ილიას სახელმწიფო უნივერსიტეტი

Dissertation thesis

The Community-Based Longitudinal Cohort Study of Mild Cognitive Impairment in Georgia

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To the Dean of the Faculty of Natural Sciences and Medicine of Ilia State University,

Assoc. Professor Elena Zhuravliova,

of the same faculty doctoral student Nino Shiukashvili

Statement

As the author of the submitted dissertation (The Community-Based Longitudinal Cohort Study of Mild Cognitive Impairment in Georgia), I declare that the work is my original work and does not contain material previously published, accepted for publication, or submitted by other authors that is not cited in the work or cited in accordance with the proper rules.

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Abstract

As the population ages, dementia is becoming one of the leading challenges for the healthcare system in both developing and developed countries. Dementia is a progressive disorder associated with the decline in different areas of cognitive function and the inability to carry out complex, as well as basic daily activities. There are several shreds of evidence, that MCI is the ultimate precondition of dementia and, based on DSM V criteria, patients with MCI, unlike dementia patients, tend to show no decline in complex daily activities.

The aim of the study is to observe the natural course of cognitive performance of healthy individuals and MCI patients in real-time for seven years period and, furthermore, find out the correlation of MCI with instrumental activities of daily living

A 7-year longitudinal community-based study was conducted in order to identify the cognitive changes over time among the population of Georgia in individuals aged 40 years or older. The investigation of participants' cognitive abilities was conducted twice using MoCA and the IADL was assessed at the end of the research for MCI and dementia patients, themselves and by their caregivers.

During follow-up visit, a changes of MoCA scores was detected in both healthy (mean change = - 0.9, SD = 2.1, t = - 3.51, $p < .002$, d = 0.73) and MCI groups group (mean change = - 1.7, SD = 2.1, t = - 5.23, $p < .003$, d = 0.81). Performing annualized change, showed 0.23-point decrease of MoCA scores in healthy individuals above 40s, whereas 0.57-point decrease was detected in patients with MCI of the same age. Patients with below cutoff for MCI overall score and MoCA-MIS showed 100% conversion to dementia. Statistically significant difference was found between the IADL scores of MCI and dementia patients and their caregivers (dementia group t=- 10.21 $p< 0.0001$; aMCI group t=-5.23, $p<0.002$; and na MCI group t=- 6.57, $p<0.001$).

Declined memory (lower MoCA-MIS scores), along with declined executive domain function (lower MoCA-EIS scores) can be a good predictor for MCI progression to dementia. MCI patients, and especially the aMCI subgroup, had some level of decreased self-awareness regarding their everyday functioning, therefore, the collecting information from caregivers/family members regarding patients' daily activities is important to make final decisions.

აბსტრაქტი

მოსახლეობის ასაკის მატებასთან ერთად, დემენცია ერთ-ერთი მნიშვნელოვანი გამოწვევა ხდება ჯანდაცვის სისტემისთვის როგორც განვითარებად, ისე განვითარებულ ქვეყნებში. დემენცია არის პროგრესირებადი დაავადება, რომელიც დაკავშირებულია კოგნიტური ფუნქციის სხვადასხვა სფეროს დაქვეითებასთან და რთული, ისევე როგორც ძირითადი ყოველდღიური აქტივობების განხორციელების შეზღუდვასთან. არსებობს რამდენიმე მტკიცებულება, რომ მსუბუქი კოგნიტური დარღვევები (Mild Cognitive Impairment) დემენციის საბოლოო წინაპირობაა და, DSM V კრიტერიუმებზე დაყრდნობით, მსუბუქი კოგნიტური დარღვევების მქონე პაციენტები, დემენციის მქონე პაციენტებისგან განსხვავებით, უფრო აქტიურები არიან და შეუძლიათ რთული ყოველდღიური საქმიანობის წარმართვა (Complex Instrumental Activities).

აღნიშნული კვლევის მიზანია დააკვირდეს ჯანმრთელი ინდივიდებისა და მსუბუქი კოგნიტური დარღვევების მქონე პაციენტებში კოგნიტური უნარების ბუნებრივი პროგრესირების კურსს რეალურ დროში 7 წლიანი ინტერვალით. გარდა ამისა, გამოიკვლიოს მსუბუქი კოგნიტური დარღვევების მქონე პაციენტების დამოუკიდებლობის ხარისხი.

ჩატარდა 7-წლიანი გრძივი კოჰორტული კვლევა, რათა გამოევლინა საქართველოს მოსახლეობაში 40 წელზე უფროსი ასაკის პირებში კოგნიტური ცვლილებების განვითარების ბუნებრივი კურსი. მონაწილეთა კოგნიტური შესაძლებლობების კვლევა ჩატარდა ორჯერ, მონტერეალის კოგნიტური შეფასების ტესტის (MoCA) გამოყენებით, ხოლო მონაწილეთა დამოუკიდებლობის ხარისხი შეფასდა IADL-კითხვარის მეშვეობით კვლევის ბოლოს, როგორც მსუბუქი კოგნიტური დარღვევების ასევე დემენციის მქონე პაციენტებში, თავად პაციენტების და მათი მომვლელების მიერ.

განმეორებითი ვიზიტის დროს, MoCA ქულების ცვლილებები გამოვლინდა როგორც ჯანმრთელ (Mean = - 0.9, SD = 2.1, t = - 3.51, p <.002, d = 0.73) და MCI ჯგუფებში (Mean = - 1.7, SD = 2.1, t = - 5.23, p <.003, d = 0.81). წლიური ცვლილების ინდექსმა (RCI) აჩვენა 40 წელზე უფროსი ასაკის ჯანმრთელ პირებში 0,23 პუნქტიანი შემცირება, ხოლო იმავე ასაკის მსუბუქი კოგნიტური დარღვევის მქონე პაციენტებში - 0,57 პუნქტიანი შემცირება. მსუბუქი კოგნიტური დარღვევის მქონე პაციენტების 100% პროგრესირდა და განუვითარდა დემენცია, რომელთა MoCA-ს საერთო ქულა და MoCA-MIS-ის ქულა ზღვარს ქვემოთ იყო. სტატისტიკურად მნიშვნელოვანი განსხვავება იქნა ნაპოვნი მსუბუქი კოგნიტური დარღვევის და დემენციის მქონე პაციენტების IADL ქულებსა და მათი მომვლელების შეფასებებს შორის (დემენციის ჯგუფი t=- 10.21 p<0.0001; aMCI ჯგუფი t=-5.23, p<0.002; და naMCI ჯგუფი t=- 6.57, p< 0.001).

მეხსიერების დაქვეითება (დაბალი MoCA-MIS ქულები), აღმასრულებელი დომეინის დაქვეითებულ ფუნქციასთან ერთად (დაბალი MoCA-EIS ქულები) შეიძლება გამოყენებულ იქნას მსუბუქი კოგნიტური დარღვევების დემენციისკენ პროგნოზირებისათვის. MCI პაციენტებს და განსაკუთრებით aMCI ქვეჯგუფს ჰქონდათ გარკვეული დონის შემცირებული თვითაღქმა მათი ყოველდღიური ფუნქციონირების და დამოუკიდებლობის ხარისხის შესახებ. შესაბამისად, მომვლელებისგან/ოჯახის წევრებისგან ინფორმაციის შეგროვება პაციენტების ყოველდღიურ საქმიანობასთან დაკავშირებით მნიშვნელოვანია საბოლოო გადაწყვეტილების მისაღებად.

Key words: Dementia, MCI, Mild cognitive impairment, MoCA, IADL

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List of abbreviations

AD – Alzheimer Disease

aMCI - amnestic MCI

BADL - Basic Activities of Daily Living

DSM - Diagnostic and Statistical Manual of Mental Disorders

IADL – Instrumental Activities of Daily Living

naMCI - Non-amnestic MCI

MCI – Mild Cognitive Impairment

MMSE - Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment test

SD - Standard Deviation

Introduction

As population ages, dementia is becoming one of the leading challenges for the health care system in both developing and developed countries (Suzman and Beard, n.d.2016). Dementia is a progressive disorder associated with the decline in different areas of cognitive function and the inability to carry out complex, as well as basic daily activities (Portet et al. 2006; Nasreddine et al. 2005). According to the World Health Organization, the number of people living with dementia is expected to double by 2050, and the increase in the numbers will be more marked in developing rather than developed countries (Figure 1):

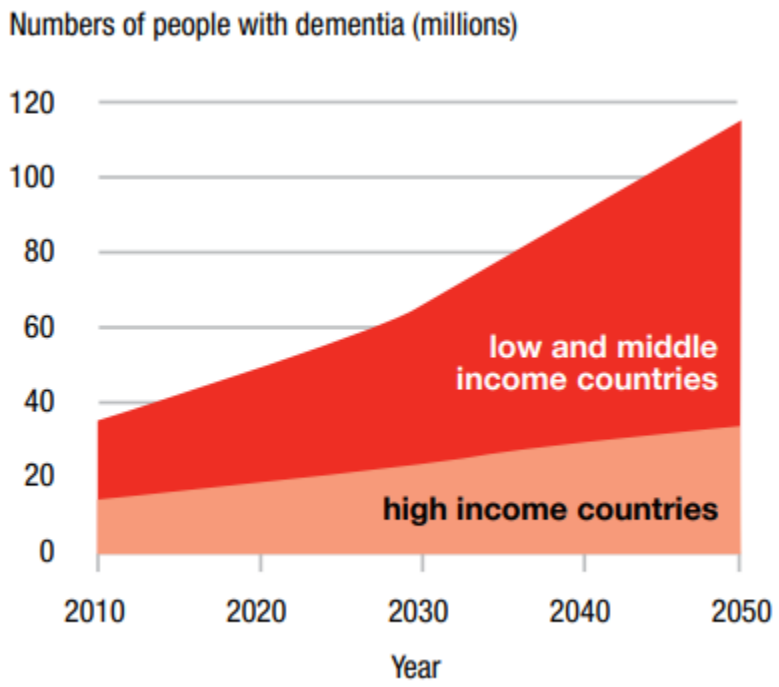


Figure 1: The growth in numbers of people with dementia in high income countries and low- and middle-income countries (Wimo and Prince 2010)

As neuropathological changes associated with dementia begin decades before the symptoms appear (Bookheimer et al. 2000; Braak et al. 1998), the half of the people go undiagnosed in the later stages leading to the increased socio-economic burden (Nichols et al. 2022). While

the patient is experiencing the prominent symptoms of dementia, there is already substantial neuronal loss and neuropathological changes over several parts of the brain with poor prognosis and decreased life expectancy (Zanetti, Solerte, and Cantoni 2009). It is noteworthy to mention that some aspects of dementia are possible to be reversed with several interventions, such as cognitive behavioral therapy (Carrion et al. 2018) or metabolic enhancement treatments (Bredesen et al. 2016). However, the prevention of the disorder is more promising once early detection of the symptoms occurs (Urakami 2016). The transitory period between a normal cognitive state to dementia is represented by Mild Cognitive Impairment (MCI) when the patient shows more than expected cognitive deficit considering the age and education keeping daily activities intact (Ronald C. Petersen et al. 1999). In order to detect early changes in cognitive abilities, brief screening tests are frequently used by the primary care physicians, such as Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) (Folstein, Folstein, and McHugh 1975; Nasreddine et al. 2005). Comparing the sensitivity and specificity of the MoCA to MMSE, MoCA showed a higher sensitivity for discriminating mild cognitive impairment from dementia. In contrast, MMSE was a sensitive tool for discriminating normal cognition from dementia with limited sensitivity for differentiating mildly impaired cognitive state (Damian et al. 2011). As cognitive abilities are closely related to language and verbal communication skills, our research team, considering the high sensitivity of MoCA to differentiate MCI from dementia, has translated MoCA into Georgian and validated it (Janelidze et al. 2017). Applying the validated MoCA, the prevalence of Mild Cognitive Impairment was established in the Georgian population (Janelidze et al. 2018).). The ongoing study's main aim is to determine the further performance of cognitive abilities among patients with MCI in follow-up.

