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Review Article

The borderland between normal aging and dementia

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Abstract

Alzheimer's disease (AD) has become a global health issue as the population ages. There is no effective treatment to protect against its occurrence or progression. Some argue that the lack of treatment response is due to delays in diagnosis. By the time a diagnosis of AD is made, neurodegenerative changes are at the stage where very few neurons can be salvaged by medication. The AD research community has developed the idea of mild cognitive impairment (MCI) in an attempt to find predementia patients who might benefit from potentially therapeutic drugs that have proven ineffective in the past. However, MCI is heterogeneous in terms of its underlying pathology and practicality for predicting dementia. This article first reviews the conceptual evolution of MCI as the borderland between normal aging and dementia, and then proposes that built environment and sociocultural context are two key elements in formulating a diagnosis of dementia. Dementia is more than a biomedical term. Cognitive impairment is considered a dynamic outcome of how an individual interacts with cognitive challenges. To focus on amyloid deposition as a single etiology for AD does not adequately capture the social implications and geriatric aspects of dementia. Moreover, MCI is nosologically questionable. Unlike a diagnosis of AD, for which a prototype has been well established, MCI is defined by operational criteria and there are no cases seen as typical MCI. Biofluid and imaging markers are under active development for early detection of amyloid deposition and neurofibrillary tangles in the brain, whereas vascular risks, chronic medical diseases, and polypharmacy continue to add to the complexity of dementia in old age. The paradigm of dementia care policy may shift to early diagnosis of AD pathology and comprehensive care for chronic diseases in the elderly population.

Keywords: *Alzheimer's disease, Dementia, Mild cognitive impairment, Normal aging*

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by slowly progressive cognitive decline. It is, however, difficult to tell the onset of AD from normal aging. Mild cognitive impairment (MCI) is a concept which has originated from the attempt to detect AD early [1], but again, it is a spectrum rather than an event with a clear onset. Here, I review the development, implications, and limitations of the concept of MCI.

In the past years, many drugs have been tested in clinical trials aimed at halting the degenerative processes of AD, including estrogen [2-4], testosterone [5], aspirin [6], nonsteroidal anti-inflammatory drugs [7,8], prednisolone [9], omega-3 fatty acids [10] and dehydroepiandrosterone [11]; however, they all failed to effectively ameliorate cognitive deterioration. Scientists argue that neuronal death may have arrived at an irreversible state by the time AD is diagnosed, and it is therefore too late to intervene with these drugs. There is a hypothesis that these drugs can be neuroprotective against AD if patients are identified earlier. Although there is no evidence to date showing that the clinical course of AD can be modified if the diagnosis is made earlier, identifying people at high risk is considered a plausible step toward finding effective treatment for AD.

This attempt at early identification of AD has resulted in tremendous enthusiasm for seeking biomarkers for early detection and defining at-risk people in clinical settings such as MCI, but it has also raised some concerns. At the individual level, people who are called at risk for AD or MCI may become apprehensive about their health, knowing that there is no cure or anything they can do to modify the course. This labeling may create more anxiety, despair, and frustration, although these people remain functional and active in different social roles. At the population level, MCI, as a new clinical entity introduced to the public through media at varied levels of scientific rigor, tends to result in

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many people of all ages flooding into clinics with complaints of mild forgetfulness. Presumably, only a small proportion of these people have the prodromal AD which we target, but considerable medical resources would need to be spent on initial screening and regular follow-up visits. The economic impact of publicizing a new clinical entity warrants careful evaluation.

A more fundamental issue is the appropriateness of MCI as a clinical entity. In the following paragraphs, I will first review how the concept of MCI has evolved before being defined by operational criteria and implemented in clinical practice; then, I will address the heterogeneity within the MCI group, particularly at the community level or in the general population. I argue that the variability in the diagnosis of MCI stems from the built environment, either physical or social. Finally, I will discuss why MCI is nosologically problematic from the viewpoints of clinical validity and categorization theory.

