering.

This paper has several points of strength. Firstly, as we know, there are no other Italian structured experiences in MCI subjects involving physical activity, reading exercises, socialization and stimulation to a greater adherence to the Mediterranean diet. Secondly, the Cesari's Questionnaire was applied to the community-dwelling older persons living in a rural area in France; as we know, it is the first time that it has been applied to MCI subjects attending an outpatients Cognitive Impairment Center. Thirdly, the sample group that we have been observing reside in their own homes and are representative of the real world. Finally, the study sample is part of the TREDEM sample which was well characterized by a large amount of data that was in part set out in previous published works [86, 97-100].

***Acknowledgements***

We are grateful to all the people who get ready to participate in this study and to Cristina Bastianello and Christopher Houston for manuscript editing. The authors have no competing interests related to the present submission.

***Conflict of interest statement***

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

*Submitted* on 30 June 2015.
*Accepted* on 8 January 2016.

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