

Mild Cognitive Impairment in Older Adults

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Abstract Mild cognitive impairment (MCI) is the intermediate stage between the cognitive changes of normal aging and dementia. MCI is important because it constitutes a high risk group for dementia. Ideally, prevention strategies should target individuals who are not even symptomatic. Indeed, the field is now moving towards identification of asymptomatic individuals who have underlying Alzheimer's disease (AD) pathology that can be detected using biomarkers and neuroimaging technologies. To this effect, the Alzheimer's Association and the National Institute on Aging have developed a new classification scheme that has categorized AD into a preclinical phase (research category), MCI due to AD, and dementia of Alzheimer's type. However, there are also ongoing research studies to understand high-risk groups for non-Alzheimer's dementia.

Keywords Aging · Mild cognitive impairment · Neuropsychiatric symptoms · Dementia · Dementia of Alzheimer's type · Cognitive impairment no dementia · Benign and malignant forgetfulness · Age-associated memory impairment · Age-associated cognitive decline · Mild neurocognitive decline · Age-associated memory impairment · Questionable dementia · Asymptomatic Alzheimer's disease

Introduction

In the late 1980s, clinical researchers investigating aging and dementia noted that some elderly persons were neither demented nor cognitively normal. This means the investigators did not have an *a priori* hypothesis of defining and characterizing the gray zone between cognitive aging and dementia. Rather, they appear to have made a serendipitous observation of the intermediate stage between the cognitive changes of aging and dementia [1, 2]. The term mild cognitive impairment (MCI) was first used by Reisberg and colleagues of New York University [3]. They defined MCI in terms of the Global Deterioration Scale (GDS). The GDS measures cognitive and functional decline on a scale of 1 (cognitively normal) to 7 (severe dementia), with MCI defined as a GDS score of 3 [2, 4]. Interest in the gray zone between normal cognitive aging and dementia dates back to as early as 1962, at which time Kral described "benign and malignant forgetfulness" [5]. Several other research groups have described similar concepts, such as age-associated memory impairment [6], aging-associated cognitive decline [7], mild neurocognitive decline [8], age-associated memory impairment [9], and questionable dementia [10], etc. Additionally, the concept of subjective cognitive impairment has also been introduced recently and is defined as a transitional stage between normal cognition and MCI [11].

Definition

MCI refers to the gray zone between the cognitive changes of normal aging and very early dementia [12, 13••]. Individuals with MCI show cognitive impairment greater than expected for their age, but are otherwise functioning independently and

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do not meet the commonly accepted criteria for dementia [1]. The original Mayo Clinic criteria for amnesic MCI are: (i) a memory complaint, preferably corroborated by an informant; (ii) impaired memory for age on psychometric testing; (iii) normal general cognitive function; (iv) intact activities of daily living; and (v) not demented [1]. Even though amnesic MCI is the most widely studied and empirically validated construct, the first international consensus on MCI has indicated that there are three additional subtypes [14].

Public Health Significance

The prevention of dementia is a public health priority [15]. In the USA alone, Alzheimer’s disease (AD) is projected to afflict as many as 14 million people by the year 2050 [16, 17]. Dementia has several devastating consequences, including substantial socioeconomic burdens. Even though life is priceless, the economic impact of AD is quite alarming. In 1993, the average cost of care for a patient with Alzheimer’s dementia in California was estimated to be over \$40,000 per year [18]. Therefore, the time-honored principles of the prevention of disease and promotion of health are particularly relevant to AD and dementia [19]. The prevention of a disease involves identifying high risk groups; indeed, MCI constitutes a high risk state for dementia, particularly for dementia of Alzheimer’s type [12]. Subjects with MCI constitute a high risk group because they develop dementia at 10–15 % per year compared with the general population of 1–2 % [20]. Delaying or preventing the onset of dementia by a mere 1 year alone could translate into 1 million fewer number of cases than predicted by the year 2050 [16]. Ideally, the prevention of disease and promotion of health should target individuals who are not even symptomatic. Indeed, the field of cognitive aging is now moving toward identification of asymptomatic individuals who have underlying AD pathology that can be detected by using biomarkers and neuroimaging technologies. To this effect, the Alzheimer’s Association and the National Institute on Aging (AA-NIA) have developed a new classification scheme that has categorized AD into a preclinical phase (research category) [21•], MCI due to AD [22•], and dementia of Alzheimer’s type [23•]. The ongoing work by the DSM-5 taskforce is anticipated to address the broader topic of neurocognitive disorders including Alzheimer’s dementia, as well as non-AD dementia [24••].