1. Domains of Cognition

Neurocognitive disorders, as a separate cluster of disorders, first appeared in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV in 1994. Unlike the neurodevelopmental deficits that present from birth or early life, neurocognitive disorders are defined as a decline from the previous functioning level with significant impairment in social and occupational functioning. After revision in 2008, DSM-5 provided the framework for the diagnosis of neurocognitive disorders based on three syndromes: delirium, mild neurocognitive disorder, and major neurocognitive disorder (Sachdev et al. 2014; Guze 1995). The definition of cognition is heterogeneous among literature, but mainly it refers to the thinking process while acquiring knowledge and using already existing information through multiple domains (Sternberg, R. J. 2009). The deficit developed during neurocognitive disorders, although it is diverse among different authors (Neuber n.d. 2002), according to DSM V, there are six principal domains along with sub-domains: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition (See Figure 1):

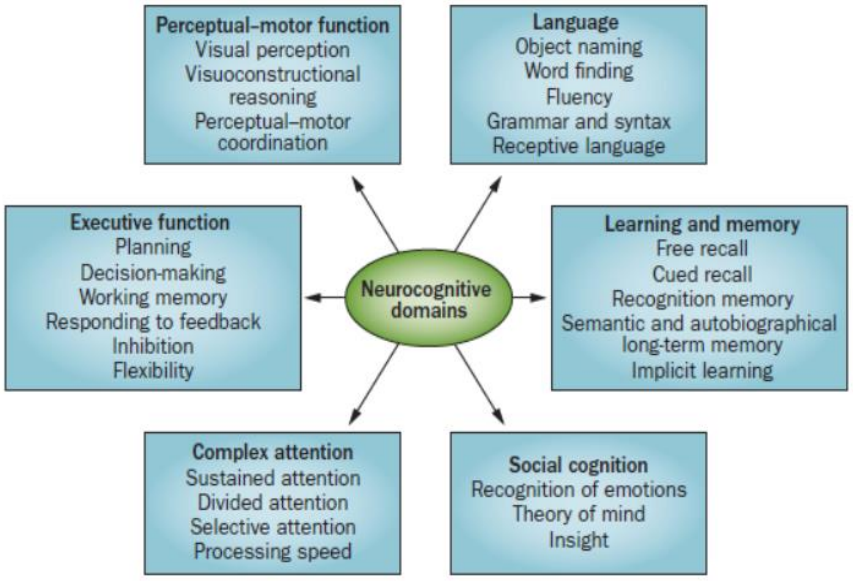


Figure 2: (Sachdev et al. 2014). Neurocognitive domains according to the DSM V (updated in 2013)

Perceptual-motor function: perception is defined as the ability to perform sensory-specific recognition of previously experienced or otherwise common stimuli. Although the ability of a person to detect a stimulus occurs in one of the five sensory modalities, the most commonly assessed perceptions under this domain are visual and auditory. Motor skills are composed of several different elements of motor activities, from balance and coordination to fine motor movements, but most motor tasks have minimal cognitive component. On the other hand, construction is the ability to copy or draw common objects. As it includes perceptual as well as motor activities, there are different opinions among researchers (Carone 2007; "Lezak. n.d.; (Shiffrin and Schneider 1984), however, the classic construction test, including the copying component, is successfully used in different diagnostic tests to assess perceptual-motor function along with executive function.

Attention and Concentration: attention and concentration, a complex, multi domain function, which is divided into two main sub-groups: selective attention and sustained attention (or vigilance). Selective attention is the ability to find out relevant and vital information while ignoring the non-relevant ones. In comparison, sustained attention is the ability to keep attention over some period of time. The tools assessing selective attention are mostly using dual tasks, such as two parallel information streams (for example, visual and auditory), while participants should prioritize the processing of one stream (Shiffrin and Schneider 1984). Sustained attention is mainly assessed with the continuous performance task (CPT) (Conners 1985), where the detection of simple stimuli, presented with some frequency among the stream of other stimuli, is the primary assignment for the participant. The balance between target and stream stimuli is the crucial factor, as 50% of frequency makes the task easier to perform, whereas the frequency of more than 50% makes the task more difficult because inhibition of the dominant response to respond to all stimuli is required, and even completely healthy people have an increased rate of mistakes.

Memory: Memory is the most complex among cognitive functions, and it is composed of several domains, such as working, episodic/declarative/explicit, procedural/motor, semantic, and prospective memories. Working memory is the ability to hold the information in consciousness for *maintenance* and *manipulation*. As the storage of information in working memory is duration and capacity limited, acquiring new information leads to the loss of previous information. Maintaining the information in working memory requires intact sensation, perception, and attention. As working memory is intensively used during executive functioning, researchers have different opinions regarding working memory assessment strategies. Typical tasks to assess working memory are simple exercises, where the participant has to recall recently given information or to recall information in the reversed format (Wechsler 1997; Gold et al. 1997; Baddeley 2000; McAvinue et al. 2013). Episodic/declarative/explicit memory interacts with working memory in order to transform information into long-term memory and recall the information from long-term memory into working memory. Transformation of the information from working into long-term memories involves a process known as encoding. The simplest task to assess this process is getting the information through the visual or auditory channels (listening/seeing) once or several times in order to recall them later (Brandt and Benedict 2001; Benedict 1997). Procedural memory is the learning of motor actions for long-term use. Although it possesses the learning part, most authors do not consider it as part of cognition but refer to it more as the motor function. Besides, procedural memory is mostly intact even in patients with amnesia and Alzheimer's Disease (AD) (Oudman et al. 2015; Strauss et al. 2006; Hirono et al. 1997). Semantic memory mainly refers to the process of long-term storage of verbal information, often referred to as long-term memory. It is less affected in healthy elderly individuals, although patients with cognitive impairment have difficulties in retrieving already encoded memories, as well as acquiring new memories (Lehrner et al. 2017; Meléndez et al. 2021). Assessment of it mainly involves visual and verbal tasks requiring the retrieval of the information previously stored in semantic memory (Heidinger and Lehrner 2020; Dresang, Dickey, and Warren 2019).

Prospective memory is the ability to remember to perform some tasks in the future in a time-based or event-based manner (for example: "taking medication at 10 AM" or "taking medication before breakfast") and, consequently, planning daily activities. A decline in prospective memory has serious consequences on an independent life, and impairment of this domain is observed even during the earliest stages of several neurological disorders (Henry 2021; Kliegel et al. 2016). There are different kinds of batteries to assess prospective memory changes, such as test batteries, single-trial measures, questionnaires, and experimental measures; however, all of them require performing a determined task at some established time along with the other ongoing tasks without reminding (Blondelle et al. 2020).

Executive functioning: Executive functioning is a part of cognitive domains, which is mainly responsible for reasoning and thinking abilities, including processing the given task, generating new ideas, thinking before performing the actions, and so forth., while staying focused (Diamond 2013). Executive function is a complex mental process mainly involving three core functions: inhibition and interference control (including self-controlling behavior and selective attention), working memory (to hold information in active form and process it), and cognitive flexibility (considering the changes of the perspective and building up another scenario/alternative reality based on the information in working memory in order to develop real-world adaptive behavior) (Miyake et al. 2000; Diamond 2013). As executive functioning requires "frontal lobe" tasks (Chayer and Freedman 2001), working and prospective memory functions, attention, and the speed to process the information, it requires sensitive tools to assess this domain, although clear boundaries between them are difficult to construct. The executive function domain declines less with the aging process, although the speed of processing the information and making relevant decisions declines over time (Bangen, Meeks, and Jeste 2013).

Language skills: In order to perceive and understand spoken language, reach the domains of semantic memory to retrieve and identify objects' names and respond to verbal instructions

with behavioral actions makes language skills a very complex domain of cognition. Some decline of language skills is observed in patients with Mild Cognitive Impairment (MCI) (Mueller et al. 2018), whereas a decline of language skills in patients with Major Cognitive disorders, like Alzheimer's Disease (AD), Lewy body disease, etc., is more prominent with significant impairment of semantic fluency rather than verbal intelligence (Henry, Crawford, and Phillips 2004).

Social Cognition: Social cognition, as a part of cognitive domains, first appeared in DSM V based on the fact that socially inappropriate behavior can be the silent indicator of starting point of some neurocognitive disorders, which later progresses into the declined ability to express empathy, recognize social issues, regulate social behavior, especially in response to feedback, etc. Although several social cognitive assessment measures are available for clinical use, social cognition is less assessed while diagnosing neurocognitive disorders, as it is the newly added domain (Henry et al. 2016).

Processing speed: The speed to perform cognitive functioning tasks is a very important ability, affected mainly by several neurological and psychiatric conditions. As the Speed of processing is tightly correlated with aging, it can be used as one of the biomarkers for cognitive aging (Deary, Johnson, and Starr 2010).

2. Normal Cognitive Aging

Based on several studies, the population worldwide is aging and, especially in developed countries, it will double by 2050 (Kanasi, Ayilavarapu, and Jones 2016; Ferrucci, Giallauria, and Guralnik 2008; M.-Y. Wang, Sung, and Liu 2022). As cognitive changes are observed not only in Mild or Major Cognitive Impairments but also detected as a part of normal aging, along

with the aging of the population, it is important to understand the process of normal aging and differentiate it from pathological conditions.