Evolution of mild cognitive impairment

Occasional forgetfulness or reduced cognitive capacity is a common and natural feature in the elderly. In 1962, Kral proposed the concept of "benign senescent forgetfulness" [12], to contrast to a rather malignant form of memory impairment, with respect to clinical manifestation and prognosis. Forgetfulness with a poor outcome was recognized first, though not necessarily as a precedent of AD. Later in 1986, a group at the US National Institute of Mental Health used the term "age-associated memory impairment" to characterize very mild memory dysfunction in the elderly compared with young adults based on formal memory tests [13]. In 1989, Blackford and La Rue proposed a refined version of age-associated memory impairment, "late-life forgetfulness," as having a decrement greater than 50% on a specified test battery. In 1994, Levy proposed "age-associated cognitive decline," for memory impairment in formal tests using norms for the elderly instead of younger individuals as a reference [14]. The aforementioned syndromes involved efforts to try to characterize memory impairment based on standardized tools in order to minimize variability in clinical judgment. Some definitions compared older people with young, and many older people were categorized as "declining" when they were in fact normal for their age.

In 1994, the concept of MCI was incorporated into the major international classification system. The Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) refers to "age-related cognitive decline" as objective functional decline due to the physiological aging process, but it has little practical value since no criteria or tests are specified. Another term proposed in the DSM-IV is "mild neurocognitive disorder (MNCD)," which includes executive and linguistic function in addition to memory. A similar term, "mild cognitive disorder (MCD)," is encompassed in the 10th revision of the International Classification of Diseases; however, it refers to memory and learning difficulty secondary to physical illnesses. Both MNCD and MCD are not designed as diagnoses for the elderly and are not suitable for identifying the population at risk for AD.

In 1997, Graham *et al*. proposed "cognitive impairment-no dementia (CIND)" in the context of the Canadian Study of Health and Aging to encompass primarily memory impairment but also other domains with a wider range of etiologies [15]. Both a formal test and clinical examination are required to meet the criteria. Although not all people with CIND have a progressive course of memory impairment, studies implemented with CIND criteria suggest that certain people with subclinical cognitive deficits are in fact in the early stages of AD. In 1999, MCI as memory impairment beyond that expected for age and education yet not dementia was characterized by Petersen *et al* [1]. The diagnosis of MCI is made if patients meet the following criteria: (1) memory complaints, (2) normal activities of daily living, (3) normal general cognitive function, (4) abnormal memory for age, and (5) not demented. Since then, many studies have applied the MCI criteria and focused on how likely and how fast people with MCI develop AD.

Although these different terms address a similar concept, prevalence estimates vary across different operational criteria. The use of a broader term such as age-associated memory impairment can result in considerably inconsistent prevalence estimates ranging from 7% to 98% in the elderly population, depending on the specific cognitive test applied [16-19]. This suggests that the spectrum of cognitive function between normal aging and dementia in the elderly is wide, and prevalence estimates simply reflect how sensitive or restrictive the particular cognitive test is in finding cases meeting the operational criteria.

Memory is one dimension of the integrated cognitive function of human beings, and there are several types of memory, including episodic, procedural, emotional, and semantic, to name a few. Episodic memory refers to the ability to recall the past events or personal experience, and it is also the major feature of AD. Isolated memory impairment is, therefore, a major focus of research. In a registry-based study, Bowen *et al.* followed a group of people with new cognitive complaints and found that people with isolated memory loss had a higher risk of developing AD than those with nonmemory cognitive complaints [20]. The diagnosis of MCI requires memory complaints as well as objective memory dysfunction to meet the criteria; however, not all cases of MCI progress to AD or other dementia and many cases even return to normal. Furthermore, in the original study of Petersen's criteria, the cutoff of 1.5 standard deviation below age- and education-matched controls was made somewhat arbitrarily. The conversion rates to AD vary by different operational cutoffs [21]. The heterogeneity in the use of the term raises various concerns, and as a result, three subtypes, amnestic, multiple domain, and single nonmemory domain MCI, have been proposed [22].

Amnestic MCI is thought to be the most common subtype and the most likely type that will convert to AD, whereas other subtypes may represent non-AD dementia or normal aging. Whether the concepts derived from patients who present to memory disorder clinics can also be applicable in the general population is questionable. Palmer *et al*. conducted a 3-year study to determine the predictive value of each MCI subtype for identifying future AD [23]. They found that the majority of cases of MCI were in people with cognitive impairment of a single nonmemory domain; the subtype carrying the highest risk of conversion to AD was not the amnestic type but the multiple domain type; a substantial proportion of people with memory impairment did not complain. All these results suggest that people with MCI who come to a clinic

seeking care for memory deficits may be different from people with MCI identified in the community. Amnestic MCI is likely overrepresented in memory clinics whereas the other two subtypes may be seen in different specialties. It is conceivable that cognitive deficits other than memory can be attributable to a variety of medical and psychiatric illnesses, which in total may be seen in a larger population than AD. Therefore, identifying people who will convert to AD simply based on the operational criteria for MCI may be inadequate. A new set of criteria has been proposed to further define MCI as MCI due to AD by incorporating pathological markers consistent with AD [24]. This change would certainly improve the predictive value of an MCI diagnosis. However, tests for these biomarkers are all expensive and not easily accessible to most primary physicians, limiting their applicability.