MCI Subtypes

Most of the empirical work regarding MCI has primarily focused on the amnesic type of MCI [1]; however, many investigators have argued that MCI is a heterogeneous entity [14]. Thus, three more MCI subtypes have been proposed [14]. The

classification is based on the presence or absence of memory domain involvement, as well as the number of cognitive domains involved, thus resulting in four categories: (i) MCI-single domain, memory type; (ii) MCI-single domain, non-memory type; (iii) multi-domain, including memory domain; and (iv) multi-domain without memory involvement. Figure 1 depicts the diagnostic algorithm that can be pursued to arrive at a diagnosis of a particular subtype of MCI. The process essentially boils down to two major steps, the first one being establishment of the diagnosis of MCI, whilst the second pertains to identification of the type and number of cognitive domains involved.

The putative etiology of MCI should be taken into consideration when considering the potential progression of MCI. For example, recent AA-NIA criteria have defined MCI in terms of etiology, i.e., MCI due to AD [22•] is considered to be the prodromal stage of Alzheimer’s dementia. In contrast, the other subtypes emphasizing impairments in non-memory domains, such as compartment-executive function and visuo-spatial skills, may have a higher likelihood of progressing to a non-AD dementia, such as frontotemporal dementia in the former or dementia with Lewy bodies in the case of the latter [25]. Therefore, the combination of clinical subtypes and putative etiologies may be useful in some people in predicting the ultimate type of dementia to which these diseases may progress.

The Epidemiology of MCI

The main focus of this section is to summarize the prevalence and incidence of MCI, as well as the conversion rate of MCI to dementia.

The incidence of MCI ranges from 1 % to 6 % per year, whilst prevalence estimates range from 3 % to 22 % per year [26–28, 29••]. The factors that may account for this variability

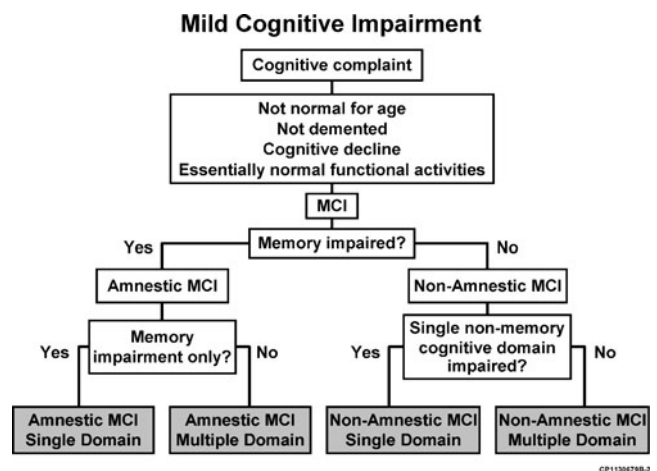


Fig. 1 Flow chart of decision process for making diagnoses of subtypes of mild cognitive impairment. From Agronin ME, Maletta GJ (eds). Principles and practice of geriatric psychiatry. Lippincott Williams & Wilkins, Philadelphia, PA; 2006, with permission

can be attributed to sampling and measurement bias [30]. The former pertains to issues of study design and sampling, for example recruiting research participants by using an advertisement can introduce non-respondent/volunteer bias [30], whilst the latter pertains to variability in the measurement of MCI. One good example to illustrate measurement bias would be studies that retrofit MCI criteria into a cohort. The ideal research design that is well-suited to compute epidemiological indices, such as prevalence and incidence, would be a population-based study that prospectively employs the operational criteria of MCI in elderly individuals [31, 32].

One of the first population-based studies that estimated the prevalence of MCI subtypes was that of the Cardiovascular Health Study. As the name implies, this cohort was assembled to examine cardiovascular risk factors [33]; hence, the investigators retrofitted the criteria for amnesic and multi-domain MCI to the cohort and reported the overall prevalence of MCI to be 22 %, with amnesic MCI accounting for 6 % and multi-domain MCI representing 16 % [33]. An Australian research group estimated prevalence in a probability sample of elderly individuals in the aged 60–64-years-old; they reported a much smaller prevalence rate than the Cardiovascular Health Study, i.e., 3.8 % and 3.1 % for MCI and aging-associated cognitive decline respectively [34]. Even though their study design was optimal, limiting the sample to the relatively younger age group is likely to have biased their findings toward underestimation of the prevalence of MCI.