Several large-scale studies show that some cognitive domains start to decline even after the 30s'; the only exception is language skills, involving vocabulary knowledge, which progresses more up to the 70s' (Figure 2):

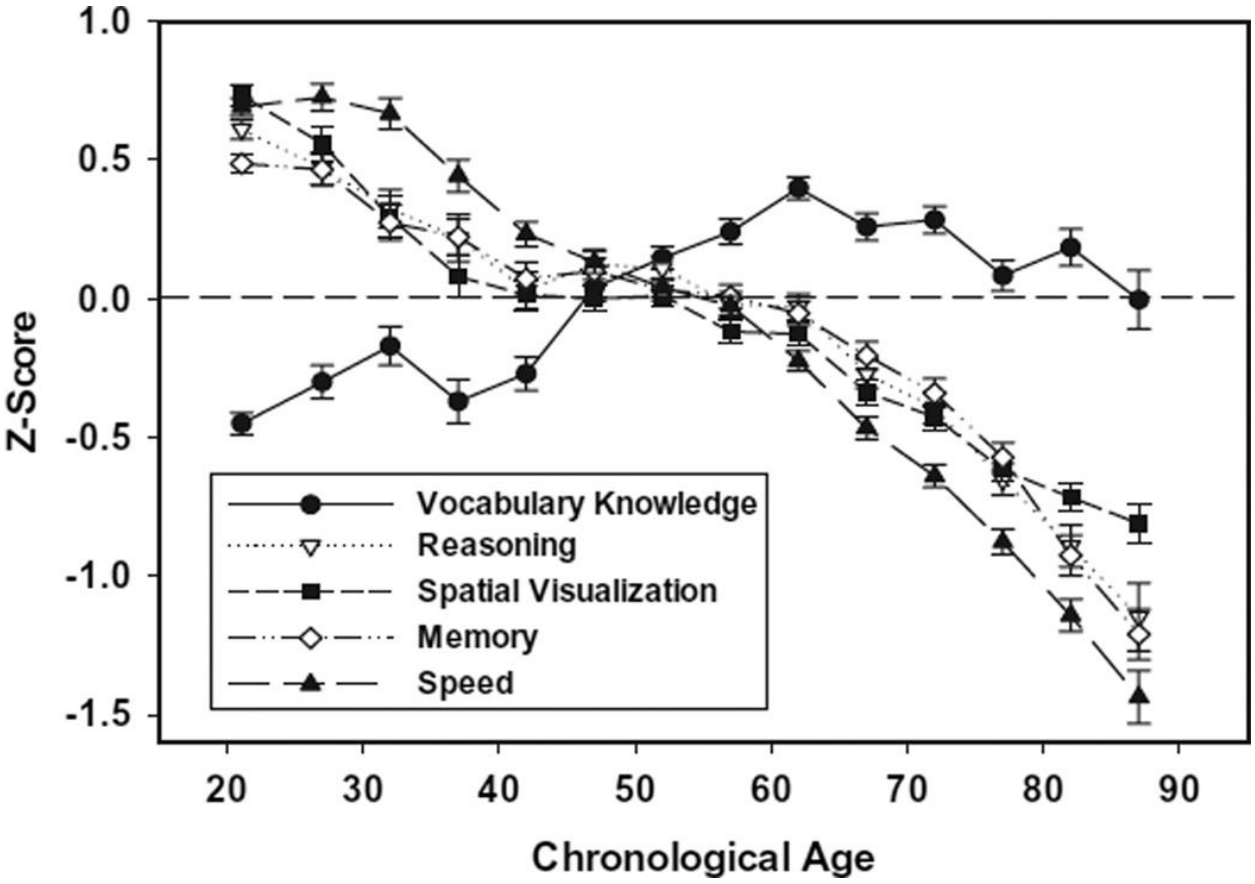


Figure 3. Means and standard errors for composite scores in five abilities as a function of age based on data from studies by Salthouse and colleagues (SALTHOUSE 2009).

The worse-performing domains during normal aging are memory along with processing speed. Researchers believe that the decline observed along with aging is mainly the result of decreased processing speed, which can affect the outcomes of many time-based cognitive assessment tests (T. A. Salthouse 1996).

Memory is another mostly affected cognitive domain in the normal aging process, which mostly are related to decreased processing speed (Small 2002) and declined ability to ignore less relevant information (Darowski et al. 2008; Holtzer, Stern, and Rakitin 2005). Episodic memory is less associated with aging and is observed to diminish throughout life, whereas semantic memory decline is more age-specific (Vallet et al. 2017). Procedural memory remains stable during the healthy aging process. Transformation of the information from working memory to long-term memory (encoding/acquisition), as well as retrieval of, especially, newly learned information from long-term into working memory, is severely affected by aging (Luo and Craik 2008), In contrast, retention of already learned information is intact in healthy individuals (Rhodes, Greene, and Naveh-Benjamin 2019).

Attention, the ability to get focused on some stimuli, declines over age; however, the ability to stay focused on a single stimulus declines slower compared to complex attention tasks with divided attention, such as talking and cooking at the same time (T. A. Salthouse et al. 1995; Carlson et al. 1995).

Language skills, along with vocabulary, is practically the only domain that is stable and even improves up to 70s' during the normal aging process (Wajman 2020; SALTHOUSE 2009; Zec et al. 2005).

Perceptual abilities remain intact along with the normal aging process, although visuospatial skills diminish over age (Howieson et al. 1993).

Executive functioning abilities are mostly declining over age. Inhibition of the response in order to form an alternative response negatively correlates with the aging process (N. S. Wecker et al. 2000). Concept formation, abstraction, and mental flexibility also decline over age, especially after the 70s' (Oosterman et al. 2010; Nancy S. Wecker et al. 2005), whereas the use of familiar information for reasoning remains more stable over age.

3. Dementia (Major Cognitive Disorder)

In the latest update of DSM V, instead of Dementia, the term – Major cognitive Disorder is used for several reasons; dementia is mainly referred to the senile cognitive impairment mostly associated with Alzheimer's Disease (AD) with consequent social stigma and limitation to give the same diagnosis for the younger patients with cognitive impairment due to other medical issues (Sachdev 2000; Sachdev et al. 2014). According to the DSM V, Major Cognitive Disorder/Dementia is defined as a disorder with significant cognitive decline from a previous level of performance in one or more cognitive domains and limited independence in, at least complex Instrumental Activities of Daily Living (IADL) with or without memory changes (Blazer 2013; Sachdev et al. 2014).

Published prevalence rates of dementia vary from 6 % to 37.4%, highly correlated with age (Jia et al. 2020; Plassman et al. 2007). A systematic review and meta-analysis conducted by Cao and colleagues in 2020 included all published data from 1985-2019 regarding dementia in a population above 50 years. While stratifying the results according to age, geographic area, and gender, the prevalence of all-cause dementia was 6.97% (CI95%: 5.46%-8.64%), the prevalence of Alzheimer type dementia was 3.24% ((CI95%: 2.28%-4.6%) and vascular type dementia - 1.16 (CI95%: 0.86%-1.57%). However, the prevalence of dementia among the population 100 years and older was 65.9%, which strongly indicates the age-correlating nature of dementia. Cao and colleagues also detected the sex-related deference among the dementia population: females were 1.9 times more prone to the development of AD-type dementia; however, the vascular type of dementia was 1.8 times more prominent in males. There was also a difference in the geographical distribution of dementia, with higher prevalence rates in Europe and North America than in Asia, Africa, and South America (Q et al. 2020). However, these geographical differences can be explained by the limited detection and diagnosis of dementia in developing countries compared with developed countries.

Another systematic review and meta-analysis conducted in 2016 by the Fiest and colleagues, including published data from 1985 to 2012, indicated a similar prevalence of dementia: pooled point and annual period prevalence estimates of dementia were 4.86% (CI95%: 4.2-5.63) and 6.91 (CI95%: 5.24-9.11). While according to the same article, the pooled incidence rate (same age and setting) was 1.72 (CI95%: 1.39-2.12) with an annual incidence proportion – 5.29 (CI95%: 3.31-8.44). Fiest and colleagues were not able to detect any geographical difference, unlike the study conducted by Cao and colleagues; however, both systematic reviews and meta-analyses showed a higher incidence of dementia among females compared to males (Km et al. 2016).

4. Mild Cognitive Impairment

According to the DSM V, Mild Cognitive impairment (MCI) is a state of cognitive decline from previous performance level in one or more cognitive domains, which do not interfere with independence in everyday complex activities of daily living. The incorporation of MCI in DSM V was followed by some criticism from clinicians due to overlapping symptoms making the blurry borders for a precise diagnosis of dementia, especially dementia of Alzheimer's type (Morris 2012). To make a clear distinction between dementia and MCI, DSM V suggested diagnostic criteria for diagnostic tests performance: MCI – 1-2 Standard Deviation (SD) below the normative mean and for Dementia – more than 2 Standard Deviations below the normative mean along with the independent daily functioning as a critical distinction between them.

Historical background of MCI

During the last 60 years, several terms appeared in literature to describe cognitive decline, which were accepted as normal senile changes, such as benign senescent forgetfulness (Kral

1962) or age-associated memory impairment (Samuel Gershon 1986). Later, researchers found that some patients, previously clustered as normal age-related cognitive decline, showed progressive impairment of cognition with dementia as the last stage.

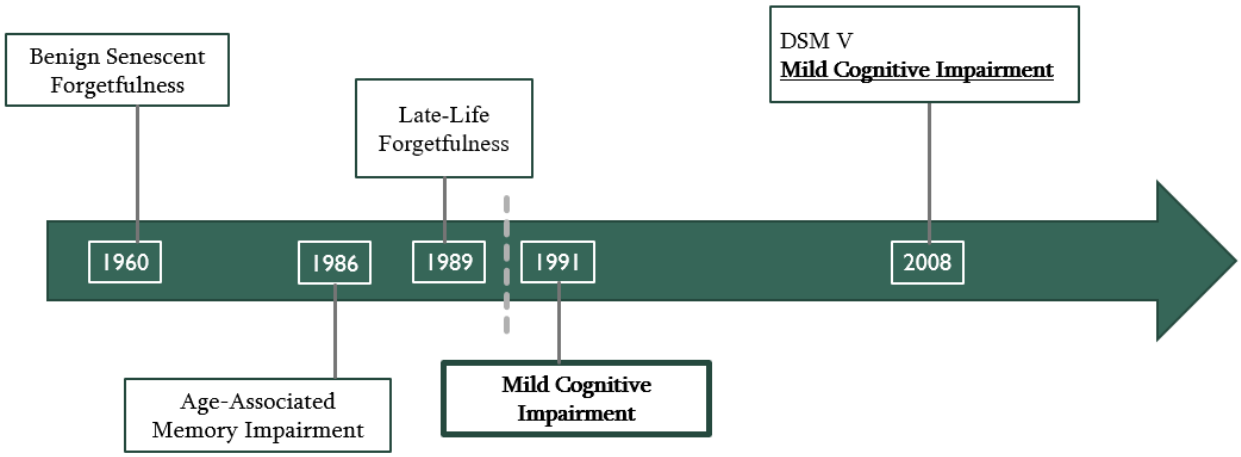


Figure 4 Historical background of the development of Mild Cognitive Impairment (MCI) as a separate disorder in literature

The term Mild Cognitive Impairment was first introduced in literature in 1991 (Flicker, Ferris, and Reisberg 1991) followed by a wide acceptance as a pathological state different from normal age-related cognitive decline (R. C. Petersen et al. 2001; Winblad et al. 2004). However, later studies showed that the population with MCI does not always progress to dementia (Koepsell and Monsell 2012; Mitchell and Shiri-Feshki 2009), which promoted the necessity of further research to find out the factors playing an important role in the transformation of Mild Cognitive Impairment to Dementia.