Built environment and cultural context

In a population study, nearly half of the AD patients had no complaints about cognitive function 3 years before diagnosis [25], suggesting that there is a discrepancy between objective cognitive impairment on tests and subjective functional impairment in daily life. Aside from the fluctuating nature of cognitive dysfunction at some point in the disease course, there are several external sources for this discrepancy: environmental support and cultural relativism.

People with episodic memory impairment are easily disoriented in the absence of cues and distracted in the presence of many stimuli. At the early stage, they still have insight about their reduced memory capacity and may develop compensatory strategies such as notes, timers, and calendars to overcome inconvenience due to forgetfulness and to avoid embarrassment in public. This is a period when the level of disability depends on the environment, particularly the built environment and social support. If there are many options for strategies within the environment to optimize cognitive performance, for instance, a portable global positioning system for navigation, they can still venture out and buy groceries independently. Mental aids can be placed in bathrooms, bedrooms, and kitchens for instructional purposes. The use of household devices can be programmed and simplified into a few buttons to prevent dangerous situations. The formation of adaptive behavior to cope with various cognitive challenges is greatly facilitated not only by advances in technology but also by support from family members. Extended family is conceptually the basic family unit in many Asian societies, although the nuclear family is becoming dominant. Children who have their own families may still live in the same neighborhood as their parents, so that they can take turns caring for them. Under these protected circumstances, daily lives are less affected by mild cognitive dysfunctions such as memory impairment since meals, transportation, leisure, health, and financial management can be taken care of by children or other family members. People are not considered diseased until the late stage of dementia, for example, when they no longer recognize people. The concept of MCI also reflects that cognitive demand is higher in a society such as the United States, where even mild impairment can severely affect quality of life. For example, driving skills are basically a requisite to mobility and a slight decrease in visuospatial attention or topographic memory may put drivers at risk. As a consequence, MCI becomes an important issue as it can lead to driving disability and thus individual immobility. On the contrary, MCI is less relevant with respect to individual mobility for the elderly who live in a rather self-contained community with no need to drive on their own. Both hardware and software in the built environment contribute in determining how much cognitive capacity is necessary to live an independent life. The difference in the built environment for individuals with comparable cognitive impairment can result in heterogeneity in defining their state of disability. While performance on neuropsychological tests may be less subjective in determining cognitive function, reliance on these standardized tests may result in a lack of consideration of the importance of local knowledge or the microenvironment which poses different levels of cognitive demand. In other words, MCI is meaningless if only low cognitive capacity is required to be functional in daily life.

Culture refers to a collective set of values and beliefs practiced and shared by a group of people. Conceivably, MCI or memory impairment is viewed in different ways depending on the cultural context. In a society which values people who "lift themselves up by their own bootstraps," even mild impairment in cognitive performance can reduce individual competence in daily activities, and therefore, these individuals seek medical evaluation. A less than ideal cognitive performance is considered abnormal when the normal range is rescaled. Similar trends can also be seen in other medical fields, such as hypertension [26]. The criteria have become more stringent for defining normal blood pressure (systolic blood pressure <120 mmHg, diastolic blood pressure <80 mmHg) and a new category such as prehypertension has been created to denote the borderline between normal and hypertension (systolic blood pressure 120–139, diastolic blood pressure 80–89). From a disease prevention perspective, there is no doubt that this approach will increase the sensitivity to find patients at a premorbid state. However, what does "pre-hypertension" mean if community hygiene and infectious diseases are major concerns in a society where more people die of diarrhea and parasitic infection than cardiovascular events? Likewise, it is ironic to talk about obesity in a country that suffers from poverty and famine. In a different culture, forgetfulness may be regarded as part of the aging process, just as we do not expect elderly people to act as swiftly as the young. MCI is not suitable to apply to people with cognitive function "appropriate" to their age in some cultural contexts. Moreover, in some cultures, cognitive impairment may be conceptualized, studied, and experienced in a totally different way from the aging processes. For example, in Cohen's book "No aging in India," aging or dementia is explained beyond individual health status and the old person is seen as a metaphor for the moral decay of the family and the nation [27].