The Prevalence and Incidence of MCI Differ by Sex

Recently, the population-based Mayo Clinic Study of Aging reported that both the prevalence [31] and incidence [29••] of MCI differ by sex. The investigators followed 1,450 cognitively normal persons, aged 70–89 years, forward in time for a median of 3.4 years. They reported that 296 of the study participants developed incident MCI. Thus, the overall age- and sex-standardized incidence rate of MCI was 6.36 % and the incidence rate was higher in men (7.24 %) than women (5.73 %). The incidence of amnesic MCI was 3.77 and that of non-amnesic MCI was 1.47 %. Additionally, the incidence rate of amnesic MCI was also higher in men than in women (4.39 % and 3.25 % respectively). Similarly, the incidence of non-amnesic MCI was higher in men (2.00 %) than in women (1.09 %). The incidence of MCI in subjects with ≤ 12 years of education was two times higher than in participants with > 12 years of education (2.03 % vs 1.02 %).

“Conversion” Rates of MCI

There are several studies that have estimated the progression rate of MCI to dementia [4, 35–37]. Their findings vary depending upon the study design and measurement instrument utilized [30]. For example, researchers from Harvard

University recruited study participants via advertisement. They then prospectively followed the cohort of subjects with MCI and reported a conversion rate of 6 % per year [37] whereas a recent multi-center, randomized, double blind, placebo-controlled clinical trial reported a conversion rate of 16 % per year [35]. Prior to that, the Mayo Clinic and other researchers also reported a conversion rate in the range of 10 % to 15 % [1]. Hence, the rather smaller rate reported by the Harvard group could be attributed to non-respondent/volunteer bias [30]. One important point that all studies highlight is that individuals with MCI develop dementia at a higher rate than the general population. It is this consistent finding that makes MCI a potential target for clinical trials.

One topic of debate and discussion is the “instability” of the MCI construct [28, 38]. Larrieu and colleagues reported a reversion rate (i.e., from MCI back to normal) to be as high as 40 % over 2–3 years of follow-up. However, they defined MCI based on only one single memory measurement, i.e., Benton Visual Retention Test [39]. A recent international consensus panel on MCI did emphasize the importance of progressive decline rather than entirely relying on poor performance at a cross-sectional point in time, which may help to minimize the “instability” of the construct [14].

Clinical Evaluation of MCI

Classic clinical scenario

A right-handed male patient aged 72 years presents with forgetfulness of recent events and future engagements. Family members and close friends also notice these changes. The patient feels that the onset of these symptoms is rather of insidious onset and has progressed gradually over a period of 2–3 years. Otherwise, he is living independently and has no difficulty carrying out activities of daily living, such as handling finances, cooking, and driving. He denies profound depression, stress, or other complicating medical issues. He requests an appointment with a physician in order to determine if his memory problem should be pursued further. The clinical evaluation, i.e., meticulous history and physical examination, including bed side cognitive screening using the Short Test of Mental Status, was suggestive of cognitive impairment but not severe enough to warrant the diagnosis of dementia. Hence, a clinical diagnosis of MCI is made. Investigations, including psychometric testing and magnetic resonance imaging (MRI), are ordered. The neuropsychological testing confirms the clinical diagnosis. Furthermore, it reveals memory impairment, particularly on measures of learning and delayed recall beyond what is expected to be normal for age; however, other cognitive domains, such as language and visuospatial skills, are relatively intact. MRI of the head reveals mild hippocampal atrophy. The above clinical

scenario is probably indicative of amnesic MCI. The patient is becoming slightly more forgetful, and this is noticeable to his family and friends. The most salient feature of the history concerns forgetfulness of insidious onset that gradually progressed over a year or so. All other cognitive domains, i.e., language, compartment-executive function, and visuospatial skills, were intact. The individual is functioning independently. This likely represents an early disease process involving the medial temporal lobe as meaningful information could no longer be stored in an efficient manner, nor is it recalled well.

There are four variables that the clinician should bear in mind when collecting clinical data from a patient with suspected cognitive impairment: (i) exploring cognitive domains; (ii) day-to-day functioning; (iii) disease course; and (iv) neuropsychiatric symptoms.