Epidemiology of MCI

The incidence and prevalence of MCI have shown some increase during the last decades, although it can be explained by the increased rate of diagnostic and screening tests of MCI

among the risk population. The literature review of the MCI incidence in the first decade of the XXI century ranges from 1% to 6% per year with a prevalence from 3% to 22% in the population older than 65 years (Bozoki et al. 2001; Bennett et al. 2002; DeCarli 2003). However, the literature review of the second and third decades of the XXI century shows increased rates of incidence ranging from 5% to 8% per year, with prevalence ranges from 5% to 29.9% among different ethnic and cultural groups (Luck et al. 2010; Hussin et al. 2019; Overton, Pihlsgård, and Elmståhl 2019; Zhang, Natale, and Clouston 2021).

One of the largest population studies conducted recently in China (2020) involved more than 50 thousand people above 65 and showed the prevalence of MCI in the same range - 15.5% (Jia et al. 2020).

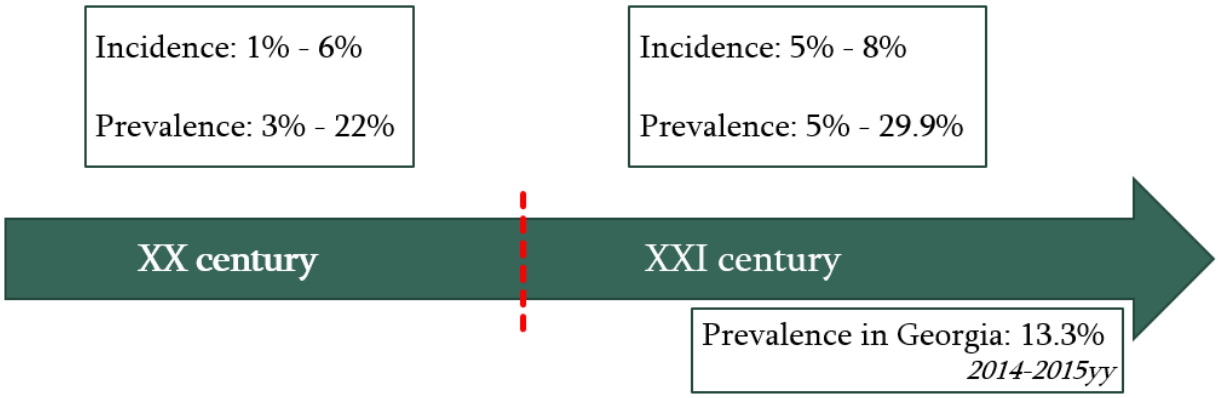


Figure 5 Prevalence of Mild Cognitive Impairment (MCI)

To determine the prevalence of MCI among the Georgian population, our research team conducted a screening of the population in 2014-2016, detecting the prevalence of MCI 13.3% among the population above 40 (Janelidze et al. 2018).

Known Risk Factors for progression of MCI to Dementia

Mild Cognitive Impairment is the preliminary stage for the development of dementia, sharing similar risk factors. Therefore, finding out factors, which increase the rate of the transformation of MCI to dementia, will dramatically change the prevalence of dementia and its burden and consequences on the public health sector.

Fewer years of education, cardiovascular and cerebrovascular disorders (such as hypertension and hyperlipidemia), diabetes, smoking, and depression are among the most common risk factors. It is noteworthy that most of the risk factors contribute to the transformation of MCI to dementia are modifiable and, therefore, capable of being prevented (Killin et al. 2016; Jia et al. 2020; Campbell et al. 2013)

Several researches indicate that education level of the patient negatively correlates with the cognitive impairment, especially verbal and non-verbal task performance (Vadikolias et al. 2012; Göthlin et al. 2018).

Several studies detected a decline in cognitive abilities among the elderly population with Major Depressive disorder. Therefore, late-life depression is a strong risk factor for normal subjects progressing to MCI (Steenland et al. 2012; Chakrabarty, Hadjipavlou, and Lam 2016).

Subtypes of MCI

According to the DSM V definition, MCI can affect any cognitive domain, although the most commonly declined cognitive domain is memory. The classification to differentiate subtypes of MCI was elaborated by Petersen, and it is still used widely among researchers (R. C. Petersen 2004). According to this classification MCI is divided into four subtypes:

- Amnestic MCI (aMCI) single domain, where only memory is affected;

- Amnestic MCI (aMCI) multiple domain, where memory and at least one other area of cognition are affected;
- Non-amnestic MCI (naMCI) single domain, where one cognitive domain other than memory is affected;
- Non-amnestic MCI (naMCI) multiple domain, where multiple domains of cognitive processes other than memory are affected.

According to several studies, amnestic MCI (aMCI) has more risk of progressing into dementia, especially dementia of AD (R. C. Petersen 2004) showing some correlations with chronic activation of the immune system (Ponomareva, Krinsky, and Gavrilova 2021). Whereas non-amnestic MCI (naMCI) has more vascular or another type of etiology.

Longitudinal studies with several-year follow-ups show heterogeneous data. Yaffe, Petersen, Lindquist, Kramer, and Miller (Yaffe et al. 2006)), with a 3.1-year follow-up, reported that among the participants who progressed to AD, 76% had a prior classification of aMCI and all participants who progressed to frontotemporal dementia had been previously classified as naMCI. Another longitudinal study with 7.5-years of follow-up also revealed that the aMCI has a higher rate of transformation in AD than naMCI (Jungwirth et al. 2012). However, a more recent longitudinal study with a 6-year follow-up conducted by Overton and colleagues in 2019 suggested that the incidence rate of overall MCI was 22.6 per 1000 person-year while showing the highest prevalence and incidence among naMCI with a single domain without age or sex difference (Overton, Pihlsgård, and Elmståhl 2019).

In patients with early-stage of Mild Cognitive Impairment (MCI), the deficit in memory encoding due to hippocampal dysfunction is compensated by the preserved executive and frontal functions (Clément, Belleville, and Mellah 2010), which helps patients to remain functional and keep independence. Along with the progression of the disorder, the frontal executive function is also affected by further progression to dementia (Dannhauser et al. 2008).

Neuropsychological Assessment of MCI

To diagnose MCI along with its subtypes and differentiate it from normal age-related cognitive functional decline, several standardized neuropsychological tests were developed to assess the degree of cognitive impairment among individuals objectively, as forgetfulness and lack of attention are very common complaints of elderly people without any cognitive disorders (Lenehan, Klekociuk, and Summers 2012). Diagnostic tests vary widely among the literature. Many previously developed diagnostic tests mainly focused on amnestic events while assessing MCI, while neglecting the non-amnestic domains of the MCI, leading to inadequate assessment and a lack the full information regarding the cognitive functional abilities of the patient (Gavett et al. 2009; Jungwirth et al. 2012; Lonie et al. 2008).). Such an approach was widely criticized among the researchers doubting the inaccurate identification of the MCI (Alladi et al. 2006; Busse et al. 2006), as the aMCI and naMCI differ in their risk factors and further progression. Therefore, the battery to assess all the cognitive domains should ideally include not only memory but also measure executive function, visuospatial function, attention and processing speed, and language abilities (Ghosh, Libon, and Lippa 2014; Summers and Saunders 2012). Although there are several assessment tests for each cognitive domain, it is important to mention that these cognitive domains are not isolated from each other, and performance in one domain might affect the results in another domain, such as, for example, memory and processing speed. Table 1 provides the diagnostic tests grouped according to the cognitive domains they assess.

Table 1: Neuropsychological tests grouped according to the neurocognitive domains

Neurocognitive Domain	Test	
Memory	Word-List Recall	California Verbal Learning Test

		Rey Auditory Verbal Learning Test
	Narrative Memory	Wechsler Memory Scale – Logical Memory
		Rivermead Behavioural Memory Test – Story Recall
	Non-Verbal	Wechsler Memory Scale – Visual Reproduction
		Rey Complex Figure Test
		Brief Visuospatial Memory Test
Visuospatial Function	Wechsler Adult Intelligence Scale – Matrix Reasoning, Block Design	
	Judgement of Line Orientation	
	Clock Drawing Test	
	Visual Object and Space Perception Battery	
	Birmingham Object Recognition Battery	
Language	Controlled Oral Word Association Test	
	Token Test	
	Boston Naming Test	
Attention and Processing Speed	Digit Symbol Modalities Test	
	Cancellation Test	

	Wechsler Adult Intelligence Scale – Digit Span, Symbol Search, Coding
	Trail Making Test-Part A
	Wechsler Memory Scale – Symbol Span
Executive Function	Wisconsin Card Sorting Test
	Delis–Kaplan Executive Function System – Trail Making, Verbal Fluency, Design Fluency, Colour-Word Interference, Sorting, Tower
Assessment of Baseline Intelligence	Advanced Clinical Solutions – Test of Premorbid IQ
	Wechsler Test of Adult Reading
	National Adult Reading Test
Measures of Global Cognitive Function	Dementia Rating Scale-2
	Clinical Rating Scale
	Alzheimer's Disease Assessment Scale – Cognitive Subscale
	Mini-Mental Status Exam
	Montreal Cognitive Assessment

Clinical Dementia Rating (CDR) scale, Alzheimer's disease Assessment Scale – Cognitive Subscale (ADAS-Cog), and Dementia Rating Scale-2 (DRS-2) were commonly used batteries to differentiate MCI from AD (Verma et al. 2015) or normal aging cognitive impairment (de Jager and Budge 2005). However, these tests showed less sensitivity and specificity to differentiate normal age-related cognitive changes from MCI.

Brief mental status examination tests, like Mini-Mental State Examination (MMSE), were widely used for screening cognitive performance worldwide (Folstein, Folstein, and McHugh 1975), however, they showed less sensitivity to differentiate normal cognitive state from MCI (Pendlebury et al. 2010). In contrast, the Montreal Cognitive Assessment (MoCA) has been suggested as a more sensitive and specific tool to differentiate MCI from the normal cognitive state, as well as from dementia (Damian et al. 2011).

