# Mild Cognitive Impairment as a Concept and Clinical Entity

## Pete Harris

*WRITER'S COMMENT:* *This paper is the collaborative result of many influences. My family history led me to become particularly interested in dementia and inspired me to volunteer at the UC Davis Alzheimer's Disease Center clinic. Here I met a number of amazing patients, family members, caregivers, and clinicians— and discovered many neurological diseases, all of which had scary sounding acronyms, such as AD, CVD, CBD, SIVD, and MCI. Although I was able to provide a supporting role in assisting doctors at the clinic, I found that I could more proactively help dementia patients through undergraduate research. At the UC Davis Center for Neuroscience, my research advisor, Dr. Owen Carmichael, has been instrumental in guiding me through research papers on dementia and related topics. When my UWP 104F professor, Dr. Mardena Creek, assigned a literature review project, I knew I wanted to write about dementia. Many thanks go to Dr. Creek and Dr. Carmichael for helping me to polish this paper, and to Ashley Stoffan for always supporting me.*

*—Pete Harris*

*INSTRUCTOR'S COMMENT:* *The literature review I assign in Writing in the Health Sciences (UWP104F) asks students to identify a cutting-edge area of research in the medical field, research that topic in the scientific literature, and synthesize their findings in an article directed to an audience of interested professionals. Pete Harris' experience working with patients suffering from dementia at the UC Davis Alzheimer's Disease Center and his undergraduate research experience at the UC Davis Center for Neuroscience contributed significantly to the success of his review paper. Already knowledgeable about dementia and committed to advancing his and others' understanding of its possible causes, Pete examined the most recent literature on Mild Cognitive*

*Impairment, analyzed his findings, and presented them in a cogent, well organized literature review that concludes by exploring not only the research but also the clinical and societal implications of his topic. Pete's mastery of the subject, combined with his passion for advancing the understanding of dementia, resulted in a sophisticated and provocative literature review. I am delighted that this excellent paper now reaches a wider audience.*

*—Mardena Creek, University Writing Program*

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## Abstract

Mild cognitive impairment (MCI) is currently identified as the transition state between normal aging and dementia. Unfortunately, the boundaries between MCI, normal aging, and dementia are unclear. This review examines the development of MCI as a concept, and suggests that the heterogeneous definition of MCI may be the reason for disparate results among studies. For this reason, it is currently not valid to consider MCI as a specific medical homogeneous condition. Future research must be done before considering MCI as a distinct clinical entity. However, despite limitations in the MCI construct, MCI still represents a useful tool for both clinical and research purposes. Clinically recognizing pathological aging sooner will allow investigators to better elucidate the origins of dementia and potentially develop successful treatments.

MILD COGNITIVE IMPAIRMENT (MCI) is a widely discussed condition thought to be a transition state between normal aging and dementia such as Alzheimer's Disease (AD). Many studies have attempted to determine the pathological changes within individuals diagnosed with MCI, as well as to determine the epidemiological factors affecting MCI risk for society as a whole (6). Unfortunately, the upper and lower boundaries separating MCI from normal aging and from AD are unclear due to heterogeneous definitions of the condition which lead to disparate results across studies (9). While some MCI patients fully progress to dementia, other individuals may actually remain stable or revert to normal cognition. Disagreement among studies creates controversy over whether MCI deserves a distinct nosological status. This

review will examine to what extent MCI is a valid concept and evaluate the usefulness of MCI as a specific clinical entity.

## MCI as a Concept

### *Conceptual Development*

MCI IS A RELATIVELY NEW TERM describing the transient condition between normal aging and dementia. However, the idea of a link between normal and pathological aging is not new: in 1962 Kral *et al.* described a condition known as "senescent forgetfulness" (15). By distinguishing between benign and malignant forgetfulness, they defined pathological aging as a condition characterized by an awareness of memory problems and depressive symptoms. In 1986, Crook *et al.* quantitatively described pathological aging using the term "age-associated memory impairment" (15). Crook *et al.* described abnormal memory function among older adults as a one–standard deviation decrease on a formal memory test. Since these two studies were published, a variety of definitions and terms have been used to describe atypical memory decline. The term MCI was first used during the late 1980s and early 1990s by a group of New York University researchers to define patients who were cognitively abnormal but did not yet manifest dementia (11). Where and how MCI fits amid these concepts is unresolved, as the absolute definition of MCI is still being debated in the literature.