Heterogeneity in dementia

The diagnosis of MCI is tied to what we know about dementia. Dementia has to be excluded to fulfill the diagnostic criteria of MCI. However, dementia is also a diagnosis with great heterogeneity. Several common criteria for the diagnosis of dementia can differ by a factor of 10 in prevalence estimates [28]. This disagreement can be attributed to different primary cognitive tests used in diagnosis. In addition, the social and occupational aspects in the diagnostic criteria for dementia are weighed differently. DSM-IV criteria for dementia of the

Alzheimer's type, for example, require that the cognitive deficits cause significant impairment in social and occupational functioning [29]. This is where clinical judgment comes into play as we do not have a standardized tool to measure this dimension. The research-oriented diagnostic criteria for AD, established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), have less to do with social and occupational functioning and also exclude other psychiatric or medical causes to increase specificity [30]. Studies showed that NINCDS-ADRDA criteria provide only fair reliability (interrater agreement kappa = 0.64) [31] and validity (sensitivity = 0.92, specificity = 0.65) [32]. Blacker *et al*. found that most disagreement originated from complicated medical, neurological, and psychiatric illnesses [33]. In addition, medical records did not always provide detailed clinical information, making interpretations and inferences less consistent across different reviewers. The authors recognized that no diagnostic tool is perfect although the consensus process may improve the diagnostic accuracy. New diagnostic criteria for AD from the National Institute on Aging-Alzheimer's Association and the International Working Group-2 have been proposed via the consensus process in recent years [34,35]. The main idea is to incorporate genetic, cerebrospinal fluid (CSF), and imaging studies into the diagnostic process to enhance its objectivity using reliable pathological markers. However, it remains unclear how these new criteria can be validated against the pathological diagnosis of AD and employed in day-to-day practice.

Functional status remains the core criterion in clinical settings. For example, the Clinical Dementia Rating (CDR) scale is often applied for case definition. The CDR scale is composed of features in problem-solving, community affairs and hobbies, which largely depend on personal educational background and facilities in the community. If people have few years of education to adequately learn problem-solving or live in an unfriendly community where they are reluctant to join programs, they are more likely to be considered functionally impaired and thus have MCI or dementia. Education has been proposed to be protective against AD [36]. It is speculated that education in early life can increase cognitive reserve. However, it remains arguable whether education can enhance performance on various cognitive tests because students are trained and given tests with similar formats during normal schooling. All in all, we should recognize that there are subjective components in the diagnostic process for AD. These components are not measured, not measurable or measured in a quasi-quantitative way. These all add to the complexity and variability of diagnosing dementia. MCI is a conceptual construct but not a diagnosis with a pathological basis like AD. It is therefore conceivable that MCI is a term with much heterogeneity and instability.

Biomedicalization of dementia

Although the current focus of AD is on the elderly population, the first case of AD reported by Alois Alzheimer at the beginning of the 20th century was a 51-year-old woman who presented with symptoms including impaired memory, aphasia, hallucinations, and bizarre behavior. Obviously, it was very unusual to see a patient with such clinical manifestations at this age. It is not known how this patient would have been viewed and treated if her age at onset was over 80 years. Senility was long deemed inevitable in old age, until the 1980s, when public awareness of dementia grew and funds for AD research from the National Institute of Health dramatically increased. Since then, senile dementia has not been considered a natural phenomenon of aging but has become a medical problem which is attributable to biological causes and subject to drug treatment. The diagnosis of attention-deficit and hyperactivity disorder in children is a similar example. Hyperactive behavior in children used to be considered normal, or at least, not a pathological condition; however, it is now an established clinical entity with formal diagnostic assessment, theory in pathophysiology and medical treatment. AD refers to a pathological condition involving loss of cognitive functions and memory in particular and was in effect originally intended to illustrate onset before very old age. Through the process of biomedicalization, senility, which has been considered appropriate to age, is now a deviance, a medical problem and a clinical entity with distinct pathology and requiring specific treatment [37]. As a result, all coexisting symptoms or illnesses, such as depression, were unsurprisingly brought in under the umbrella of dementia, regardless of whether they may simply reflect a normal emotional response to the social construct. All features that come along with dementia tend to be seen as part of the constellation of symptoms and signs in AD or an indicator of disease stage.