Diagnosing Cognitive Impairment

During the last decade, several researchers developed clinical and biological markers to predict the transformation of MCI into dementia. Several neuroimaging studies were conducted using MRI to map the hippocampal and entorhinal cortexes to predict the progression of MCI (Devanand et al. 2012; 2007; Orso et al. 2020; Moscoso et al. 2019) or SPECT scan with visual ratings and region of interest (ROI) analyses (Devanand et al. 2010). Apoprotein E and plasma tau-protein were also used to predict Alzheimer's disease in memory-impaired individuals (R. C. Petersen et al. 1995; Mielke et al. 2018). Analysis of cerebrospinal fluid and detection of several markers to predict this transformation or combination of neuroimaging studies along with CSF biomarkers were also conducted by several researchers (Papaliagkas et al. 2009; Lonie et al. 2010; Devanand et al. 2008; Davatzikos et al. 2011; Vemuri et al. 2009). However, testing the biomarkers or conducting several neuroimaging studies can only be done for research purposes or in tertiary hospitals in order to help clinicians, mainly primary care physicians, to detect MCI among the general population and assess the risk factors for dementia development for further close monitoring and follow-up.

Therefore, the brief neuropsychological tests were developed for screening and differentiation purposes.

5. Montreal Cognitive Assessment (MoCA) Test

The MoCA is a 30-point screening test that requires a maximum of 10-15 minutes to administer and briefly assesses several aspects of cognitive function, including executive functioning, attention, language, abstraction, delayed recall, and orientation. MoCA was first developed and introduced by Nasreddine and colleagues in 2005 (Nasreddine et al. 2005) with high sensitivity and specificity to differentiate MCI from Dementia and normal cognitive state (Smith, Gildeh, and Holmes 2007).

MoCA one-page test assesses several cognitive domains, such as:

Visuospatial function/abstraction – a patient is asked to connect dots, draw the clock according to their visuospatial imagination and copy a three-dimension cube from the paper;

Language/Verbal fluency – a patient is asked to recognize three familiar animals (like camel, lion, rhinoceros), repeat complex sentences; counting as many words the words starting with some special letter;

Memory/delayed recall – patient is asked to repeat five familiar nouns with a 5-minute delay;

Attention - a patient is asked to repeat the digits forward and backward; serial subtraction of some numbers; the patient is asked to tap while hearing only indicated letter;

Executive function – a patient is asked to connect the dots and letters with order (modified Trail-Making Test Part B (Smith Watts et al. 2019), to draw the clock, to repeat digits forward and backward; tap while heating indicated letter; serial subtraction, verbal fluency;

Orientation – patient is asked to state day, date and location

Calculating MoCA results, the maximum score is 30; however, considering the education as an important factor for fostering cognitive abilities, one extra score is added for the participants with education less than 12 years (Nasreddine et al. 2005).

While defining the criteria for Mild Cognitive Impairment, Petersen and colleagues (R. C. Petersen et al. 1999), suggested setting the cutoff score below 1.5 SD, considering age and education adjustment. Since then, several researchers have conducted studies to define the cutoff score, which fluctuated from 1 SD below average (Ritchie, Artero, and Touchon 2001; Lonie et al. 2010) to 2 SD below average (De Ronchi et al. 2005)

To apply MoCA assessment proper understanding of the language is mandatory along with some culture-specific details. Our research team has translated MoCA into Georgian and tested its validity among Georgian-speaking populations (Janelidze et al. 2017). While putting the cutoff score for screening purposes (cutoff score for MCI - below 22) Georgian MoCA showed 100% of sensitivity and 69% of specificity.

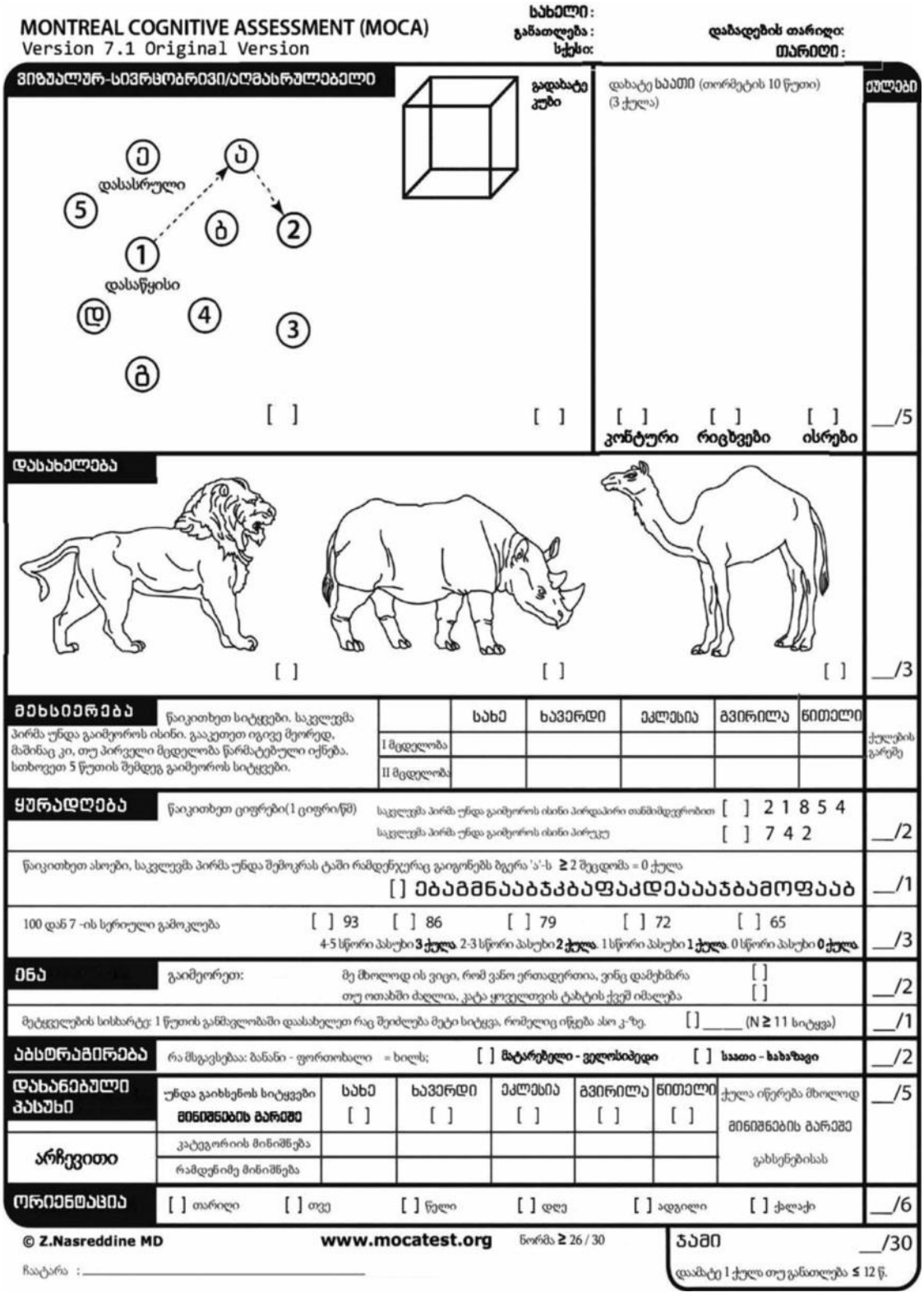


Figure 6 Montreal Cognitive Assessment Test (MoCA) - Georgian translated and validated version

6. Instrumental Activities of Daily Living (IADL)

Worsening of cognitive as well as physical abilities associated with the aging process makes functional status (Activities of Daily Living) a significant part of the examination of elderly patients to determine the level of their independence in order to make decisions regarding the treatment plan and care.

Activities of Daily Living (ADL) have two subdomains, such as Basic Activities of Daily Living (BADL) and instrumental activities of daily living (IADL). BADL includes self-maintenance skills such as bathing, getting dressed, or eating, whereas IADL is a complex activity like cooking, doing laundry, taking medications, managing finances, public transportation, or shopping (Lawton and Brody 1969).

Basic Activities of Daily Living (BADLs)	Instrumental Activities of Daily Living (IADLs)
Feeding	Using the telephones
Transferring	Shopping
Toileting	Preparing food
Dressing	Housekeeping
Bathing	Doing laundry
Continence	Handling Medications
	Handling finances

Table 2 Main activities related to the Basic (BALD) and Instrumental Activities of Daily Living (IADL)

Lawton IADL scale (McMahon, n.d.) is easy to administer, it only takes 5-10 minutes and contains eight domains to assess Instrumental Activities of Daily Living (IADL) measured from 0 to 8 score. The most commonly used scoring is dichotomous (0 = less able, 1 = more able). Considering the specific gender responsibilities/activities, women are scored on all eight areas of function, but for men, the areas of food preparation, housekeeping, and laundering are excluded. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women, and 0 through 5 for men ("Lawton And Brody Instrumental Activities Of Daily Living (IADL) Scale" n.d.)

Patient Name:_____ **Date:**_____
Patient ID #_____

LAWTON - BRODY
INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

A. Ability to Use Telephone		**E. Laundry**	
1. Operates telephone on own initiative-looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
		2. Launders small items-rinses stockings, etc.	1
2. Dials a few well-known numbers	1	3. All laundry must be done by others	0
3. Answers telephone but does not dial	1		
4. Does not use telephone at all	0		
B. Shopping		**F. Mode of Transportation**	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food Preparation		**G. Responsibility for Own Medications**	
1. Plans, prepares and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosage	0
3. Heats, serves and prepares meals, or prepares meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0		
D. Housekeeping		**H. Ability to Handle Finances**	
1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1	1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income	1
2. Performs light daily tasks such as dish washing, bed making	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Incapable of handling money	0
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		
Score		**Score**	
		Total score_____	
A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.			

Source: *try this:* Best Practices in Nursing Care to Older Adults, The Hartford Institute for Geriatric Nursing, New York University, College of Nursing, www.hartfordign.org.

Figure 7 Instrumental Activities of Daily Living (IADL) - Lawton Scale

According to the DSM V and supported by several studies, MCI is not associated with a deficit in IADL (Farias, Mungas, and Jagust 2005). However, a couple of researchers criticize this formulation, as the patients with MCI lack self-awareness, which might lead to reporter bias (Albert et al. 1999; Tabert et al. 2002). To support this idea, there are Zanetti and colleagues, and later Okonkwo (Okonkwo et al. 2008; Zanetti et al. 1999)) conducted a cross-assessment of MCI patients and their relatives to find out the difference between self-reflection of the MCI patients and compared it with the information provided by their relatives. Research showed that MCI patients had less insight regarding their performance, and there was a prominent decline in daily activities based on the data provided by caregivers or close relatives. Some researchers also developed the idea that IADL can be impaired prior to the onset of dementia and should therefore be included in the diagnosis of progressive MCI (Nygård 2003). However, it is unclear whether there are IADL domains that are consistently affected across patients with MCI. A systematic review of the literature showed a heterogeneous correlation between IADL and MCI (Jekel et al. 2015).

7. Beck's Depression Inventory

The Beck Depression Inventory (BDI) is a 21-item, inventory that measures characteristic attitudes and symptoms of depression (BECK et al. 1961). The inventory is self-performed and the patient has to report regarding their feelings and thoughts during past two weeks. Each item (21 items in total) is rated from 0-3 and based on the results the person is diagnosed to have normal mood (0-10), mild mood disturbances (11-16) borderline clinical depression (17-20), moderate depression (21-30), Severe depression (31-40) and extreme depression (over 40). Although it is widely used all over the world for screening and diagnosing depression, however, like all other self-reporting inventories, it also has a reporter bias, as the respondent can minimize or exaggerate their symptoms.