### *Heterogeneous Definitions*

RESEARCHERS ARE STILL REFINING the definition of MCI. In a 1997 study, Petersen *et al.* describes MCI in terms of patient complaints regarding defective memory, demonstration of abnormal memory functioning for age, preserved general cognitive functioning, intact activities of daily living, and no clinical dementia (13). Recognizing the heterogeneity of the concept, researchers added that the memory impairment must go beyond that expected for age and education-matched normal healthy subjects (12). In addition, they recognized that progression to multiple types of dementia such as AD, frontotemporal dementia, and vascular dementia might be related to multiple types of MCI. In other words, different types of MCI may represent distinct clinical etiologies. For example, MCI that primarily affects memory, or "amnestic" MCI, is currently thought to

be the precursor to AD. A new classification scheme recognizes four types of MCI: solely amnestic, amnestic with deficits in other cognitive domains such as attention or visuospatial domains, nonamnestic single-domain, and nonamnestic multiple domains (8). Researchers hope to resolve discrepancies in the variability of MCI by matching specific types of MCI to their underlying etiologies (11).

A review of the literature reveals two general types of definitions: those that specify MCI exclusively as memory impairment, and those that encompass other cognitive domains (5). Whether researchers diagnose patients based on the more specific or broader definition of MCI has huge implications for the results of the clinical studies. The chosen definition of MCI affects the underlying etiology and measurement of decline, estimates of prevalence, and potential treatments.

## MCI as a Clinical Entity

### *Pathophysiology and Measures of Decline*

Neuropsychological tests seek to describe the cognitive symptoms bridging healthy aging and dementia. However, variability and a lack of consistent standards in neuropsychological testing have created discrepancies between studies. Crook *et al.* were the first to define pathological aging by making specific quantitative measurements with a neuropsychological memory test (15). While they defined pathological aging as a one–standard deviation decrease from normal elderly subjects, other studies have used as many as two standard deviations (6). Differences also exist in the number of tests administered. If one test forms the basis of the results, instability in the results may be caused by instability in the psychometric measure rather than in a heterogeneous definition of MCI (11). If more than one memory test is used, however, there is no consensus as to how many measures are needed or how much of a memory decline represents cognitive impairment. Additionally, difficulties on a psychometric test of memory may involve other cognitive processes such as deficits in executive function, attention, and comprehension, further compromising the results (15). Also, measurement of memory impairment in the elderly is difficult as there is often a lack of test scores to produce statistically normal distributions (6). The confusion resulting from neuropsychological methods may be clarified by examining MCI from a biological perspective.

Different types of MCI may be the result of different etiologies. For example, amnestic MCI, the proposed precursor to AD, is likely caused by the same underlying pathology as AD. Whereas normal brains have very little senile plaque density and limited neuronal loss, AD patients have much more severe deficits (5). In a study by Price *et al.*, patients with a clinical dementia rating of 0.5, which may indicate amnestic MCI, showed signs of pathology at a level of severity between normal elderly controls and patients with AD (14). If results are compared between studies that only focus on amnestic MCI, those results should be congruent. Studies showing patients regressing to normal cognition after diagnosis may not have taken the distinct etiology behind the specific type of MCI into account. For example, there are several causes of MCI that can result in transient loss of cognitive abilities; if these causes are not recognized, then people are mistakenly diagnosed with amnestic MCI, which negatively affects the validity of the results. Reversible causes of MCI include upper airway obstruction or depression, as well as various metabolic, nutritional, and sensory deficits (9). Logical transient impairments exist to explain why individuals diagnosed with MCI may revert to normal cognition. Results can be clarified by understanding the underlying pathology between types of MCI. For example, Petersen *et al.* use relatively restrictive amnestic MCI diagnostic criteria, and diagnosed subjects have higher rates of progression to AD with fewer patients reverting to normal cognition (11). Unfortunately, some researchers report that even within specific types such as amnestic MCI, heterogeneity still exists (5). In this regard, brain imaging may be an important tool to resolve whether a patient will progress to dementia.

Brain imaging is a much more objective measure of change than neuropsychological testing, because it relies on actual changes to brain structure rather than possibly transient cognitive symptoms. While imaging methods should help to clarify differences in results, a recent imaging study by Apostolova *et al.* further revealed heterogeneity even within the relatively specific amnestic MCI category (1). Researchers longitudinally followed twenty patients diagnosed with MCI. They created three categories: MCI-c (develop AD), MCI-nc (remain stable), and MCI-i (improve). Volumetric analysis revealed that MCI-c patients have significantly reduced hippocampal volumes over three years, thus showing the predictive validity of brain imaging. Although researchers theoretically screened out all cases of MCI that should have reverted to normal

cognition, a significant percentage actually did (roughly one-third). The concept of MCI remains plagued from heterogeneity found within neuropsychological, pathological, and brain imaging perspectives.