Cognitive Domains

Sometimes, it may be helpful for the clinician to bear in mind the major cognitive domains whilst eliciting history, i.e., inquire about memory, language, visuospatial, executive-compartment function, and human face- and object-recognition networks [40]. Such an approach will elucidate whether cognitive domains other than memory are significantly impaired in the patient. For example, after inquiring about recent events, the clinician may ask about any loss of sense of direction, such as getting lost in one's neighborhood or having difficulty finding the bathroom in one's own house.

Day-to-Day Functions

In addition to gathering clinical data on cognitive domains, the clinician should make sure that the patient is presently functioning independently. This is accomplished by inquiring about instrumental activities of daily living, such as balancing a checkbook or making travel reservations.

Temporal Course of the Illness

Finally, the clinician should determine the temporal profile of the illness. If the memory problem is of insidious onset and gradual progression, then one should think of possible underlying neurodegenerative processes, whereas if there has been a rather acute onset of cognitive changes then vascular or infectious contributions may be considered.

From a cognitive domain perspective, the clinician should inquire about forgetfulness of recent events and future engagements (memory domain), problems of comprehension and expression (language), problems with sense of direction, and behavior changes, such as disinhibited behavior or apathy. One may want to ask about major events, such as severe weather or other widely discussed political, cultural, or sporting events, depending on the patient's cultural background.

The clinician can get an idea about the patient's baseline interests and hobbies from the patient and family and make inquiries based on recent experiences. For example, if the patient is a known sports fan, then inquiring about recent games might be informative. If the patient maintains an interest in current events and politics, then inquiring about recent happenings may be helpful. Also, the clinician should inquire about recent important engagements, such as a family gathering or a critical appointment with the doctor, that were missed because of forgetfulness.

Corroborating data from the family is helpful, not only in determining comparison with baseline function of the patient, but also in validating the history provided by the patient. Patients with memory problems may give little detail about recent events and tend to be vague.

Physical Examination

The physical examination often renders important clinical data regarding the etiology of cognitive problems. For instance, rigidity, bradykinesia, and tremor in an individual complaining of "memory" problems could be indicative of Parkinson's disease or any other Parkinsonian syndrome. Aphasia and right hemiparesis in a right-handed person presenting with acute "memory" complaint could be indicative of left-sided cerebrovascular accident. Fever, nuchal rigidity, and seizure could be suggestive of herpes simplex encephalitis in someone presenting with subacute memory loss.

Mental Status Examination

The mental status examination is a critical part of the clinical evaluation which plays an important role in the diagnostic process. This evaluation also aids the clinician in considering the need for more detailed neuropsychological evaluations. The clinician can use any of the standard bedside tests, such as the Mini-Mental State Examination or the Kokmen Short Test of Mental Status [41]. The clinician also has to be familiar with the limitations of these tests. These tests use the learning of three or four words, with a relatively short recall interval. The Short Test of Mental Status has the advantage of assessing learning by taking into account the number of trials the subject requires to learn the four words accurately [42].

It is important that bedside mental status examinations screen for problems with attention or language. If observation of affect is suggestive of significant depression or anxiety, the mental status examination should be augmented by screening for psychiatric symptoms using a psychiatric inventory, such as the Geriatric Depression Scale, Hamilton Depression/Anxiety Rating Scale, Beck Depression/Anxiety Inventory, or similar screening instruments.

Investigations

Psychometric Testing

A meticulous history and examination may indicate the need for neuropsychological testing standardized for age and education level. Psychometric testing is essentially an extension of the bedside mental status examination. Both verbal and nonverbal functions should be addressed to effectively evaluate a memory problem. One example, the Rey Auditory Verbal Learning Test, is often used in such patients. In this test, a patient is given 5 trials to learn 15 unrelated words. The score of each trial is recorded, which later will be used to generate the learning curve of the patient. After 30 minutes, the patient is asked to recall the learned material and should be able to recall 50 % or more of the material acquired. This test evaluates the patient's ability to encode learned material and subsequently transfer this from a working memory to recent memory. The learning curves generated from such a test have a characteristic pattern, for example in patients with AD, the learning curve will be flat, i.e., a curve with a slope approaching zero. Alternatively, in cognitively normal individuals, the learning curve will have a positive slope indicating the ability of an individual to learn more with each successive trial. Patients with depression display cognitive inefficiency such that they are able to learn but require more effort than normal individuals. The learning curve is somewhat flat and falls to the right of a normal curve (Fig. 2).