To summarize:

Mild Cognitive Impairment (MCI), as a pathological condition, first appeared in DSM V only in 2008, which underlies that it is a recently developed diagnosis with limited information in the literature and the necessity for further research in this direction;

There are several pieces of evidence that the prevalence and incidence of this disorder increases over time as population ages;

There are several shreds of evidence, that MCI is the ultimate precondition of dementia and, dementia is one of the critical socio-economic burdens for the public health sector for aging society;

As the formal diagnosing of the disorder is recently developed, there are little researches regarding its natural development, risk factors, and consequences;

MoCA, a brief neuropsychological test with high sensitivity to differentiate MCI from normal cognitive state and dementia, is one of the widely used batteries. Besides, there is evidence that aMCI progresses to dementia more frequently than naMCI.

Although DSM V defines MCI as a mild decline of some cognitive domains along with intact complex/instrumental activities of daily living (IADL), some research is challenging this idea and hypothesizes the opposite.

Based on our preliminary data and the discussion above, we hypothesize that changes in cognitive abilities over time can be a good predictor for further progression of the MCI to dementia. Thus, the aim of the study is to observe the natural course of cognitive performance of healthy individuals and MCI patients in real-time for seven years period and, furthermore, find out the correlation of MCI with instrumental activities of daily living.

- **Find out cognitive performance of healthy and MCI patients over time;**

- Determine more vulnerable MoCA cognitive domains over time;
- Find out the disability level among MCI individuals
- Determine the least performed domain of IADL among MCI patients.

Materials and Methods

A community-based longitudinal cohort study was conducted in order to identify the cognitive changes over time among the population of Georgia in individuals aged 40 years or older.

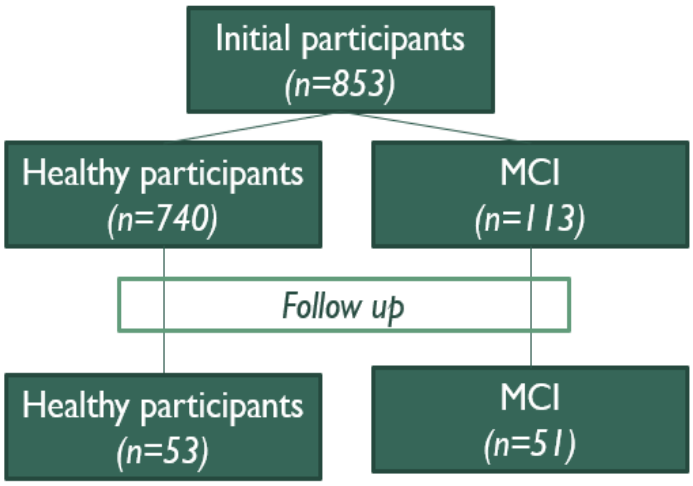
Inclusion criteria: everybody above 40 years of age.

Exclusion criteria: patients with dementia or other neurological conditions.

The investigation of participants' cognitive abilities was conducted twice. For the initial investigation, the information and data from the previous study of Mild Cognitive Impairment in Georgia (Janelidze et al. 2018) were used, which was conducted as a cross-sectional one-phase study in 2014-2015 years to identify subjects with MCI among an urban and rural population of Georgia with institutional ethical approval from the Tbilisi State Medical University (Tbilisi, Georgia) along with informed consents from individuals before enrollment in the study. The study included participants from rural and urban areas of the country with random contact with households. Where there was no response, the household was replaced by the next in order.

From 851 subjects, 103 participants (52 healthy and 51 MCI) were randomly chosen for this study for follow-up.

The follow-up meeting was conducted in 2021-2022 years. The demographic data, including the age and education of the participants, were used from the database of the initial study.



Cognitive testing

To assess participants' cognitive abilities, Montreal Cognitive Assessment (MoCA) test was used.

The MoCA is a 30-point screening test that requires a maximum of 10-15 minutes to administer and briefly assesses several aspects of cognitive function, including executive functioning, attention, language, abstraction, delayed recall, and orientation.

During the first phase of the study, all participants' cognitive abilities were evaluated with the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005), which was previously translated into the Georgian language and validated with the same team of the researchers showing its reliability and accuracy for evaluation of MCI among Georgian population (Janelidze et al. 2018).

During initial assessment, the individuals with MoCA scores < 16 were excluded from the analysis, classifying them as moderately to severely cognitively impaired (Ganguli et al. 2010). After randomly choosing the participants from the initial database, repeated MoCA was conducted during the follow-up visits after seven years (range 6.5-7.5 years).

Cognitive Domain Index Scores

To evaluate participants' cognitive abilities, MoCA cognitive domain index score (MoCA CDIS) was used. In order to calculate MoCA CDIS scores, the method used by Nasreddine, Julayanont, and colleagues (Julayanont et al. 2014) was used:

Cognitive Domain	MoCA tasks used to calculate	Total score
MIS – Memory Index Score	adding the number of words remembered in free delayed recall	0-5
EIS – Executive Index Score	Adding the scores of: • modified Trail-Making Test Part B • clock drawing • digit span forward and backward • letter A tapping • serial-7 subtraction • letter fluency • abstraction	0-13
VIS – Visuospatial Index Score	Adding the scores of: • cube copy • clock drawing • naming	0-7
LIS – Language Index Score	Adding the scores of: • Naming • sentence repetition • letter fluency	0-6
AIS – Attention Index Score	Adding the scores of: • digit span forward and backward • letter A tapping • serial-7 subtraction • sentence repetition,	0-18

	• the words recalled in both immediate recall trials	
OIS – Orientation Index Score	Sum of points for the orientation section of the MoCA	0-6

Based on the above-mentioned index scores the participants were categorized as single domain aMCI, multiple domain aMCI, single domain naMCI or multiple domain naMCI for further analysis.

Instrumental Activities of Daily Living (IADL) Assessment

To assess the participants' abilities for daily living and performing complex activities, the IADL assessment test was used in the MCI patient group during follow-up visits. While performing the MCI patient assessment, the caregiver, family member, or close relative was given another copy of the IADL test to fill up independently. A difference was calculated by subtracting patient IADLs results from the family member score. A higher score indicated that the family member was reporting more impairment of complex instrumental daily activities compared to the patients' report.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS version 25.0. To compare intergroup variability Chi-square test, Fisher's test or t-tests were used for demographic data. Age and education were used as covariates while performing ANCOVA along with the MCI. The statistical significance level was set at $p < 0.05$. Reliable Change Index (RCI) with confidence intervals (95%) was used to establish the clinical significance of the cognitive change from the test-retest results among healthy individuals (Jacobson and Truax 1991). To define the annual

change in MoCA scores, a calculation was done for both groups by taking the difference between each participant's initial and follow-up score and dividing it by the number of total years between the assessments. Independent t-tests were used to compare MoCA scores and CDIS. The area under the curve (ROC) was calculated for MoCA scores and CDIS to identify the patient who had progressed to dementia by the end of the study. Analysis of variance (ANOVA) was used to determine the statistical significance of the results. Student t-test was used to compare the average values and determine their statistical significance.

The correlation of the initial (2014-2015) and the newly performed (2021-2022) results, as well as a correlation between different cognitive domains and IADLs scores, were calculated with Pearson's Correlation coefficient.

Results

General results of cognitive decline

The time period between initial and follow-up MoCA was approximately 7 years (range: 6.5-7.5 years, SD=0.2). The sample was made of 103 participants, from which 52 participant were cognitively intact (MoCA=28.3, SD=1.5) and 51 were diagnosed to have MCI during initial examination according the MoCA scores (MoCA=20.1, SD=1.9).

	Healthy (n=52)		**MCI (n=51)**		
	M (SD)	**Range**	**M (SD)**	**Range**	***p* value**
Initial age	58.8 (9.2)	35-74	55.3 (8.1)	39-76	0.002
Follow-up age	65.8 (9.1)	42-81	62.4 (8.4)	46-83	0.03
Education (years)	12.5 (0.5)	9.1-17	10.6 (0.7)	9-15.5	0.06
Gender, n (% female)	31 (59.6)		28 (54.9)		0.1
Initial MoCA score	28.3 (1.5)		20.5 (1.9)		0.005
Follow-up MoCA score	27.4 (2.8)		18.8 (2.1)		0.004

Table 3 Demographic Characteristics for initial stage and follow-up

There were some group differences in age and education among healthy and MCI groups and both of them revealed to be statistically significant while used as covariates for the study

(F=4.4, p=0.03). During follow-up visit, a significant decrease of MoCA scores was detected in both healthy (mean change = - 0.9, SD = 2.1, t = - 3.51, p < .002, d = 0.73) and MCI groups healthy (mean change = - 1.7, SD = 2.1, t = - 5.23, p < .003, d = 0.81).

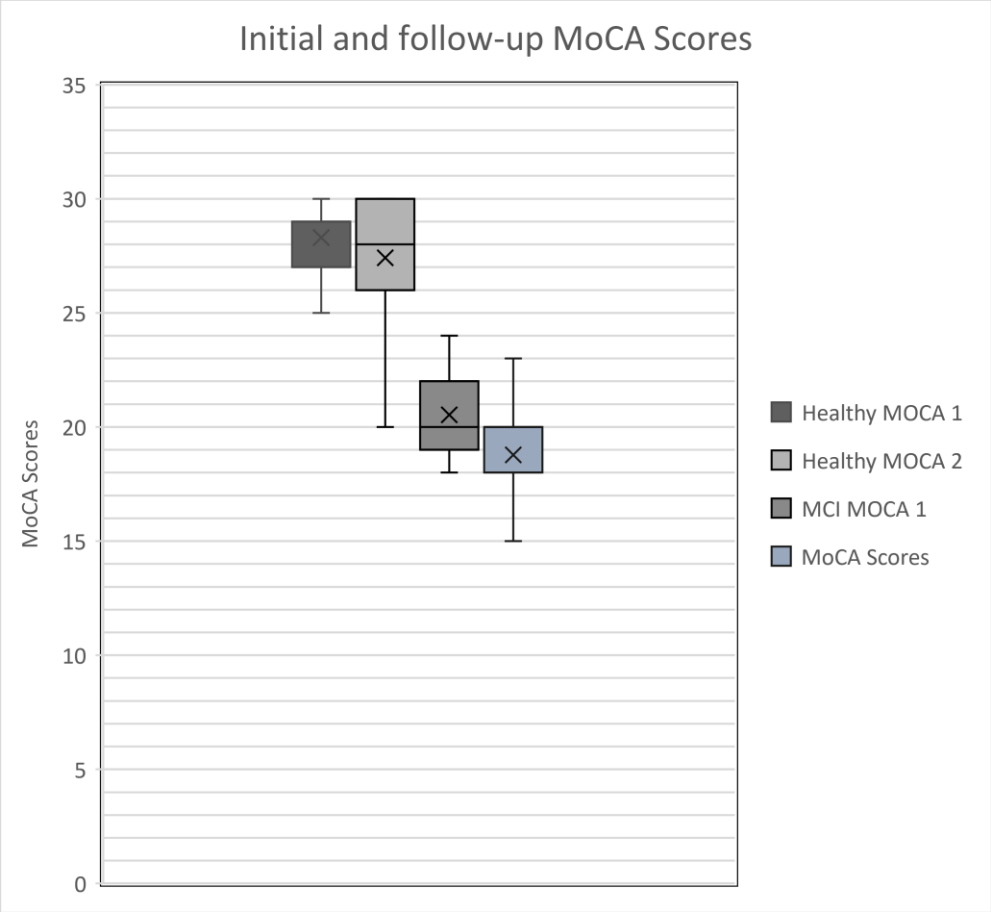


Figure 8 MoCA performance over time.