## *Prevalence*

Varying definitions of MCI cause estimates of its prevalence within the general elderly population to vary greatly. More specific definitions of MCI focusing solely on memory impairment, such as the Petersen criteria, yield smaller estimates of around 3% (5). On the other hand, broader definitions encompassing any type of cognitive impairment causes estimates to be higher at 16.8% (9). Additional variability occurs in the reported statistical rates of progression to dementia. Studies using broad definitions typically have a high percentage of patients who remain stable or even revert to normal cognition. Gauthier *et al.* cite a study in which 44% of patients diagnosed with MCI returned to normal cognition within a year (8). Some investigators argue that this implies a lack of stability in the concept itself over time (9). However, other researchers argue that studies have not properly screened out transient causes of MCI and matched specific etiologies correctly to a specific MCI type (11). According to the restrictive amnestic MCI criteria, fewer patients reverted and rates of conversion to dementia were predicted at 10-15% per year (11). Another problem is that longitudinal studies often have not followed patients longer than three years. Petersen argues that longer studies would show higher amounts of conversion. Additionally, studies concerning older adults invariably have significant attrition rates because of patient death. If these patients lived longer, they might have eventually progressed to dementia; lack of this information creates further variability in measuring the prevalence of conversion from MCI to dementia (5).

Although the etiology-specific MCI approach helps to resolve some of the reported variability in prevalence, evidence still exists for heterogeneity within the most restrictive types of MCI. In a study by Busse *et al.*, researchers explored the prevalence and predictive validity of the various sub-classifications of MCI (3). They delineated patients into three sub-classes: "MCI-amnestic," "MCI–multiple domains slightly impaired," and "MCI–single nonamnestic domain." Normal nondemented individuals over seventy-five were classified based on clinician interviews and

neuropsychological tests such as the mini-mental state exam. Subjects were longitudinally followed for three years to see if subtypes eventually progressed to dementia. Researchers found that none of the three subtypes significantly predicted dementia. Additionally, results failed to support the idea that different subsets of MCI will progress to different dementias. The fact that Busse *et al.* followed etiology-specific criteria and failed to find significant predictability of conversion to dementia provides sufficient evidence for the heterogeneity of MCI even within subtypes.

## Treatment

WHETHER TO ADMINISTER TREATMENT is perhaps the most controversial issue in MCI research. Although it is established that MCI is a heterogeneous condition even in the most specific types, pathological evidence and common sense indicate that drugs used for dementia may be helpful in treating the condition or prolonging progression (5). Acetyl cholinesterase inhibitors (AchEIs) are used to combat the degradation of acetylcholine found in the neuronal junctions of the AD brain (9). Focusing on amnestic MCI, the proposed precursor to AD, the temptation for neurologists to prescribe AchEIs is great. Yet arguments can be made both for and against treatment of amnestic MCI.

Multiple reasons for not treating MCI are apparent. As previously discussed, when examining the general population, a significant percentage of diagnosed MCI patients will revert to normal cognition or will not progress. The diagnosis of MCI in these patients may inappropriately create a heavy psychological and medical burden on the person or his or her family (9). Also, since MCI is not a homogeneous clinical entity, doctors might inappropriately prescribe a specific drug treating the wrong pathology (9). Additionally, current clinical trials using AchEIs indicate that benefits are limited and transient (2). According to Gauthier *et al.*, treatment has been predominantly unsuccessful over the last three years (8). Treatment may not be successful until MCI is better understood.

Compelling reasons to treat MCI also exist. Since MCI has milder pathology and clinical symptoms compared to dementia, drugs with little efficacy combating dementia may be more effective if introduced at earlier stages of the disease (5). Although there is a possibility of wrongly diagnosing a patient with MCI, a diagnosis should not be withheld.

Whether the patient progresses or not, he or she deserves the chance to plan financially and emotionally for the possibility of dementia (11). Patients should have a chance to make decisions about their future, such as whether to retire. Petersen *et al.* argue that the experienced clinician will be able to gauge the chance for progression using a battery of neuropsychological and imaging methods and counsel the patient accordingly (11). If the cause of MCI is transient, such as depression, this will be discovered and treated appropriately. Treatment is also supported from a pharmacoeconomic perspective (17). If treatment of MCI can postpone dementia for even a short amount of time, this may result in economic benefits of up to $5300 per year. Delaying the onset of dementia is thus advantageous to the individual and family members by lessening the reported economic and emotional care-giving burden (7). Recognizing the debate from both sides, Roach argues that if medication improves cognitive function and quality of life, however slightly, attempting treatment is reasonable (16). Further research must be done to better define MCI to help clinicians determine when to treat patients, and to create more efficacious treatments.