Neuroimaging of the Brain

A computerized tomography (CT) or MRI scan of the brain may be done in order to visualize the medial temporal lobe structures that are involved in MCI. A MRI of the brain will be more sensitive in imaging medial temporal lobe structures. A CT scan of the head may have a number of artifacts, as the medial temporal lobe structures are located near the calvarium. Techniques for the detection of MCI or AD through neuroimaging have

improved in recent years. Automated imaging techniques have been shown to be highly useful in the evaluation of MCI and AD [43].

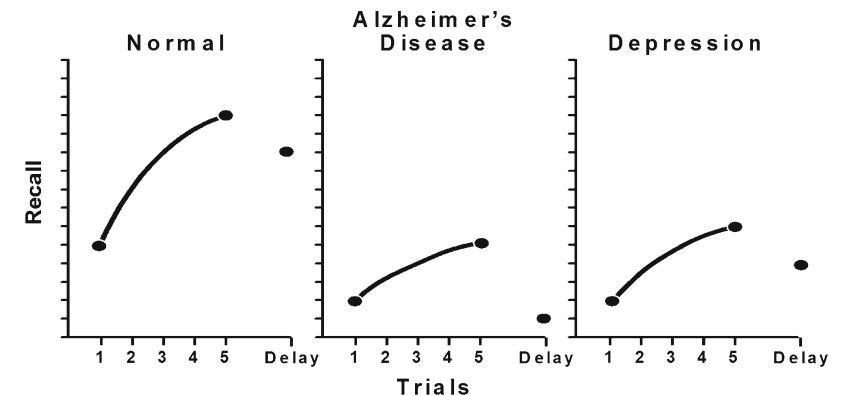
In selected cases, one should consider using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) scans. In the early stages of the disease, a MRI of the head may not show any gross abnormality, whereas a decreased blood flow pattern on SPECT or decreased glucose utilization on PET could be noted in areas of the brain reported as normal on MRI. As these tests are expensive, they should be reserved for special circumstances.

Molecular Imaging

Pittsburgh Compound B Imaging

Several agents have been developed in recent years but Pittsburgh Compound B (PiB) is the most intensely investigated. PiB is a tracer used in PET scans that labels fibrillar amyloid and allows for the assessment of cerebral amyloid burden in living persons; therefore, it may prove to be very useful in imaging amyloid in normal cognitive aging and dementia [44]. More information is necessary about PiB imaging before it is used in clinical settings. Several groups around the world are investigating PiB among selected convenience samples and most of these studies are cross-sectional associations. Current data suggest that 20–30 % of cognitively normal subjects have positive PiB scans, whilst about 60 % of MCI subjects have PiB-positive scans [45]. A few studies have begun to examine the serial properties of PiB imaging over time [46, 47]. Investigators from Washington University in St Louis, MO, reported the outcome of following 159 cognitively normal persons that had PiB imaging at baseline and were followed for a mean (SD) of 2.4 (1.3) years [48]. Twenty-three subjects progressed from 0 to 0.5 on the Clinical Dementia Rating Scale, and 9 of these subjects developed dementia of Alzheimer's type. They concluded that preclinical AD as measured by PiB may predict symptomatic AD. However, given the small AD

Fig. 2 Learning curves: Normal vs AD vs Depression. From Agronin ME, Maletta GJ (eds). Principles and practice of geriatric psychiatry. Lippincott Williams & Wilkins, Philadelphia, PA; 2006, with permission



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events and shorter follow-up of their study, larger studies with longer follow-up duration are indicated.

Treatment of Mild Cognitive Impairment

As the focus of AD research moves toward prevention, numerous clinical trials designed to determine pharmacotherapy options for MCI are underway [49].

Clinical trials involving MCI patients are promising because such trials will likely uncover new information in the detection and intervention of the disease while it is still in a transitional clinical stage. The therapeutic agents being tested are similar to those under consideration for the treatment of AD, namely cholinesterase inhibitors, antioxidants, anti-inflammatories, nootropics, and glutamate receptor modulators. There is no specific medication treatment for MCI. Nonetheless, it is important for a clinician working with MCI subjects to be aware of AD treatment options that may be of some benefit in MCI patients; hence, these medications are discussed below.