Note. Healthy MOCA 1 = Initial MoCA scores of the healthy individuals; Healthy MOCA 2 = follow-up scores of the healthy individuals; MCI MOCA 1= Initial scored of the patients with Mild Cognitive Impairment; MCI MOCA 2= follow-up scored of the patients with Mild Cognitive Impairment

As the education and age are important factors effecting cognitive abilities, education (F= 12.4, p= 0.02, η2= 0.14) and age (F= 6.5, p= 0.001, η2= 0.10) were adjusted as covariates during

follow-up, MoCA scores by healthy and MCI group interaction was significant (F= 4.5, p= 0.001, η2= 0.25) along with main effects for groups (F= 42.1, p= 0.04, η2= 0.21). While adjusting education and age as the covariates, the changes of MoCA scores among healthy individuals was -1.1 (28.3 vs 27.2) and among MCI group was -1.92 (20.5 vs 18.58).

Reliable Change Index (RCI) was calculated for healthy group and the results are represented in the following table:

	Test–retest reliability	SEM	SE diff.	RC
Initial to follow-up	0.93	0.56	0.81	± 1.1

Table 4 Test–Retest Reliability Coefficients and Reliable Change Indices Based on Standard Error of Measurement (SEM) for Healthy Group

Note: SEM = standard error of measurement; SE diff. = standard error of the difference; RC = reliable change at 95% confidence interval.

Test–retest reliability coefficients based on the correlation between the mean MoCA score at baseline and follow-up visit.

Considering the RCI cutoff point (±1.1), the statistically significant decline of the MoCA scores were detected in 19.2 % (n=10) of healthy group during 7 years, whereas in MCI group 49.01% (n=25) experienced statistically significant decline of MoCA scores and the rest patients stayed cognitively intact after 7-year follow-up.

Performing annualized change, showed 0.23-point decrease of MoCA scores in healthy individuals above 40s, whereas 0.57-point decrease was detected in patients with MCI of the same age.

Analyzing according to CDIS

We have done data stratification based on MoCA follow-up results in MCI patients. Comparing MoCA Cognitive Domain Index Scores of the patients converted to dementia during follow-up and MCI patients who stayed stable during follow-up visits is shown below:

Cognitive domain index scores Total points	Total MCI patients (n=51)		P value[a]
	MCI-NC (n=32)	MCI-AD (n=19)	
Memory index score (15)	9.24 ± 0.57	7.62 ± 0.55	0.001
Orientation index score (6)	5.23 ± 0.24	4.34 ± 0.25	0.001
Executive index score (13)	8.54 ± 0.64	7.54 ± 0.87	0.002
Language index scores (6)	5.01 ± 0.17	3.86 ± 0.21	0.085
Visuospatial index scores (7)	5.55 ± 0.24	4.22 ± 0.13	0.023
Attention index scores (18)	14.26 ± 0.87	12.94 ±0.83	0.004

Table 5 MoCA Cognitive Domain Index Scores in MCI-NC and MCI-AD Groups

MCI-NC = mild cognitive impairment non-converters; MCI-AD = mild cognitive impairment AD converters

Education-corrected MoCA scores is adding 1 point if education level of participants ≤12 years
Data are expressed as means ± SE, with total point in parentheses.

[a] *two-tailed t-test was conducted for continuous data as appropriate.*

To find out the impact of education on MoCA cognitive domains, education adjustment was done with subsequent positive correlation with VIS, EIS, and LIS. As years of intermediate school years was varying in Georgia over years (10, 11, 12 years during different time points), the education adjustment was done as "intermediate education" and "higher education":

Cognitive domain (total points)	Education level	Mean	SD	Cutoff
Memory (5)	All	3.85	1.33	2.5
	intermediate	3.67	1.44	2.5
	Higher	3.92	1.17	2.5
Executive Index Score (13)	intermediate	10.58	1.62	8.5
	Higher	13.34	0.85	11.5
Visuospatial Index Score (7)	intermediate	5.50	1.24	4.5
	Higher	6.97	0.86	5.5
Language Index Score (6)	intermediate	4.77	1.12	3.5
	Higher	5.76	0.49	5.5

Table 6 Education- Adjusted Cutoff Scores for Each Cognitive Domain

While applying the above-mentioned criteria, we have detected that the patients with multidomain amnestic MCI were progressing to dementia most commonly (75.2%), followed by single domain aMCI (68.3%). Analyzing the cognitive domains, memory (MIS) (94.2%) and executive (EIS) (75.3%) domains were the most commonly affected functions.

Subtype of MCI	Impaired cognitive domains	% AD conversion
Single domain	Amnestic	68.3
	Non amnestic	15.1

	Visuospatial	0.0
	Executive	10.1
	Language	0.0
Multiple domains	Amnestic *plus*	75.2
	Visuospatial	100.0
	Executive	91.5
	Language	56.2
	Visuospatial & Executive	88.4
	Visuospatial & Language	75.1
	Executive & Language	68.4
	Visuospatial & Executive & Language	79.1
	Non amnestic	0
	Visuospatial & Executive	0
	Visuospatial & Language	0
	Executive & Language	0.0
	Visuospatial & Executive & Language	0

Table 7 MCI Subtypes and Conversion Rates

Cognitive Domain Index Scores (CDIS) to Predict dementia conversion in Individuals with MCI

MoCA overall score and MoCA-MIS scores were good indicators to predict the conversion of MCI to dementia during seven years follow-up. The area under the ROC curve for the overall MoCA score was 0.78 (95% CI: 0.65-0.82, p=0.001), whereas, for the MoCA-MIS, it was 0.71 (95% CI: 0.66-0.76, p=0.001. EIS, OIS, and AIS were also good predictors for dementia conversion; however, LIS results were not statistically significant.

Cognitive domain index scores	AUC	95 % CI	P value
MoCA overall score	0.78	0.653-0.821	<0.001
Orientation index score	0.659	0.622-0.744	0.001
Memory index score	0.71	0.662-0.763	0.001
Executive index score	0.629	0.597-0.714	0.007
Attention index score	0.636	0.59-0.697	0.016
Visuospatial index score	0.60	0.508-0.701	0.026
Language index score	0.576	0.482-0.671	0.118

Table 8 Area Under the Curves (AUC) for the Cognitive Domain Index Scores to Predict Mild Cognitive Impairment to Dementia Conversion

To predict the conversion of MCI to dementia the algorithm suggested by the Nasreddine, Julayanont and colleagues was used (Julayanont et al. 2014). According to this algorithm cutoff scores of MoCA-overall-scores less than 20 (out of 30) and MoCA-MIS scores less than 7 (out of 15) is used to predict the conversion of MCI to dementia. The calculated results are shown below:

	% Converted to Dementia	Annualized conversion rate
Below cutoff for MCI overall score and MoCA-MIS	100%	14.3 %
MCI overall score **OR** MoCA-MIS below cutoff (one indicator only)	78.4%	11.2 %
Above cutoff for MCI overall score and MoCA-MIS	57.9%	8.3 %
Average		11.3 %

Table 9 The Percentage of Conversion Rate from MCI to Dementia according to the Cognitive Domain Scores

IADL correlation with cognitive decline

In order to assess the MCI patients' abilities for performing complex/ instrumental activities of daily living, IADL checklist was used. While performing the MCI patient assessment, the caregiver, family member, or close relative was given another copy of the IADL test to fill up independently. The information providers mostly were spouses (73.1%), adult children (25.3%), or other family members (1.6%). The average time the family member spent with the participant was 80.9 hours/per week.

Analysis of variance (ANOVA) was used to determine whether there was a statistically significant difference between the aMCI, naMCI, and dementia groups reported by the patients themselves or their caregiver/family member. The IADL score results of the patient and family member are indicated below:

Diagnostic group	Average IADL score	*p* value
Family member report results		
aMCI	5.3 ± 1.2	0.001
naMCI	7.1 ± 0.9	0.001
Dementia	0.5 ± 0.6	0.003
Patient report results		
aMCI	6.8 ± 0.5	0.02
naMCI	7.5 ± 0.8	0.001
Dementia	5.1 ± 2.5	0.0001

Table 10 Family member and Patient reported results of IADL scores

While performing t-test showed that caregivers/family members reported significantly more decline in everyday functioning, compared to the self-report among dementia group (t=-10.21 $p< 0.0001$), among the aMCI group (t=-5.23, p<0.002) and among the naMCI group (t=-6.57, p<0.001).

To find the difference between IADL scores reported by the patients and their caregiver/family member: patients' IADL score results were subtracted from the caregiver/family member reported score. A higher score indicated that the family member was reporting more impairment of complex instrumental daily activities compared to the patients' report.

The ANOVA was used to find out the statistical significance of the mean IADL difference scores among three groups of patients, reporting themselves and caregiver/family members reporting scores. The overall F statistics were significant (p<0.001).

Diagnostic group	IADL score difference	*p value*
aMCI	1.5	0.003
naMCI	0.4	0.01
Dementia	4.6	0.002

Table 11 IADL scores difference for each diagnostic group

The mostly affected IADL domains were the MCI patients' ability to handle finances and the mode of transportation.

Correlation between patient and family member reported everyday function and specific domains of cognition

In order to find the degree of association between the measurements of cognitive domains and self and family member-reported IADL scores, the Pearson Correlation test was used. Lower MIS scores were significantly correlated with the family member-reported decreased IADL

scores (r=0.62, p<0.002). However, the patient self-reported everyday functioning scores were not significantly associated with any of the objective cognitive domain declines.

Discussion

The community-based study provides information about MoCA changes during a 7-year period and mainly includes an aged population with the age range of 41 to 90 years. According to the MoCA scores on follow-up, the sample was divided as cognitively healthy, with MCI, or with Dementia.