## Conclusion

THE CONCEPT OF MCI is still widely disputed in the literature. The heterogeneity of the definition makes the relationship between MCI, other types of cognitive decline, and dementia unclear. Further research must be done before conclusions can be made about the validity of MCI as a distinct nosological status. However, despite the limitations of MCI, the concept of pathological aging and its clinical characterization have proven to be very useful tools.

The construct of MCI has been useful from societal, clinical, and research perspectives. Recognizing the concept of MCI or pathological aging in general as different from normal aging is a tremendous step forward. If successful treatments for MCI can be found, society's attitude toward the elderly may change and older adults may not perceive dementia as a necessary process of aging. New attitudes, in turn, may spur more research to discover even more effective treatments. Investigative and clinical efforts to characterize pre-dementia states allow the opportunity to identify disorders, advise patients, and eventually treat mild conditions before they fully progress to dementia.

Although relatively little has been firmly established in MCI research, studies reveal a very high interest in the screening and treatment of this possible disorder. In a 2006 pilot study by Dale *et al.*, investigators interviewed older adults over 35 years of age to test their willingness to be screened for MCI (4). An astounding 98% of subjects said they would agree to MCI testing if a family member indicated that they have memory problems. Furthermore, if subjects were hypothetically diagnosed with MCI, 92% of patients would be willing to take medication even if it delayed the onset of dementia by only one year. The high interest in treating this disease is disconcerting given the current state of knowledge about MCI. Considering the variability in MCI definitions and their implications on clinical medicine, further research needs to be done.

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## References

1.   Apostolova MD, *et al.* 2006. Conversion of mild cognitive impairment to Alzheimer Disease predicted by hippocampal atrophy maps. *Arch Neurology* **63(5)**: 693–9.

2.   Blacker D. 2005. Mild cognitive impairment: No benefit from Vitamin E, little from Donepezil. *New Engl J Med* **352**: 2439–41.

3.   Busse A, *et al.* 2003. Subclassifications for mild cognitive impairment: Prevalence and predictive validity. *Psychol Med* **33**: 1029–38.

4.   Dale W, *et al.* 2006. High interest in screening and treatment for mild cognitive impairment in older adults: A pilot study. *J Amer Geriatr Socty* **54**: 1388–94.

5.   DeCarli C. 2003. Mild cognitive impairment: Prevalence, prognosis, aetiology, and treatment. *Lancet Neurology* **2**: 15–21.

6.   Ganguli M. 2006. Mild cognitive impairment and the 7 uses of epidemiology. *Alzheimer's Disease & Assoctd Disorders* **20(2)**: 52–7.

7.   Garand L, *et al.* 2005. Caregiving burden and psychiatric morbidity in spouses and persons with mild cognitive impairment. *Int J Geriatr Psychiatry* **20(6)**: 512–22.

8.   Gauthier S, *et al.* 2006. Mild cognitive impairment. *Lancet* **367**: 1262–70.

9.    Gauthier S, Touchon J. 2005. Mild cognitive impairment is not a clinical entity and should not be treated. *Arch Neurology* **62(7)**: 1164–6.

10.    Modrego PJ, *et al.* 2005. Conversion from mild cognitive impairment to probable Alzheimer's Disease predicted by brain magnetic resonance spectroscopy. *American J Psychiatry* **162**: 667–75.

11.    Petersen R, Morris J. 2005. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurology* **62(7)**: 1160–3.

12.    Petersen R, *et al.* 1999. Mild cognitive impairment: Clinical characterization and outcome.  *Arch Neurology* **56(3)**: 303–8.

13.    Petersen R, *et al.* 1997. Aging, memory, and mild cognitive impairment. *Int Psychogeriatrics* **9(1)**: 65–9.

14.    Price J, Morris J. 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's Disease.  *American Neurolog Assoc* **45**: 358–68.

15.    Ritchie K, Touchon J. 2000. Mild cognitive impairment: Conceptual basis and current nosologicial status.  *Lancet* **255** (9199): 225–8.

16.    Roach ES. 2005. Treating mild cognitive impairment: The absence of evidence. *Arch Neurology* **62(7)**: 1167.

17.    Wimo A, Winblad B. 2003. Pharmacoeconomics of mild cognitive impairment. *Acta Neurologica Scandinavica* **107(179)**: 94–99.

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