Most medications that are used to treat AD are cholinomimetics (reversible inhibitors of acetylcholinesterase enzyme activity) and were developed based on the rationale that the cholinergic system is involved in learning processes. The first FDA-approved cholinomimetic agent was tacrine (Cognex[®]) [50]. It is rarely used currently because of its hepatotoxic side effect profile. Currently, there are three FDA-approved cholinomimetics: (i) donepezil (Aricept[®]); (ii) rivastigmine (Exelon[®]); and (iii) galantamine (Razadyne[®]) [51–56]. These medications are not curative but they have been shown to minimize morbidity in AD. These medications may also be helpful in managing some neuropsychiatric and behavioral symptoms in AD patients [54]. Side effects of cholinomimetics can be understood by recalling the multiple systemic functions of the cholinergic system. Through their primary action of increased cholinergic activity, these medications can lead to bradycardia, increased gastric acid secretions, and increased gastrointestinal motility. Further considerations pertain to drug–drug interactions, for example cholinomimetics are known to interact with some anesthetics.

Memantine (Namenda[®]) is a US Food and Drugs Administration (FDA)-approved N-methyl-D-aspartate receptor antagonist of glutamate activity used in patients with moderate-to-severe dementia. Clinical trials to determine the efficacy of memantine in such patients were conducted based on the rationale that glutamate contributes to neurodegenerative disorders by overstimulating the N-methyl-D-aspartate receptor [55, 56].

Apart from the above agents, other medications targeting the monoaminergic neurotransmitter system, such as selective serotonin reuptake inhibitors, adrenergic agents, peptides, and nootropics [57], have been considered for the symptomatic

treatment of cognitive impairment. Limited data have suggested that nicotine treatment may reduce symptoms of MCI and clinical trials are being conducted to explore this treatment option [58]. Another group that has attracted research interest is the anti-oxidants. At least one randomized, placebo-controlled, double-blind multi-center trial indicates that vitamin E may delay the progression of moderate to severe AD [35]. However, more recent studies have indicated that vitamin E is not efficacious in the treatment or prevention of AD or MCI [59]. Furthermore, a meta-analysis indicated that high-dose vitamin E may increase all-cause mortality and thus should be avoided [60].

In review articles, Geda and Petersen, and others [12, 61–63] discussed several clinical trials on MCI, including one conducted by the Alzheimer's Disease Cooperative Study (ADCS), and other pharmaceutical company-sponsored trials. The ADCS completed a randomized, double-blind, placebo-controlled study involving three arms to assess the safety and efficacy of high-dose vitamin E and donepezil [35]. The objective was to assess the safety and efficacy of vitamin E (2000 IU per day) and donepezil (10 mg per day), and was powered to decrease the conversion rate of MCI to AD from the anticipated 45 % down to 30 % over the course of 3 years. Seven hundred and sixty-nine subjects were randomized in the trial and the annual conversion rate from MCI to AD was approximately 16 % per year. Over the course of the study, donepezil reduced the risk of progressing to AD for the first 18 months of the trial, whilst vitamin E had no therapeutic effect. The secondary cognitive measures supported the overall group progression rates. No unexpected adverse events were observed. This trial was an important first step in elucidating techniques to delay progression from MCI to AD. Furthermore, a meta-analysis pooled the data from four randomized clinical trials in MCI. There were 3,574 subjects with MCI; of these, 1,784 were treated with cholinesterase inhibitors (ChEIs) and 1,790 were given placebo. Two hundred and seventy-five (15.4 %) of those treated with ChEIs progressed to AD while 366 (20.4 %) of those treated with placebo progressed to AD [relative risk (95 % confidence interval) = 0.75 [0.66–0.87]; $p < 0.001$] [63]. These results indicate that the ChEI treatment may have some role in delaying the progression of MCI to AD.

Conclusion

The study of aging and dementia has led to the description of MCI. The construct of MCI, particularly amnesic MCI, has stimulated research as it is a high risk group for dementia. In the past decade, there has been an exponential increase in the epidemiology, clinical, neuroimaging, and interventional research targeting MCI. The field of cognitive aging is now moving toward identification of asymptomatic individuals who have underlying AD pathology that can be detected using

biomarkers and neuroimaging technologies. To this effect, the AA-NIA has developed a new classification scheme that has categorized AD into a preclinical phase (research category), MCI due to AD, and dementia of Alzheimer's type. The AA-NIA criteria will catalyze the research work to prevent Alzheimer's dementia. Similarly, non-amnesic MCI may be a precursor of non-Alzheimer's dementia; thus, several investigations are underway to identify high-risk groups for Lewy body dementia and other non-AD dementias.

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- Of major importance

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