General Outcomes

MoCA scores of the initially cognitively healthy individuals remained stable in 80.8% of cases during a 7-year period, whereas 19.2% of the healthy individuals experienced clinically significant decline of the MoCA scores. These results are consistent with the already published findings stating the slight decline in the cognitive abilities of the healthy population over the years (Unger, van Belle, and Heyman 1999; Krishnan et al. 2017; Kramer et al. 2007; Cooley et al. 2015), whereas there were none of the individuals showed improvement of cognitive abilities proved with MoCA scored over seven years. These findings have a logical explanation, as the time-frame for our study (7 years) and the studies showing no changes of cognitive abilities (2.5-3.5 years) is different, whereas the longitudinal studies covering more than 4 years prove statistically significant decline of mental abilities among initially healthy individuals mainly measured with Mini-Mental State Examination (MMSE) (Hensel, Angermeyer, and Riedel-Heller 2007; Gluhm et al. 2013). Based on the data from the validation of MoCA among the Georgian population (Janelidze et al. 2017), the sensitivity and specificity of the MoCA were 0.88 and 0.95 compared to 0.43 and 0.67 MMSE results. Considering this information, we can conclude that the MoCA results used during this study are more precise than the studies where measurement is done using MMSE.

In the study, 19.2% of cognitively intact individuals showed a 0.23-points annual decrease in the MoCA scores. While analyzing the initial data of these individuals, 86% of them experienced depression diagnosed with Beck's Depression Inventory. As no more in-depth investigation of these individuals was performed, it is possible that the decreased cognitive scores were due to the associated depression (a condition sometimes termed pseudodementia). In the study conducted at a two-year interval (Perini et al. 2019), it is stated that the increased level of psychological stress, such as anxiety or depression, may represent an important predictor for further changes in cognitive health. The follow-up visit with the participants was conducted during the 2021-2022 years, which coincides with the COVID-19 pandemic and post-covid period. According to several studies and systematic reviews, depression has increased by more than 21% during and after Covid pandemic (Lee et al. 2021; Li et al. 2021). Pandemics and the consequent increased level of depression can explain the increased level of conversion from normal cognitive state to MCI.

The average MoCA score for the Mild Cognitive Impairment group was 21.1, which is consistent with the standard criteria initially given by Nasreddine and other colleagues (Nasreddine et al. 2005; Luis, Keegan, and Mullan 2009). The time frame between the two consequent measurements was 7.5 years on average, which totally excludes the possibility of under-detection of the cognitive change due to the relatively shorter intervals between the measurements (Timothy A. Salthouse 2014).

Demographic factors were considered while interpreting the results, such as the age and education of the patients. As all of the patients were Caucasians, no ethnic/race adjustment was made (Rossetti et al. 2011; Waldron-Perrine and Axelrod 2012),), although considering the study for Krishnan and the colleagues, there were no statistically significant differences among different races (Krishnan et al. 2017). However, it does not exclude the possibility that the MoCA scores over time might differ in certain socioeconomic groups, which was not the target of our study. The healthy individuals' group was somewhat older than the MCI group,

which might also explain the higher decline in cognitive abilities compared to the literature data (Cooley et al. 2015).

Based on the **Reliable Change Index**, the MoCA score difference between the initial and follow-up assessment must be ±1.1 in order to represent a statistically meaningful difference, which means that the changes in the cognitive abilities among two different time points are the reflection of a real cognitive impairment. Considering these measurements, approximately one-fifth of healthy individuals (19.2 %) and approximately half (49.01%) of the patients initially diagnosed with MCI exhibited clinically significant decline over seven years. These are consistent with the previously detected findings, showing diverse outcomes of cognitive changes: keeping stable cognition, declining cognition, or even improving it over time. In our study, both groups showed either stable scores or a decline in the MoCA scores; none of them showed a clinically significant improvement in the scores (Ganguli et al. 2004; Rossetti et al. 2011). However, these findings might include some sample or timing bias, as there were only a limited number of participants included in the study, and the time between measurements was up to 7 years without any measurements between them.

Cognitive domains

During this study, we found out that all MCI patients exhibiting low MoCA overall scores (below 20/30) and low MoCA-MIS scores (below 7/15) at the time of initial visit had converted to dementia (100%) during follow-up after seven years with an annualized conversion rate of 14.3%. MCI patients with higher MoCA overall scores (above 20/30) and higher MoCA- MIS scores (above 7/15) at the time of the initial visit showed better outcomes during follow-up, with an 8.3 % annualized conversion rate to dementia. While using MoCA CDIS to differentiate MCI subtypes, we found that multi domain amnestic MCI patients had a higher rate of dementia conversion. These results are consistent with the previous findings, confirming that the tests assessing learning and retention (Arnaiz et al. 2004), along with the

smaller volume of hippocampal formation (P. N. Wang et al. 2006) are the best predictors for progression to dementia; besides, patients with multi domain, rather than single-domain amnestic MCI have higher rates to progress to dementia (Matthias H. Tabert et al. 2006). Declined memory (lower MoCA-MIS scores), along with declined executive domain function (lower MoCA-EIS scores) can be a good predictor for MCI progression to dementia in 7 years perspective (Aggarwal et al. 2005; Traykov et al. 2007; Grober et al. 2008).

Dementia annualized conversion rate for all participants with MCI in this study (14.3%) is lower than in previous, relatively short-term studies (1.5-year follow-up 46.1% (Julayanont et al. 2014), 1-year follow-up 23.8% (Maioli et al. 2007), 18.2% (P. N. Wang et al. 2006). However, it is noteworthy that all these studies were conducted among patients of memory or neurological clinic, thus already having some major memory or neurological issues with higher conversion rates (Ronald C. Petersen et al. 2009), unlike this study, which included participants from the general population without major neurological background. Also, there were no intermediate cognitive examinations conducted among these patients, and the exact timing of the conversion from MCI to dementia is unknown. Besides, the MCI patients in the above mentioned study were experiencing multiple domain aMCI, which indicates a more widespread brain disorder and increases the risks of conversion to dementia (P. N. Wang et al. 2006; Molinuevo et al. 2011). During the current study, we also found out that executive function is declined and can be used as one of the indicators to predict the conversion of MCI to dementia. As executive function compensates for the memory impairment, its dysfunction would more likely lead to loss of independence of the patient and, therefore, will meet dementia criteria (Johns et al. 2012).

Daily Activities

Patients with aMCI, naMCI, or dementia reported less functional decline compared to the caregiver/family member reported results. Besides, results of self-reported daily activities were

not varying much among the patients with aMCI (average score - 6.8), naMCI (average score - 7.5), or dementia (average score - 5.1). These results are consistent with the research conducted previously, where the patients with different cognitive decline report a similar level of functional activities and report limited self-awareness regarding the loss to perform complex daily activities (Farias, Mungas, and Jagust 2005; Hartle et al. 2022). These results are explained by the fact that patients with any kind of cognitive decline have a tendency to very significantly underestimate their functional losses compared to the results of their caregivers/family members. Based on DSM V criteria, patients with MCI tend to show no decline in complex daily activities; however, the result of the present study showed that the patients with MCI also show some degree of decreased self-awareness while comparing the results of their self-reports and the results of their caregiver/family members. Specifically, caregivers/family members reported more decline in the complex daily activities among the dementia group (difference score = 4.6) compared to the MCI group. However, there was a discrepancy among the results of amnestic MCI patients compared to non-amnestic MCI patients' self-reports and caregiver/family member reports. aMCI patients' self-reported results, compared to the caregiver/family member scores, showed a higher difference (difference score = 1.5), whereas naMCI patients and caregiver/family member reports were not dramatically different (difference score = 0.4). Based on these results, we can assume that there is little functional change among naMCI patients compared to the aMCI patients.

While examining the discrepancies between self-reporting and caregiver/family member reporting, the dementia group showed a significantly higher difference score than the MCI (both aMCI and naMCI) groups. Meaning that dementia patients rated themselves as having less decline in complex everyday functioning compared to their caregiver/family member reports. This finding indicates the decreased self-awareness and insight of dementia patients regarding self-functioning. Furthermore, it correlates with other studies supporting the idea that caregivers/family members of dementia patients are more accurate while assessing the patient's cognitive and functioning abilities and pointing out their importance in being the

detectors of the first symptoms of dementia (Montgomery et al. 2018; Nosheny et al. 2019). Although the difference scores of MCI patients did not show higher values, the difference still was statistically significant, indicating the MCI patients, and especially the aMCI subgroup, had some level of decreased self-awareness regarding their everyday functioning, unlike the findings of the Farias and colleagues, where they indicated about the discrepancy between dementia patients and caregiver/family member scores, however, their findings in MCI group was not statistically significant (Farias, Mungas, and Jagust 2005, 1). However, the findings from other researchers show the necessity not only to rely on the findings of the caregivers/relatives regarding the functioning of elderly patients but also objectively assess their true functioning status due to statistically significant differences between the objective and subjective information (Figueredo and Jacob-Filho 2018).

Limitations

There were several limitations of the study. The sample was randomly selected from the already existing database of the previous study (Janelidze et al. 2018), which, although initially included up to 900 participant and was a good presentation of the population, only 103 participants were randomly selected for this study. During follow-up the decision regarding cognitive changes was made considering only MoCA scores, which restricts our understanding of the patients' objective cognitive status at follow-up. In order to use MoCA as the screening tool for the prediction of the cognitive decline, it would be recommended to perform the test annually among MCI patients in order to see the consistent changes of the MoCA scores and identify the alarming factors. Besides, there were no neurological examination of the patients with MCI on follow-up, which also limited the study outcome.

Conclusion

In conclusion there were several factors we were to identify during this research

1. The individuals, initially classified as cognitively intact were mostly stable over 7 years of period.

2. Up to 20% of the healthy individuals experienced statistically significant decline in MoCA scores

3. almost half of the patients initially diagnosed with MCI experienced statistically significant decline in MoCA scores during the same period.

4. RCI of ±1.1 indicated that the changes are clinically significant and showed meaningful difference.

5. Depression might be the important risk factor for healthy individuals for transformation to MCI state, especially during and after pandemics.

6. Declined memory (lower MoCA-MIS scores), along with declined executive domain function (lower MoCA-EIS scores) can be a good predictor for MCI progression to dementia.

7. MCI patients, and especially the aMCI subgroup, had some level of decreased self-awareness regarding their everyday functioning, therefore, the collecting information from caregivers/family members regarding patients' daily activities is important to make final decisions.

In conclusion, we found that there was clinically significant decline of the MoCA scores over 7 years period both in initially healthy individuals, as well as among the patients initially diagnosed MCI. Age and education were important predictors of the MoCA scores change over time. The mental state, like anxiety and depression seemed to be participating the important role in the changes of the cognitive abilities over time. MoCA can be used as the routine assessment tool to screen and diagnose patients' cognitive function.

MoCA-MIS scores can be used to identify the MCI patients with higher risk to progress to dementia. Because of decreased self-awareness of MCI patients, there is a need to interview the caregiver/family member in order to have a holistic understanding regarding patients' state.

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