Ever since the paradigm of AD was established, there has been a growing body of evidence supporting the notion that AD is a disease entity. However, aside from some rare genetic causes of AD, there has never been a definite etiology. Some studies demonstrated that not all patients with the brain plaques and tangles typically shown in AD develop dementia [38,39], and conversely, disseminated vascular lesions or small infarcts in the brain seemed no less contributory than amyloid deposition to typical presentations of AD [40]. The amyloid hypothesis of AD pathophysiology is no longer certain. The discrepancy between pathology and clinical presentation further increases the complexity of AD. Our understanding of AD has arrived at the stage where it is unlikely a single disease and, instead, is a general category. Biomedicalization does not seem to lead to a definite biological answer.

MCI is a diagnosis made on top of our understanding of AD. Since the biological underpinning of AD is somewhat undecided, transforming MCI or the concept of a transitional phase into a biomedical entity is even more challenging. As a recent study showed, many patients with clinically diagnosed amnestic MCI exhibit mixed pathologies [41]. What has been neglected throughout the course of biomedicalization is how the sociocultural context frames the nosology of AD or MCI. The implications of an MCI diagnosis need to be reconsidered.

Mild cognitive impairment as a nosological entity

A clinical syndrome consists of a cluster of symptoms and signs placed in a distinctive time course. The constituents of MCI are not derived from a group of patients with unique clinical features observed in clinical settings but rather a conceptual set of attributes.

This makes an MCI diagnosis different from how we define AD. To be qualified as a clinical syndrome, there should be ways we can ensure the validity beyond a cluster of symptoms and signs.

Several validators for clinical syndromes have been proposed: (1) identification and description by "clinical intuition" or by cluster analysis, (2) demonstration of boundaries between related syndromes by discriminant function analysis, (3) follow-up studies establishing a distinctive course or outcome, (4) therapeutic trials establishing a distinctive treatment response, (5) evidence of familial clusters, and (6) association with more fundamental abnormalities - histological, biochemical, or molecular [42]. A diagnosis of MCI is based on artificial criteria but not identified by clinical intuition. Boundaries for MCI are blurred and related syndromes are distributed all over the spectrum of symptomatology without a "point of rarity". People with MCI are more likely to develop AD during follow-ups, but it is also common to see reversion to normal among these patients [43]. Overall, the clinical course of MCI is more heterogeneous than distinctive. There is no documented treatment for MCI, although it remains unknown whether current therapeutic options for AD can be effectively applied to MCI. MCI is not considered a familial or inheritable disorder, and transition to AD does not vary with family history [44]. Although there was a study using a set of revised MCI criteria in an attempt to increase the predictive ability, its validation was made against clinical judgment of AD, which also did not help in making MCI a distinctive entity [45]. Finally, unlike AD, there is no way we can validate MCI by histological pathology. Therefore, MCI seems well formulated but lacks validators; MCI has become a syndrome that cannot be accurately identified. Although accurately identifying a clinical syndrome does not always precede etiological discovery, it undoubtedly increases the likelihood of a successful elucidation of its etiology.

In addition to the above problems, there is also a lack of a prototype to make MCI an independent category. The prototype theory was first introduced to cognitive psychology by Rosch and Barbara [46]. They concluded that the natural way we categorize objects is based on recognizing the prototype but not on logical classification. Taking AD as an example, the prototype is the first case reported by Alois Alzheimer. Alzheimer noticed the unique pattern of cognitive impairment and behavioral changes, and he correlated these clinical features with pathological findings in the brain. The typical case or prototype was then established, which allowed physicians to diagnose patients by comparing with the AD prototype. AD experts accumulated clinical experience over time and subsequently formed the basis of consensus criteria. Although current concepts of AD are much different from that in Alzheimer's era, the origin can be traced back to that prototype case. Parkinson's disease is an another example. When James Parkinson first described cases of paralysis agitans, he thought that these patients were cognitively intact with pure motor dysfunction. To date, there is a growing body of evidence showing that many nonmotor features such as dementia, depression, sleep disorders, and autonomic dysfunction are part of the Parkinson's disease course. The concept may evolve and branch into different categories, but there is always a prototype fertilizing the nosology.

Petersen recognized the variability in making an MCI diagnosis, ranging from rating scales to sources of subjects [47]. Nevertheless, many investigators argued that just because there are instability rates of 25%–40% in the longitudinal outcomes of patients with MCI does not mean the construct of MCI criteria is inaccurate. Using an MCI diagnosis for patients with memory dysfunction may still have practical value for longitudinal follow-ups. No matter how unstable the MCI diagnosis may be in terms of AD risks, memory function in these people is lower than normal. The current criteria for MCI are still broad and not specific. At the clinical level, it is difficult to distinguish which cases of MCI will progress to AD and which will return to normal. There is no prototype MCI case as a reference for physicians to compare, contrast, and comprehend. Although it is known that many MCI patients have AD pathology and subsequently convert to AD, treating MCI as a nosological entity is still debatable. Although an MCI diagnosis in combination with other biomarkers is highly predictive of AD, this is in reality a diagnosis of AD or preclinical AD, not something unique and separable from AD.

Early detection of dementia

Clinical neuroscientists are striving to identify the at-risk group who will develop AD. However, defining the transitional phase between normal aging and AD has brought both hope and apprehension, especially when the sociocultural context is taken into consideration. During the past two decades, several biomarkers of AD have emerged, such as amyloid and tau protein in the CSF, hippocampal atrophy on brain magnetic resonance imaging, and glucose metabolism and even amyloid on positron emission tomography. These biomarkers have been incorporated into new diagnostic criteria [34,35,48], may be used to differentiate patients with AD from healthy elderly people. However, when these markers begin to progress and how fast these markers change over time are not known. There has not been enough evidence from prospective studies to show the trajectories of these biomarkers. Tracking AD biomarkers over time together with repeated cognitive tests may allow us to find the earliest pathological changes and evaluate the possibility of using biomarkers for early detection of AD, thereby limiting our dependence on the imperfectly defined syndrome of MCI.

Biomarkers seem to be reliable and objective tools for the diagnosis of AD, but defining AD purely on a biological basis is not without concern. Previous studies have shown discordance between the clinical severity and pathological severity of AD and found that nonbiological factors, such as education and occupation, also play important roles in cognitive expression. Cognitive reserve theory was, therefore, developed to account for the observed discordance [49]. Based on this theory, given the same amount of AD pathological burden, people with higher education or greater reserve are more resistant to cognitive impairment. However, the neural basis of cognitive reserve remains elusive and whether the progression of AD pathology can be altered by cognitive reserve is not clear.

In addition to our lack of understanding of AD biomarker dynamics and clinicopathological discrepancy, early detection of AD is also hampered by the fact that many elderly people have multiple comorbidities, particularly cardio- and cerebrovascular diseases. Overt stroke or microinfarcts in the brain can lead to

cognitive dysfunction. Typical vascular pathology is commonly found in postmortem brain examinations of patients with an AD diagnosis and in fact mixed pathologies account for most dementia cases in the community [50]. To better define dementia of the Alzheimer type, further clarification of the role of vascular risks and other chronic medical diseases is warranted.

Conclusion

MCI is a concept which has been used in an attempt to identify patients with AD early in the disease course. This attempt reflects the failure of multiple clinical trials for AD and the hope for effective treatment if given earlier. Various terms including MCI have been proposed to signify the transition phase between normal aging and dementia. Several subtypes have been identified among people with MCI defined by the same criteria, and MCI patients seen in the clinic are different from those in the community. The diagnosis of MCI or dementia depends on not only cognitive tests but also the interaction between individuals and their local environment and sociocultural context. The level of required cognitive capacity varies with the cognitive demands in the environment. Different cultures have their own interpretation of cognitive impairment and the border separating normalcy from deviance is quite blurred.

Dementia of the Alzheimer type represents a referent diagnosis for MCI; however, the established criteria for AD are sensitive but not specific. Biomedicalization of AD is intended to explain the disease on a more biological and objective basis, but in fact, this approach has created more complexity. Although cerebral amyloid deposition and neurofibrillary tangles are the key components in AD pathology, the etiology of AD is still under investigation. MCI is a diagnosis without validators and the lack of a prototypical MCI case makes the diagnosis unstable. Treating MCI as a nosological entity to feature an intermediate stage between normal aging and dementia may be an intuitive but complicated approach.

The development of biofluid and imaging markers has improved our understanding of the temporality of AD pathological progression. A longitudinal research design is thus crucial in studying cognitive decline in relation to pathological changes in aging and dementia. Low cognitive reserve and high vascular burden may contribute to dementia through different pathways, and understanding their roles will have an enormous impact in AD prevention.

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Conflicts of interest

There are no conflicts of interest.

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